

# What is Data Mining?

A data mining analysis was performed using a version of the AERS spontaneous reporting database. This database is the primary data resource for the study and identification of adverse drug reactions in the United States, and currently contains over 2.9 million such reports. AERS has over 10,000 Preferred Terms (PTs) and over 4,000 decoded generic drug names.

The fundamental method used in this consult is DuMouchel's Multi-item Gamma Poisson Shrinker (MGPS) method. MGPS is a disproportionality method that utilizes an empirical Bayesian model to detect the magnitude of drug-event associations in drug safety databases. MGPS calculates adjusted reporting ratios for pairs of drug event combinations. The adjusted reporting ratio values are termed the EBGM or the "Empirical Bayes Geometric Mean." EBGM values indicate the strength of the reporting relationship between a particular drug and event pair.

In order to reduce potential confounding, the MGPS program systematically stratifies the data in AERS by 1280 categories, including 39 by year, 11 by age group, and 3 by gender to help adjust for background differences in relative reporting ratios by these variables.

MGPS adjusts for multiplicity and controls type I (false positive) errors, by systematically "shrinking" observed-expected ratios that cannot be precisely estimated because of small counts towards 1 as a function of how much information exists about the drug-event combination. In general, the fewer events there are for a drug-event combination, the greater the shrinkage. Typically, drug-event combinations with three or fewer reports for the event are shrunk a large amount, while drug-event combinations with 20 or more reports for an event are shrunk by a small amount.

Analyses of the relative frequency of reports as of May 2006 were conducted by first designing three distinct data mining configurations that were used to generate three distinct MGPS data mining analyses.

The *All Reports* output table assessed all of the more than 2.9 million reports, and almost 24 million combinations of pairs of items and single items by year contained in AERS. The *Fatal* output table assessed the data from the over 240 thousand reports in which the patient died. This table contains the values for over 7.4 million combinations of items and single items by year. The *Disabled* output table assessed the data from the over 90 thousand reports in which the patient became disabled. This table contains the values for over 4.4 million combinations of items and single items by year.

While all suspect drugs were included in the analyses, results are only presented for the following 16 drugs: telithromycin, azithromycin, clarithromycin,

dirithromycin, erythromycin, cefditoren, cefixime, cefpodoxime, ceftibuten, cefuroxime, gemifloxacin, moxifloxacin, trovafloxacin, nitrofurantoin, amoxicillin and clavulanate, and acetaminophen. We only presented results for drug - PT pairs for severe adverse events where EBGM  $\geq 2$  and  $N \geq 2$  for at least one year. PTs most likely related to the indications being treated (e.g., pneumonia, meningitis, otitis, pain) were excluded, with the exception of gout because gout appeared to be a surrogate for a serious drug-drug interaction between colchicine and clarithromycin. To focus the analysis, we selected the event codes that reflected a more severe problem (e.g., we selected "Hepatic failure" instead of "Aspartate Aminotransferase Increased", "Toxic epidermal necrolysis" instead of "Rash"). The 168 PTs of interest and outcomes selected and the groups of event codes are listed in page 81 of the Memorandum.

MGPS was able to detect known toxicities across multiple drugs and drug classes and multiple events as exemplified by the detection of hepatotoxicity with acetaminophen and trovafloxacin, our positive comparators for liver toxicity in this review. Most of the antimicrobials that we studied show some unique class specific risks. Our results for a drug are in general, consistent with the results with other drugs in the same class. (See Figures 6 and 7 on pages 37 to 55 of the Memorandum.)

Telithromycin shows some *uniquely* strong signals for eye events, myasthenia and exacerbation of myasthenia, ischemic hepatitis, and syncope (See Figure 3-5 of the Memorandum). The diplopia eye events with telithromycin seem to be acetylcholine mediated and may be related to telithromycin's myasthenia events signals. The eye events with telithromycin may pose problems in patients who drive or operate machineries. For other reasons, fluoroquinolones may also pose problems in patients who drive or operate machineries. The myasthenia and exacerbation of myasthenia events may pose serious problems for patients at risk of developing these events.

For many events, including hepatic failure, drug-drug interactions, and QT prolongation and torsades de pointes, the telithromycin signals were so far similar or lower to those of several other drugs. Telithromycin seems to have so far less relative reporting of deafness, tinnitus, and gout than other macrolides, less Clostridium infection than cephalosporins, fluoroquinolones, macrolides, amoxicillin and clavulanate and nitrofurantoin; less cholestasis than "amoxicillin and clavulanate," macrolides, fluoroquinolones, and nitrofurantoin; less pancreatitis than acetaminophen, "amoxicillin and clavulanate," and macrolides. As well as other antimicrobials, telithromycin shows so far less neuropathy, polyneuropathy, and toxic lung signals than nitrofurantoin, and less psychiatric disorders than fluoroquinolones and macrolides. (See Figures 6 and 7 of the Memorandum)

Using MGPS we detected some growing hepatotoxicity signals across all reports and with reports having a fatal outcome with acetaminophen, telithromycin, nitrofurantoin, "amoxicillin and clavulanate," and some macrolides (See Figure 9

on page 72, Table 6 [all reports] on page 18 and Table 7 on page 20 [reports having a fatal outcomes] of the Memorandum).

## Data Mining at the FDA

### *General Information*

#### What is Data Mining?

- *Definition:* a systematic analysis method used to simultaneously extract new and useful information hidden in large, complex databases.
- *Impact:* once meaningful patterns identified, information can be evaluated to forecast future trends and/or intervene as appropriate.
- Goal of Data Mining at the FDA:

to detect “higher than expected” drug-event combinations in post marketing reports.

to help monitor the safety of drugs, biologics, and vaccines after they have been approved for use.

- *Method implemented by the FDA:* a Bayesian data mining system called the Multi-item Gamma Poisson Shrinker (MGPS) (<sup>i</sup>, <sup>ii</sup>)

#### What Opportunities Does MGPS Provide?

Even when specific questions are not asked

- MGPS provides a large collection of positive and negative controls
- Provides reminders of what other experts know that serve to assess biologic plausibility of results
- Provides clues to complex safety issues quickly
- Signals important information that might be missed if the question is not asked
- Aids in predicting future trends or behaviors (e.g., of drugs in same class)
- Enables decision-makers to make proactive, knowledge driven decisions

#### What is MGPS?

- MGPS calculates adjusted reporting ratios.
- *Independence Assumption:* drug-event combinations are reported with no greater relative frequency for drug X than for any other drug. Example: if 3% of all reports contain acetaminophen as a drug, and 7% of all reports contain “rash”

as an event, then the expected count for “acetaminophen-rash” as a drug-event combination would be 0.21% ( $0.03 * 0.07$ ) of the total number of reports.

- Adjustments:
- MGPS systematically stratifies a huge database by more than 1,300 categories (9 for age, 3 for sex [male, female, unknown]), and 39 for year of report) to help adjust for background differences in relative reporting ratio by these variables.
- MGPS fits all interaction model for stratification variables.
- MGPS systematically “shrinks” observed-expected ratios that cannot be precisely estimated because of small counts. This process guards against generating multiple false-positive signals due to multiple independent comparisons.
- For every drug and event in AERS, MGPS evaluates all drug-event pairs.
- Calculations are limited to AERS data. No external denominators are incorporated in the calculations.

## Definitions

- EBGM (Empirical Bayes Geometric Mean): adjusted estimate for the relative reporting ratio. Example: if EBGM=3.9 for acetaminophen-hepatic failure, then this drug-event combination occurred in the data 3.9 times more frequently than expected under the assumption of no association between the drug and the event.
- EB05 and EB95 are the lower and upper bounds of the 2-sided 90% confidence interval around EBGM.
- Comparing (EB05, EB95) intervals for the same event code or outcome between two or more drugs:

If the (EB05, EB95) intervals for two drugs overlap, it means the independence assumption is questionable for both. In other words, there may be an association between an adverse event and the both drugs in question.

Non-overlapping (EB05, EB95) intervals for a specific event code or outcome for two different drugs can be explained by considering that the proportional frequency of reported drug events is higher for one drug than for the other drug, displaying more “lack of independence” for one drug than the other for that particular event code.

Non-overlapping (EB05, EB95) intervals between two or more drugs for the same event can provide some information about the degree of relative toxicity between

these drugs, though the exact degree of this relationship is not yet known. However, a drug is not proven to be more or less toxic than another simply because of EBGM scores or overlapping or non-overlapping (EB05, EB95) intervals in these patient records.

Overlapping (EB05, EB95) intervals are “inseparable” in the sense that there is not enough information regarding one drug’s relative association with that particular event code versus another.

### **Limitations of MGPS**

- Data mining simply identifies adjusted disproportionality of drug-event reporting patterns in databases.
- The absence of a “signal” (higher-than-expected reporting relationship between a drug and event) does not rule out a safety problem.
- Potential for confounding due to multiple indications.
- Data mining cannot prove or refute causal associations between drugs and events.
- MGPS does not estimate incidence or prevalence.
- There is a potential for masking and leakage of signals in situations of polypharmacy. MGPS does not adjust for polypharmacy.
- No dosage and formulation information is incorporated in the MGPS analyses.
- To further study the adverse-event risk, the signals generated by MGPS can be evaluated by individual case review and compared with various analyses from other sources (e.g. clinical trials, general practice databases, literature reports).

### **Limitations of AERS**

- Passive reporting system. Reports to companies from patients or healthcare providers are still voluntarily submitted.
- No measure of exposure or background rate systematically linked to the AERS data.
- Potential for confounding due to multiple drugs being prescribed to individual patients.
- Reporter bias.

- No certainty that a reported event is causal.
- Incorrect reporting (missing fields, indications entered as adverse events, etc.)
- Under-reporting and waivers.

Waivers: Although pharmaceutical companies of marketed products are required to submit to the FDA reports of adverse events for their drugs, a company can request a waiver of this requirement for non-serious, expected adverse events for drugs and certain biologics.

- Over-reporting of specific drug-events due to publicity or litigation.
- Duplicate reporting of the same drug-event by different manufacturers for events associated with multiple drugs manufactured by various manufacturers.
- Inconsistencies and changes over time in reporting, naming, coding, and data processing practices.
- Coding errors and misspellings.
- Changes over time in prescribing paradigms.

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i DuMouchel W, Pregibon D. Empirical bayes screening for multi-item associations. Proceedings of the conference on knowledge discovery and data; 2001 Aug 26-29; San Diego (CA): ACM Press: 67-76.

ii Szarfman A, Machado SG, O'Neill RT. Use of Screening Algorithms and Computer Systems to Efficiently Signal Higher-Than-Expected Combinations of Drugs and Events in the US FDA's Spontaneous Reports Database. Drug Safety 2002; 25:381-392.



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

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# MEMORANDUM

**DATE:** Saturday, August 12, 2006

**TO:** Janice Soreth, M.D., Director of the Division of Anti-Infective and Ophthalmology Products, Office of New Drugs, HFD-520

**SUBJECT:** NDA 21-144, KETEK (Telithromycin) 400MG Tablets® (Sanofi-Aventis): Data Mining Analysis of Adverse Events and Outcomes Reported for Telithromycin and 15 Comparator Drugs (AERS Data)

**ISSUED BY:** Ana Szarfman, M.D., Ph.D., Medical Officer, Division of Cardiovascular and Renal products, Office of New Drugs, HFD-110 and Division of Biometrics VI, Office of Biostatistics, Office of Translational Sciences, HFD-705 and

Jonathan Levine, Ph.D., Expert Mathematical Statistician, Division of Biometrics VI, Office of Biostatistics, Office of Translational Sciences, HFD-705; and Division of Cardiovascular and Renal products, Office of New Drugs, HFD-110

**THROUGH:** Norman Stockbridge, MD, Director of the Division of Cardiovascular and Renal Products, HFD-110

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## **1. Purpose of this Review**

This review is the response to a consult request of May 2 2006 from Dr. Janice Soreth, Director of the Division of Anti-Infective and Ophthalmology Products.

Dr. Soreth requested data mining analyses to study competing profiles of relative reporting of adverse events of telithromycin and comparator drugs in the Adverse Event Reporting System (AERS) database.

## **2. Methods**

### **2.1. *Data Source***

The data mining analyses were performed using the CBAERS version<sup>(1)</sup> of AERS maintained by FDA. AERS is a spontaneous reporting database. This database is the primary data resource for the study and identification of adverse drug reactions in the United States. Created in 1968, the U.S. Food and Drug Administration (FDA) has maintained the AERS database containing reports of adverse drug events submitted to the FDA by the pharmaceutical industry and the public. AERS currently contains over 2.9 million such reports and the FDA continues to receive approximately 1,000 new reports each day. AERS has over 10,000 Preferred Terms (PTs) and 4,000 decoded generic drug names in use at least once. The large number and complexity of these reports and the sparsity of the data necessitate the use of statistical algorithms combined with modern computer technology to supplement traditional methods of detecting drug safety problems from this large database.

### **2.2. *Multi-item Gamma Poisson Shrinker (MGPS) Data Mining Method***

The fundamental method used in this consult is DuMouchel's Multi-item Gamma Poisson Shrinker (MGPS) method.<sup>(2,3)</sup> MGPS is a-disproportionality method designed to search in a disciplined and systematic way for potential drug safety problems in very large databases, such as AERS and to monitor the safety of drugs after they have been approved for use.<sup>(2,3)</sup> MGPS utilizes an empirical Bayesian model to detect the magnitude of drug-event associations in drug safety databases. MGPS calculates adjusted reporting ratios for pairs of drug-event combinations and for higher-order (e.g. triplet, quadruplet) combinations of drugs and events that are significantly more frequent than their pair-wise associations would predict.<sup>(2,3)</sup> The adjusted reporting ratio values are termed the EBGM or the "Empirical Bayes Geometric Mean." EBGM values indicate the strength of the reporting relationship between a particular drug and event pair.

This report focuses on drug-event pairs. In this report, we use the terms “EBGM value” and “data mining score” interchangeably.

The MGPS program systematically stratifies the data in AERS by 1280 categories, including 39 by year, 11 by age group, and 3 by gender to help adjust for background differences in relative reporting ratios by these variables. This stratification reduces potential confounding, including confounding due to database changes over time and prescribing paradigm changes over time and confounding due to independent relationships between a drug and a stratum variable and an event and the same stratum variable.<sup>(4)</sup> The MGPS program calculates lower and upper bounds of 90% confidence limits for each EBGM value, denoted EB05 and EB95 respectively.

### **2.2.1. MGPS Method in Plain English**

Disproportionality analysis can be used to calculate a relative reporting ratio (RR). In disproportionality analysis, the goal is to determine if a drug-event combination is reported with no greater relative frequency for drug X than for any other drug.

For example, if 2% of all reports contain acetaminophen as a drug, and 5% of all reports contain “rash” as an event, then the expected count for “acetaminophen-rash” as a drug-event combination would be 0.10% ( $0.02 * 0.05$ ) of the total number of reports.

If in fact 1% of all acetaminophen reports contain “rash” as an event, the RR can be estimated to be 10 ( $1.0\%/0.10\%$ ), indicating that rash is ten times a likely to be reported for acetaminophen than it is for all drugs in AERS.

A problem with this estimate of RR is that it can yield very large, high variability, estimates of RR when only one or two reports of an event have been observed for a drug. For example, if AERS only contained 100 reports for acetaminophen, having **one** of these reports be for rash **will produce an RR of 10** ( $1\%/0.10\%$ ), and having **two** reports be for rash **will produce an RR of 20** ( $2\%/0.10\%$ ). Another problem is that no attempt is made to adjust for multiple estimates of RR, so that using RR to make decisions about the true RR will be associated with many false positives.

In order to avoid the problem associated with the naïve estimate of RR, the FDA has implemented MGPS. The FDA is currently applying the MGPS data mining algorithm to the AERS database. MGPS and AERS are incorporated into the web based visual data mining environment (“WebVDME”).

The MGPS algorithm simultaneously and systematically analyzes the records contained in the AERS database and then quantifies potential drug-event associations by producing a set of values or scores, which can be ranked to indicate varying strengths of reporting relationships between drugs and events. These scores, denoted the Empirical Bayes Geometric Mean (EBGM), provide a stable estimate of the relative reporting ratio of an event for a particular drug relative to all other drugs in the database being analyzed. MGPS also calculates lower and upper 90% confidence limits<sup>(5)</sup> for EBGM values, denoted EB05 and EB95 respectively. General information on data mining at the FDA using MGPS is provided in the Appendix on page 76 and the general experience with MGPS is provided in the Appendix on page 80.

To further study the adverse-event risk, the signals generated by MGPS can be evaluated by individual case review and compared with various analyses from other sources (e.g. clinical trials, general practice databases, literature reports).

### ***2.2.2. How MGPS Helps Guard Against Generating Too Many False Positives?***

The MGPS uses the information contained in the AERS database to derive an improved estimate of the relative reporting ratio. Like the simple RR estimator, the MGPS algorithm estimates adjusted reporting ratios by assuming independence of drugs and events. Unlike the simple RR estimator, MGPS adjusts for multiplicity and controls type I (false positive) errors, by systematically “shrinks” observed-expected ratios that cannot be precisely estimated because of small counts towards 1 as a function of how much information contains about the drug-event combination. In general, the fewer events there are for a drug-event combination, the greater the shrinkage. Typically, drug-event combinations with three or fewer reports for the event are shrunk a large amount, while drug-event combinations with 20 or more reports for an event are shrunk by a small amount.

These features of the MGPS help guard against generating multiple false-positive signals due to multiple independent comparisons. These features enable using the adverse event profile of one drug to inform about drugs with similar chemical structures and about the competing relative reporting of adverse events of drugs in a similar drug class.

### ***2.3. MGPS Runs***

Analyses of the relative frequency of reports as of May 2006, were conducted by first designing three distinct data mining configurations prior to applying the MGPS algorithm to the FDA’s CBAERS database.<sup>(6)</sup> The three distinct configurations that we generated produced three distinct MGPS data mining analyses.

The *All Reports* output table assessed the data from over 2.9 million reports, and almost 24 million combinations of pairs of items and single items. The values include observed (N) and expected (E) counts and the EBGM, and the 90% confidence interval (EB05, EB95) of every drug-event, drug-drug, and event-event pairs by year. The values also include the N for every single drug by year and every single event by year.<sup>(7)</sup>

The *Fatal* output table assessed the data from over 240 thousand reports the patient died. This table contains the values for over 7.4 million combinations of items and single items.<sup>(8)</sup>

The *Disabled* output table assessed the data from over 90 thousand reports in which the patient became disabled. This table contains the values for over 4.4 million combinations of items and single items.<sup>(9)</sup>

Overall, these configurations generated over 35 million rows of values by drug, event, drug-event, and year, and by associated outcomes by drug, event, drug-event, and year.

To focus our analyses we selected from these output tables a set of specific drugs and events (See next sections).

## **2.4. Drugs**

Table 1 below lists the drugs selected for analysis by the DAIOP plus nitrofurantoin, a drug added by the reviewers of this document. The drugs selected as comparators are known to have particularly unique adverse event profiles (e.g., cephalosporins and *Clostridium difficile* colitis, fluoroquinolones and Central Nervous System adverse events).

Table 1: List of 16 drugs selected for analysis by DAIOP

Indication	Drug	Class
Anti-Infective	Ketolide	Telithromycin
	Macrolide	Azithromycin
		Clarithromycin
		Dirithromycin
		Erythromycin
		Cephalosporin
	Cephalosporin	Cefixime
		Cefpodoxime
		Ceftibuten
		Cefuroxime
		Fluoroquinolone
	Moxifloxacin	
	Trovafloxacin	
Nitrofurantoin*	Nitrofurantoin*	
Penicillin	Amoxicillin and clavulanate	
Analgesic	Anilide	Acetaminophen

\*Nitrofurantoin was selected as a comparator drug because of high data mining scores (EBGM values) for hepatotoxic events noted for this drug during this analysis of AERS.

## 2.5. Events

### 2.5.1. Event Codes Used in the Data Mining Runs

The Preferred Terms (PTs) selected in the data mining runs consisted of the Recoded Hepatotoxic Event Codes (described in Section 2.5.2 and in Table 2) as well as any other PT in CBAERS.

### 2.5.2. Recoded Hepatotoxic Event Codes Used in Data Mining Runs

To increase the sensitivity of the analysis of hepatotoxicity we recoded 29 MedDRA Preferred Terms (PTs) having similar event codes into 8 single PTs prior to running MGPS (see Table 2).

The rationale for combining medically similar codes is that these terms may represent misclassification among these codes or changes in coding practices through time. Under similar circumstances, a report containing an event code could have also been legitimately coded using other similar event codes, depending on the individual submitting the report or the individual coding the report. Therefore, combining these codes under this assumption would improve

the estimation of the drug-combined event confidence intervals for all the drugs being analyzed, resulting in narrower confidence intervals for hepatotoxic events.

Table 2: Recoding of “hepatotoxic” event codes prior to running MGPS

Original Event Code (Preferred Term)	Recoded Event Code
Cholestasis	Cholestasis
Cholelithiasis	
Hepatitis cholestatic	
Jaundice cholestatic	
Coma hepatic	Hepatic failure
Hepatic encephalopathy	
Hepatic failure	
Hepatic necrosis	
Hepatitis fulminant	
Liver transplant	
Autoimmune hepatitis	
Cytolytic hepatitis	
Hepatitis	
Hepatitis acute	
Hepatocellular damage	Hepatocellular damage
Hepatocellular damage aggravated	
Hepatitis toxic	Hepatotoxicity
Hepatotoxicity	
Ammonia increased	Hyperammonaemia
Hyperammonaemia	
Bilirubin conjugated increased	Hyperbilirubinaemia
Bilirubinuria	
Blood bilirubin increased	
Hyperbilirubinaemia	
Jaundice	
International normalized ratio increased	
Prothrombin level decreased	
Prothrombin time prolonged	

### 2.5.3. Selection of the Events of Interest for this Review

First, we included only PTs with at least one of the selected drugs having an EBG  $\geq 2$  and an  $N \geq 2$  in any given year. Next, we removed PTs most likely related to the indications being treated (e.g., pneumonia, meningitis, otitis, pain). There was only one exception to this rule. Gout was selected as a term because after drilling down to the narratives of the “Fatal” run we identified that Gout was a surrogate for a serious drug-drug interaction between colchicine and clarithromycin that leads to a high proportion of fatal outcomes. Lastly, to focus

the analysis, we selected the event codes that reflected a more severe problem (e.g., we selected “Hepatic failure” instead of “Aspartate Aminotransferase Increased”, “Toxic epidermal necrolysis” instead of “Rash”). The 168 events of interest and outcomes selected are listed in the Appendix on page 81.

## **2.6. *Recoded Event Classes***

To aid with pattern recognition in graphical displays, we grouped similar PTs into Recoded Event Classes (See Appendix on page 81.). This was done to simplify the analysis of complex drug safety patterns.

## **2.7. *Estimated Reporting Rates***

For the sake of completeness, we have, in some cases, calculated crude estimated reporting rates for the drugs and the years we received the number of estimated prescriptions dispensed for a drug (See Appendix on page 85).

We have serious reservations about these estimates. There is no way to adjust these rates for differences in underreporting and in duration of treatment, and for errors in the estimates of number of prescriptions.

Drug exposure data used as a denominator are an estimate of the number of prescriptions filled or dispensed for a particular drug, not an absolute indication of exposure to that drug. A myriad of issues, such as noncompliance, abuse, incorrect use, and sporadic use (as is the case with over-the-counter drugs such as acetaminophen or with prescription drugs such as nitrofurantoin) or dispensed as a prescription or over-the-counter (as is the case with acetaminophen) can generate unreliable exposure estimates. Drug exposure data and background rates of events for a particular population experiencing adverse drug events (e.g., baseline rates of hepatic failure in pneumonia patients of a certain age receiving specific concomitant drugs) are difficult to obtain or are nonexistent.<sup>(10)</sup>

Differences in estimated crude rates for two drugs may also be due to differences in treatment duration. For example, estimated reporting rates failed to detect a strong signal of hepatotoxicity with nitrofurantoin (the average reporting rate for Hepatic failure was 0.6 cases per million prescriptions dispensed and for Hepatitis 1.13 cases per million prescriptions dispensed.) This is a signal much clearly seen with MGPS. In situations such as with nitrofurantoin, where treatment is sporadic or longer than with other antimicrobials, EBGM values are unaffected by uncertain differences in treatment duration (Table 9).

In situations where drug exposure data are below the limits of detection of a method as is the case with ceftibuten with <1,000 prescriptions per year in 1997, detecting 6 cases of clostridial infections or 8 cases of toxic skin reactions, may

not automatically trigger an estimation of crude reporting rates (the reporting rate for Clostridial infections in 1997 was >6,000 cases per million prescriptions dispensed and for Toxic skin >8,000 cases per million prescriptions dispensed.) EBGM values are less affected by low drug exposure (Table 9).

Overall, differences in estimated crude rates for two drugs could be completely due to differences in the underreporting rate. While certain types of underreporting can also be a problem in MGPS analyses, in many situations EBGM values are unaffected by differences in underreporting (<sup>11</sup>)

## **2.8. *Time Periods of the Data Analyzed***

For the MGPS analyses we assessed all the CBAERS data collected between January 1968 through May 2006. For the estimated reporting rates we assessed all the CBAERS data collected between January 1991 and May 2006. This corresponds to the time period we received number of prescriptions dispensed.

## **3. Results**

### **3.1. *Year of First AERS Report by Drug***

Table 3 presents the year of first report for the 16 drugs included in this analysis. The AERS database started to collect data in 1968. Note in Table 3 that the year of the first reports by a drug being analyzed in this review ranges from 1969 for acetaminophen, erythromycin, and nitrofurantoin to 2004 for gemifloxacin. Differences between the year of the first report for a drug and the year of approval for marketing in the US reflect the submission to AERS of foreign or domestic reports prior to US approval for marketing.

Table 3: Year of the First AERS Report for Each Drug

Generic Name	Year of First AERS Report
Acetaminophen	1969
Erythromycin	1969
Nitrofurantoin	1969
Cefuroxime	1984
Amoxicillin and clavulanate	1984
Cefixime	1989
Clarithromycin	1991
Azithromycin	1992
Cefpodoxime	1992
Dirithromycin	1995
Ceftibuten	1996
Trovafloxacin	1998
Moxifloxacin	1999
Cefditoren	2001
Telithromycin	2002
Gemifloxacin	2004

### 3.2. Total Number of Reports

#### 3.2.1. All Reports Output Table

Table 4 presents the total number of reports for the *All Reports*, *Fatal*, and *Disabled* output tables for the 16 drugs included in this analysis.

As seen in Table 4 the total number of unique reports for all 16 drugs totaled 78,414 reports as of May 2006 (the cut-off date for this analysis). The total number of reports among these drugs (also denoted “marginal totals for the drugs”) vary widely, ranging from 226 to 13,759 with telithromycin having 1,736 reports. Dirithromycin, cefditoren, ceftibuten, and gemifloxacin have the lowest number of reports among the drugs analyzed with total number of reports less than 1,000. Cefpodoxime, cefixime, moxifloxacin, nitrofurantoin, trovafloxacin, cefuroxime, “amoxicillin and clavulanate”, and erythromycin all have a total number of reports between 1,000 and 10,000. Clarithromycin was the most commonly reported antimicrobial in this group, with 12,070 reports, second to acetaminophen with 13,759 reports.

#### 3.2.2. Fatal and Disabled Output tables

Table 4. Total number of unique reports for the *All Reports*, *Fatal*, and *Disabled* data mining output tables for the 16 drugs included in this analysis

Generic name	Total All Reports	Fatal Outcome		Disabled		Fatal or Disabled	
		Total	%	Total	%	Total	%
Acetaminophen	13,759	3,492	25.38%	140	1.02%	3,617	26.29%
Cefuroxime	5,744	443	7.71%	145	2.52%	582	10.13%
Amoxicillin and clavulanate	8,030	591	7.36%	224	2.79%	798	9.94%
Trovafloxacin	4,586	289	6.30%	84	1.83%	373	8.13%
Moxifloxacin	3,898	223	5.72%	125	3.21%	345	8.85%
Nitrofurantoin	4,567	223	4.88%	118	2.58%	338	7.40%
Clarithromycin	12,070	574	4.76%	284	2.35%	851	7.05%
Azithromycin	9,917	412	4.15%	332	3.35%	737	7.43%
Erythromycin	9,218	321	3.48%	128	1.39%	447	4.85%
<b>Telithromycin</b>	<b>1,736</b>	<b>56</b>	<b>3.23%</b>	<b>49</b>	<b>2.82%</b>	<b>105</b>	<b>6.05%</b>
Cefpodoxime	1,313	39	2.97%	22	1.68%	61	4.65%
Ceftibuten	593	17	2.87%	7	1.18%	24	4.05%
Cefditoren	523	14	2.68%	9	1.72%	23	4.40%
Cefixime	2,321	57	2.46%	17	0.73%	74	3.19%
Gemifloxacin	773	6	0.78%	4	0.52%	10	1.29%
Dirithromycin	226	0	0.00%	1	0.44%	1	0.44%
<b>Total</b>	<b>78,414</b>	<b>6,663</b>	<b>8.50%</b>	<b>1,655</b>	<b>2.11%</b>	<b>8,258</b>	<b>10.53%</b>

\* **Telithromycin values are in green. In red, higher proportions for the comparator than telithromycin; in blue, lower proportions for the comparator.**

As seen in Table 4, of the 16 drugs evaluated, **telithromycin ranked 10<sup>th</sup> in percentage of reports where the patient died** (3.23% of reports with AERS outcome variable equal to fatal). The proportion of fatal outcome was highest with acetaminophen with over 25% of the reports having a fatal outcome, followed by cefuroxime and “amoxicillin and clavulanate” with over 7%, trovafloxacin and moxifloxacin with over 5%, nitrofurantoin, azithromycin, and Clarithromycin with over 4%; and erythromycin and telithromycin with over 3%.

Compared to telithromycin only dirithromycin, cefditoren, ceftibuten, gemifloxacin, cefpodoxime, and cefixime have a lower proportion of fatal outcome, all below 3%. Dirithromycin does not have any report of fatal outcome.

Figure 1 shows the **progression of number of reports for all reports and for reports with a fatal outcome** for each drug. Note that AERS is barely collecting

new reports for dirithromycin since 1997, for ceftibuten since 1998, and for trovafloxacin since 2001. We expect this finding with trovafloxacin due to marketing restrictions following reports of serious hepatotoxic reactions with this drug.

As seen in Table 4, of the 16 drugs evaluated, **telithromycin ranked 3<sup>rd</sup> in percentage of reports where the patient had a disability** (3.35% of reports with AERS outcome variable equal to disability). The proportion of disability outcome was highest with azithromycin and moxifloxacin with over 3% of the reports having a disability outcome, followed by telithromycin with 2.82%. The rest of the drugs have a lower proportion of disability outcome than telithromycin, all below 3%.

As seen in Table 4, of the 16 drugs evaluated, **telithromycin ranked 9th in percentage of reports where the patient died or had a disability** (6.05% of reports with AERS outcome variable equal to fatal or disability).

Figure 2 shows the progression of number of reports for all types of reports and for reports with disability for each drug.

### **3.3. Total Numbers in the MGPS Subset Tables Used in this Review**

Our selection of the 168 events still allowed us to assess a huge proportion of all reports for the 16 drugs.

By selecting the 168 event codes we assessed 34,563 unique reports for the 16 drugs (44% of the 78,414 reports in the *All Reports* data mining output table), 4,669 (70% of 6,663 reports in the *Fatal* output table, and 950 (57% of the 1,655) in the *Disability* output table for these 16 drugs.

The *All Reports* analysis by cumulative year assessed 18,390 unique **drug-event** combinations, the *Fatal* 6,918 **fatal-drug-event** combinations, and the Disabled 4,820 **disabled-drug-event** combinations. The All Reports analysis also included 1,031 **drug-any outcome** unique combinations by year.

This review focuses on the cumulative data mining outputs by year of these 34,563 reports that included 31,159 (18,390 + 6,918 + 4,820 + 1,031) unique **drug-event** and **outcome** combinations.

We are not considering the **negative signals** of dirithromycin in our MGPS comparative analyses. The small number of reports with this drug leads to volatility and consequent shrinkage with MGPS.

### **3.4. Ranking of Telithromycin Among the 16 Drugs Across Recorded Event Classes**

Figure 3 to Figure 5 show an overview of the ranking of telithromycin across Recorded Event Classes among the 16 drugs as well as the Max EBGM (EB05, EB95) values for telithromycin across each recorded event class. In this analysis, a rank of 16 corresponds to having the highest Max EBGM value among the 16 drugs in any given year, while a rank of 1 corresponds to having the lowest Max EBGM value among the 16 drugs. If a drug has no reported events for a particular recorded event class it is given a rank of zero.

#### **3.4.1. Ranking Across the “All Reports” output**

Inspection of Figure 3 on page 31 shows that telithromycin had the highest score for three recorded event classes: *Eye*, *Myasthenia*, and *“Ischemic hepatitis.”* For the remaining 43 event classes, one or more drugs had a higher score than telithromycin. For ten of the event classes, telithromycin has no events.

#### **3.4.2. Ranking Across the “Fatal Outcome” output**

Figure 4 shows the same overview as in Figure 3 but across fatal outcome. In this analysis, a rank of 15 corresponds to having the highest EBGM value among the 15 drugs with fatal outcomes, while a rank of 1 corresponds to having the lowest EBGM value among the 15 drugs. Inspection of Figure 4 shows that telithromycin had the highest score for three event classes: *Syncope*, *Myasthenia*, and *“Ischemic hepatitis.”* For the remaining 43 recorded event classes, one or more drugs had a higher score than telithromycin. For 21 of the recorded event classes, telithromycin has no events.

#### **3.4.3. Ranking Across “Disabled Outcome” output**

Figure 5 shows the same display as in Figure 3 and Figure 4 but across the disability outcome. Inspection of Figure 5 shows that telithromycin had the highest score for two event classes: *Eye* and *Myasthenia*. For the remaining 42 event classes, one or more drugs had a higher score than telithromycin. For 21 of the event classes, telithromycin has no events.

### **3.5. Events More Likely to be Associated with a Drug, Drugs, or Classes of Drugs, or with a Fatal or Disability Outcome**

Figure 6 and Figure 7 present spatial maps of composite summary displays of the Max EBGM values and Figure 8 of the number of reports for the ***integrated data from three different MGPS output tables*** for the 16 drugs and 168 event codes, including:

- *All Reports*
- *Fatal* outcome
- *Disabled*

The event axis of Figure 6 is organized by related Recorded Event Classes.

The event axis of Figure 7 and Figure 8 are first organized by related Recorded Event Classes and then split into related Events or Outcomes of Interest (See details in the Appendix on page 81).

The drug axis of Figure 6, Figure 7 and Figure 8 are organized by drug class and then split into the individual drugs as listed in Table 1.

Figure 6 shows the Max EBGM values in any given year ***with Recoded Event Classes***

Figure 7 shows the Max EBGM values in any given year with ***Events of Interest<sup>(12)</sup>***

Figure 8 shows the ***total number of reports in 2006 for the drug-event associations in*** Figure 7 plus the marginal totals for each drug and each selected event and outcome.

### ***3.5.1. Interpreting Figure 6 and Figure 7***

By comparing the column (drug) values in these graphs with the rows (event by type of analysis including for all reports, and for fatal and disability reports), it is possible to get a sense of which events are more likely to be associated with which drug, drugs, or classes of drugs, or with a fatal or disability outcome.

These types of display provide some insight into the safety trade-offs associated with choosing one antibiotic over another. In the discussion we present scenarios in which a clinician might opt to use one antimicrobial instead of another based upon differing side effect profile.

#### **3.5.1.1. Examples**

Several eye events have strong EBGM signals with telithromycin. Single eye events have weak EBGM signals with clarithromycin (only one PT: diplopia), with erythromycin (only one PT: visual disturbance), with moxifloxacin (only one PT:

“Optic neuritis retrobulbar”), and with “amoxicillin and clavulanate” (one PT: optic neuropathy) but do not have any signal above an EBGM >2 with any of the cephalosporins that we studied or with acetaminophen. Figure 7 shows that most eye events are also associated with disability outcomes.

Strong EBGM signals for Clostridium infection with cephalosporins, and weak EBGM signals with macrolides and fluoroquinolones. Clostridium infection with these drugs is also associated with fatal and disability outcomes. Clostridium infection reports are just starting to arrive with telithromycin (a total of 4 cases), none reported as having a fatal outcome.

Strong EBGM signals for anaphylactic reactions with cephalosporins, moxifloxacin, and “amoxicillin and clavulanate”. Anaphylactic reactions with these drugs have strong fatal outcome signals. So far, anaphylactic reactions have weak EBGM signals with macrolides and telithromycin, so far without fatal outcome signals with telithromycin.

Macrolides and moxifloxacin have strong EBGM signals for torsade de points and or QT prolongation. These events have strong fatal outcome signals, so far without cases of fatal outcome with telithromycin.

### 3.6. *Telithromycin Confidence Intervals*

The following subsections show the details of the overlapping/non-overlapping status of (EB05, EB95) intervals of Telithromycin with regard to the comparator drugs. <sup>(13)</sup>

#### 3.6.1. *CI for Fatal Outcome Across All Events in the CBAERS data*

As seen on Table 5, of the 16 drugs evaluated, MGPS showed that telithromycin’s confidence intervals for fatal outcomes were below the confidence intervals of 9 comparator drugs. <sup>(14)</sup>

Table 5. EBGM (EB05, EB95) Values for Fatal Outcome by Drug (All data collected as of May 2006)

Generic name	N	EBGM (EB05, EB95)
Acetaminophen	3,492	2.38 (2.31, 2.44)
Cefuroxime	443	1.05 (.97, 1.14)
Trovafloxacin	289	0.84 (.76, .93)
Amoxicillin And Clavulanate	591	0.81 (.75, .86)
Nitrofurantoin	223	0.71 (.64, .8)
Clarithromycin	574	0.65 (.61, .7)

<b>Azithromycin</b>	<b>412</b>	<b>0.54 (.5, .58)</b>
<b>Ceftibuten</b>	<b>17</b>	<b>0.53 (.36, .77)</b>
<b>Moxifloxacin</b>	<b>223</b>	<b>0.52 (.47, .58)</b>
<b>Erythromycin</b>	<b>321</b>	<b>0.51 (.46, .56)</b>
<b>Cefpodoxime</b>	<b>39</b>	<b>0.5 (.38, .64)</b>
<b>Cefixime</b>	<b>57</b>	<b>0.45 (.36, .55)</b>
<b>Telithromycin</b>	<b>56</b>	<b>0.31 (.25, .39)</b>
<b>Cefditoren</b>	<b>14</b>	<b>0.28 (.18, .42)</b>
<b>Gemifloxacin</b>	<b>6</b>	<b>0.08 (.04, .16)</b>
<b>Fatal Outcome with All Drugs</b>	<b>240,155</b>	

\* **Telithromycin values are in green. In red, non-overlapping higher (EB05, EB95) interval for the comparator; in blue, overlapping (EB05, EB95) interval; in black, non-overlapping and lower (EB05, EB95) than teithromycin.**

### **3.6.2. CI for Selected Hepatotoxic Events**

#### **3.6.2.1. All Reports**

As described in Table 6, the data mining analysis showed that telithromycin confidence intervals were below 7 comparator drug event combinations, and were overlapping 16 or above other 16 comparator drug- event combinations.

##### **3.6.2.1.1. Hepatic failure**

As described in Table 6, of the 16 drugs evaluated, MGPS showed that telithromycin's confidence intervals were below the confidence intervals of 2 comparator drugs (acetaminophen and trovafloxacin), were overlapping with 2 drugs (nitrofurantoin and "amoxicillin and clavulanate"), and were above 5 drugs (clarithromycin, azithromycin, moxifloxacin, erythromycin, and gemifloxacin.)

##### **3.6.2.1.2. Hepatitis**

Telithromycin's confidence intervals were overlapping with 4 drugs ("amoxicillin and clavulanate," trovafloxacin, nitrofurantoin, and dirithromycin), and were above 6 drugs (acetaminophen, erythromycin, azithromycin, clarithromycin, moxifloxacin, and gemifloxacin).

##### **3.6.2.1.3. Hyperbilirubinaemia**

Telithromycin confidence were below the confidence intervals of "amoxicillin and clavulanate", were overlapping with 7 drugs, and were above 2 drugs with data.

### 3.6.2.1.4. Cholestasis

Telithromycin's confidence intervals were below the confidence intervals of 4 comparator drugs ("amoxicillin and clavulanate," erythromycin, nitrofurantoin, and clarithromycin), and were overlapping with 6 drugs (trovafloxacin, azithromycin, acetaminophen, dirithromycin, moxifloxacin, and gemifloxacin.)

Table 6. By event variations in overlapping and non-overlapping confidence intervals for telithromycin compared to each comparator Across All Reports\*

Event Code	Generic name	N	EBGM (EB05, EB95)
Hepatic failure	Acetaminophen	12,88	14.3 (13.65, 14.97)
	Trovafloxacin	136	5.44 (4.71, 6.25)
	Nitrofurantoin	71	4.83 (3.96, 5.85)
	Telithromycin	41	3.67 (2.82, 4.7)
	Amoxicillin and Clavulanate	141	3.13 (2.72, 3.59)
	Clarithromycin	101	1.8 (1.53, 2.11)
	Azithromycin	97	1.68 (1.42, 1.98)
	Moxifloxacin	40	1.39 (1.07, 1.79)
	Erythromycin	33	1.09 (.82, 1.44)
	Gemifloxacin	2	0.44 (.15, 1.1)
	All Reports	13,481	
Hepatitis	Amoxicillin and Clavulanate	317	6.31 (5.75, 6.92)
	Trovafloxacin	160	6.26 (5.48, 7.13)
	Nitrofurantoin	173	5.82 (5.13, 6.59)
	Telithromycin	59	5.79 (4.64, 7.17)
	Acetaminophen	347	3.85 (3.52, 4.2)
	Erythromycin	258	3.69 (3.33, 4.08)
	Dirithromycin	6	3 (1.51, 5.5)
	Azithromycin	150	2.61 (2.28, 2.97)
	Clarithromycin	169	2.43 (2.14, 2.76)
	Moxifloxacin	45	1.66 (1.29, 2.1)
	Gemifloxacin	1	0.3 (.07, .93)
	All Reports	17,676	
Hyperbilirubinaemia	Amoxicillin and Clavulanate	502	6.42 (5.97, 6.91)
	Nitrofurantoin	202	4.97 (4.42, 5.57)
	Erythromycin	442	4.9 (4.53, 5.3)
	Telithromycin	64	4.54 (3.68, 5.55)
	Trovafloxacin	230	4.5 (4.03, 5)
	Acetaminophen	535	3.69 (3.43, 3.95)
	Clarithromycin	274	2.5 (2.26, 2.76)

	Azithromycin	196	1.87 (1.66, 2.1)
	Moxifloxacin	56	1.35 (1.08, 1.68)
	Dirithromycin	3	1.3 (.51, 2.85)
	Gemifloxacin	2	0.38 (.13, .94)
	All Reports	27,017	
Cholestasis	Amoxicillin and Clavulanate	561	13.7 (12.78, 14.68)
	Erythromycin	348	8.58 (7.83, 9.38)
	Nitrofurantoin	66	3.2 (2.6, 3.9)
	Clarithromycin	143	2.74 (2.38, 3.14)
	Trovafloxacin	61	2.74 (2.22, 3.37)
	Azithromycin	123	2.64 (2.27, 3.05)
	Acetaminophen	157	2.15 (1.88, 2.45)
	Telithromycin	16	1.59 (1.05, 2.34)
	Dirithromycin	2	1.55 (.51, 3.84)
	Moxifloxacin	29	1.12 (.82, 1.5)
	Gemifloxacin	2	0.5 (.16, 1.23)
		All Reports	13,975

\* Telithromycin values are in green. In red, non-overlapping higher (EB05, EB95) interval for the comparator; in blue, overlapping confidence interval; in black, non-overlapping and lower confidence intervals than Teithromycin.

### 3.6.2.2. Fatal Outcomes

Telithromycin confidence intervals for four different hepatotoxic event codes across fatal outcome were mostly overlapping the confidence intervals of comparator drug-event combinations with data (Table 7).

Note also that the confidence intervals for fatal outcomes are higher for Hepatic failure than for all other events in this analysis.

#### 3.6.2.2.1. Hepatic failure

Telithromycin's confidence intervals overlapped with all the drugs with data.

#### 3.6.2.2.2. Hepatitis

Telithromycin's confidence intervals overlapped with 6 drugs with data.

#### 3.6.2.2.3. Hyperbilirubinaemia

Telithromycin confidence intervals overlapped with 8 drugs, and were above the confidence interval of one comparator drug (erythromycin).

### 3.6.2.2.4. Cholestasis

Telithromycin's confidence intervals were below the confidence interval of one comparator drug ("amoxicillin and clavulanate.") Telithromycin confidence intervals overlapped with 8 drugs.

Table 7: By event variations in overlapping and non-overlapping confidence intervals for telithromycin compared to each comparator Across All Reports with a Fatal Outcome Collected as of May 2006\*

Event Code	Generic name	N	EBGM (EB05, EB95)
Hepatic failure	Trovafloxacin	69	5.6 (4.56, 6.82)
	Acetaminophen	819	5.46 (5.15, 5.78)
	Nitrofurantoin	35	4.36 (3.28, 5.71)
	Amoxicillin and Clavulanate	81	3.82 (3.18, 4.57)
	Telithromycin	9	3.39 (1.95, 5.63)
	Moxifloxacin	21	2.56 (1.78, 3.6)
	Clarithromycin	50	2.38 (1.88, 2.99)
	Azithromycin	34	2.18 (1.64, 2.86)
	Gemifloxacin	2	1.97 (.69, 4.79)
	Erythromycin	19	1.62 (1.11, 2.31)
	All Reports	7,589	5.58 (5.47, 5.68)
Hepatitis	Amoxicillin and Clavulanate	38	5.6 (4.23, 7.36)
	Nitrofurantoin	19	5.54 (3.67, 8.46)
	Azithromycin	22	4.5 (3.14, 6.34)
	Trovafloxacin	13	3.96 (2.48, 6.13)
	Telithromycin	4	3.25 (1.39, 7.73)
	Clarithromycin	17	2.65 (1.77, 3.84)
	Moxifloxacin	7	2.61 (1.4, 4.53)
	Acetaminophen	67	2.2 (1.79, 2.67)
	Erythromycin	4	0.96 (.43, 1.9)
	All Reports	2,161	1.34 (1.29, 1.39)
Hyperbilirubinaemia	Nitrofurantoin	22	4.73 (3.29, 6.7)
	Trovafloxacin	35	3.91 (2.94, 5.11)
	Telithromycin	6	3.48 (1.75, 6.62)
	Amoxicillin and Clavulanate	44	3.16 (2.46, 4.02)
	Acetaminophen	226	3.03 (2.72, 3.38)
	Clarithromycin	37	2.93 (2.23, 3.8)

	Azithromycin	24	2.63 (1.87, 3.62)
	Gemifloxacin	2	2.22 (.75, 5.79)
	Moxifloxacin	5	1.02 (.5, 1.91)
	Erythromycin	7	1 (.54, 1.73)
	All Reports	4,392	1.68 (1.64, 1.73)
Cholestasis	Amoxicillin and Clavulanate	74	13.86 (11.37, 16.73)
	Trovafloxacin	10	2.87 (1.7, 4.61)
	Erythromycin	8	2.59 (1.45, 4.36)
	Clarithromycin	14	2.56 (1.64, 3.85)
	Nitrofurantoin	6	2.45 (1.26, 4.41)
	Gemifloxacin	2	2.43 (.79, 8.03)
	Azithromycin	9	2.43 (1.4, 3.98)
	Moxifloxacin	6	2.05 (1.06, 3.68)
	Telithromycin	1	1.14 (.31, 3.2)
	Acetaminophen	29	1.13 (.83, 1.51)
	All Reports	1,761	1.22 (1.17, 1.26)

**\*In red, non-overlapping higher (EB05, EB95) interval for the comparator; in blue, overlapping confidence interval; in black, non-overlapping and lower (EB05, EB95) than Teithromycin.**

### 3.7. Progression of Signals for Selected Hepatotoxic PTs and of Fatal Outcomes

Figure 9 expands the displays in the previous sections by showing the progression of the EBGm values, confidence intervals, and number of reports by calendar year for selected hepatotoxic PTs for all reports and for reports with a fatal outcome. This display shows as well the total number of reports for all reports and for fatal outcomes for each PT and drug analyzed (marginal totals).

Some points to highlight in Figure 9:

The proportion of fatal outcome is the highest with “Hepatic failure” with over 50% of fatal outcomes. The other 4 events being analyzed have lower proportions of fatal outcomes. This is also being reflected in Table 7 showing EBGm values for fatal outcome of 5.58 (5.47, 5.68) with Hepatic failure, 1.68 (1.64, 1.73) with Hyperbilirubinaemia, 1.34 (1.29, 1.38) with Hepatitis, and 1.22 (1.17, 1.26) with Cholestasis.

Telithromycin’s EBGm values for “Hepatic failure,” “Hepatitis,” and Hyperbilirubinaemia are increasing over time. Telithromycin’s EBGm values are a little stronger with Hepatitis than with “Hepatic failure.” Azithromycin showed some initial higher EBGm values with “Hepatic failure,” that seem to stabilize

over some period of years, and then slowly increase afterwards. Clarithromycin shows higher EBGM values for fatal outcomes than for the analysis across all reports. Trovafloxacin's EBGM reached maximum values and very high scores for fatal outcome for most event codes analyzed the first year of marketing of this drug.

After initial low EBGM values for nitrofurantoin and "amoxicillin and clavulanate" their EBGM values started to increase and stayed high. This pattern is repeated with acetaminophen that reached the highest EBGM values among all the drugs in this analysis. With acetaminophen we also see a pattern of decreasing EBGM values in the last few years that may reflect more knowledge in the community about acetaminophen role in serious liver toxicity.

"Amoxicillin and clavulanate" shows very strong signals for Cholestasis with strong signals for fatal Cholestasis soon after AERS started receiving reports for this drug. Although the overall proportion and EBGM values of fatal outcome with Cholestasis are relatively low, the EBGM values of fatal outcome with Cholestasis with "amoxicillin and clavulanate" are quite high (See Figure 9 and Table 7).

#### **4. Discussion**

The graphical techniques were used should help assess in a disciplined manner the competing relative reporting of adverse events and outcomes of the drugs selected for analysis.

These displays permit the reader to verify if the effects detected by MGPS for a drug and for a group of drugs with similar modes of activity make sense from a pharmacological and clinical perspective.

Understanding the data behind the differing and continuously evolving safety profiles of drugs is important for helping make better treatment selections and regulatory decisions.

We used mostly un-reviewed report counts in these analyses. The sheer number of reports that needs to be analyzed to get a summary analysis precludes a hands-on review of every report.

Both case review and data mining provide insight into the adverse drug events. Case review may give insight into the correctness of the diagnosis, and occasionally into the causal relationship between the drug and the event, but it cannot provide any insight into how the reporting frequency of the adverse event compares to background reporting rates, or to reporting rates for other drugs.

In the early years of marketing of new drugs, little is known about their full therapeutic or toxic potential. For example, it took many years to understand the therapeutic potential of erythromycin, now known to be effective in treating Legionnaire's disease, and of clarithromycin now known as effective in treating *Helicobacter pylori* gastritis and disseminated *Mycobacterium avium-intracellulare* infections, or that fluoroquinolones are effective in treating leprosy.

Similarly, it also took many years to understand their toxic potentials. For example, erythromycin and other macrolides are now known as capable of inducing serious drug-drug interactions.<sup>(15)</sup> Drug-drug interactions can also affect telithromycin. Telithromycin has already shown that it can develop drug-drug interactions with several HMG-CoA Reductase Inhibitors and with Tacrolimus, and has the potential of inducing additional drug-drug interactions already seen with macrolides.

From what we know so far, in patients with myasthenia gravis, hepatic disorders including ischemic hepatitis and hepatic failure, in patients who drive or operate machineries, and in patients with underlying risk factors for drug-drug interactions, or for QT prolongation and torsades de pointes telithromycin is not a good treatment choice.

Azithromycin, clarithromycin, erythromycin, and moxifloxacin have shown strong signals for QT prolongation and torsades de pointes having fatal and disability outcomes. These drugs are not good choices for patients with underlying risk factors for developing these serious problems. So far, telithromycin does not have reports of fatal or disability outcomes with these events, but this profile may change when more information is collected.

Telithromycin, azithromycin, clarithromycin, erythromycin, nitrofurantoin, and trovafloxacin show signals of hepatic problems with fatal and/or disability outcomes but, have much lower signals with anaphylactic reactions than cephalosporins, moxifloxacin, and "amoxicillin and clavulanate". Anaphylactic reactions with cephalosporins, moxifloxacin, and "amoxicillin and clavulanate" are associated with fatal outcomes. So far, telithromycin is not associated with fatal outcome signals for anaphylactic reactions.

Azithromycin, clarithromycin, and erythromycin show signals for hearing problems with disability outcomes. In contrast to aminoglycosides that are associated with both nephrotoxicity and ototoxicity, the macrolides in general seem to be less associated with nephrotoxicity than with ototoxicity. In cases where ototoxicity is a concern, specially in patients with decrease hearing, neither aminoglycosides nor macrolides may be good choices. Telithromycin seems to be less ototoxic so far than other macrolides, but this profile may change when more information is collected.

In patients prone to develop toxic skin reactions such as “Toxic epidermal necrolysis” and/or “Stevens-Johnson syndrome” or vasculitis, cephalosporins, “amoxicillin and clavulanate”, and azithromycin may not be good treatment choices.

In patients with either pulmonary fibrosis and eosinophilic pneumonia, neuropathy, nephritis, and hepatic disorders, many of these events with fatal and disability outcomes, nitrofurantoin is not a good treatment choice.

Some cephalosporins and aminoglycosides are associated with nephrotoxicity. In cases where development of nephrotoxicity is a concern, fluoroquinolones other than ciprofloxacin, and macrolides in general seem to be appropriate choices.

In patients receiving colchicine, macrolides especially clarithromycin, are not good choices as concomitant drugs.

From what we see so far, in patients at risk of developing Clostridium difficile-associated infections, macrolides and telithromycin could be good choices.

Azithromycin has strong signals for Drug ineffective, Drug effect decreased, and Therapeutic response decreased, some with fatal outcome signals. The narratives of these cases describe the failure of azithromycin to treat Streptococcus pyogenes and Streptococcus pneumoniae infections.

#### **4.1. Risk Summary**

We analyzed some of the multidimensional aspects of the adverse event profiles of 16 drugs, specifically their competing relative reporting of adverse events and outcomes.

Telithromycin ranked 10<sup>th</sup> in percentage of reports where outcome = fatal, and 3<sup>rd</sup> in percentage of reports where outcome = disability across the 16 drugs that are the focus of this review.

Telithromycin had the highest Max EBGM values **across all reports** for three recoded event classes: *eye*, *myasthenia*, and *ischemic hepatitis*. For the remaining 43 event classes, one or more drugs had a higher score than telithromycin. For ten of the event classes, telithromycin has no events.

Telithromycin had the highest Max EBGM values **across reports with an outcome = fatal** for three recoded event classes: *syncope*, *myasthenia*, and *ischemic hepatitis*. For the remaining 43 recoded event classes, one or more

drugs had a higher score than telithromycin. For 21 of the recoded event classes, telithromycin has no events.

Telithromycin had the highest Max EBGM values ***across reports with an outcome = disability*** for two event classes: *eye* and *myasthenia*. For the remaining 42 event classes, one or more drugs had a higher score than telithromycin. For 21 of the event classes, telithromycin has no events.

Of the 16 drugs evaluated, MGPS showed that telithromycin's confidence intervals for fatal outcomes across any event were below the confidence intervals of 9 comparator drugs.<sup>(16)</sup>

Telithromycin confidence intervals for four different hepatotoxic event codes across all reports were below 7 comparator drug- hepatotoxic event combinations, were overlapping with 16 comparator drug- hepatotoxic event combinations and were above other 16 comparator drug- hepatotoxic event combinations, as follows:

For Hepatic failure, telithromycin's confidence intervals were below the confidence intervals of 2 comparator drugs (acetaminophen and trovafloxacin), were overlapping with 2 drugs (nitrofurantoin and "amoxicillin and clavulanate"), and were above 5 drugs (clarithromycin, azithromycin, moxifloxacin, erythromycin, and gemifloxacin.)

For Hepatitis, telithromycin's confidence intervals were overlapping with 4 drugs ("amoxicillin and clavulanate," trovafloxacin, nitrofurantoin, and dirithromycin), and were above 6 drugs (acetaminophen, erythromycin, azithromycin, clarithromycin, moxifloxacin, and gemifloxacin).

For Hyperbilirubinaemia, telithromycin (EB05, EB95) were below the (EB05, EB95) intervals of "amoxicillin and clavulanate", were overlapping with 7 drugs, and were above 2 drugs with data.

For Cholestasis, telithromycin's (EB05, EB95) intervals were below the (EB05, EB95) intervals of 4 comparator drugs ("amoxicillin and clavulanate," erythromycin, nitrofurantoin, and clarithromycin), and were overlapping with 6 drugs (trovafloxacin, azithromycin, acetaminophen, dirithromycin, moxifloxacin, and gemifloxacin.)

Telithromycin confidence intervals for four different hepatotoxic event codes across fatal outcome were mostly overlapping the confidence intervals of comparator drug-event combinations with data.

For Fatal Hepatic failure telithromycin's confidence intervals were overlapping with all the drugs with data.

For Fatal Hepatitis telithromycin's confidence intervals were overlapping with 6 drugs with data.

For Hyperbilirubinaemia telithromycin confidence were overlapping with 8 drugs, and were above the (EB05, EB95) interval of one comparator drug (erythromycin).

For Cholestasis telithromycin's confidence intervals were below the confidence interval of one comparator drug ("amoxicillin and clavulanate.") Telithromycin confidence were overlapping with 8 drugs with data.

## **4.2. Conclusions**

We generated and analyzed the MGPS outputs included in this review to help discern the relative reporting patterns of 16 drugs to aid drug safety and risk/benefit analyses and regulatory decisions. These analyses describe the different relative reporting profiles of telithromycin and comparator drugs in the Adverse Event Reporting System (AERS) across all reports, and the subset of reports having a fatal or a disability outcome.

Our selection of drugs and events still provide us with a huge number of reports to analyze. Indeed, we analyzed 34,563 unique reports comprising 44% of the 78,414 reports in the "All Reports Analysis" across all events for the 16 drugs; 4,669 unique reports comprising 70% of the 6,663 reports across all events in the fatal outcome analysis; and 950 unique reports comprising 57% of the 1,655 reports across all events in the disability outcome analysis.

MGPS detected known toxicities across multiple drugs and drug classes and multiple events as exemplified by the detection of hepatotoxicity with acetaminophen and trovafloxacin, our positive comparators for liver toxicity in this review. Most of the antimicrobials that we studied with MGPS show some unique class specific risks. Our results for a drug are in general, consistent with the results with other drugs in the same class.

Telithromycin shows some uniquely strong signals for eye events, myasthenia and exacerbation of myasthenia, and ischemic hepatitis. The diplopia eye events with telithromycin seem to be acetylcholine mediated and may be related to telithromycin's myasthenia events signals. The eye events with telithromycin may pose problems in patients who drive or operate machineries. For other reasons, fluoroquinolones may also pose problems in patients who drive or

operate machineries. The myasthenia and exacerbation of myasthenia events may pose serious problems for patients at risk of developing these events.

For many events, including hepatic failure, drug-drug interactions, and QT prolongation and torsades de pointes, the telithromycin signals were so far similar or lower to those of several other drugs. Telithromycin seems to have less relative reporting of deafness, tinnitus, and gout (<sup>17</sup>) than other macrolides, less Clostridium infection than cephalosporins, fluoroquinolones, macrolides, amoxicillin and clavulanate and nitrofurantoin; less cholestasis than “amoxicillin and clavulanate,” macrolides, fluoroquinolones, and nitrofurantoin; less pancreatitis than acetaminophen, “amoxicillin and clavulanate,” and macrolides. As well as other antimicrobials, telithromycin shows less neuropathy, polyneuropathy, and toxic lung signals than nitrofurantoin, and less psychiatric disorders than fluoroquinolones and macrolides.

Using MGPS we detected some growing hepatotoxicity signals across all reports and with reports having a fatal outcome with acetaminophen, telithromycin, nitrofurantoin, and “amoxicillin and clavulanate,” and macrolides.

While performing this analysis with MGPS we identified a serious drug-drug interaction between colchicine and clarithromycin that lead to a high proportion of fatal outcomes.

Overall, the analysis indicates that all of the drugs studied are associated with one or more serious adverse events, and that the associated adverse events differ from drug to drug. In particular, telithromycin was associated with several serious adverse events. Of these adverse events, only eye events were associated with a uniquely high risk of occurring with telithromycin.

Are any of these antimicrobials too toxic to be marketed? Assuming that all 15 antimicrobials were all equally effective, we would want to prescribe the one with the most benign adverse event profile. Not all antimicrobials are equally effective at treating a particular infection. Moreover, some patients are allergic to amoxicillin and cephalosporins, or have developed hearing problems, or are prone to develop drug-drug interactions, greatly reducing their treatment options. If a particular antimicrobial was uniquely effective in treating a particular serious infection, the benefit-risk ratio would be strongly in its favor. If an antimicrobial is not uniquely effective in treating a particular serious infection, it would seem prudent not to use such an antimicrobial as first line therapy unless other treatment options are known to be less effective or more toxic.

MGPS revealed the growing accumulation of toxicity cases with many antimicrobials and with acetaminophen. The toxicities include the increasing hepatic failure signals of nitrofurantoin, a drug only indicated to treat urinary tract infections; the fatal cholestasis signals with amoxicillin and clavulanate; the high

number of cases and strong signals of fatal hepatotoxicity with acetaminophen; and the fatal decreased of coverage of *Streptococcus pyogenes* and *Streptococcus pneumoniae* infections. These other drug toxicities are also of great concern to these reviewers.

## 5. Figures

**Cumulative Number of Reports by Drug and by Year  
All Reports and  
Only Reports with an Outcome = Fatal**

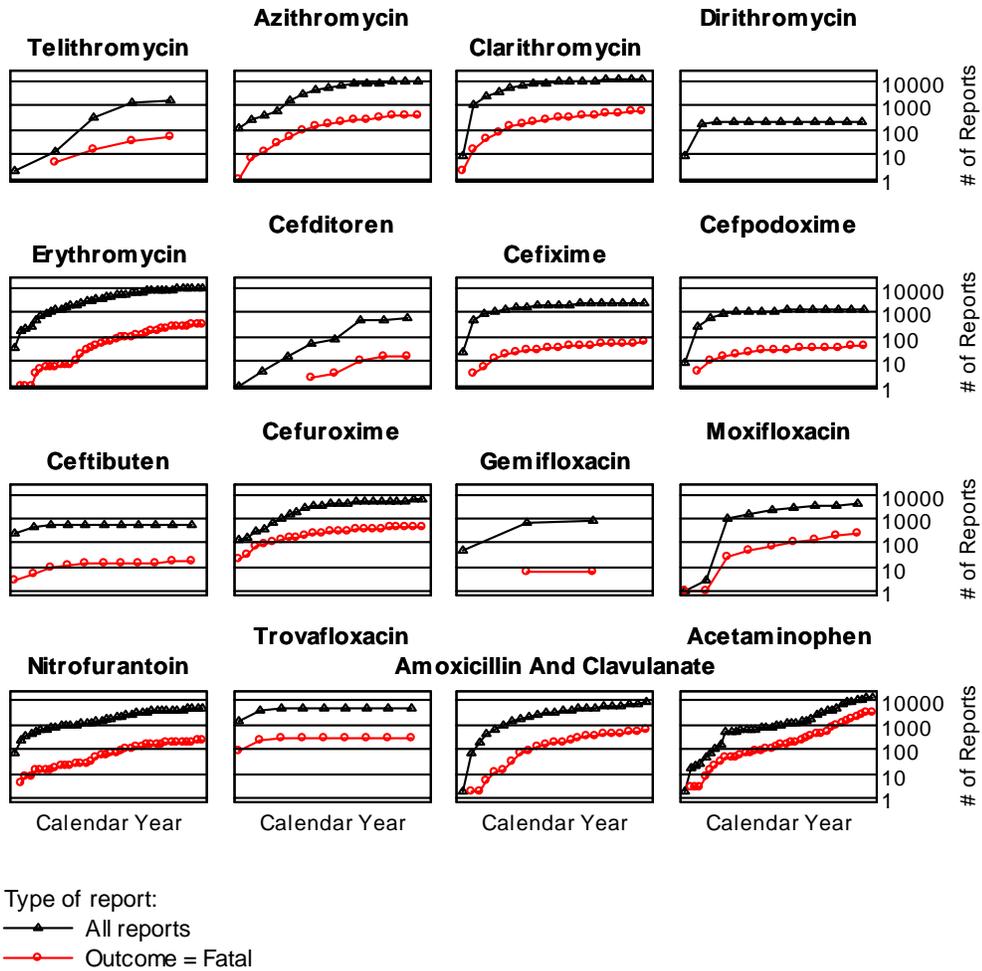


Figure 1: Cumulative Number of Reports for Each Drug by Calendar Year for All Drugs and for Reports with a Fatal Outcome

**Cumulative Number of Reports by Drug and by Year  
All Reports and  
Only Reports with an Outcome = Disability**

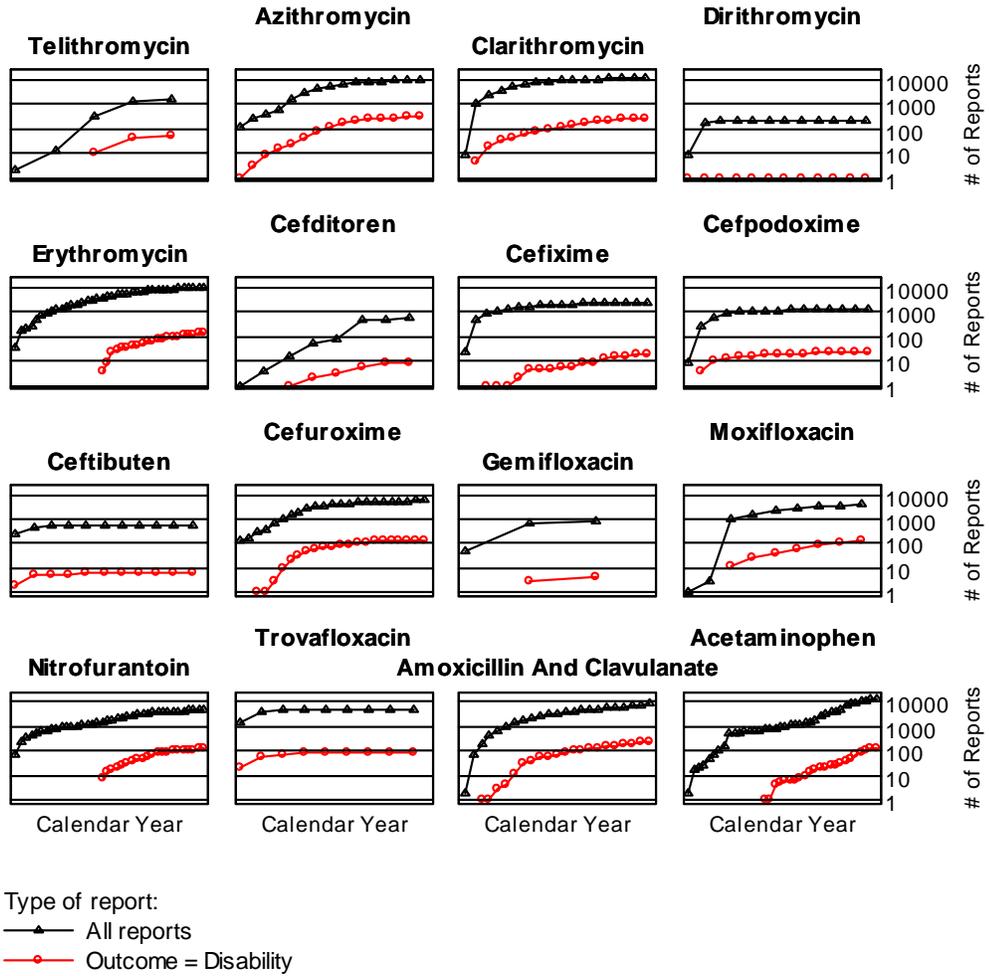
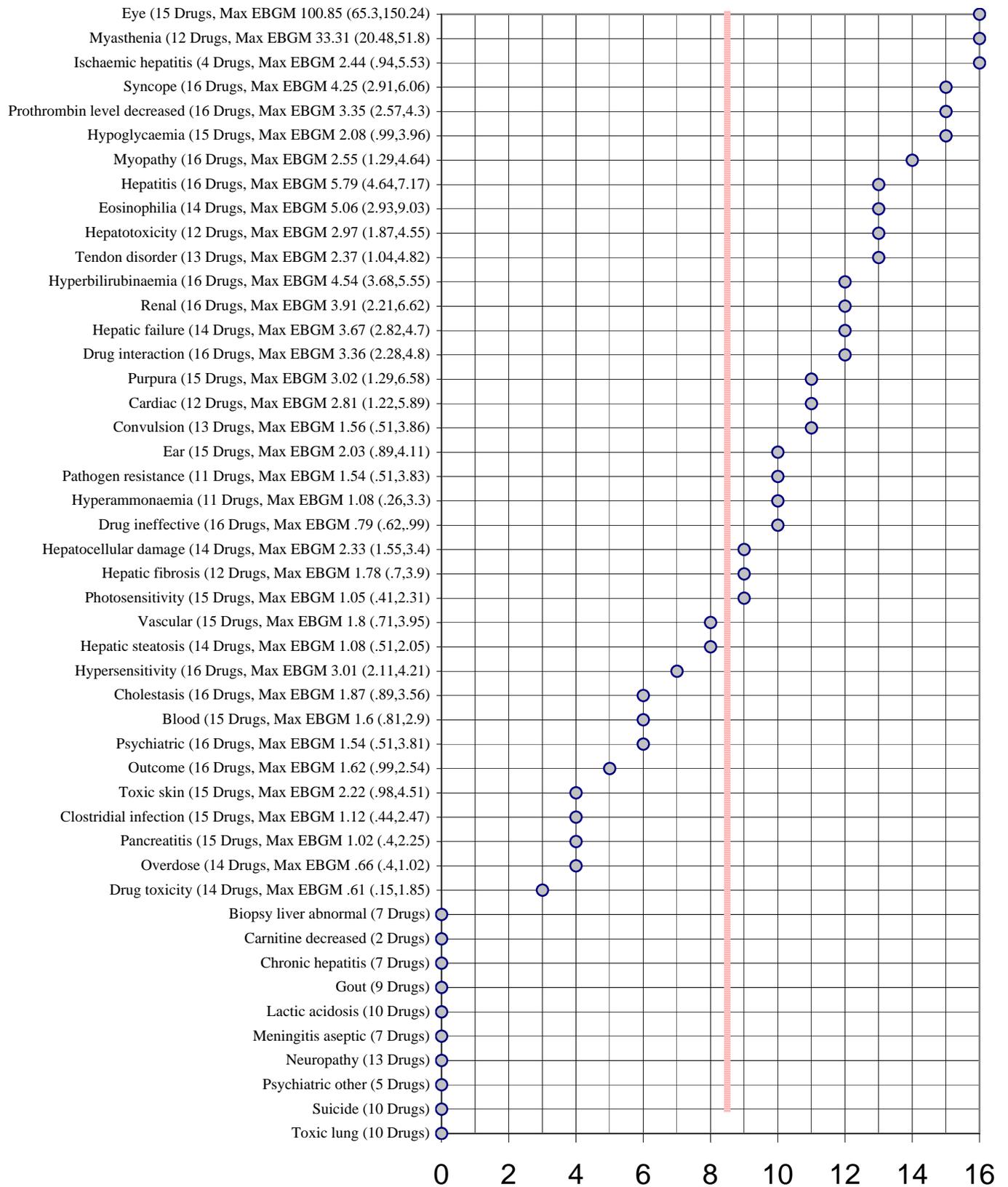


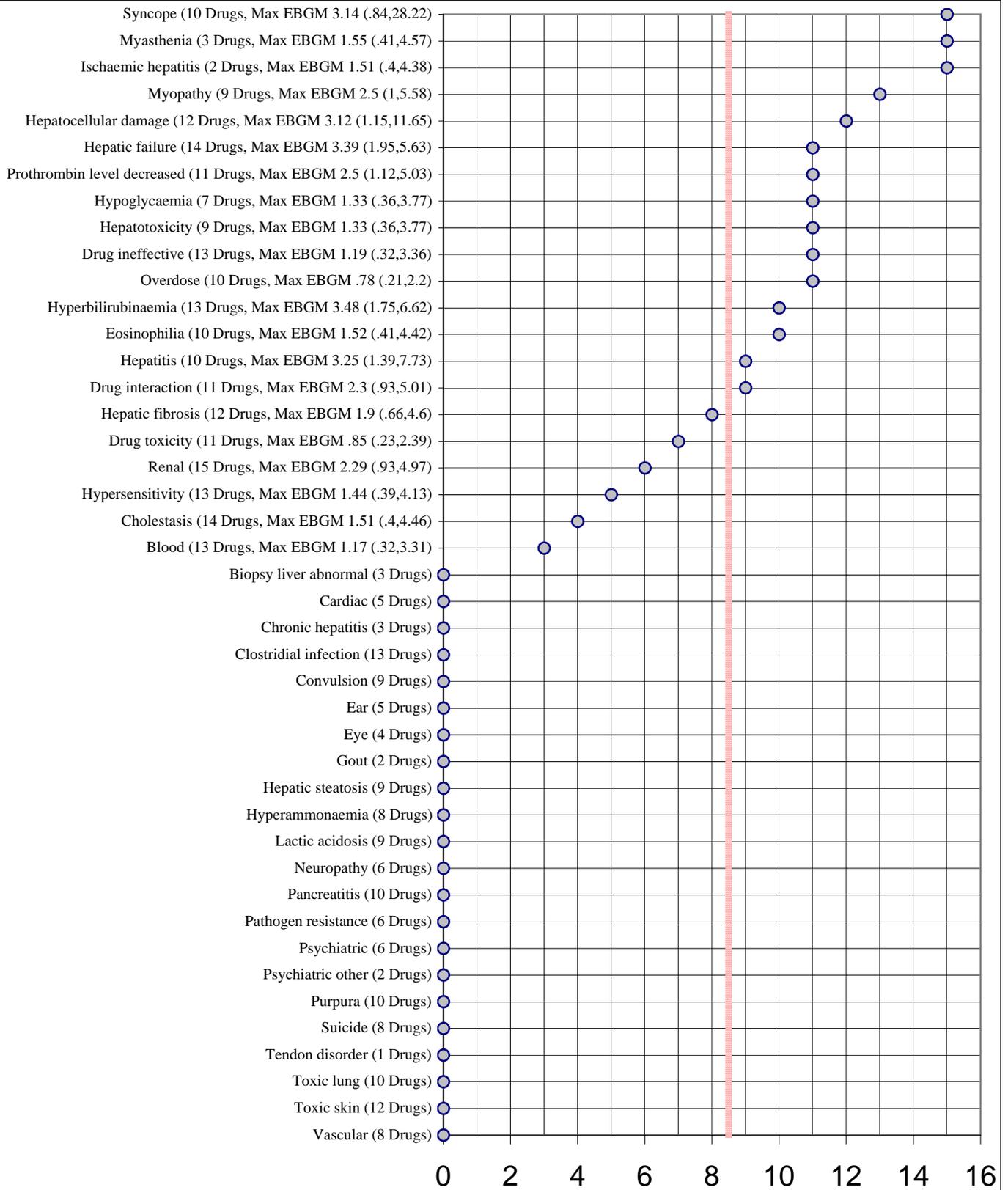
Figure 2: Cumulative Number of Reports for Each Drug by Calendar Year for All Drugs and for Reports with a Disability Outcome

Figure 3. Ranking of Telithromycin Among the 16 Drugs Across Recorded Event Classes in the "All Reports" output



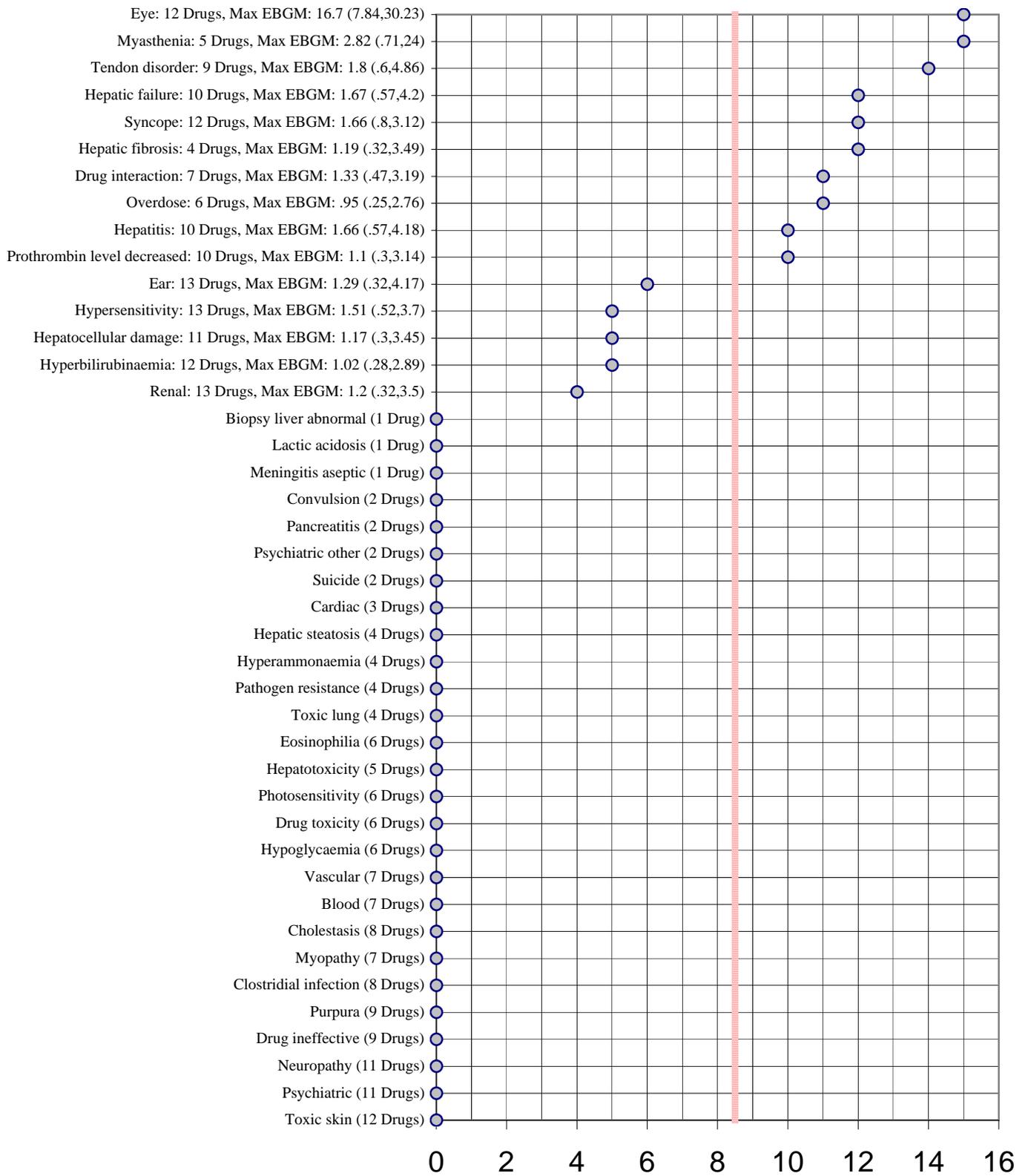
**Rank of Telithromycin Among 16 Drugs**  
*Higher Rank Indicates Higher Signal Score*

Figure 4. Ranking of Telithromycin Among the 16 Drugs Across Recorded Event Classes in the "Fatal" output



**Rank of Telithromycin Among 16 Drugs  
for Reports With Outcome=Death**  
Higher Rank Indicates Higher Signal Score

Figure 5. Ranking of Telithromycin Among the 16 Drugs Across Recorded Event Classes in the "Disability" output



**Rank of Telithromycin Among 16 Drugs  
for Reports With Outcome=Disability**

*Higher Rank Indicates Higher Signal Score*

Figure 6. Data Mining Summary Display Showing Maximum EBGm Values in Any Given Year with *Recoded Event Classes and Serious Outcomes* with Telithromycin and 15 comparators

Figure 6. Data Mining Summary Display Showing Maximum EBGM Values in Any Given Year with Recoded Event Classes and Serious Outcomes with Telithromycin and 15 comparators (data collected as of May 2006)

- 1 - All Reports
- 2 - Only Reports with an Outcome = Fatal
- 3 - Only Reports with an Outcome = Disability

	Telithromycin	Azithromycin	Clarithromycin	Dirithromycin	Erythromycin	Cefditoren	Cefixime	Cefpodoxime	Ceftibuten	Cefuroxime	Gemifloxacin	Moxifloxacin	Trovafoxacin	Nitrofurantoin	Amoxicillin And Clavulanate	Acetaminophen
Blood / 1	1.6	3.26	5.69	1.1	1.51	1.98	1.69	1.51	1.31	4.36		2.6	2.21	3.51	3.13	8.67
Blood / 2	1.17	2.54	3.83		1.43	1.5	2.07	1.23		1.54		2.64	3.52	4.15	4.26	3.78
Blood / 3		1.26	2.08		0.66					1.28				1.71	1.02	2
Cardiac / 1	2.81	4.21	7.24	1.36	55.91			1.29		1.27		6.49	0.42	0.5	0.45	4.98
Cardiac / 2		4.4	10.76		27.92							18.98				2.52
Cardiac / 3			6.6		1.57							5.36				
Drug ineffective / 1	0.79	19.06	0.45	0.76	0.54	72.23	1.56	0.92	2.4	0.5	0.54	0.35	0.58	0.29	0.52	2.54
Drug ineffective / 2	1.19	2.41	0.77		1		0.87	1	1.47	0.72		3.37	1.15	1.8	0.75	0.58
Drug ineffective / 3		1.76	0.77		0.75			1.03	1.99	0.9		0.63			0.78	0.89
Drug interaction / 1	3.36	4.55	5.92	1.03	6.35	0.66	0.9	1.18	0.77	1.36	0.75	1.6	1.77	1.07	1.4	4.3
Drug interaction / 2	2.3	5.9	10.77		12.03		0.96			1.73		3.15	2.64	0.99	1.42	3.57
Drug interaction / 3	1.33	2.02	7.03		18.23			1.05							1.85	1.25
Ear / 1	2.03	17.03	4.63	1.29	16.91	0.46	1.17	1.79	1.85	1.49		4.57	3.5	1.63	2.52	1.65
Ear / 2		1.3			15.42							1.51	1.44			0.73
Ear / 3	1.29	7.83	3.56	1.41	10.78		1.05		2.48	1.58		3.33	2.78	1.99	2.36	1.2
Eosinophilia / 1	5.06	5.11	3.98	1	2.09	2.2	1.71	2.18		3.16		1.15	7.44	43.86	3.99	2.27
Eosinophilia / 2	1.52	2.8	1.95				1.56			0.95		2.05	1.37	1.49	2.54	1.1
Eosinophilia / 3		1.51	2.57		1.92					1.61			5.27		2.46	
Eye / 1	100.8	1.67	2.29		2.28	0.37	1.16	0.8	1.36	1.41	0.33	2.53	1.77	1.39	2.85	0.97
Eye / 2		1.24	1.49										1.95			0.36
Eye / 3	16.7	2.23	1.39		2.38		1.12	1.2		0.76		2.33	2	1.25	1.74	1.79
Clostridial infection / 1	1.12	3.83	3.02		2.62	66.15	38.4	41.96	23.46	43.39	4.48	7.26	3.15	0.87	24.23	0.4
Clostridial infection / 2		1.98	3.93		5.81	8.15	36.29	24.6	2.39	22.21	1.54	7.53	2.35	2.07	13.26	
Clostridial infection / 3		1.23			1.15		4.84	17.26	1.43	38.93		1.18			3.18	
Drug toxicity / 1	0.61	1.44	6.16	1.26	1.53		0.73	0.66		0.83	0.65	0.76	1.2	2.06	0.93	11.65
Drug toxicity / 2	0.85	1.24	6.3		1.63		1.85				2.01	0.48	0.47	1.27	0.9	3.61
Drug toxicity / 3		0.91	1.5		1.94							1.67			1.29	1.24
Gout / 1		5.33	2.96		0.68					2.19	0.89	0.62	0.75		2.49	0.75
Gout / 2			42.87												1.55	
Hepatotoxicity / 1	2.97	1.92	2.92		1.64	1.16			1.07	1.67		2.51	7.62	2.84	3.83	13.1
Hepatotoxicity / 2	1.33	1.25	1.3							1.16		3.61	3.55	1.31	2.69	4.37
Hepatotoxicity / 3		1.03	1.09		1.27									1.26		1.21
Hepatic failure / 1	3.67	2.46	1.8		1.16	0.59	0.65	1.4		0.99	0.53	1.39	5.44	4.83	3.84	33.14
Hepatic failure / 2	3.39	2.18	3.02		2.76	1.64	1.47	2.21		1.1	1.98	2.56	6.29	4.36	3.82	9.66
Hepatic failure / 3	1.67	1.57	1.46					1.22		0.71		0.95	1.59	2.88	3.1	20.46

Cutpoints:

Min.	<=1.5	<=2	<=4	>4	Max.
EBGM	0	1.5	2	4	195.24

**Figure 6. Data Mining Summary Display Showing Maximum EBGGM Values in Any Given Year with Recoded Event Classes and Serious Outcomes with Telithromycin and 15 comparators (data collected as of May 2006)**

**1 - All Reports**

**2 - Only Reports with an Outcome = Fatal**

**3 - Only Reports with an Outcome = Disability**

	Telithromycin	Azithromycin	Clarithromycin	Dirithromycin	Erythromycin	Cefditoren	Cefixime	Cefpodoxime	Ceftibuten	Cefuroxime	Gemifloxacin	Moxifloxacin	Trovafoxacin	Nitrofurantoin	Amoxicillin And Clavulanate	Acetaminophen
Hepatitis / 1	5.79	4.17	3.22	3.1	4.79	1.34	1.12	2.79	0.97	1.51	0.3	1.66	6.27	5.82	6.32	5.41
Hepatitis / 2	3.25	4.5	3.31		1.67					1.07		2.61	3.99	6.93	5.6	3.59
Hepatitis / 3	1.66	1.64	3.99		1.9			1.17				0.91	5.68	1.33	5.98	2.17
Hepatocellular damage / 1	2.33	2.23	2.26		6.4	15.79	1.71	9.01	0.73	1.53		0.71	3.85	2.68	3.75	15.37
Hepatocellular damage / 2	3.12	2.81	2.05		1.22		1.23	7.77		1.56		1.85	1.05	1.15	3.77	3.63
Hepatocellular damage / 3	1.17	1.4	1.27		6.36			1.33		1.64		1.2	8.07	3.67	1.49	4.83
Biopsy liver abnormal / 1		0.99	0.91									0.9	5.15	4.81	5.12	0.73
Biopsy liver abnormal / 2													1.33	1.52	4.84	
Biopsy liver abnormal / 3													3.39			
Hyperammonaemia / 1	1.08	1.01	1.07			0.97		1.78			0.94	1.26	3.14	1.64	1.43	10.43
Hyperammonaemia / 2		1.71	1.15								1.53	2.31	4.2	2.21	0.92	7.53
Hyperammonaemia / 3		1.26	1.4					1.48					2.6			
Hyperbilirubinaemia / 1	4.54	2.47	2.77	1.36	12.21	1.9	1.49	1.92	1.19	1.78	1.8	1.69	4.5	5.01	6.7	4.64
Hyperbilirubinaemia / 2	3.48	2.63	5.71		1.27		2.56		1.42	1.38	3.12	1.02	3.92	5.7	3.75	3.78
Hyperbilirubinaemia / 3	1.02	3.43	3.45		1.51	4.07		1.22		1.8		0.94	6.54	1.76	9.34	1.64
Prothrombin level decreased / 1	3.35	3.17	2.21	0.58	1.06	0.41	1.69	1.3	1.56	1.01	1.39	3.02	3.18	0.97	1.84	6.16
Prothrombin level decreased / 2	2.5	3.46	2.21		0.93		2.59			1		1.81	3.55	1.82	1.59	6.77
Prothrombin level decreased / 3	1.1	1.58	2.44					1.39		0.88		0.91	2.37	0.82	0.89	15.96
Chronic hepatitis / 1		0.91	1.09									1.49	3.63	1.31	2.77	2.89
Chronic hepatitis / 2												1.47			4.07	1.79
Hepatic fibrosis / 1	1.78	2.75	2.64		0.48			1.18	1.75	2.1		0.48	1.88	7.19	2.54	9.9
Hepatic fibrosis / 2	1.9	1.96	1.56		1.72			1.52	2.46	2.51		0.97	2.39	7.19	2.09	3.27
Hepatic fibrosis / 3	1.19		1.38												1.94	1.43
Lactic acidosis / 1		0.53	0.93		0.34	0.99				0.47		0.26	0.18	0.73	0.69	2.9
Lactic acidosis / 2		1.37	1.07		0.94					0.79		0.92	0.63	0.82	1.2	4.42
Lactic acidosis / 3															1.02	
Cholestasis / 1	1.87	4.69	8.42	1.55	15.22	1.23	2.62	2	1.77	2.21	0.61	1.12	3.57	3.51	28.74	2.15
Cholestasis / 2	1.51	2.43	2.56		7.78		2.53	1.93	1.5	1.65	2.45	2.05	2.88	2.51	19.1	1.46
Cholestasis / 3		1.66	3.63		2.22			1.39		0.95		1.46	1.54		20.35	
Hepatic steatosis / 1	1.08	1.36	0.94		1.52			1.59	0.75	1.01	1.13	0.61	0.51	2.98	1.46	2.54
Hepatic steatosis / 2		2.18	1.14					1.35				1.48	1.23	1.9	1.12	3.65
Hepatic steatosis / 3			1.2										2.02		1.53	1.38
Ischaemic hepatitis / 1	2.44											1.1			0.96	1.04
Ischaemic hepatitis / 2	1.51														1.32	
Hypersensitivity / 1	3.01	5.61	2.96	2.91	2.31	28.65	2.38	4.33	3.44	17.08	2.12	10.61	4.59	4.7	7.07	1.66

Cutpoints:

	Min.	<=1.5	<=2	<=4	>4	Max.
EBGM	0	1.5	2	4	195.24	

**Figure 6. Data Mining Summary Display Showing Maximum EBGGM Values in Any Given Year with Recoded Event Classes and Serious Outcomes with Telithromycin and 15 comparators (data collected as of May 2006)**

**1 - All Reports**  
**2 - Only Reports with an Outcome = Fatal**  
**3 - Only Reports with an Outcome = Disability**

	Telithromycin	Azithromycin	Clarithromycin	Dirithromycin	Erythromycin	Cefditoren	Cefixime	Cefpodoxime	Ceftibuten	Cefuroxime	Gemifloxacin	Moxifloxacin	Trovafoxacin	Nitrofurantoin	Amoxicillin And Clavulanate	Acetaminophen
Hypersensitivity / 2	1.44	4.21	2.83		1.97	1.52	1.66	1.47		6.64		3.45	2.58	0.93	11.82	0.96
Hypersensitivity / 3	1.51	4.09	3.09		1.79		1.32	2.22	1.44	7.99		2.59	2.06	1.58	1.96	1.73
Meningitis aseptic / 1		1.17	2.18							1.15		0.92		1.22	4.29	0.86
Meningitis aseptic / 3																1.32
Pathogen resistance / 1	1.54	14.31	9.97		1.87		1.07	1.2	1.27	3.61		0.88	3.17		2.03	
Pathogen resistance / 2		1.84	2.99				1.51			4.04		1.8	2.1			
Pathogen resistance / 3		1.14	1.43					1.49							1.27	
Carnitine decreased / 1						47.34										1.27
Hypoglycaemia / 1	2.08	0.8	3.11	0.78	1.62	1.29	1.15	1.22	0.33	0.64		1.39	1.51	0.26	0.75	1.42
Hypoglycaemia / 2	1.33		2.17		1.81							0.89	2.09		0.78	3
Hypoglycaemia / 3			1.31		1.08							1.04		1.09	0.82	2.37
Tendon disorder / 1	2.37	2.47	0.91		1.21		1.89	1.16		1.01	0.9	11.89	7.13	0.95	1.06	0.56
Tendon disorder / 2												1.52				
Tendon disorder / 3	1.8	1.03	1.03		1.1		1.31					13.46	1.74	1.07	1.51	
Myopathy / 1	2.55	1.19	3.54	1.33	3.62	1.62	0.49	1.98	0.68	0.58	0.35	0.78	0.96	0.59	1.45	1.4
Myopathy / 2	2.5	1.31	3.39		14.26						1.48	0.66	1.15		1.07	1.16
Myopathy / 3		0.92	2.75		1.87	1.2				1.41				0.87	0.59	
Myasthenia / 1	33.31	8.93	2.1		1.08		3.86	1.27		1.21		3.34	1.67	2.17	1.17	0.56
Myasthenia / 2	1.55														1.42	1.37
Myasthenia / 3	2.82		1.3							1.44		1.29			1.16	
Neuropathy / 1		1.88	3.13		0.5		0.9	1.29	0.49	0.96	0.63	2.24	1.05	20.28	0.74	0.51
Neuropathy / 2			1.3		1.21								1.31	2.15	0.57	0.39
Neuropathy / 3		0.65	2.37		1.02		0.93		1.09	1.82	1.29	1.14	1.34	3.43	1.17	
Convulsion / 1	1.56	1.14	0.82		2.08		0.57	0.52	1.75	2.04		0.95	2.48	2.1	1.04	0.85
Convulsion / 2		0.94	1.45		3.07					3.01		1.32	2.45	1.44	1.53	0.65
Convulsion / 3		0.98														1.2
Overdose / 1	0.66	1.55	1.18	1.36	1.07		1.59	1.15	1.26	0.89		1.81	1.16	0.75	0.39	20.46
Overdose / 2	0.78	0.73	0.55		1.46		1.12			0.26		1.34		0.33	0.71	5.68
Overdose / 3	0.95	3.87			0.91								1.32		1.14	16.34
Pancreatitis / 1	1.02	2.43	2.08	1.33	2.73	2	1.09	2.1		0.87	0.58	1.23	1.66	1.26	2.74	3.18
Pancreatitis / 2		2.56	2.75		1.25					1.15	1.49	1.52	0.8	1.38	1.32	2.29
Pancreatitis / 3			1.53												0.99	
Psychiatric / 1	1.54	1.87	5.58	1.17	2.37	1.1	1.51	1.78	3.01	1.02	1.68	7.98	4.24	1.52	2.73	2.21
Psychiatric / 2		2.65	1.96									1.54	3.54		2.54	2.53
Psychiatric / 3		1.04	1.99		1.66		1.2	1.2		1.22		1.73	1.76	0.69	1.49	1.01

Cutpoints:

Min.	<=1.5	<=2	<=4	>4	Max.
EBGM	0	1.5	2	4	195.24

**Figure 6. Data Mining Summary Display Showing Maximum EBGGM Values in Any Given Year with Recoded Event Classes and Serious Outcomes with Telithromycin and 15 comparators (data collected as of May 2006)**

**1 - All Reports**

**2 - Only Reports with an Outcome = Fatal**

**3 - Only Reports with an Outcome = Disability**

	Telithromycin	Azithromycin	Clarithromycin	Dirithromycin	Erythromycin	Cefditoren	Cefixime	Cefpodoxime	Ceftibuten	Cefuroxime	Gemifloxacin	Moxifloxacin	Trovafoxacin	Nitrofurantoin	Amoxicillin And Clavulanate	Acetaminophen
Psychiatric other / 1		0.59	1.44		0.86										1.06	2.9
Psychiatric other / 2			1.26													1.94
Psychiatric other / 3		1.04			1.21											
Suicide / 1		0.29	0.69		0.4		0.14		0.6	0.47		0.14		0.55	0.76	14.79
Suicide / 2		0.59	0.76		0.5					0.18		0.25		0.77	0.7	2.8
Suicide / 3			0.85													16.57
Purpura / 1	3.02	2.71	20.7		2.68	2.7	2.85	4.32	3.48	2.27	0.86	3.3	0.87	2.9	10.21	2.56
Purpura / 2		1.81	1.68		1.09		2.06			0.97		2.22	1	2.43	3.05	1.31
Purpura / 3		2.04	1.65		1.21					1.85		1.3	1.32	2.3	2.29	1.33
Renal / 1	3.91	6.09	3.79	1.18	2.56	1.63	2.84	1.98	2.69	4.66	1.14	3.25	3.17	4.73	3.29	56.76
Renal / 2	2.29	1.87	2.8		2.37	1.59	1.47	4.09	2.73	3.12	2.45	1.47	2.37	1.56	3.33	6.84
Renal / 3	1.2	1.66	3.33		2.26	1.2	2.96	1.44		1.41		1.71	0.92	1.46	1.68	3.03
Toxic lung / 1		1.79	0.71		0.27	1.18	1.38					0.98	0.52	48.36	0.6	0.67
Toxic lung / 2		0.88	0.76		1.11	1.45	1.46					1.3	0.72	26.56	0.44	0.36
Toxic lung / 3		1.51												25.08	0.76	0.91
Toxic skin / 1	2.22	5.46	2.68		3.45	12.47	3.18	15.39	2.34	5.5	1.81	2.87	1.23	2.47	24.12	5.21
Toxic skin / 2		3.17	3.03		4.81	3.6	1.16	4.04		6.59		3.35	2.35	2.9	17.66	2.06
Toxic skin / 3		2.02	1.65		2.15	2.89	2.55	2.1		4.36		1.83	1.07	1.52	5.47	1.96
Photosensitivity / 1	1.05	1.95	1.34		0.9	0.85	0.97	0.59	2.09	0.55	3.73	2.31	2.29	2.08	0.78	0.27
Photosensitivity / 3		1.09	0.7		1.31						3.01		1.11	0.93		
Syncope / 1	4.25	2.01	1.58	1.04	2.03	0.27	1.14	0.88	1.07	2.83	1.06	4.85	3.19	1.48	1.41	1.62
Syncope / 2	3.14	2.05	3.04		1.56					2.22		2.02	0.88	1.09	1.15	1.28
Syncope / 3	1.66	1.82	1.17		1.45			1.11	1.41	0.91		2.2	1.99	0.66	1.21	1.33
Vascular / 1	1.8	3.09	2.49	1.75	1.27	1.16	1.81	13.33		4.1	0.96	2.61	1.78	3.92	10.23	1.43
Vascular / 2		1.68	2.2		0.97		1.5						1.3	1.07	1.58	0.35
Vascular / 3		1.1	1.53							1.99		2.02	2.28		3.56	1.27
Outcome / 1	1.62	2.52	1.76	1.6	2.52	1.98	1.66	3.09	1.13	2.87	1.1	1.47	3.57	4.71	1.69	2.89

Cutpoints:

Min.	<=1.5	<=2	<=4	>4	Max.
EBGM	0	1.5	2	4	195.24

Figure 7. Data Mining Summary Display Showing Maximum EBGm Values in Any Given Year with *Recoded Event Classes, Events of Interest, and Serious Outcomes* with Telithromycin and 15 comparators

**Figure 7. Data Mining Summary Display Showing Maximum EBGm Values in Any Given Year with Recoded Event Classes, Events of Interest, and Serious Outcomes with Telithromycin and 15 comparators (data collected as of May 2006)**

**1 - All Reports**

**2 - Only Reports with an Outcome = Fatal**

**3 - Only Reports with an Outcome = Disability**

	Telithromycin	Azithromycin	Clarithromycin	Dirithromycin	Erythromycin	Cefditoren	Cefixime	Cefpodoxime	Ceftibuten	Cefuroxime	Gemifloxacin	Moxifloxacin	Trovafloxacin	Nitrofurantoin	Amoxicillin And Clavulanate	Acetaminophen
Blood/ Bleeding time abnormal / 1	1.6	1.53	0.87		0.93		0.98	0.84		2.43		1.15	2.21	3.32	1.07	4.78
Blood/ Coagulopathy / 1	1.17	2.54	1.94		1.2		2.07	1.23		1.33		2.15	3.52	4.15	2.12	3.78
Blood/ Coagulopathy / 2			1.26		0.66									1.03	1.02	2
Blood/ Coagulopathy / 3	1.34	3.26	1.81		0.57	1.26		0.9		4.36		2.6	1.62	2.49	1.64	0.83
Blood/ Haemolysis / 1		1.58			1.19	1.5				1.54		1.9		1.95	1.4	
Blood/ Haemolysis / 2														1.35		
Blood/ Haemolysis / 3	1.51	1.71	2.64	1.1	1.51	1.9	1.69	1.51	1.31	2.43		1.04	0.94	3.51	3.13	0.72
Blood/ Haemolytic anaemia / 1		2.3	3.83		0.99					1.07		1.21		2.62	4.26	0.8
Blood/ Haemolytic anaemia / 2		1.26	2.08							1.28				1.71		
Blood/ Haemolytic anaemia / 3		1.32	5.69		1.04	1.98		1.24				1.53	0.76	1.15	1.75	0.65
Blood/ Anaemia haemolytic autoimmune / 1			2.89		1.43							1.4				
Blood/ Anaemia haemolytic autoimmune / 2										1.24		2.45				
Blood/ Anaemia haemolytic autoimmune / 3												2.64				
Blood/ Intravascular haemolysis / 1	1.23	0.34	4									0.64			1.1	0.71
Blood/ Intravascular haemolysis / 2			1.73													0.53
Blood/ Intravascular haemolysis / 3			1.23													1.24
Blood/ Haemolytic uraemic syndrome / 1												0.88				4.98
Blood/ Haemolytic uraemic syndrome / 2												1.25				2.52
Blood/ Haemolytic uraemic syndrome / 3			1.67													2.06
Cardiac/ Myocardial fibrosis / 1			2.52													
Cardiac/ Myocardial fibrosis / 2																
Cardiac/ Myocardial fibrosis / 3			1.67													
Cardiac/ Cardiotoxicity / 1			2.52													
Cardiac/ Cardiotoxicity / 2	2.81	4.21	6.37		40.59			0.84		0.65		6.49	0.24	0.49	0.45	1.03
Cardiac/ Torsade de pointes / 1		4.4	2.25		27.54							18.98				0.97
Cardiac/ Torsade de pointes / 2			2.04		1.43							5.36				
Cardiac/ Torsade de pointes / 3												5.4	0.42	0.5	0.35	1
Cardiac/ Electrocardiogram QT prolonged / 1	1.52	4.09	7.24	1.36	19.41					1.27		12.56				0.97
Cardiac/ Electrocardiogram QT prolonged / 2		2.92	10.76		4.41											
Cardiac/ Electrocardiogram QT prolonged / 3			6.6		1.57											
Cardiac/ Electrocardiogram QT corrected / 1	2.34	2.77	3.36		55.91			1.29				6.31			0.34	1.25
Cardiac/ Electrocardiogram QT corrected / 2		1.31	1.43		6.77							2.08				2.37
Cardiac/ Electrocardiogram QT corrected / 3			1.38													
Cardiac/ Sudden cardiac death / 1		1.15	1.23		53.16							2.53				0.96
Cardiac/ Sudden cardiac death / 2		1.36	1.47		27.92							3.01				0.5
Cardiac/ Sudden cardiac death / 3																
Drug ineffective/ Drug ineffective / 1	0.79	1.21	0.39	0.76	0.52	1.83	1.56	0.92	2.4	0.38	0.54	0.35	0.58	0.29	0.52	2.54
Drug ineffective/ Drug ineffective / 2	1.19	2.41	0.77		1		0.87	1	1.3	0.72		3.37	0.62	1.8	0.75	0.45
Drug ineffective/ Drug ineffective / 3		1.76	0.77		0.75			1.03	1.99	0.9		0.63			0.78	0.87

Cutpoints:

EBGM	Min.	<=1.5	<=2	<=4	>4	Max.
	0	1.5	2	4	195.24	

**Figure 7. Data Mining Summary Display Showing Maximum EBGM Values in Any Given Year with Recoded Event Classes, Events of Interest, and Serious Outcomes with Telithromycin and 15 comparators (data collected as of May 2006)**

**1 - All Reports**

**2 - Only Reports with an Outcome = Fatal**

**3 - Only Reports with an Outcome = Disability**

	Telithromycin	Azithromycin	Clarithromycin	Dirithromycin	Erythromycin	Cefditoren	Cefixime	Cefpodoxime	Ceftibuten	Cefuroxime	Gemifloxacin	Moxifloxacin	Trovafloxacin	Nitrofurantoin	Amoxicillin And Clavulanate	Acetaminophen
Drug ineffective/ Drug effect decreased / 1	15.82	0.19			0.54		0.65		1.39	0.3		0.22	0.29	0.24	0.27	0.3
Drug ineffective/ Drug effect decreased / 2	1.01								1.47			1.72	1.15			0.51
Drug ineffective/ Drug effect decreased / 3	1															0.89
Drug ineffective/ Drug ineffective for unapprove / 1						72.23										
Drug ineffective/ Therapeutic response decreased / 1	0.77	19.06	0.45			0.64				0.5					0.28	0.49
Drug ineffective/ Therapeutic response decreased / 2																0.58
Drug interaction/ Drug interaction / 1	3.36	4.55	5.92	0.8	6.35	0.66	0.9	1.18	0.77	1.36	0.75	1.6	1.77	1.07	1.4	2.36
Drug interaction/ Drug interaction / 2	2.3	5.9	10.77		12.03		0.96			1.73		3.15	2.64	0.65	1.42	1.7
Drug interaction/ Drug interaction / 3	1.33	2.02	7.03		12.68			1.05							1.85	0.94
Drug interaction/ Drug interaction potentiation / 1	1.06	1.84	4.79		1.16					1.18					1.1	1.02
Drug interaction/ Drug interaction potentiation / 2			2.2													
Drug interaction/ Drug level increased / 1	1.3	0.9	4.31		1.9		0.87			0.91		0.73			0.86	4.28
Drug interaction/ Drug level increased / 2			1.37												0.85	3.16
Drug interaction/ Drug level increased / 3		1.63													1.22	1.25
Drug interaction/ Drug level above therapeutic / 1	1.33	1.31	2.88	1.03	3.28		0.2	0.31		0.75		0.58	0.62	0.3	0.88	4.3
Drug interaction/ Drug level above therapeutic / 2		0.93	1.4		2.69					0.87				0.99	0.72	3.57
Drug interaction/ Drug level above therapeutic / 3			2.97		18.23											1.16
Drug interaction/ Antidepressant drug level above / 1			3.38													
Ear/ Ototoxicity / 1		2.3	1.03		14.01							1.64				
Ear/ Ototoxicity / 2		1.17	1.22		2.5							1.26				
Ear/ Ototoxicity / 3																
Ear/ Deafness / 1	1.59	9.76	3.15	1.29	7.25		0.57	0.89	1.85	1.49		1.6	1.24	1.63	0.77	0.62
Ear/ Deafness / 2		1.3			15.42											
Ear/ Deafness / 3	1.2	7.83	2.06	1.41	9.33		1.05		2.48	1.58		2.46	2.78	1.78	0.51	0.7
Ear/ Deafness permanent / 1		1.23	2.19		2.58					1.11						
Ear/ Deafness permanent / 2					9.56											
Ear/ Deafness permanent / 3		1.46	1.28		1.35					1.45						
Ear/ Deafness neurosensory / 1		3.38	0.62		2.31					1.13		1.76		1.22		
Ear/ Deafness neurosensory / 2												1.51				
Ear/ Deafness neurosensory / 3		3.09	0.8													
Ear/ Deafness transitory / 1		17.03	4.63		16.91			1.23				1.29	1.18	1.45		1.46
Ear/ Deafness transitory / 2					1.86											
Ear/ Deafness transitory / 3			1.31		10.02											
Ear/ Deafness bilateral / 1	1.32	1.13			1.3					1.33		2.69				1.65
Ear/ Deafness bilateral / 2		1.13			1.27							1.22				1.2
Ear/ Deafness bilateral / 3												1.66				1.05

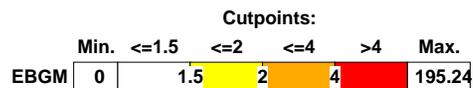
Cutpoints:

Min.	<=1.5	<=2	<=4	>4	Max.
EBGM	0	1.5	2	4	195.24

**Figure 7. Data Mining Summary Display Showing Maximum EBG M Values in Any Given Year with Recoded Event Classes, Events of Interest, and Serious Outcomes with Telithromycin and 15 comparators (data collected as of May 2006)**

**1 - All Reports**  
**2 - Only Reports with an Outcome = Fatal**  
**3 - Only Reports with an Outcome = Disability**

	Telithromycin	Azithromycin	Clarithromycin	Dirithromycin	Erythromycin	Cefditoren	Cefixime	Cefpodoxime	Ceftibuten	Cefuroxime	Gemifloxacin	Moxifloxacin	Trovafloxacin	Nitrofurantoin	Amoxicillin And Clavulanate	Acetaminophen	
Ear/ Deafness unilateral / 3		2.53	1.15		1.22							1.58					
Ear/ Hearing impaired / 1	2.03	3.67	1.94		1.64				1.17	1.79	1.11	1.46		2.05	0.71	2.52	0.62
Ear/ Hearing impaired / 3	1.29	3.19	1.14		1.09									1.64	0.91	2.36	
Ear/ Hypoacusis / 1	1.69	4.47	1.1											2.87			0.64
Ear/ Hypoacusis / 3		6.36												3.29			
Ear/ Tinnitus / 1	0.95	3.47	1.54		2.11		0.39	0.74	1.1	0.61		1.76	0.91	0.88	0.37	1.33	
Ear/ Tinnitus / 3	0.88	5.51	3.56		10.78				1.3	0.91		3.33	1.47	1.99	0.7	0.98	
Ear/ Vertigo / 1	1.78	2.11	1.91	0.95	0.87	0.46	0.89	1.45	0.75	1.26		4.57	3.5	1.48	1.82	1.63	
Ear/ Vertigo / 2		1.24										1.32	1.44			0.73	
Ear/ Vertigo / 3	1.11	1.48	0.96							1.16			2.52			0.86	1.08
Eosinophilia/ Eosinophilia / 1	2.14	2.04	2.05	1	2.09	1.36	0.88	2.18		2.51		0.98	4.64	4.1	3.56	0.85	
Eosinophilia/ Eosinophilia / 2	1.52	2.8	1.95							0.95		2.05	1.17		2.46	1.1	
Eosinophilia/ Eosinophilia / 3		1.34	2.57		1.92					1.61			2.14		2.46		
Eosinophilia/ Eosinophil count increased / 1	5.06	3.99	3.34		1.11	1.04	1.71	1.84		3.16		0.91	7.44	1.47	2.17	1.46	
Eosinophilia/ Eosinophil count increased / 2													1.37	1.49			
Eosinophilia/ Eosinophil count increased / 3		1.51			1.23								5.27				
Eosinophilia/ Eosinophilic pneumonia / 1	1.14	5.11	3.98			2.2	1.42			0.61		1.15		43.86	1.1	2.27	
Eosinophilia/ Eosinophilic pneumonia / 2														1.47			
Eosinophilia/ Eosinophilic pneumonia / 3			1.18														
Eosinophilia/ Drug rash with eosinophilia an / 1	1.6						1.39					1.03			3.99	0.86	
Eosinophilia/ Drug rash with eosinophilia an / 2							1.56								2.54		
Eye/ Visual brightness / 1	100.8																
Eye/ Visual brightness / 3	3.14																
Eye/ Visual disturbance / 1	12.2	0.74	0.88		2.28		0.52	0.6		0.8	0.33	1.99	1.77	0.57	0.36	0.71	
Eye/ Visual disturbance / 2		1.17											1.95			0.36	
Eye/ Visual disturbance / 3	9.07	0.78	1.31		0.84			1.2		0.43		1.05	2	1.25	0.66	1.16	
Eye/ Vision blurred / 1	17.78	1	0.94		1.2	0.37		0.54	0.77	0.96		0.9	0.79	0.9	0.48	0.35	
Eye/ Vision blurred / 2		1.24														0.34	
Eye/ Vision blurred / 3	12.1	0.84	0.47		2.38							1.02	1.74	1.18		1.79	
Eye/ Visual acuity reduced / 1	3.04	0.36	1.18		0.96		0.81		1.03	1.41		1.58	0.25	0.41	0.46	0.28	
Eye/ Visual acuity reduced / 3			1.39		1.13		1.08					1.29			0.46		
Eye/ Accommodation disorder / 1	45.4									1.12		0.94			0.69	0.48	
Eye/ Accommodation disorder / 3	1.26																
Eye/ Strabismus / 1	3.22	0.86	1.25										0.79	0.95	0.63	0.92	
Eye/ Strabismus / 3		0.99													0.94	1.22	



**Figure 7. Data Mining Summary Display Showing Maximum EBGm Values in Any Given Year with Recoded Event Classes, Events of Interest, and Serious Outcomes with Telithromycin and 15 comparators (data collected as of May 2006)**

**1 - All Reports**

**2 - Only Reports with an Outcome = Fatal**

**3 - Only Reports with an Outcome = Disability**

	Telithromycin	Azithromycin	Clarithromycin	Dirithromycin	Erythromycin	Cefditoren	Cefixime	Cefpodoxime	Ceftibuten	Cefuroxime	Gemifloxacin	Moxifloxacin	Trovafoxacin	Nitrofurantoin	Amoxicillin And Clavulanate	Acetaminophen
Eye/ Diplopia / 1	20.39	1.25	1.75		0.51		1.16	0.8		0.92		1.45	1.43	0.94	0.73	0.68
Eye/ Diplopia / 3	16.7	2.23	0.79				1.12			0.76		0.73	1.98	1.22	0.55	1.29
Eye/ Blindness transient / 1	3.01	0.31			1.03							1.39			0.85	0.94
Eye/ Blindness transient / 3	1.28														1.13	
Eye/ Optic neuropathy / 1			2.29									1.32			2.85	0.72
Eye/ Optic neuropathy / 3			1												1.74	
Eye/ Optic neuritis retrobulbar / 1	1.33							1.36				2.53		1.39		0.97
Eye/ Optic neuritis retrobulbar / 3												2.33				
Eye/ Tunnel vision / 1	2.67	0.9														
Eye/ Visual field defect / 1	1.92	1.67	0.71							0.5		1.21	0.7	0.35	0.2	0.31
Eye/ Visual field defect / 2													1.5			
Eye/ Visual field defect / 3	1.25	1.6	0.49										1.4	0.98		0.99
Eye/ Retinopathy / 1	1.86		2.16													
Eye/ Retinopathy / 2			1.49													
Clostridial infection/ Clostridial infection / 1	0.8	3.83	2.35			66.15	1.34	2.15	1.34	6.89		4.08	2.47		7.95	0.4
Clostridial infection/ Clostridial infection / 2		1.98					1.51		1.55	2.46		1.37	1.43		2.53	
Clostridial infection/ Clostridial infection / 3															2.61	
Clostridial infection/ Clostridium colitis / 1	1.12	3.09	3.02		2.62	57.96	38.4	41.96	23.46	43.39	4.48	7.26	3.15	0.87	24.23	0.21
Clostridial infection/ Clostridium colitis / 2		1.88	3.93		5.81	8.15	36.29	24.6	2.39	22.21	1.54	7.53	2.35	2.07	13.26	
Clostridial infection/ Clostridium colitis / 3		1.23			1.15		4.84	17.26	1.43	38.93		1.18			3.18	
Drug toxicity/ Drug toxicity / 1	0.33	1.42	2.34	1.26	1.53		0.73	0.66		0.83	0.65	0.72	1.2	2.06	0.93	11.65
Drug toxicity/ Drug toxicity / 2	0.85	1.24	2.54		1.63		1.85				2.01	0.48	0.47	1.27	0.9	3.6
Drug toxicity/ Drug toxicity / 3		0.91	1.5									1.67			1.29	1.24
Drug toxicity/ Therapeutic agent toxicity / 1	0.61	1.44	6.16		1.44					0.28		0.76	0.19	0.6	0.21	2.53
Drug toxicity/ Therapeutic agent toxicity / 2			6.3													3.61
Drug toxicity/ Therapeutic agent toxicity / 3					1.94											
Gout/ Gout / 1		5.33	2.96		0.68					2.19	0.89	0.62	0.75		1.96	0.75
Gout/ Gout / 2			42.87													
Gout/ Gouty arthritis / 1										1.3					2.49	
Gout/ Gouty arthritis / 2															1.55	
Hepatotoxicity/ Hepatotoxicity / 1	2.97	1.92	2.92		1.64	1.16			1.07	1.67		2.51	7.62	2.84	3.83	13.1
Hepatotoxicity/ Hepatotoxicity / 2	1.33	1.25	1.3							1.16		3.61	3.55	1.31	2.69	4.37
Hepatotoxicity/ Hepatotoxicity / 3		1.03	1.09		1.27									1.26		1.21
Hepatic failure/ Hepatic failure / 1	3.67	2.46	1.8		1.16	0.59	0.65	1.4		0.99	0.53	1.39	5.44	4.83	3.84	33.14
Hepatic failure/ Hepatic failure / 2	3.39	2.18	3.02		2.76	1.64	1.47	2.21		1.1	1.98	2.56	6.29	4.36	3.82	9.66

Cutpoints:

	Min.	<=1.5	<=2	<=4	>4	Max.
EBGM	0	1.5	2	4	195.24	

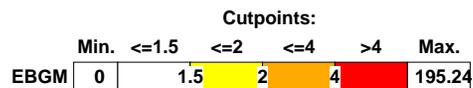
**Figure 7. Data Mining Summary Display Showing Maximum EBGm Values in Any Given Year with Recoded Event Classes, Events of Interest, and Serious Outcomes with Telithromycin and 15 comparators (data collected as of May 2006)**

**1 - All Reports**

**2 - Only Reports with an Outcome = Fatal**

**3 - Only Reports with an Outcome = Disability**

	Telithromycin	Azithromycin	Clarithromycin	Dirithromycin	Erythromycin	Cefditoren	Cefixime	Cefpodoxime	Ceftibuten	Cefuroxime	Gemifloxacin	Moxifloxacin	Trovafoxacin	Nitrofurantoin	Amoxicillin And Clavulanate	Acetaminophen
Hepatic failure/ Hepatic failure / 3	1.67	1.57	1.46					1.22		0.71		0.95	1.59	2.88	3.1	20.46
Hepatitis/ Hepatitis / 1	5.79	4.17	3.22	3.1	4.79	1.34	1.12	2.79	0.97	1.51	0.3	1.66	6.27	5.82	6.32	5.41
Hepatitis/ Hepatitis / 2	3.25	4.5	3.31		1.67					1.07		2.61	3.99	6.93	5.6	3.59
Hepatitis/ Hepatitis / 3	1.66	1.64	3.99		1.9			1.17				0.91	5.68	1.33	5.98	2.17
Hepatocellular damage/ Hepatocellular damage / 1	2.33	2.23	2.26		6.4	15.79	1.71	9.01	0.73	1.53		0.71	3.85	2.68	3.75	15.37
Hepatocellular damage/ Hepatocellular damage / 2	3.12	2.81	2.05		1.22		1.23	7.77				1.85	1.05	1.15	3.77	3.63
Hepatocellular damage/ Hepatocellular damage / 3	1.17	1.4	1.27		6.36			1.33		1.64		1.2	8.07	3.67	1.49	4.83
Biopsy liver abnormal/ Biopsy liver abnormal / 1		0.99	0.91									0.9	5.15	4.81	5.12	0.73
Biopsy liver abnormal/ Biopsy liver abnormal / 2													1.33	1.52	4.84	
Biopsy liver abnormal/ Biopsy liver abnormal / 3													3.39			
Hyperammonaemia/ Hyperammonaemia / 1	1.08	1.01	1.07			0.97		1.78			0.94	1.26	3.14	1.64	1.43	10.43
Hyperammonaemia/ Hyperammonaemia / 2		1.71	1.15								1.53	2.31	4.2	2.21	0.92	7.53
Hyperammonaemia/ Hyperammonaemia / 3		1.26	1.4					1.48					2.6			
Hyperbilirubinaemia/ Hyperbilirubinaemia / 1	4.54	2.47	2.77	1.36	12.21	1.9	1.49	1.92	1.19	1.78	0.45	1.35	4.5	5.01	6.7	4.64
Hyperbilirubinaemia/ Hyperbilirubinaemia / 2	3.48	2.63	5.71		1.27		2.56		1.42	1.38	2.23	1.02	3.92	5.7	3.75	3.78
Hyperbilirubinaemia/ Hyperbilirubinaemia / 3	1.02	3.43	3.45		1.51	4.07		1.22		1.8		0.94	6.54	1.76	9.34	1.64
Hyperbilirubinaemia/ Ocular icterus / 1	2.39	1.94	0.92								1.8	1.69		2.12	4.64	2.96
Hyperbilirubinaemia/ Ocular icterus / 2											3.12			1.55		1.56
in level decreased/ Prothrombin level decreased / 1	3.35	3.17	2.21	0.58	1.06	0.41	1.69	1.3	1.56	1.01	1.39	3.02	3.18	0.97	1.84	6.16
in level decreased/ Prothrombin level decreased / 2	2.5	3.46	2.21		0.93		2.59			1		1.81	3.55	1.82	1.59	6.77
in level decreased/ Prothrombin level decreased / 3	1.1	1.58	2.44					1.39		0.88		0.91	2.37	0.82	0.89	15.96
Chronic hepatitis/ Chronic hepatitis / 1		0.91	1.09									1.49	3.63	1.31	2.77	2.89
Chronic hepatitis/ Chronic hepatitis / 2												1.47			4.07	1.79
Hepatic fibrosis/ Hepatic cirrhosis / 1	1.07	1.26	1.43		0.48				1.75	2.1		0.42	1.61	7.19	2.54	9.9
Hepatic fibrosis/ Hepatic cirrhosis / 2	1.9	1.39	1.56		1.72				2.46	2.51		0.97	2.39	7.19	2.09	3.27
Hepatic fibrosis/ Hepatic cirrhosis / 3	1.19		1.38												1.94	1.43
Hepatic fibrosis/ Hepatic fibrosis / 1	1.78	2.75	1.06				1.18			1.99		0.48	1.88	2.47	2.04	2.03
Hepatic fibrosis/ Hepatic fibrosis / 2		1.96						1.52						1.5	1.69	1.61
Hepatic fibrosis/ Hepatic atrophy / 1	1.19	1.36	2.64										0.98	2.06		1.79
Hepatic fibrosis/ Hepatic atrophy / 2		1.36												1.48		1.54
Lactic acidosis/ Lactic acidosis / 1		0.35	0.93		0.34					0.47		0.26	0.18	0.73	0.69	2.9
Lactic acidosis/ Lactic acidosis / 2		1.37	1.07		0.94					0.79		0.92	0.63	0.82	1.06	1.62
Lactic acidosis/ Lactic acidosis / 3															1.02	
Lactic acidosis/ Blood lactic acid increased / 1		0.53				0.99									0.41	2.43
Lactic acidosis/ Blood lactic acid increased / 2															1.2	4.42



**Figure 7. Data Mining Summary Display Showing Maximum EBGm Values in Any Given Year with Recoded Event Classes, Events of Interest, and Serious Outcomes with Telithromycin and 15 comparators (data collected as of May 2006)**

**1 - All Reports**

**2 - Only Reports with an Outcome = Fatal**

**3 - Only Reports with an Outcome = Disability**

	Telithromycin	Azithromycin	Clarithromycin	Dirithromycin	Erythromycin	Cefditoren	Cefixime	Cefpodoxime	Ceftibuten	Cefuroxime	Gemifloxacin	Moxifloxacin	Trovafloxacin	Nitrofurantoin	Amoxicillin And Clavulanate	Acetaminophen
Cholestasis/ Cholangitis / 1		2.33	8.42		4.67		1.14			1.43		1.02	2.21	3.51	11.54	0.73
Cholestasis/ Cholangitis / 2		1.96	1.5										1.21		1.19	
Cholestasis/ Cholangitis / 3													1.33			
Cholestasis/ Cholecystitis / 1	1.12	1.04	1.4	1.27	1.95	1.1	1.42	1.31	1.08	1.36		0.5	3.21		2.76	0.58
Cholestasis/ Cholecystitis / 2			1.58					1.54		1.54		1.87	1.86			0.84
Cholestasis/ Cholecystitis / 3					2.22								1.24		1.59	
Cholestasis/ Cholestasis / 1	1.87	4.69	2.99	1.55	15.22	1.23	2.62	2	1.77	2.21	0.61	1.12	2.75	3.42	28.74	2.15
Cholestasis/ Cholestasis / 2	1.25	2.43	2.56		7.78		2.53	1.93	1.5	1.65	2.45	2.05	2.88	2.51	19.1	1.25
Cholestasis/ Cholestasis / 3		1.66	3.63		1.41			1.39		0.95		1.46	1.54		20.35	
Cholestasis/ Gallbladder disorder / 1	1.55	1.69	1.33		1.92		1.04	1.05		0.88		0.43	3.57	0.85	2.75	1.08
Cholestasis/ Gallbladder disorder / 2	1.51	1.18	1.07				1.5						2.34	1.43		1.46
Cholestasis/ Gallbladder disorder / 3															5.29	
Hepatic steatosis/ Hepatic steatosis / 1	1.08	1.36	0.94		1.52		1.59	0.75	1.01	1.13	0.61	0.51	2.98	1.46	2.54	4.11
Hepatic steatosis/ Hepatic steatosis / 2		2.18	1.14				1.35				1.48	1.23	1.9	1.12	3.65	2.09
Hepatic steatosis/ Hepatic steatosis / 3			1.2										2.02		1.53	1.38
Ischaemic hepatitis/ Ischaemic hepatitis / 1	2.44											1.1			0.96	1.04
Ischaemic hepatitis/ Ischaemic hepatitis / 2	1.51														1.32	
Hypersensitivity/ Anaphylactic shock / 1	2.27	2.68	1.07		1.17	3.55	1.3		1.08	17.08		4.55	0.97		7.07	1.33
Hypersensitivity/ Anaphylactic shock / 2		3.1	1.41		1.2					6.64		2.77	1.12		11.82	0.55
Hypersensitivity/ Anaphylactic shock / 3		1.19								7.05		1.17			1.96	
Hypersensitivity/ Anaphylactic reaction / 1	2.25	1.92	1.2	1.28	0.78	1.43	1		0.85	11.73	2.12	10.6	1.54	1.89	3.24	0.88
Hypersensitivity/ Anaphylactic reaction / 2	1.44	1.5								5.28		3.45	2.58		1.91	0.2
Hypersensitivity/ Anaphylactic reaction / 3		4.09								2.28		1.74	1.26			1.19
Hypersensitivity/ Anaphylactoid reaction / 1		2.44	1.18		0.91	2.98	0.85	1.4	0.44	4.74		10.61	4.59	1.6	1.82	1.31
Hypersensitivity/ Anaphylactoid reaction / 2		1.59	0.93		1.24		1.66	1.42		4.29				0.85	3.2	
Hypersensitivity/ Anaphylactoid reaction / 3		1.37			1.16					2.59			1.24		1.41	
Hypersensitivity/ Angioneurotic oedema / 1	3.01	5.61	1.36	2.91	1.85	0.84	2.16	0.94	1.04	1.95	0.93	3.91	0.37	1.3	2.45	1.26
Hypersensitivity/ Angioneurotic oedema / 2		1.15	1.59		1.03			1.47		6.41		2.05	1.23		1.4	
Hypersensitivity/ Angioneurotic oedema / 3		2.08			1.27		1.32			2.18				1.18		
Hypersensitivity/ Laryngospasm / 1		1.53	1.44		0.88	1.17	0.28	1.02	0.66	0.92		6.1	0.46	0.75	0.55	1.16
Hypersensitivity/ Laryngospasm / 2					1.5										1.92	0.81
Hypersensitivity/ Pharyngeal oedema / 1	1.83	4.2	2.21		0.56			3.18		3.68		4.11	1.18	1.16	2.02	1.03
Hypersensitivity/ Pharyngeal oedema / 3		2.56	3.09									1.21	1.29		1.23	
Hypersensitivity/ Drug hypersensitivity / 1	1.1	4.02	2.96		1.72	28.65	0.64	4.33	0.94	4.6	0.92	2.05	2	3.95	5.21	1.3
Hypersensitivity/ Drug hypersensitivity / 2		1.92	2.83		1.23	1.52				1.28		2.06	1.52		2.08	0.96

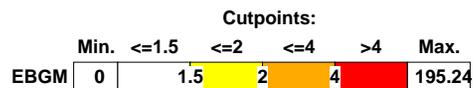
Cutpoints:

Min.	<=1.5	<=2	<=4	>4	Max.
EBGM	0	1.5	2	4	195.24

**Figure 7. Data Mining Summary Display Showing Maximum EBGm Values in Any Given Year with Recoded Event Classes, Events of Interest, and Serious Outcomes with Telithromycin and 15 comparators (data collected as of May 2006)**

**1 - All Reports  
2 - Only Reports with an Outcome = Fatal  
3 - Only Reports with an Outcome = Disability**

	Telithromycin	Azithromycin	Clarithromycin	Dirithromycin	Erythromycin	Cefditoren	Cefixime	Cefpodoxime	Ceftibuten	Cefuroxime	Gemifloxacin	Moxifloxacin	Trovafoxacin	Nitrofurantoin	Amoxicillin And Clavulanate	Acetaminophen
Hypersensitivity/ Drug hypersensitivity / 3		1.25	1.53		1.11							1.28	1.06		1.32	1.07
Hypersensitivity/ Hypersensitivity / 1	2.63	2.55	1.38	1.16	2.31	2.1	1.35	1.25	1.66	2.38	0.97	5.47	2.13	2.22	2.52	1.66
Hypersensitivity/ Hypersensitivity / 2		4.21	2.22		1.97			1.33		3.99		3.11	1.67	0.93	2.95	0.71
Hypersensitivity/ Hypersensitivity / 3	1.51	1.95	1.6		1.79			2.22	1.44	7.99		2.59	1.28	1.58	1.76	1.73
Hypersensitivity/ Serum sickness / 1	1.72	2.16	0.99		1.89	1.05	2.38	4.05	3.44	1.67		1.85	1.55	4.7	1.48	0.44
Hypersensitivity/ Serum sickness / 2					1.7											1.47
Hypersensitivity/ Serum sickness / 3		1.19					1.24			2.49			2.06			
Hypersensitivity/ Jarisch-Herxheimer reaction / 1		4.15			1.34					1.36					1.31	
Meningitis aseptic/ Meningitis aseptic / 1		1.17	2.18							1.15		0.92		1.22	4.29	0.86
Meningitis aseptic/ Meningitis aseptic / 3															1.32	
Pathogen resistance/ Pathogen resistance / 1	1.54	14.31	9.97		1.87		1.07	1.2	1.27	3.61		0.88	3.17		2.03	
Pathogen resistance/ Pathogen resistance / 2		1.84	2.99				1.51					1.8	2.1			
Pathogen resistance/ Pathogen resistance / 3		1.14	1.43						1.49						1.27	
Carnitine decreased/ Carnitine decreased / 1						47.34										1.27
Hypoglycaemia/ Hypoglycaemic coma / 1			3.11									1.31			0.75	
Hypoglycaemia/ Hypoglycaemic coma / 2			1.33													
Hypoglycaemia/ Hypoglycaemic coma / 3			1.31													
Hypoglycaemia/ Hypoglycaemia / 1	2.08	0.8	1.83	0.78	1.62	1.29	1.15	1.22	0.33	0.64		1.39	1.51	0.26	0.62	1.42
Hypoglycaemia/ Hypoglycaemia / 2	1.33		2.17		1.81							0.89	2.09		0.78	3
Hypoglycaemia/ Hypoglycaemia / 3			1.2		1.08							1.04		1.09	0.82	2.37
Tendon disorder/ Tendon disorder / 1	2.37	1.31	0.91				0.9			1.01		7.68	0.65	0.73	1.06	0.56
Tendon disorder/ Tendon disorder / 3	1.8		1.03									7.38		0.99	1.51	
Tendon disorder/ Tendon rupture / 1	0.7	0.35	0.41		1.14			1.16			0.9	11.89	0.63		0.91	
Tendon disorder/ Tendon rupture / 2												1.52				
Tendon disorder/ Tendon rupture / 3												13.46				
Tendon disorder/ Tendonitis / 1	1.14	1.23	0.8		1.21		1.89			0.89		6.87	2.65	0.95	1	
Tendon disorder/ Tendonitis / 3	1.03				1.1		1.31					4.73	1.74	1.07	1.27	
Tendon disorder/ Tenosynovitis / 1		2.47			0.63			1.03				1.87	7.13		0.83	0.56
Tendon disorder/ Tenosynovitis / 3		1.03										1.21				
Myopathy/ Myopathy / 1	2.55	1	2.15		1.79		0.38			0.39		0.78	0.85	0.59	0.89	0.49
Myopathy/ Myopathy / 2			1.47		14.26										0.92	0.63
Myopathy/ Myopathy / 3		0.92	1.34							1.41				0.87	0.59	
Myopathy/ Rhabdomyolysis / 1	1.35	1.19	3.54	1.33	3.62	1.62	0.49	1.98	0.68	0.58	0.35	0.28	0.96		1.45	1.4
Myopathy/ Rhabdomyolysis / 2	2.5	1.31	3.39		1.3						1.48	0.66	1.15		1.07	1.16
Myopathy/ Rhabdomyolysis / 3		0.86	2.75		1.87	1.2				1.03						



**Figure 7. Data Mining Summary Display Showing Maximum EBGm Values in Any Given Year with Recoded Event Classes, Events of Interest, and Serious Outcomes with Telithromycin and 15 comparators (data collected as of May 2006)**

**1 - All Reports**

**2 - Only Reports with an Outcome = Fatal**

**3 - Only Reports with an Outcome = Disability**

	Telithromycin	Azithromycin	Clarithromycin	Dirithromycin	Erythromycin	Cefditoren	Cefixime	Cefpodoxime	Ceftibuten	Cefuroxime	Gemifloxacin	Moxifloxacin	Trovafloxacin	Nitrofurantoin	Amoxicillin And Clavulanate	Acetaminophen
Myasthenia/ Myasthenia gravis / 1	33.31	3.7	2.1		1.08		1.37	1.27		1.21		1.7	1.67		1.17	
Myasthenia/ Myasthenia gravis / 2	1.55														1.42	
Myasthenia/ Myasthenia gravis / 3	2.82		1.3							1.44					1.16	
Myasthenia/ Myasthenic syndrome / 1	1.23	8.93	1.1		0.87		3.86					3.34	1.51	2.17		0.56
Myasthenia/ Myasthenic syndrome / 2																1.37
Myasthenia/ Myasthenic syndrome / 3												1.29				
Myasthenia/ Myasthenia gravis crisis / 1	10.74															
Neuropathy/ Neuropathy peripheral / 1		1.03	0.9		0.44		0.5	1.29	0.49	0.55	0.63	0.74	1.05	20.28	0.46	0.3
Neuropathy/ Neuropathy peripheral / 2			1.16		1.21									1.91	0.57	0.39
Neuropathy/ Neuropathy peripheral / 3			2.37		1.02		0.93		1.09	1.82	1.29	1.14		3.43	1.17	
Neuropathy/ Polyneuropathy / 1		0.78	0.91							0.75		1.17	1.01	4.4		0.25
Neuropathy/ Polyneuropathy / 2			1.3										1.31	2.15		
Neuropathy/ Polyneuropathy / 3		0.65	0.74									0.95				
Neuropathy/ Guillain-Barre syndrome / 1		1.88	3.13		0.5		0.9			0.96		2.24	0.88	1.71	0.74	0.51
Neuropathy/ Guillain-Barre syndrome / 3			2.26												0.91	
Convulsion/ Clonic convulsion / 1		0.78	0.77		0.51		0.57	0.52		1.16		0.95	2.48	0.37	1.01	0.32
Convulsion/ Clonic convulsion / 2		0.94	1.45							1.14		1.32	2.45		1.51	0.65
Convulsion/ Clonic convulsion / 3		0.98														1.2
Convulsion/ Epilepsy / 1	1.56	1.14	0.62		0.53				1.75			0.36	0.36	2.1	1.04	0.85
Convulsion/ Epilepsy / 2			1.02											1.44	1.53	0.64
Convulsion/ Epilepsy / 3																1.09
Convulsion/ Petit mal epilepsy / 1		0.32	0.82		2.08					2.04					0.84	0.83
Convulsion/ Petit mal epilepsy / 2					3.07					3.01						
Overdose/ Overdose / 1	0.66	1.32	1.18	1.06	0.34		0.38	0.46		0.39		1.81	0.14	0.56	0.39	10.73
Overdose/ Overdose / 2	0.78	0.45	0.27		0.19		1.12			0.26		1.02			0.35	5.4
Overdose/ Overdose / 3	0.95	1.19													0.74	4.1
Overdose/ Multiple drug overdose / 1	0.2		0.64		1.07		1.59		1.26	0.56				0.75		7.81
Overdose/ Multiple drug overdose / 2					1.17											2.48
Overdose/ Multiple drug overdose / 3																15.9
Overdose/ Multiple drug overdose acciden / 1																20.46
Overdose/ Multiple drug overdose acciden / 2																3.79
Overdose/ Multiple drug overdose intent / 1			0.98							0.89						2.97
Overdose/ Multiple drug overdose intent / 2																1.53
Overdose/ Intentional overdose / 1	1.55	0.3	0.79	0.35				0.3		0.22		0.19	1.16	0.31	0.32	9.04
Overdose/ Intentional overdose / 2	0.73	0.2		0.24										0.33		5.68

Cutpoints:

Min.	<=1.5	<=2	<=4	>4	Max.
EBGM	0	1.5	2	4	195.24

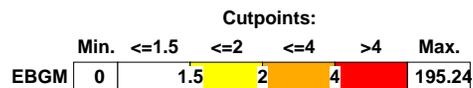
**Figure 7. Data Mining Summary Display Showing Maximum EBGm Values in Any Given Year with Recoded Event Classes, Events of Interest, and Serious Outcomes with Telithromycin and 15 comparators (data collected as of May 2006)**

**1 - All Reports**

**2 - Only Reports with an Outcome = Fatal**

**3 - Only Reports with an Outcome = Disability**

	Telithromycin	Azithromycin	Clarithromycin	Dirithromycin	Erythromycin	Cefditoren	Cefixime	Cefpodoxime	Ceftibuten	Cefuroxime	Gemifloxacin	Moxifloxacin	Trovafoxacin	Nitrofurantoin	Amoxicillin And Clavulanate	Acetaminophen
Overdose/ Intentional overdose / 3	3.87												1.32			16.34
Overdose/ Accidental overdose / 1	1.28	0.85		1.36	0.56		0.24	1.15	0.36	0.36		0.68	0.91	0.26	0.38	5.75
Overdose/ Accidental overdose / 2	0.3	0.55			1.46							1.34			0.71	3.49
Overdose/ Accidental overdose / 3					0.91										1.14	1.07
Pancreatitis/ Pancreatitis / 1	0.67	2.43	2.08	0.78	2.73		0.41	1.24		0.87	0.58	0.41	1.66	1.02	2.15	2.2
Pancreatitis/ Pancreatitis / 2		2.56	2.75							1.15	1.49		0.8		1.32	1.9
Pancreatitis/ Pancreatitis / 3			1.53												0.99	
Pancreatitis/ Pancreatitis acute / 1	1.02	1.05	1.6	1.33	2.16	2	1.09	2.1		0.5		1.13		1.26	2.74	0.95
Pancreatitis/ Pancreatitis acute / 2		0.99	1.43		1.21									1.38	1.04	1.28
Pancreatitis/ Pancreatitis acute / 3			1.09													
Pancreatitis/ Pancreatic necrosis / 1												1.23				2.37
Pancreatitis/ Pancreatic necrosis / 2												1.52				1.58
Pancreatitis/ Pancreatitis chronic / 1			1.69									1.08			0.97	2.54
Pancreatitis/ Pancreatitis chronic / 2												1.47				2.29
Pancreatitis/ Pancreatitis necrotising / 1		0.65	1.43		0.88							0.87			0.81	3.18
Pancreatitis/ Pancreatitis necrotising / 2		1.19	1.66		1.25							1.35			1.11	1.97
Pancreatitis/ Pancreatitis necrotising / 3	0.21	0.53	2.73		0.4	0.52	0.32		0.42			2.45	2	1.2	0.64	0.74
Psychiatric/ Psychotic disorder / 1		1.56	1									1.24	1.35			0.22
Psychiatric/ Psychotic disorder / 2			1.68		0.75					0.81			1.01		1.49	
Psychiatric/ Psychotic disorder / 3			5.58									3.67	1.48			0.72
Psychiatric/ Acute psychosis / 1		0.79										0.87			0.81	3.18
Psychiatric/ Delusion / 1	0.5	0.88	2.37		0.69					0.8	1.66	1.25	1.37	0.47	0.88	2.21
Psychiatric/ Delusion / 2												1.34			2.54	0.57
Psychiatric/ Delusion / 3		0.77	1.99		0.95										1.08	
Psychiatric/ Hallucination / 1	0.99	0.86	2.18	1.17	1.22	0.99	0.57	1.78	0.91	0.57	1.68	3.19	4.24	1.52	0.75	0.96
Psychiatric/ Hallucination / 2			1.96									0.99	3.54		1.21	1.34
Psychiatric/ Hallucination / 3			1.54		1.21							1.17	1.76	0.69	0.52	0.76
Psychiatric/ Hallucination, auditory / 1	0.52	1.11	3.11		0.8					1.02		0.52	0.69		0.5	0.47
Psychiatric/ Hallucination, auditory / 3			1.68													1.01
Psychiatric/ Hallucination, visual / 1	1.54	1.29	1.92		2.37					0.76		1.41	1.41	0.81	1.13	0.88
Psychiatric/ Hallucination, visual / 2													1.43			1.08
Psychiatric/ Hallucination, visual / 3			0.97							1.22			1.33		1.32	
Psychiatric/ Depersonalisation / 1		1.83	4.22		0.89				3.01	1		7.98	3.57	0.36	0.56	0.65
Psychiatric/ Depersonalisation / 3			1.11													
Psychiatric/ Hostility / 1		0.66	0.5		0.72		0.41	1.1		0.71			1.4	0.24	2.58	0.47
Psychiatric/ Hostility / 2																1.06



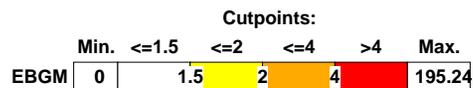
**Figure 7. Data Mining Summary Display Showing Maximum EBGm Values in Any Given Year with Recoded Event Classes, Events of Interest, and Serious Outcomes with Telithromycin and 15 comparators (data collected as of May 2006)**

**1 - All Reports**

**2 - Only Reports with an Outcome = Fatal**

**3 - Only Reports with an Outcome = Disability**

	Telithromycin	Azithromycin	Clarithromycin	Dirithromycin	Erythromycin	Cefditoren	Cefixime	Cefpodoxime	Ceftibuten	Cefuroxime	Gemifloxacin	Moxifloxacin	Trovafoxacin	Nitrofurantoin	Amoxicillin And Clavulanate	Acetaminophen
Psychiatric/ Mania / 1	0.4	0.52	3.68		0.96			0.53				0.38	0.29		0.63	0.18
Psychiatric/ Mania / 2			1.89												1.32	
Psychiatric/ Thinking abnormal / 1	0.93	0.73	1.63	0.76	0.79		0.45	0.3	0.49	0.92		1.79	1.9	0.28	2.65	1.51
Psychiatric/ Thinking abnormal / 2			1.72													2.53
Psychiatric/ Thinking abnormal / 3		0.97	0.54		1.66							1.73	1.31			
Psychiatric/ Personality disorder / 1	1.03	1.53	1.4		2.04		1.51	1.04	0.7	0.7		0.43	1.62	0.53	2.73	0.59
Psychiatric/ Personality disorder / 2		2.65														
Psychiatric/ Personality disorder / 3					1.03		1.2	1.2							0.82	
Psychiatric/ Panic attack / 1	0.65	1.87	1.65		1.26						1.2	2.15	1.02		1.03	0.52
Psychiatric/ Panic attack / 2													1.47			1.26
Psychiatric/ Panic attack / 3		1.04	1.23									1.08	1.02			
Psychiatric/ Panic reaction / 1		0.77	2.1			1.1						2.37	0.78		0.74	1.6
Psychiatric/ Panic reaction / 2												1.54				1.38
Psychiatric/ Panic reaction / 3												1.29				
Psychiatric other/ Intentional self-injury / 1		0.59	1.44		0.86										1.06	2.9
Psychiatric other/ Intentional self-injury / 2			1.26													1.94
Psychiatric other/ Intentional self-injury / 3		1.04			1.21											
Suicide/ Suicide attempt / 1		0.29	0.69		0.4		0.14		0.6	0.47		0.14		0.44	0.44	14.79
Suicide/ Suicide attempt / 2			0.19							0.18					0.7	2.56
Suicide/ Suicide attempt / 3			0.85													1.63
Suicide/ Completed suicide / 1		0.23	0.61		0.36							0.07		0.55	0.76	13.76
Suicide/ Completed suicide / 2		0.59	0.76		0.5							0.25		0.77	0.7	2.8
Suicide/ Completed suicide / 3																16.57
Purpura/ Thrombocytopenic purpura / 1	1.02	2.64	20.7									2.43			1.82	2.52
Purpura/ Thrombocytopenic purpura / 2			1.48													
Purpura/ Thrombocytopenic purpura / 3		1.35														
Purpura/ Idiopathic thrombocytopenic pu / 1	1.15	2.63	1.99		1.36	2.29	1.79	1.48	2.41	1.76		2.4	0.58	2.04	2.07	1.62
Purpura/ Idiopathic thrombocytopenic pu / 2			1.1		1.09									2.43	0.96	
Purpura/ Idiopathic thrombocytopenic pu / 3			1.65												2.29	
Purpura/ Henoch-Schonlein purpura / 1	1.3	2.71	5.17			1.31	1.21	4.32	1.3			2.85		1.93	5.09	2.07
Purpura/ Henoch-Schonlein purpura / 2															2.79	
Purpura/ Vascular purpura / 1	1.89	1.91	1.94		2.68		1.74	1.99		2.04		1.37		1.6	10.21	2.56
Purpura/ Vascular purpura / 2															1.35	
Purpura/ Vascular purpura / 3	3.02	2.57	2.1		0.96	2.7	2.85	3.41		2.27		1.14	0.87	1.51	5.7	1.64
Purpura/ Purpura / 1			1.68				2.06					1.77		1.58	3.05	0.98



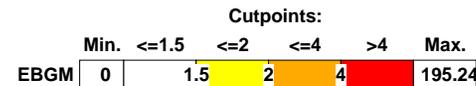
**Figure 7. Data Mining Summary Display Showing Maximum EBGGM Values in Any Given Year with Recoded Event Classes, Events of Interest, and Serious Outcomes with Telithromycin and 15 comparators (data collected as of May 2006)**

1 - All Reports

2 - Only Reports with an Outcome = Fatal

3 - Only Reports with an Outcome = Disability

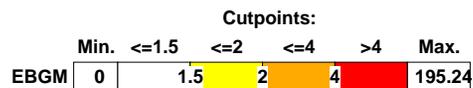
	Telithromycin	Azithromycin	Clarithromycin	Dirithromycin	Erythromycin	Cefditoren	Cefixime	Cefepodoxime	Ceftibuten	Cefuroxime	Gemifloxacin	Moxifloxacin	Trovafoxacin	Nitrofurantoin	Amoxicillin And Clavulanate	Acetaminophen
Purpura/ Purpura / 3		2.04			1.15					1.85			1.32	2.3		1.33
Purpura/ Petechiae / 1	0.93	2.65	1.85		1.19	1.9	1.33	2.75	3.48	1.5	0.86	3.3	0.74	2.9	2.39	1.32
Purpura/ Petechiae / 2		1.81	0.88		1.09		1.45			0.97		2.22	1			1.31
Purpura/ Petechiae / 3			0.98		1.21					1.22		1.3		1.83		
Renal/ Nephritis / 1		6.09	1.64		1.61	1.3	2.14	1.1		3.78		0.69	3.17	1.8	2.45	0.94
Renal/ Nephritis / 2		1.48	1.1							3.12			1.33		1.04	0.73
Renal/ Nephritis / 3		1.66	0.96					1.44							1.6	
Renal/ Nephropathy / 1		1.12	0.93		1.15	1.31		1.29		2.35					1.44	1.01
Renal/ Nephropathy / 2										1.4						1.02
Renal/ Nephropathy toxic / 1		1.07	2.11		0.76					1.02		0.79	1.57		1.13	2.99
Renal/ Nephropathy toxic / 2			1.15							1.23		1.37	2.37		1.8	1.51
Renal/ Glomerulonephritis / 1	1.08	2.47	1.15		1.05		1.59			1.68		1.15	1.13	0.66	0.8	0.34
Renal/ Glomerulonephritis / 2										1.28			1.41		1.28	
Renal/ Glomerulonephritis / 3										1						
Renal/ Nephritis interstitial / 1	3.91	1.48	3.79		1.26		2.84	1.03	2.69	4.66	0.91	3.25	0.94	4.73	3.29	1.08
Renal/ Nephritis interstitial / 2									2.38	2.2	1.56				3.33	0.69
Renal/ Nephritis interstitial / 3	1.2	1.08	1.65				1.38					1.71			1.68	1.81
Renal/ Renal failure / 1	1.82	0.99	1.5		0.72	0.75	0.85	0.88	1.34	2.26	0.34	0.76	1.07	0.82	1.18	5.34
Renal/ Renal failure / 2	1.08	1.2	1.77		2.12	1.59	1.47	0.84		2.48	1.29	1.47	1.76	1.49	1.14	3.45
Renal/ Renal failure / 3	0.82	0.25	3.33		0.73					1.11		0.74	0.6	1.14	1.18	1.82
Renal/ Renal failure acute / 1	1.52	2.63	1.7	1.18	1.16	1.63	2.02	1.64	0.65	2.07	0.35	0.9	1.29	0.54	2.45	5.15
Renal/ Renal failure acute / 2	1.83	1.87	2.1		2.37		1.37	4.09		1.74	1.37	0.94	1.84	0.36	2.21	1.61
Renal/ Renal failure acute / 3		1.11	2.46		0.96	1.2	2.45			1.12			0.83		1.55	2.65
Renal/ Renal impairment / 1	1.57	1.3	1.22		1.05	1.56	0.4	1.07	1.24	2.34		0.59	1.33	1	1.45	2.76
Renal/ Renal impairment / 2	1.12		1.45		2.21			1.28		0.54		0.95	1.25	1.56	3.06	1.99
Renal/ Renal impairment / 3			1.19		2.26					1.41			0.92	1.46	0.69	1.64
Renal/ Renal papillary necrosis / 1	1.29	1.11														56.76
Renal/ Renal papillary necrosis / 3																1.71
Renal/ Renal tubular necrosis / 1	0.64	2.33	2.21		0.59		1.76	1.27	1.71	2.66		0.49	0.66		1.75	12.47
Renal/ Renal tubular necrosis / 2		0.89	1.94						2.73	1.82		1.13	1.03		2.11	6.84
Renal/ Renal tubular necrosis / 3		0.6	1.09							1.35					0.83	0.93
Renal/ Nephrosclerosis / 1												0.78				4.25
Renal/ Nephrosclerosis / 2																3.37
Renal/ Nephrotic syndrome / 1		2.52	0.96		0.19		1.43			0.82		0.48	1.18	0.49	2.01	1.31
Renal/ Nephrotic syndrome / 2		1.35			1.32											0.98



**Figure 7. Data Mining Summary Display Showing Maximum EBGGM Values in Any Given Year with Recoded Event Classes, Events of Interest, and Serious Outcomes with Telithromycin and 15 comparators (data collected as of May 2006)**

- 1 - All Reports
- 2 - Only Reports with an Outcome = Fatal
- 3 - Only Reports with an Outcome = Disability

	Telithromycin	Azithromycin	Clarithromycin	Dirithromycin	Erythromycin	Cefditoren	Cefixime	Cefepodoxime	Ceftibuten	Cefuroxime	Gemifloxacin	Moxifloxacin	Trovafoxacin	Nitrofurantoin	Amoxicillin And Clavulanate	Acetaminophen
Renal/ Nephrotic syndrome / 3	1.14	1.54	1.41		1.6		2.51	1.98	1.85	2.43		0.77	0.46	0.8	1.59	1.18
Renal/ Dialysis / 1	1.31	1.31	2.36		1.6		2.51	1.98	1.85	2.43		0.77	0.46	0.8	1.03	2.5
Renal/ Dialysis / 2	2.29	1.36	1.56		2.32					1.11		0.94	1	1.11	1	2.24
Renal/ Dialysis / 3		0.76	1.46		1.03		2.96					1.35				2.34
Renal/ Haemodialysis / 1	0.34	1.02	2.44		2.56			1.46	1.06	2.65	1.14	0.47	0.73		1.04	3.3
Renal/ Haemodialysis / 2	1.18	1.69	2.8		1.19					2.02	2.45	1.12	1.28		0.91	2.46
Renal/ Haemodialysis / 3		1.34	0.95							1.24						3.03
Toxic lung/ Pulmonary fibrosis / 1		1.79	0.71		0.27	1.18	1.38					0.98	0.52	48.36	0.6	0.67
Toxic lung/ Pulmonary fibrosis / 2		0.88	0.76		1.11	1.45	1.46					0.69	0.72	26.56	0.44	0.36
Toxic lung/ Pulmonary fibrosis / 3		1.51												25.08	0.76	0.91
Toxic lung/ Pulmonary toxicity / 1												0.75		15.45		
Toxic lung/ Pulmonary toxicity / 2												1.3				
Toxic skin/ Erythema multiforme / 1		3.4	1.99		1.41	6.86	3.18	4.06	2.34	1.51	1.81	1.19	1.23	2.47	2.45	1.24
Toxic skin/ Erythema multiforme / 2			3.03		1.34					1.74			1.43	2.05	2.03	0.53
Toxic skin/ Erythema multiforme / 3		2.02	1.33							4.36		1.15		1.11	5.17	
Toxic skin/ Stevens-Johnson syndrome / 1	2.22	5.46	2.62		2.51	12.47	2.49	3.92	1.45	4.69	1.21	2.87	0.91	2.33	4.63	2.7
Toxic skin/ Stevens-Johnson syndrome / 2		3.17	1.98		4.81	1.45	1.16	1.39		5.15		3.35	2.35	2.9	7.12	1.96
Toxic skin/ Stevens-Johnson syndrome / 3		2.02	1.65		0.9	2.89	1.12	2.1		2.98		1.83	1.07	1.52	1.9	1.96
Toxic skin/ Toxic epidermal necrolysis / 1	1.03	1.64	2.68		3.45	4.24	2.67	6.75	1.39	5.5		2.48	0.8	1.39	6.99	5.21
Toxic skin/ Toxic epidermal necrolysis / 2		2.22	2.97		4.62	3.6		4.04		6.59		2.47	0.55	0.6	9.4	2.06
Toxic skin/ Toxic epidermal necrolysis / 3		1.53	1.6		2.15	1.21	2.55	1.3		2.32		1.23			4.1	0.97
Toxic skin/ Toxic skin eruption / 1	1.02	1.72	2.56		2.23	2.11	1.71	15.39		2.83		1.36		0.84	24.12	2.47
Toxic skin/ Toxic skin eruption / 2		1.36	1.34		1.45							1.38			17.66	1.42
Toxic skin/ Toxic skin eruption / 3		1.17													2.13	
Photosensitivity/ Photosensitivity reaction / 1	1.05	1.95	1.34		0.9	0.85	0.97	0.59	2.09	0.55	3.73	2.31	2.29	2.08	0.78	0.27
Photosensitivity/ Photosensitivity reaction / 2		1.09	0.7		1.31						3.01		1.11	0.93		
Photosensitivity/ Photosensitivity reaction / 3	2.16	1.55	1.29	1.04	1.29		0.49	0.88	0.74	1.88	1.06	4.07	0.91	1.11	0.89	0.67
Syncope/ Syncope / 1	1.84	0.55	2.39		1.56					0.89		1.37		0.77	1.15	1.14
Syncope/ Syncope / 2	1.18	0.9	0.54		1.11					0.89		2.2	0.74	0.66	1.21	0.6
Syncope/ Syncope / 3	4.25	2.01	1.58		2.03	0.27	0.81	0.7	0.84	2.83	0.21	2.09	0.75	1.48	1.41	1.62
Syncope/ Loss of consciousness / 1	3.07	1.47	1.37		1.39					2.22		2.02	0.88	1.09	1.13	1.23
Syncope/ Loss of consciousness / 2	1.33	1.82	1.08		1.1				1.41	0.8		2.12	0.77		1.2	1.33
Syncope/ Loss of consciousness / 3	2.67	1.2	1.11				1.14					4.85	0.56	1.1	0.92	0.99
Syncope/ Syncope vasovagal / 1	3.14	2.05														
Syncope/ Syncope vasovagal / 2																
Syncope/ Syncope vasovagal / 3			1.17													



**Figure 7. Data Mining Summary Display Showing Maximum EBMG Values in Any Given Year with Recoded Event Classes, Events of Interest, and Serious Outcomes with Telithromycin and 15 comparators (data collected as of May 2006)**

**1 - All Reports**

**2 - Only Reports with an Outcome = Fatal**

**3 - Only Reports with an Outcome = Disability**

	Telithromycin	Azithromycin	Clarithromycin	Dirithromycin	Erythromycin	Cefditoren	Cefixime	Cefpodoxime	Ceftibuten	Cefuroxime	Gemifloxacin	Moxifloxacin	Trovafloxacin	Nitrofurantoin	Amoxicillin And Clavulanate	Acetaminophen
Syncopal/ Dizziness / 1	2.55	0.83	1.19	0.83	0.95	0.25	0.48	0.73	1.07	0.59	0.56	4.31	3.19	1.1	0.45	0.99
Syncopal/ Dizziness / 2		1.06	3.04							0.94		0.94	0.29	1	0.65	1.28
Syncopal/ Dizziness / 3	1.66	1.2	0.89		1.45			1.11		0.91		1.96	1.99	0.66	0.51	0.73
Vascular/ Vasculitis / 1	1.31	1.34	2.09	1.75	1.21		0.95	2.48		1.59		1.29	1.78	2.17	3.57	1.43
Vascular/ Vasculitis / 2		1.68	2.2		0.97									1.07	1.58	0.35
Vascular/ Vasculitis / 3		1.1	1.53							1.99		1.03	2.28		0.74	1.27
Vascular/ Vasculitis necrotising / 1		0.8	1.43		1.22										2.12	
Vascular/ Vasculitis necrotising / 3															1.28	
Vascular/ Leukocytoclastic vasculitis / 1	1.8	3.09	2.49		1.27	1.16	1.81	13.33		4.1	0.96	2.61	1.6	3.92	10.23	1.09
Vascular/ Leukocytoclastic vasculitis / 2							1.5						1.3		1.33	
Vascular/ Leukocytoclastic vasculitis / 3		1.06										2.02	1.27		3.56	
Outcome/ 1	1.33	0.92	1.22		0.51	0.41	0.45	0.52	0.59	1.74	0.1	1.47	0.84	0.72	1.06	2.89
Outcome/ 2	0.97	1.12	0.88	1.35	0.8	1.11	0.37	0.9	0.82	1.17	0.15	0.7	0.72	1.54	1.07	1.17
Outcome/ Life-threatening	1.28	1.27	1.05	0.46	1.57	1.63	0.62	1.5	0.53	2.87	1.1	1.47	0.96	1.38	1.69	1.41
Outcome/ Hospitalized	1.62	1.86	1.76	1.6	1.19	1.98	1.66	2.62	1.13	1.57	0.56	1	0.75	1.59	1.66	2.45
Outcome/ Congenital Anomaly	0.33	1.06	0.81		1.23		0.5	0.58	0.33	1.03		0.3	0.05	4.71	0.35	1.15
Outcome/ Required Intervention to Prevent	0.33	2.52	1.6	0.73	2.52	1.25	0.7	3.09	0.34	1.72	0.26	0.52	3.57	1.34	0.97	1.7

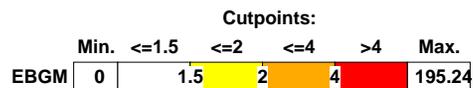


Figure 8. Number of Reports and Marginal Totals in 2006 with Events of Interest with Telithromycin and 15 comparators

**Figure 8. Number of Reports and Marginal Totals in 2006  
with Events of Interest with Telithromycin and 15 comparators  
(data collected as of May 2006)**

**1 - All Reports**

**2 - Only Reports with an Outcome = Fatal**

**3 - Only Reports with an Outcome = Disability**

	Telithromycin	Azithromycin	Clarithromycin	Dirithromycin	Erythromycin	Cefditoren	Cefixime	Cefpodoxime	Ceftibuten	Cefuroxime	Gemifloxacin	Moxifloxacin	Trovaflaxacin	Nitrofurantoin	Amoxicillin And Clavulanate	Acetaminophen	All Reports
Blood/ Bleeding time abnormal / 1																3	16
Blood/ Bleeding time abnormal / 3																	1
Blood/ Coagulopathy / 1	6	20	18		16		6	2		19		10	18	12	20	202	5559
Blood/ Coagulopathy / 2	1	9	8		2		3	1		4		5	10	8	12	131	2093
Blood/ Coagulopathy / 3			2		1									1	1	3	259
Blood/ Haemolysis / 1	2	16	12		2	1		1		15		10	6	7	10	5	1749
Blood/ Haemolysis / 2		2			1	1				2		2		2	2		357
Blood/ Haemolysis / 3														1	1		49
Blood/ Haemolytic anaemia / 1	4	28	51	1	16	2	7	4	2	25		4	6	40	40	17	4783
Blood/ Haemolytic anaemia / 2		4	10		1					2		1		5	12	6	674
Blood/ Haemolytic anaemia / 3		1	3							1				1			120
Blood/ Anaemia haemolytic autoimmune / 1		4	14		1	2		1				3	1	1	3	2	462
Blood/ Anaemia haemolytic autoimmune / 2			3		1							1					69
Blood/ Anaemia haemolytic autoimmune / 3																	12
Blood/ Intravascular haemolysis / 1										1		3					121
Blood/ Intravascular haemolysis / 2												2					25
Blood/ Intravascular haemolysis / 3																	1
Blood/ Haemolytic uraemic syndrome / 1	1	1	13									1			2	4	672
Blood/ Haemolytic uraemic syndrome / 2			2													2	189
Blood/ Haemolytic uraemic syndrome / 3			1													1	45
Cardiac/ Myocardial fibrosis / 1												1				13	280
Cardiac/ Myocardial fibrosis / 2												1				13	232
Cardiac/ Myocardial fibrosis / 3																	4
Cardiac/ Cardiotoxicity / 1			2													5	214
Cardiac/ Cardiotoxicity / 2			2														55
Cardiac/ Cardiotoxicity / 3																	8
Cardiac/ Torsade de pointes / 1	6	49	82		121			1		2		41	1	1	2	8	2458
Cardiac/ Torsade de pointes / 2		7	4		12							9				4	294
Cardiac/ Torsade de pointes / 3			2		1							3					35
Cardiac/ Electrocardiogram QT prolonged / 1	6	61	134	1	145					1		70	2	2	3	20	4343
Cardiac/ Electrocardiogram QT prolonged / 2		5	12		11							9				6	345
Cardiac/ Electrocardiogram QT prolonged / 3			5		2							1					279
Cardiac/ Electrocardiogram QT corrected / 1	7	15	10		17			1				28			1	13	1473
Cardiac/ Electrocardiogram QT corrected / 2		1	1		3							2				8	96
Cardiac/ Electrocardiogram QT corrected / 3			1														11

Cutpoints:

	Min.	<=1	<=100	<=1000	>1000	Max.
N	1	1	100	1000	659953	

**Figure 8. Number of Reports and Marginal Totals in 2006  
with Events of Interest with Telithromycin and 15 comparators  
(data collected as of May 2006)**

**1 - All Reports**

**2 - Only Reports with an Outcome = Fatal**

**3 - Only Reports with an Outcome = Disability**

	Telithromycin	Azithromycin	Clarithromycin	Dirithromycin	Erythromycin	Cefditoren	Cefixime	Cefpodoxime	Ceftibuten	Cefuroxime	Gemifloxacin	Moxifloxacin	Trovafloxacin	Nitrofurantoin	Amoxicillin And Clavulanate	Acetaminophen	All Reports
Cardiac/ Sudden cardiac death / 1		1	2		10							5				2	358
Cardiac/ Sudden cardiac death / 2		1	2		10							5				2	338
Cardiac/ Sudden cardiac death / 3																	9
Drug ineffective/ Drug ineffective / 1	59	720	185	18	198	38	300	40	126	160	19	61	143	73	225	1371	177180
Drug ineffective/ Drug ineffective / 2	1	17	8		6		1	1	1	6		14	2	2	8	24	4413
Drug ineffective/ Drug ineffective / 3		11	2		2			1	2	3		2			2	1	1682
Drug ineffective/ Drug effect decreased / 1		56	7		6		1		3	3		7	14	1	5	27	12525
Drug ineffective/ Drug effect decreased / 2		1							1			2	1			3	336
Drug ineffective/ Drug effect decreased / 3		2														1	292
Drug ineffective/ Drug ineffective for unapprove / 1						11											112
Drug ineffective/ Drug ineffective for unapprove / 2																	12
Drug ineffective/ Drug ineffective for unapprove / 3																	3
Drug ineffective/ Therapeutic response decreased / 1	1	12	3			1				1					1	6	2691
Drug ineffective/ Therapeutic response decreased / 2																1	144
Drug ineffective/ Therapeutic response decreased / 3																	50
Drug interaction/ Drug interaction / 1	50	470	1026	3	484	1	24	21	6	90	6	92	125	43	151	285	35312
Drug interaction/ Drug interaction / 2	3	41	95		51		1			7		11	16	1	12	67	2754
Drug interaction/ Drug interaction / 3	2	10	28		24			1							5	2	1007
Drug interaction/ Drug interaction potentiation / 1	1	3	10		1					1					1	1	309
Drug interaction/ Drug interaction potentiation / 2			2														50
Drug interaction/ Drug interaction potentiation / 3																	10
Drug interaction/ Drug level increased / 1	3	7	33		6		1			2		6			6	71	2554
Drug interaction/ Drug level increased / 2			2												1	48	761
Drug interaction/ Drug level increased / 3		2													1	1	64
Drug interaction/ Drug level above therapeutic / 1	1	56	247	2	143		3	3		20		4	14	5	9	298	13248
Drug interaction/ Drug level above therapeutic / 2		3	11		11					2				2	1	213	1965
Drug interaction/ Drug level above therapeutic / 3			4		8											1	178
Drug interaction/ Antidepressant drug level above / 1			3														29
Drug interaction/ Antidepressant drug level above / 2																	14
Drug interaction/ Antidepressant drug level above / 3																	1
Ear/ Ototoxicity / 1		4	1		5							2					190
Ear/ Ototoxicity / 2																	7
Ear/ Ototoxicity / 3		1	1		2							1					82
Ear/ Deafness / 1	2	202	85	1	168		3	1	5	17		11	14	13	12	18	6454
Ear/ Deafness / 2		1			6												146

Cutpoints:

	Min.	<=1	<=100	<=1000	>1000	Max.
N	1	1	100	1000	659953	

**Figure 8. Number of Reports and Marginal Totals in 2006  
with Events of Interest with Telithromycin and 15 comparators  
(data collected as of May 2006)**

**1 - All Reports**

**2 - Only Reports with an Outcome = Fatal**

**3 - Only Reports with an Outcome = Disability**

	Telithromycin	Azithromycin	Clarithromycin	Dirithromycin	Erythromycin	Cefditoren	Cefixime	Cefpodoxime	Ceftibuten	Cefuroxime	Gemifloxacin	Moxifloxacin	Trovafloxacin	Nitrofurantoin	Amoxicillin And Clavulanate	Acetaminophen	All Reports
Ear/ Deafness / 3	1	70	10	1	29		1		3	3		6	9	6	2	2	1797
Ear/ Deafness permanent / 1		1	3		9					1							279
Ear/ Deafness permanent / 2					3												9
Ear/ Deafness permanent / 3		1	1		1					1							77
Ear/ Deafness neurosensory / 1		12	1		3					1		3		1			452
Ear/ Deafness neurosensory / 2												1					16
Ear/ Deafness neurosensory / 3		8	1									1					216
Ear/ Deafness transitory / 1		4	10		69		1					1	1	3		1	565
Ear/ Deafness transitory / 2					1												5
Ear/ Deafness transitory / 3			1		4												45
Ear/ Deafness bilateral / 1	1	1			1					1		3				2	109
Ear/ Deafness bilateral / 2																	2
Ear/ Deafness bilateral / 3		1			1							1				1	49
Ear/ Deafness unilateral / 1		7	1		1							3				2	370
Ear/ Deafness unilateral / 2																	2
Ear/ Deafness unilateral / 3		3	1		1							2					124
Ear/ Hearing impaired / 1	4	29	9		3		1	2	1	2		7	3		5	6	1252
Ear/ Hearing impaired / 2																	30
Ear/ Hearing impaired / 3	1	11	2		1							2	1		3		293
Ear/ Hypoacusis / 1	3	10	1									7				1	604
Ear/ Hypoacusis / 2																	27
Ear/ Hypoacusis / 3		4										3					121
Ear/ Tinnitus / 1	7	134	70		63		2	2	2	13		29	15	15	10	59	11927
Ear/ Tinnitus / 2																	80
Ear/ Tinnitus / 3	1	32	13		10				1	1		10	3	3	1	2	1199
Ear/ Vertigo / 1	15	49	43	1	22	1	3	3	1	19		65	55	16	18	26	9619
Ear/ Vertigo / 2		1										1	1				1
Ear/ Vertigo / 3	1	6	2							2			5		2	2	892
Eosinophilia/ Eosinophilia / 1	7	40	58	1	70	2	5	8		39		7	39	61	74	26	6913
Eosinophilia/ Eosinophilia / 2	1	4	3							1		2	1		4	2	289
Eosinophilia/ Eosinophilia / 3		2	3		2					1			2		3		150
Eosinophilia/ Eosinophil count increased / 1	11	28	18		2	1	2	2		5		2	28	2	10	14	1252
Eosinophilia/ Eosinophil count increased / 2													1	1			80
Eosinophilia/ Eosinophil count increased / 3		2			1								3				53
Eosinophilia/ Eosinophilic pneumonia / 1	1	17	15			2	1			1		2		40	2	6	774

Cutpoints:

	Min.	<=1	<=100	<=1000	>1000	Max.
N	1	1	100	1000	659953	

**Figure 8. Number of Reports and Marginal Totals in 2006  
with Events of Interest with Telithromycin and 15 comparators  
(data collected as of May 2006)**

**1 - All Reports**

**2 - Only Reports with an Outcome = Fatal**

**3 - Only Reports with an Outcome = Disability**

	Telithromycin	Azithromycin	Clarithromycin	Dirithromycin	Erythromycin	Cefditoren	Cefixime	Cefpodoxime	Ceftibuten	Cefuroxime	Gemifloxacin	Moxifloxacin	Trovafloxacin	Nitrofurantoin	Amoxicillin And Clavulanate	Acetaminophen	All Reports
Eosinophilia/ Eosinophilic pneumonia / 2			1											1			50
Eosinophilia/ Eosinophilic pneumonia / 3																	19
Eosinophilia/ Drug rash with eosinophilia an / 1	2						1			1		1			6	1	143
Eosinophilia/ Drug rash with eosinophilia an / 2							1								2		17
Eye/ Visual brightness / 1	16																35
Eye/ Visual brightness / 3	2																4
Eye/ Visual disturbance / 1	104	47	74		18		2	3		13	1	47	72	14	16	32	19009
Eye/ Visual disturbance / 2		1											2			1	237
Eye/ Visual disturbance / 3	10	6	6		3			1		1		3	6	4	1	4	1979
Eye/ Vision blurred / 1	248	26	29		11	1		1	1	4		19	21	5	8	25	11160
Eye/ Vision blurred / 2		1															181
Eye/ Vision blurred / 3	14	5	2		4							3	5	2		5	1287
Eye/ Visual acuity reduced / 1	23	7	19		4		1		1	6		24	2	1	6	5	5064
Eye/ Visual acuity reduced / 2																	71
Eye/ Visual acuity reduced / 3			6		1		1					4			1		1135
Eye/ Accommodation disorder / 1	14									1		1			1	1	674
Eye/ Accommodation disorder / 2																	5
Eye/ Accommodation disorder / 3	1																60
Eye/ Strabismus / 1	4	2	3											1	1	2	500
Eye/ Strabismus / 2													1				18
Eye/ Strabismus / 3		1														1	92
Eye/ Diplopia / 1	72	20	31		5		4	2		4		12	14	6	10	18	5361
Eye/ Diplopia / 2																	109
Eye/ Diplopia / 3	8	6	2				1			1		1	2	2	1	2	647
Eye/ Blindness transient / 1	7	1			1							4			1	2	871
Eye/ Blindness transient / 2																	28
Eye/ Blindness transient / 3	1														1		134
Eye/ Optic neuropathy / 1			4									2			5	1	276
Eye/ Optic neuropathy / 2																	4
Eye/ Optic neuropathy / 3			1												2		94
Eye/ Optic neuritis retrobulbar / 1	1								1			3		1		1	193
Eye/ Optic neuritis retrobulbar / 2																	2
Eye/ Optic neuritis retrobulbar / 3												2					42
Eye/ Tunnel vision / 1	3	1															159
Eye/ Tunnel vision / 2																	3

		Cutpoints:					
		Min.	<=1	<=100	<=1000	>1000	Max.
N	1	1	1	100	1000	659953	

**Figure 8. Number of Reports and Marginal Totals in 2006  
with Events of Interest with Telithromycin and 15 comparators  
(data collected as of May 2006)**

**1 - All Reports**

**2 - Only Reports with an Outcome = Fatal**

**3 - Only Reports with an Outcome = Disability**

	Telithromycin	Azithromycin	Clarithromycin	Dirithromycin	Erythromycin	Cefditoren	Cefixime	Cefpodoxime	Ceftibuten	Cefuroxime	Gemifloxacin	Moxifloxacin	Trovafloxacin	Nitrofurantoin	Amoxicillin And Clavulanate	Acetaminophen	All Reports
Eye/ Tunnel vision / 3										2		6	3	1	1	4	23
Eye/ Visual field defect / 1	5	15	7														2812
Eye/ Visual field defect / 2													1				44
Eye/ Visual field defect / 3	1	5	1										2	1		1	599
Eye/ Retinopathy / 1	3		4														608
Eye/ Retinopathy / 2			1														14
Eye/ Retinopathy / 3																	111
Clostridial infection/ Clostridial infection / 1	1	10	5			21	1	2	1	7		9	3		18	1	534
Clostridial infection/ Clostridial infection / 2		2					1		1	2		1	1			3	117
Clostridial infection/ Clostridial infection / 3																2	21
Clostridial infection/ Clostridium colitis / 1	3	48	97		84	43	462	201	22	1103	8	53	24	14	299	2	6948
Clostridial infection/ Clostridium colitis / 2		4	12		13	3	18	6	2	83	1	8	5	4	45		993
Clostridial infection/ Clostridium colitis / 3		1			1		2	4	1	38		1			5		163
Drug toxicity/ Drug toxicity / 1	3	33	68	1	15		2	1		5	3	19	20	8	19	422	9586
Drug toxicity/ Drug toxicity / 2	1	5	20		4		2				2	1	1	2	3	311	3803
Drug toxicity/ Drug toxicity / 3		2	3									3			2	2	356
Drug toxicity/ Therapeutic agent toxicity / 1	1	11	118		13					1		3	1	4	1	47	3761
Drug toxicity/ Therapeutic agent toxicity / 2			9													36	573
Drug toxicity/ Therapeutic agent toxicity / 3					1												64
Gout/ Gout / 1		11	21		3					7	1	1	2		3	5	1784
Gout/ Gout / 2			16														83
Gout/ Gout / 3																	146
Gout/ Gouty arthritis / 1									1						3		113
Gout/ Gouty arthritis / 2															1		8
Gout/ Gouty arthritis / 3																	15
Hepatotoxicity/ Hepatotoxicity / 1	13	12	22		5	1			1	4		17	41	6	21	150	2210
Hepatotoxicity/ Hepatotoxicity / 2	1	2	2							1		6	6	1	4	54	468
Hepatotoxicity/ Hepatotoxicity / 3		1	1		1									1		1	69
Hepatic failure/ Hepatic failure / 1	41	97	101		33	2	5	9		21	2	40	136	71	141	1288	13481
Hepatic failure/ Hepatic failure / 2	9	34	50		19	2	4	5		11	2	21	69	35	81	819	7589
Hepatic failure/ Hepatic failure / 3	2	5	3					1		1		1	2	5	8	23	558
Hepatitis/ Hepatitis / 1	59	150	169	6	258	3	13	22	3	50	1	45	160	173	317	347	17676
Hepatitis/ Hepatitis / 2	4	22	17		4					4		7	13	19	38	67	2461
Hepatitis/ Hepatitis / 3	2	3	6		3			1				1	7	2	16	3	620
Hepatocellular damage/ Hepatocellular damage / 1	17	45	60		63	8	8	23	1	18		12	52	24	82	306	8749

Cutpoints:

	Min.	<=1	<=100	<=1000	>1000	Max.
N	1	1	100	1000	659953	

**Figure 8. Number of Reports and Marginal Totals in 2006  
with Events of Interest with Telithromycin and 15 comparators  
(data collected as of May 2006)**

**1 - All Reports**

**2 - Only Reports with an Outcome = Fatal**

**3 - Only Reports with an Outcome = Disability**

	Telithromycin	Azithromycin	Clarithromycin	Dirithromycin	Erythromycin	Cefditoren	Cefixime	Cefpodoxime	Ceftibuten	Cefuroxime	Gemifloxacin	Moxifloxacin	Trovafloxacin	Nitrofurantoin	Amoxicillin And Clavulanate	Acetaminophen	All Reports
Hepatocellular damage/ Hepatocellular damage / 2	3	8	7		3		1	4		2		3	2	2	15	60	1239
Hepatocellular damage/ Hepatocellular damage / 3	1	4	2		3			1		2		2	6	4	2	7	1716
Biopsy liver abnormal/ Biopsy liver abnormal / 1		2	1									1	10	3	5	2	290
Biopsy liver abnormal/ Biopsy liver abnormal / 2													1	1	3		54
Biopsy liver abnormal/ Biopsy liver abnormal / 3													2				13
Hyperammonaemia/ Hyperammonaemia / 1	1	8	3			1		2			1	5	13	2	4	117	1337
Hyperammonaemia/ Hyperammonaemia / 2		3	1								1	3	7	2	1	90	405
Hyperammonaemia/ Hyperammonaemia / 3		1	1					1					2				51
Hyperbilirubinaemia/ Hyperbilirubinaemia / 1	64	196	274	3	442	8	25	20	6	87	2	56	230	202	502	535	27017
Hyperbilirubinaemia/ Hyperbilirubinaemia / 2	6	24	37		7		5		1	10	2	5	35	22	44	226	4392
Hyperbilirubinaemia/ Hyperbilirubinaemia / 3	1	8	14		3	3		1		4		1	10	2	25	3	758
Hyperbilirubinaemia/ Ocular icterus / 1	4	3	1								2	2		2	6	8	296
Hyperbilirubinaemia/ Ocular icterus / 2											2			1		2	33
Hyperbilirubinaemia/ Ocular icterus / 3																	12
in level decreased/ Prothrombin level decreased / 1	40	205	202	1	53	1	20	11	6	41	6	103	118	24	112	585	19812
in level decreased/ Prothrombin level decreased / 2	4	22	14		3		4			6		8	20	6	15	363	2932
in level decreased/ Prothrombin level decreased / 3	1	3	4					1		1		1	3	1	1	9	380
Chronic hepatitis/ Chronic hepatitis / 1		1	1									2	5	1	4	7	200
Chronic hepatitis/ Chronic hepatitis / 2												1			3	2	44
Chronic hepatitis/ Chronic hepatitis / 3																	12
Hepatic fibrosis/ Hepatic cirrhosis / 1	3	10	11		3				2	11		2	9	27	17	75	3020
Hepatic fibrosis/ Hepatic cirrhosis / 2	2	3	3		1				2	6		1	6	7	6	38	1038
Hepatic fibrosis/ Hepatic cirrhosis / 3	1		2												2	1	213
Hepatic fibrosis/ Hepatic fibrosis / 1	3	8	3					1		3		1	4	3	6	13	740
Hepatic fibrosis/ Hepatic fibrosis / 2		2						1						1	2	6	179
Hepatic fibrosis/ Hepatic fibrosis / 3																	37
Hepatic fibrosis/ Hepatic atrophy / 1	1	2	4										1	2		2	207
Hepatic fibrosis/ Hepatic atrophy / 2		1												1		2	78
Hepatic fibrosis/ Hepatic atrophy / 3																	68
Lactic acidosis/ Lactic acidosis / 1		5	8		2					1		2	1	4	7	62	4079
Lactic acidosis/ Lactic acidosis / 2		4	4		1					1		1	1	1	4	33	1486
Lactic acidosis/ Lactic acidosis / 3																1	98
Lactic acidosis/ Blood lactic acid increased / 1		1				1									1	28	1023
Lactic acidosis/ Blood lactic acid increased / 2															1	25	159
Lactic acidosis/ Blood lactic acid increased / 3																	37

Cutpoints:

	Min.	<=1	<=100	<=1000	>1000	Max.
N	1	1	100	1000	659953	

**Figure 8. Number of Reports and Marginal Totals in 2006  
with Events of Interest with Telithromycin and 15 comparators  
(data collected as of May 2006)**

**1 - All Reports**

**2 - Only Reports with an Outcome = Fatal**

**3 - Only Reports with an Outcome = Disability**

	Telithromycin	Azithromycin	Clarithromycin	Dirithromycin	Erythromycin	Cefditoren	Cefixime	Cefpodoxime	Ceftibuten	Cefuroxime	Gemifloxacin	Moxifloxacin	Trovafloxacin	Nitrofurantoin	Amoxicillin And Clavulanate	Acetaminophen	All Reports
Cholestasis/ Cholangitis / 1		8	8		3		1			2		2	5	6	15	2	729
Cholestasis/ Cholangitis / 2		2	1										1		1		160
Cholestasis/ Cholangitis / 3													1				28
Cholestasis/ Cholecystitis / 1	1	5	11	1	10	1	1	2	1	7		2	15		14	6	2386
Cholestasis/ Cholecystitis / 2			1					1		2		2	2			1	267
Cholestasis/ Cholecystitis / 3					1								1				92
Cholestasis/ Cholestasis / 1	16	123	143	2	348	4	20	10	4	55	2	29	61	66	561	157	13975
Cholestasis/ Cholestasis / 2	1	9	14		8		3	2	1	5	2	6	10	6	74	29	1761
Cholestasis/ Cholestasis / 3		5	8		2			1		1		2	2		32		481
Cholestasis/ Gallbladder disorder / 1	5	15	8		4		1	1		1		2	22	1	11	13	1818
Cholestasis/ Gallbladder disorder / 2	1	1	1				1						3	1		4	177
Cholestasis/ Gallbladder disorder / 3															3		163
Hepatic steatosis/ Hepatic steatosis / 1	5	22	14		3		4	1	1	6	1	5	22	6	28	102	4125
Hepatic steatosis/ Hepatic steatosis / 2		6	3				1				1	2	4	1	5	58	1052
Hepatic steatosis/ Hepatic steatosis / 3			1										2		2	1	180
Ischaemic hepatitis/ Ischaemic hepatitis / 1	3														1	1	126
Ischaemic hepatitis/ Ischaemic hepatitis / 2	1														1		60
Ischaemic hepatitis/ Ischaemic hepatitis / 3																	5
Hypersensitivity/ Anaphylactic shock / 1	10	49	12		4	8	2		1	59		53	8		81	35	3625
Hypersensitivity/ Anaphylactic shock / 2		6	2		1					6		4	2		18	1	446
Hypersensitivity/ Anaphylactic shock / 3		1								4		1			2		73
Hypersensitivity/ Anaphylactic reaction / 1	15	49	18	1	3	4	1		1	49	8	149	20	5	50	33	4960
Hypersensitivity/ Anaphylactic reaction / 2	1	2								6		5	6		3	1	389
Hypersensitivity/ Anaphylactic reaction / 3		5								2		2	1			1	83
Hypersensitivity/ Anaphylactoid reaction / 1		47	37		59	4	13	11	1	177		67	44	47	72	59	15143
Hypersensitivity/ Anaphylactoid reaction / 2		2	3		3		2	1		17				1	13		1129
Hypersensitivity/ Anaphylactoid reaction / 3		1			1					3					2		156
Hypersensitivity/ Angioneurotic oedema / 1	22	101	69	5	32	2	23	5	3	53	3	62	6	18	93	55	12080
Hypersensitivity/ Angioneurotic oedema / 2		1	2		1			1		6		2	1		2		270
Hypersensitivity/ Angioneurotic oedema / 3		3			1		1			3				1			199
Hypersensitivity/ Laryngospasm / 1		11	45		14	1	1	4	1	11		13	1	5	7	19	4733
Hypersensitivity/ Laryngospasm / 2					1										2	1	114
Hypersensitivity/ Laryngospasm / 3																	55
Hypersensitivity/ Pharyngeal oedema / 1	4	34	16		1			4		10		21	7	2	11	9	1865
Hypersensitivity/ Pharyngeal oedema / 2																	62

Cutpoints:

	Min.	<=1	<=100	<=1000	>1000	Max.
N	1	1	100	1000	659953	

**Figure 8. Number of Reports and Marginal Totals in 2006  
with Events of Interest with Telithromycin and 15 comparators  
(data collected as of May 2006)**

**1 - All Reports**

**2 - Only Reports with an Outcome = Fatal**

**3 - Only Reports with an Outcome = Disability**

	Telithromycin	Azithromycin	Clarithromycin	Dirithromycin	Erythromycin	Cefditoren	Cefixime	Cefpodoxime	Ceftibuten	Cefuroxime	Gemifloxacin	Moxifloxacin	Trovaflaxacin	Nitrofurantoin	Amoxicillin And Clavulanate	Acetaminophen	All Reports	
Hypersensitivity/ Pharyngeal oedema / 3		3	2															75
Hypersensitivity/ Drug hypersensitivity / 1	8	106	45		9	12	1	8	1	22	4	32	22	15	64	54		5529
Hypersensitivity/ Drug hypersensitivity / 2		3	4		1	1				1		3	2		3	6		379
Hypersensitivity/ Drug hypersensitivity / 3		2	3		1							1	1		2	1		358
Hypersensitivity/ Hypersensitivity / 1	42	298	212	3	291	11	52	24	13	208	4	216	94	144	267	127		37058
Hypersensitivity/ Hypersensitivity / 2		10	6		4			1		11		5	3	1	9	7		861
Hypersensitivity/ Hypersensitivity / 3	2	8	2		3			2	1	11		4	2	3	3	4		762
Hypersensitivity/ Serum sickness / 1	3	34	26		15	1	76	38	15	44		6	6	30	62	4		5698
Hypersensitivity/ Serum sickness / 2					1										1			57
Hypersensitivity/ Serum sickness / 3		1					1			3			2					92
Hypersensitivity/ Jarisch-Herxheimer reaction / 1		4			1					1					1			27
Hypersensitivity/ Jarisch-Herxheimer reaction / 2																		1
Meningitis aseptic/ Meningitis aseptic / 1		4	4							1		2		1	11	2		511
Meningitis aseptic/ Meningitis aseptic / 2																		19
Meningitis aseptic/ Meningitis aseptic / 3															1			20
Pathogen resistance/ Pathogen resistance / 1	2	25	13		4		1	1	1	5		2	5		6			640
Pathogen resistance/ Pathogen resistance / 2		2	3				1			3		2	2					241
Pathogen resistance/ Pathogen resistance / 3		1	1						1						1			20
Carnitine decreased/ Carnitine decreased / 1						4										1		24
Carnitine decreased/ Carnitine decreased / 2																		4
Carnitine decreased/ Carnitine decreased / 3																		2
Hypoglycaemia/ Hypoglycaemic coma / 1			8									3			1			553
Hypoglycaemia/ Hypoglycaemic coma / 2			1															63
Hypoglycaemia/ Hypoglycaemic coma / 3																		29
Hypoglycaemia/ Hypoglycaemia / 1	10	31	129	1	25	4	9	6	1	5		38	29	6	15	109		16893
Hypoglycaemia/ Hypoglycaemia / 2	1		9		4							1	5		3	62		1279
Hypoglycaemia/ Hypoglycaemia / 3			2		1							1	1	1	1	3		338
Tendon disorder/ Tendon disorder / 1	4	5	4				1			2		32	2	1	4	3		1426
Tendon disorder/ Tendon disorder / 2																		12
Tendon disorder/ Tendon disorder / 3	2		1									8		1	3			369
Tendon disorder/ Tendon rupture / 1	1	1	1		2			1			1	35	1		2			1094
Tendon disorder/ Tendon rupture / 2												1						18
Tendon disorder/ Tendon rupture / 3												10						331
Tendon disorder/ Tendonitis / 1	2	5	2		2		2			1		31	11	1	3			1317
Tendon disorder/ Tendonitis / 2																		22

**Cutpoints:**

	Min.	<=1	<=100	<=1000	>1000	Max.
N	1	1	100	1000	659953	

**Figure 8. Number of Reports and Marginal Totals in 2006  
with Events of Interest with Telithromycin and 15 comparators  
(data collected as of May 2006)**

**1 - All Reports**

**2 - Only Reports with an Outcome = Fatal**

**3 - Only Reports with an Outcome = Disability**

	Telithromycin	Azithromycin	Clarithromycin	Dirithromycin	Erythromycin	Cefditoren	Cefixime	Cefpodoxime	Ceftibuten	Cefuroxime	Gemifloxacin	Moxifloxacin	Trovaflaxacin	Nitrofurantoin	Amoxicillin And Clavulanate	Acetaminophen	All Reports
Tendon disorder/ Tendonitis / 3	1				1		1					9	3	1	2		455
Tendon disorder/ Tenosynovitis / 1		8			1			1				3	13		2	1	901
Tendon disorder/ Tenosynovitis / 2																	8
Tendon disorder/ Tenosynovitis / 3		1										1					99
Myopathy/ Myopathy / 1	6	12	43		23		1			2		2	4	3	8	6	4312
Myopathy/ Myopathy / 2		2	2		6					2					1	2	316
Myopathy/ Myopathy / 3		2	4							2				1	1		715
Myopathy/ Rhabdomyolysis / 1	15	49	134	1	37	6	1	4	1	3	1	11	6		20	61	13174
Myopathy/ Rhabdomyolysis / 2	3	3	13		2						1	1	1		2	25	1245
Myopathy/ Rhabdomyolysis / 3	3	3	11		5	1				1							3320
Myasthenia/ Myasthenia gravis / 1	16	9	4		1		1	1		1		3	4		2		422
Myasthenia/ Myasthenia gravis / 2	1														1		34
Myasthenia/ Myasthenia gravis / 3	2		1							1					1		49
Myasthenia/ Myasthenic syndrome / 1	1	17	3		1		4					10	10	3		4	1041
Myasthenia/ Myasthenic syndrome / 2																	11
Myasthenia/ Myasthenic syndrome / 3												1					72
Myasthenia/ Myasthenia gravis crisis / 1	3																11
Myasthenia/ Myasthenia gravis crisis / 3																	1
Neuropathy/ Neuropathy peripheral / 1		17	39		18		4	3	1	12	1	11	20	179	15	5	12520
Neuropathy/ Neuropathy peripheral / 2			3		2									1	1	2	778
Neuropathy/ Neuropathy peripheral / 3			7		3		1		1	4	1	3		10	4		2142
Neuropathy/ Polyneuropathy / 1		4	4							1		4	3	4		1	1234
Neuropathy/ Polyneuropathy / 2			1										1	1			77
Neuropathy/ Polyneuropathy / 3		1	1									1					272
Neuropathy/ Guillain-Barre syndrome / 1		8	12		1		1			2		6	1	3	3	1	1056
Neuropathy/ Guillain-Barre syndrome / 2																	86
Neuropathy/ Guillain-Barre syndrome / 3			2										1		1		164
Convulsion/ Clonic convulsion / 1		11	12		5		2	1		7		4	18	1	11	5	3142
Convulsion/ Clonic convulsion / 2		1	2							1		1	4		2	2	223
Convulsion/ Clonic convulsion / 3		1														1	123
Convulsion/ Epilepsy / 1	3	7	4		1				2			2	1	4	8	11	2343
Convulsion/ Epilepsy / 2			1											1	2	1	265
Convulsion/ Epilepsy / 3																	124
Convulsion/ Petit mal epilepsy / 1		1	1		3					3					2	3	697
Convulsion/ Petit mal epilepsy / 2					2					2							22

Cutpoints:

	Min.	<=1	<=100	<=1000	>1000	Max.
N	1	1	100	1000	659953	

**Figure 8. Number of Reports and Marginal Totals in 2006  
with Events of Interest with Telithromycin and 15 comparators  
(data collected as of May 2006)**

**1 - All Reports**

**2 - Only Reports with an Outcome = Fatal**

**3 - Only Reports with an Outcome = Disability**

	Telithromycin	Azithromycin	Clarithromycin	Dirithromycin	Erythromycin	Cefditoren	Cefixime	Cefpodoxime	Ceftibuten	Cefuroxime	Gemifloxacin	Moxifloxacin	Trovafloxacin	Nitrofurantoin	Amoxicillin And Clavulanate	Acetaminophen	All Reports
Convulsion/ Petit mal epilepsy / 3	13	57	74	2	25		9	5		16		33	3	4	34	1549	26545
Overdose/ Overdose / 1	1	4	2		1		2			1		3			4	671	7968
Overdose/ Overdose / 2	1	3													1	9	800
Overdose/ Overdose / 3	1		4		3		2		1	1				1		464	3754
Overdose/ Multiple drug overdose / 1					2											314	2734
Overdose/ Multiple drug overdose / 2																4	22
Overdose/ Multiple drug overdose / 3																28	194
Overdose/ Multiple drug overdose acciden / 1																27	171
Overdose/ Multiple drug overdose acciden / 2																	1
Overdose/ Multiple drug overdose acciden / 3																	105
Overdose/ Multiple drug overdose intenti / 1			1							1							834
Overdose/ Multiple drug overdose intenti / 2																	79
Overdose/ Multiple drug overdose intenti / 3																	4
Overdose/ Intentional overdose / 1	60	16		1	23			1		5		1	26	5	10	1141	15742
Overdose/ Intentional overdose / 2	1	1			1									1		458	5045
Overdose/ Intentional overdose / 3	4												1			6	154
Overdose/ Accidental overdose / 1	40	40	2	2	34		8	2	3	9		4	7	2	23	604	11568
Overdose/ Accidental overdose / 2	1	1			7							1			2	308	2928
Overdose/ Accidental overdose / 3					1											1	227
Pancreatitis/ Pancreatitis / 1	5	56	101	1	57		3	7		17	2	6	26	13	61	65	11160
Pancreatitis/ Pancreatitis / 2		8	12							3	1		1		4	23	1187
Pancreatitis/ Pancreatitis / 3			3												1		274
Pancreatitis/ Pancreatitis acute / 1	3	9	11	1	6	2	1	3		1		6		2	16	16	2149
Pancreatitis/ Pancreatitis acute / 2		1	2		1									1	1	7	349
Pancreatitis/ Pancreatitis acute / 3			1														63
Pancreatitis/ Pancreatic necrosis / 1												1				3	60
Pancreatitis/ Pancreatic necrosis / 2												1				2	25
Pancreatitis/ Pancreatic necrosis / 3												1			1	4	170
Pancreatitis/ Pancreatitis chronic / 1			2													3	31
Pancreatitis/ Pancreatitis chronic / 2												1					13
Pancreatitis/ Pancreatitis chronic / 3																	
Pancreatitis/ Pancreatitis necrotising / 1		1	3		1							1			1	12	421
Pancreatitis/ Pancreatitis necrotising / 2		1	2		1							1			1	9	213
Pancreatitis/ Pancreatitis necrotising / 3																	19
Psychiatric/ Psychotic disorder / 1	1	16	97		14	1	1			7		33	22	4	13	18	9525
Psychiatric/ Psychotic disorder / 2		2	1									1	1			1	386

Cutpoints:					
Min.	<=1	<=100	<=1000	>1000	Max.
N	1	1	100	1000	659953

**Figure 8. Number of Reports and Marginal Totals in 2006  
with Events of Interest with Telithromycin and 15 comparators  
(data collected as of May 2006)**

**1 - All Reports**

**2 - Only Reports with an Outcome = Fatal**

**3 - Only Reports with an Outcome = Disability**

	Telithromycin	Azithromycin	Clarithromycin	Dirithromycin	Erythromycin	Cefditoren	Cefixime	Cefpodoxime	Ceftibuten	Cefuroxime	Gemifloxacin	Moxifloxacin	Trovafoxacin	Nitrofurantoin	Amoxicillin And Clavulanate	Acetaminophen	All Reports
Psychiatric/ Psychotic disorder / 3			4		1					1			1		2		467
Psychiatric/ Acute psychosis / 1		1	10									5	2			1	283
Psychiatric/ Acute psychosis / 2																	17
Psychiatric/ Acute psychosis / 3																	15
Psychiatric/ Delusion / 1	1	10	32		4					4	3	7	7	1	6	9	3076
Psychiatric/ Delusion / 2												1			2	1	148
Psychiatric/ Delusion / 3		1	2		1										1		149
Psychiatric/ Hallucination / 1	9	42	183	2	60	2	8	10	3	23	8	56	111	20	36	75	18585
Psychiatric/ Hallucination / 2			5									1	6		3	10	675
Psychiatric/ Hallucination / 3			5		2							1	3	1	1	1	714
Psychiatric/ Hallucination, auditory / 1	1	6	17		1					1		2	1		1	6	1602
Psychiatric/ Hallucination, auditory / 2																	73
Psychiatric/ Hallucination, auditory / 3			2													1	108
Psychiatric/ Hallucination, visual / 1	5	11	13		6					1		7	4	1	9	12	1886
Psychiatric/ Hallucination, visual / 2													1			2	88
Psychiatric/ Hallucination, visual / 3			1							1			1		1		133
Psychiatric/ Depersonalisation / 1		26	75		10				4	8		20	34	2	3	5	3599
Psychiatric/ Depersonalisation / 2																	34
Psychiatric/ Depersonalisation / 3			1														130
Psychiatric/ Hostility / 1		13	20		13		2	7		6			4	2	23	11	6875
Psychiatric/ Hostility / 2																2	210
Psychiatric/ Hostility / 3																	276
Psychiatric/ Mania / 1	1	9	75		3			1				2	2		8	4	4663
Psychiatric/ Mania / 2			2												1		118
Psychiatric/ Mania / 3																	193
Psychiatric/ Thinking abnormal / 1	3	26	75	1	26		4	1	1	4		16	30	3	15	41	10829
Psychiatric/ Thinking abnormal / 2			3													9	346
Psychiatric/ Thinking abnormal / 3		1	1		2							3	1				587
Psychiatric/ Personality disorder / 1	1	26	44		25		16	5	1	4		1	8	4	34	10	6031
Psychiatric/ Personality disorder / 2		2															163
Psychiatric/ Personality disorder / 3					1		1	1							1		232
Psychiatric/ Panic attack / 1	3	14	9		2						2	20	4		3	10	2985
Psychiatric/ Panic attack / 2													1			2	80
Psychiatric/ Panic attack / 3		3	2									2	1				439
Psychiatric/ Panic reaction / 1		2	5			1						6	1		1	6	588

Cutpoints:

	Min.	<=1	<=100	<=1000	>1000	Max.
N	1	1	100	1000	659953	

**Figure 8. Number of Reports and Marginal Totals in 2006  
with Events of Interest with Telithromycin and 15 comparators  
(data collected as of May 2006)**

**1 - All Reports**

**2 - Only Reports with an Outcome = Fatal**

**3 - Only Reports with an Outcome = Disability**

	Telithromycin	Azithromycin	Clarithromycin	Dirithromycin	Erythromycin	Cefditoren	Cefixime	Cefpodoxime	Ceftibuten	Cefuroxime	Gemifloxacin	Moxifloxacin	Trovafloxacin	Nitrofurantoin	Amoxicillin And Clavulanate	Acetaminophen	All Reports
Psychiatric/ Panic reaction / 2												1				1	10
Psychiatric/ Panic reaction / 3												1					60
Psychiatric other/ Intentional self-injury / 1		2	5		1										2	28	935
Psychiatric other/ Intentional self-injury / 2			1													10	175
Psychiatric other/ Intentional self-injury / 3		1			1												35
Suicide/ Suicide attempt / 1		6	41		11		1		1	13		2		2	13	416	13241
Suicide/ Suicide attempt / 2			1							1					1	88	3431
Suicide/ Suicide attempt / 3			1													3	431
Suicide/ Completed suicide / 1		4	10		2							1		1	2	801	10283
Suicide/ Completed suicide / 2		4	10		2							1		1	2	792	9811
Suicide/ Completed suicide / 3																4	31
Purpura/ Thrombocytopenic purpura / 1	1	4	13									4			3	6	244
Purpura/ Thrombocytopenic purpura / 2			1														21
Purpura/ Thrombocytopenic purpura / 3		1															4
Purpura/ Idiopathic thrombocytopenic pu / 1	1	20	22		7	2	6	3	3	13		10	1	8	18	12	2948
Purpura/ Idiopathic thrombocytopenic pu / 2			1		1									2	1		275
Purpura/ Idiopathic thrombocytopenic pu / 3			1												1		71
Purpura/ Henoch-Schonlein purpura / 1	1	9	12			1	1	2	1			5		2	12	9	365
Purpura/ Henoch-Schonlein purpura / 2															2		24
Purpura/ Henoch-Schonlein purpura / 3																	13
Purpura/ Vascular purpura / 1	2	4	5		10		2	2		3		2		3	25	9	555
Purpura/ Vascular purpura / 2																	36
Purpura/ Vascular purpura / 3															1		11
Purpura/ Purpura / 1	5	24	48		19	4	17	11		27		8	8	17	104	44	5275
Purpura/ Purpura / 2			3				2			1		2		2	7	4	419
Purpura/ Purpura / 3		2			1					1			1	1		1	109
Purpura/ Petechiae / 1	2	34	33		14	2	5	7	6	13	1	21	5	22	30	31	3978
Purpura/ Petechiae / 2		3	1		1		1			1		3	1			13	442
Purpura/ Petechiae / 3			1		1					1		1		2			98
Renal/ Nephritis / 1		29	20		22	1	4	2		31		1	8	10	19	7	2490
Renal/ Nephritis / 2		1	1							4			1		1	1	193
Renal/ Nephritis / 3		1	1					1							2		111
Renal/ Nephropathy / 1		3	2		1	1		1		3					3	3	499
Renal/ Nephropathy / 2										1						1	94
Renal/ Nephropathy / 3																	34

Cutpoints:

	Min.	<=1	<=100	<=1000	>1000	Max.
N	1	1	100	1000	659953	

**Figure 8. Number of Reports and Marginal Totals in 2006  
with Events of Interest with Telithromycin and 15 comparators  
(data collected as of May 2006)**

**1 - All Reports**

**2 - Only Reports with an Outcome = Fatal**

**3 - Only Reports with an Outcome = Disability**

	Telithromycin	Azithromycin	Clarithromycin	Dirithromycin	Erythromycin	Cefditoren	Cefixime	Cefpodoxime	Ceftibuten	Cefuroxime	Gemifloxacin	Moxifloxacin	Trovafloxacin	Nitrofurantoin	Amoxicillin And Clavulanate	Acetaminophen	All Reports
Renal/ Nephropathy toxic / 1		2	7		2					2		2	3		4	20	1039
Renal/ Nephropathy toxic / 2			1							1		1	2		2	4	182
Renal/ Nephropathy toxic / 3																	44
Renal/ Glomerulonephritis / 1	1	10	5		3		2			4		2	2	1	2	1	932
Renal/ Glomerulonephritis / 2										1			1		1		94
Renal/ Glomerulonephritis / 3										1							67
Renal/ Nephritis interstitial / 1	10	14	27		2		4	1	3	11	1	19	5	7	19	14	1740
Renal/ Nephritis interstitial / 2									2	2	1				4	1	117
Renal/ Nephritis interstitial / 3	1	1	2				1					2			2	2	120
Renal/ Renal failure / 1	18	57	119		37	4	5	6	3	80	2	39	33	23	78	371	23939
Renal/ Renal failure / 2	3	17	34		12	2	3	1		38	1	15	18	11	27	238	8198
Renal/ Renal failure / 3	1	1	13		3					3		2	1	2	4	9	2793
Renal/ Renal failure acute / 1	23	71	157	2	55	4	23	13	2	55	2	38	35	12	148	220	21341
Renal/ Renal failure acute / 2	4	15	33		14		3	5		18	1	6	11	1	37	71	5286
Renal/ Renal failure acute / 3		4	9		2	1	2			3			1		5	7	1031
Renal/ Renal impairment / 1	7	23	61		29	3	2	5	3	35		13	28	13	43	100	12753
Renal/ Renal impairment / 2	1		10		8			1		2		3	6	4	17	44	2553
Renal/ Renal impairment / 3			3		2					3			1	2	2	4	1563
Renal/ Renal papillary necrosis / 1	1	1														21	153
Renal/ Renal papillary necrosis / 2																	14
Renal/ Renal papillary necrosis / 3																1	7
Renal/ Renal tubular necrosis / 1	1	11	11		3		3	2	2	13		3	2		15	45	2763
Renal/ Renal tubular necrosis / 2		1	2						2	3		1	1		4	24	574
Renal/ Renal tubular necrosis / 3		1	1							1					1	2	645
Renal/ Nephrosclerosis / 1												1				11	377
Renal/ Nephrosclerosis / 2																11	178
Renal/ Nephrosclerosis / 3																	44
Renal/ Nephrotic syndrome / 1		8	8		1		3			3		1	4	1	12	11	2120
Renal/ Nephrotic syndrome / 2		1			1											1	147
Renal/ Nephrotic syndrome / 3		1	2												2	1	119
Renal/ Dialysis / 1	6	18	25		6		4	3	2	6		11	3	2	11	76	4273
Renal/ Dialysis / 2	3	4	5		3					1		2	2	1	3	50	1237
Renal/ Dialysis / 3		1	3		1		2					2				4	337
Renal/ Haemodialysis / 1	1	18	32		8			2	1	8	3	6	5		13	112	4362
Renal/ Haemodialysis / 2	1	5	10		1					3	2	3	3		3	73	1339

Cutpoints:

	Min.	<=1	<=100	<=1000	>1000	Max.
N	1	1	100	1000	659953	

**Figure 8. Number of Reports and Marginal Totals in 2006  
with Events of Interest with Telithromycin and 15 comparators  
(data collected as of May 2006)**

**1 - All Reports**

**2 - Only Reports with an Outcome = Fatal**

**3 - Only Reports with an Outcome = Disability**

	Telithromycin	Azithromycin	Clarithromycin	Dirithromycin	Erythromycin	Cefditoren	Cefixime	Cefpodoxime	Ceftibuten	Cefuroxime	Gemifloxacin	Moxifloxacin	Trovafloxacin	Nitrofurantoin	Amoxicillin And Clavulanate	Acetaminophen	All Reports
Renal/ Haemodialysis / 3		2	1							1						5	293
Toxic lung/ Pulmonary fibrosis / 1		4	6		1	1	2					7	3	223	6	10	3924
Toxic lung/ Pulmonary fibrosis / 2		1	2		1	1	1					1	1	32	1	3	1291
Toxic lung/ Pulmonary fibrosis / 3		1												17	1	1	345
Toxic lung/ Pulmonary toxicity / 1												1		5			333
Toxic lung/ Pulmonary toxicity / 2												1					126
Toxic lung/ Pulmonary toxicity / 3																	17
Toxic skin/ Erythema multiforme / 1		69	49		39	10	39	26	10	27	3	7	8	28	80	35	5925
Toxic skin/ Erythema multiforme / 2			4		1					2			1	2	3	1	179
Toxic skin/ Erythema multiforme / 3		2	1							3		1		1	3		108
Toxic skin/ Stevens-Johnson syndrome / 1	6	144	93		67	13	18	21	4	72	2	34	10	26	105	121	7886
Toxic skin/ Stevens-Johnson syndrome / 2		7	7		11	1	1	1		16		6	3	6	25	23	1000
Toxic skin/ Stevens-Johnson syndrome / 3		6	4		1	2	1	2		6		2	1	2	4	3	352
Toxic skin/ Toxic epidermal necrolysis / 1	3	24	58		42	7	10	18	2	54		17	6	9	100	109	4246
Toxic skin/ Toxic epidermal necrolysis / 2		6	16		16	3		4		31		5	1	1	54	39	1557
Toxic skin/ Toxic epidermal necrolysis / 3		3	3		3	1	2	1		4					5	1	217
Toxic skin/ Toxic skin eruption / 1	2	9	14		4	2	2	5		6		6		1	72	26	1332
Toxic skin/ Toxic skin eruption / 2		1	1		1							1			7	2	76
Toxic skin/ Toxic skin eruption / 3		1													2		33
Photosensitivity/ Photosensitivity reaction / 1	3	40	38		16	1	7	2	3	9	7	17	16	10	15	7	6985
Photosensitivity/ Photosensitivity reaction / 2																	39
Photosensitivity/ Photosensitivity reaction / 3		2	1		2						2		1	1			298
Syncope/ Syncope / 1	23	90	157	2	112		8	9	3	77	3	136	43	38	59	90	28841
Syncope/ Syncope / 2	2	1	10		5					3		2		1	4	16	1480
Syncope/ Syncope / 3	1	4	1		2					2		4	1	1	3	1	980
Syncope/ Loss of consciousness / 1	66	89	60		15	1	2	1	1	32	2	91	19	9	46	167	15725
Syncope/ Loss of consciousness / 2	7	8	9		1					5		10	2	1	8	67	2546
Syncope/ Loss of consciousness / 3	2	8	3		1				1	1		6	1		2	3	793
Syncope/ Syncope vasovagal / 1	4	6	4				1					14	1	1	3	3	1007
Syncope/ Syncope vasovagal / 2	2	2															49
Syncope/ Syncope vasovagal / 3			1														46
Syncope/ Dizziness / 1	148	278	422	4	226	4	21	19	11	95	14	384	648	106	107	340	95015
Syncope/ Dizziness / 2		3	7							1		2	3	1	3	11	1772
Syncope/ Dizziness / 3	5	19	11		6			1		4		13	13	2	3	3	3768
Vascular/ Vasculitis / 1	4	19	43	2	20		3	7		19		8	14	13	55	17	5169

Cutpoints:

	Min.	<=1	<=100	<=1000	>1000	Max.
N	1	1	100	1000	659953	

**Figure 8. Number of Reports and Marginal Totals in 2006  
with Events of Interest with Telithromycin and 15 comparators  
(data collected as of May 2006)**

**1 - All Reports**

**2 - Only Reports with an Outcome = Fatal**

**3 - Only Reports with an Outcome = Disability**

	Telithromycin	Azithromycin	Clarithromycin	Dirithromycin	Erythromycin	Cefditoren	Cefixime	Cefpodoxime	Ceftibuten	Cefuroxime	Gemifloxacin	Moxifloxacin	Trovafloxacin	Nitrofurantoin	Amoxicillin And Clavulanate	Acetaminophen	All Reports
Vascular/ Vasculitis / 2		2	4		1									1	3	1	482
Vascular/ Vasculitis / 3		2	2							3		1	3		1	1	371
Vascular/ Vasculitis necrotising / 1		1	2		1										3		191
Vascular/ Vasculitis necrotising / 2																	24
Vascular/ Vasculitis necrotising / 3															1		13
Vascular/ Leukocytoclastic vasculitis / 1	3	14	11		2	1	2	6		7	1	10	5	6	34	8	993
Vascular/ Leukocytoclastic vasculitis / 2							1								1		67
Vascular/ Leukocytoclastic vasculitis / 3		1										2	1		3		50
Outcome/ 1	56	412	574		321	14	57	39	17	443	6	223	289	223	591	3492	240155
Outcome/ 2	49	332	284	1	128	9	17	22	7	145	4	125	84	118	224	140	90238
Outcome/ Life-threatening	80	448	561	2	244	25	33	81	12	362	7	338	179	106	536	586	107455
Outcome/ Hospitalized	390	2713	3417	33	1668	158	541	419	120	1765	41	1096	752	1040	3369	5000	659953
Outcome/ Congenital Anomaly	3	28	30		24		1	5	2	5		4	1	37	9	63	9165
Outcome/ Required Intervention to Prevent	18	1260	758	2	339	16	23	52	6	147	5	124	1111	97	214	1073	105594
All Reports / 1	1736	9917	12070	226	9218	523	2321	1313	593	5744	773	3898	4586	4567	8030	13759	
All Reports / 2	56	412	574		321	14	57	39	17	443	6	223	289	223	591	3492	
All Reports / 3	49	332	284	1	128	9	17	22	7	145	4	125	84	118	224	140	

Cutpoints:

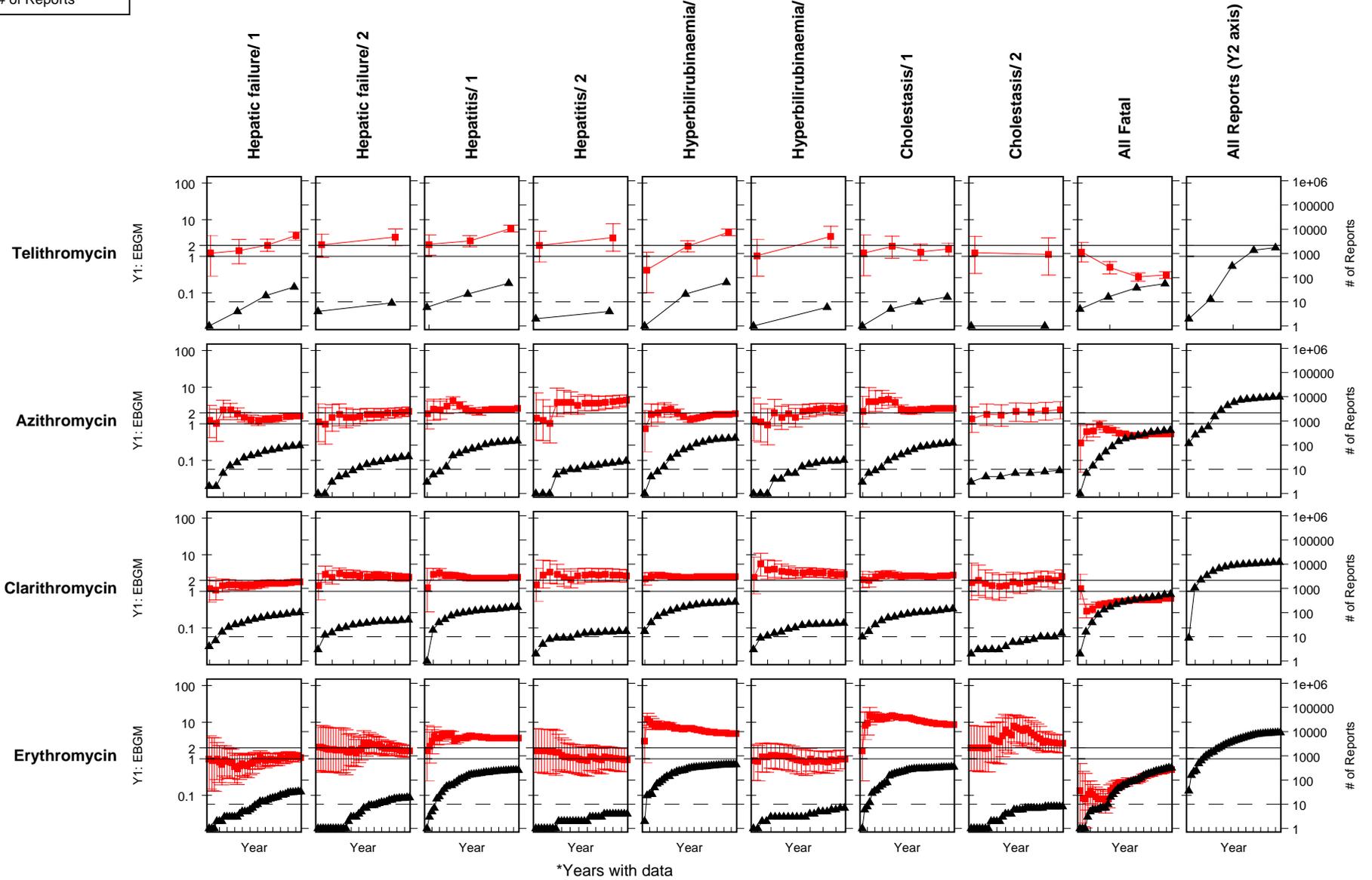
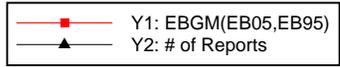
	Min.	<=1	<=100	<=1000	>1000	Max.
N	1	1	100	1000	659953	

Figure 9. Progression of EBGm values and Number of Reports Showing Selected Hepatotoxic Events and Fatal Outcome with Telithromycin and Comparators by Calendar Year

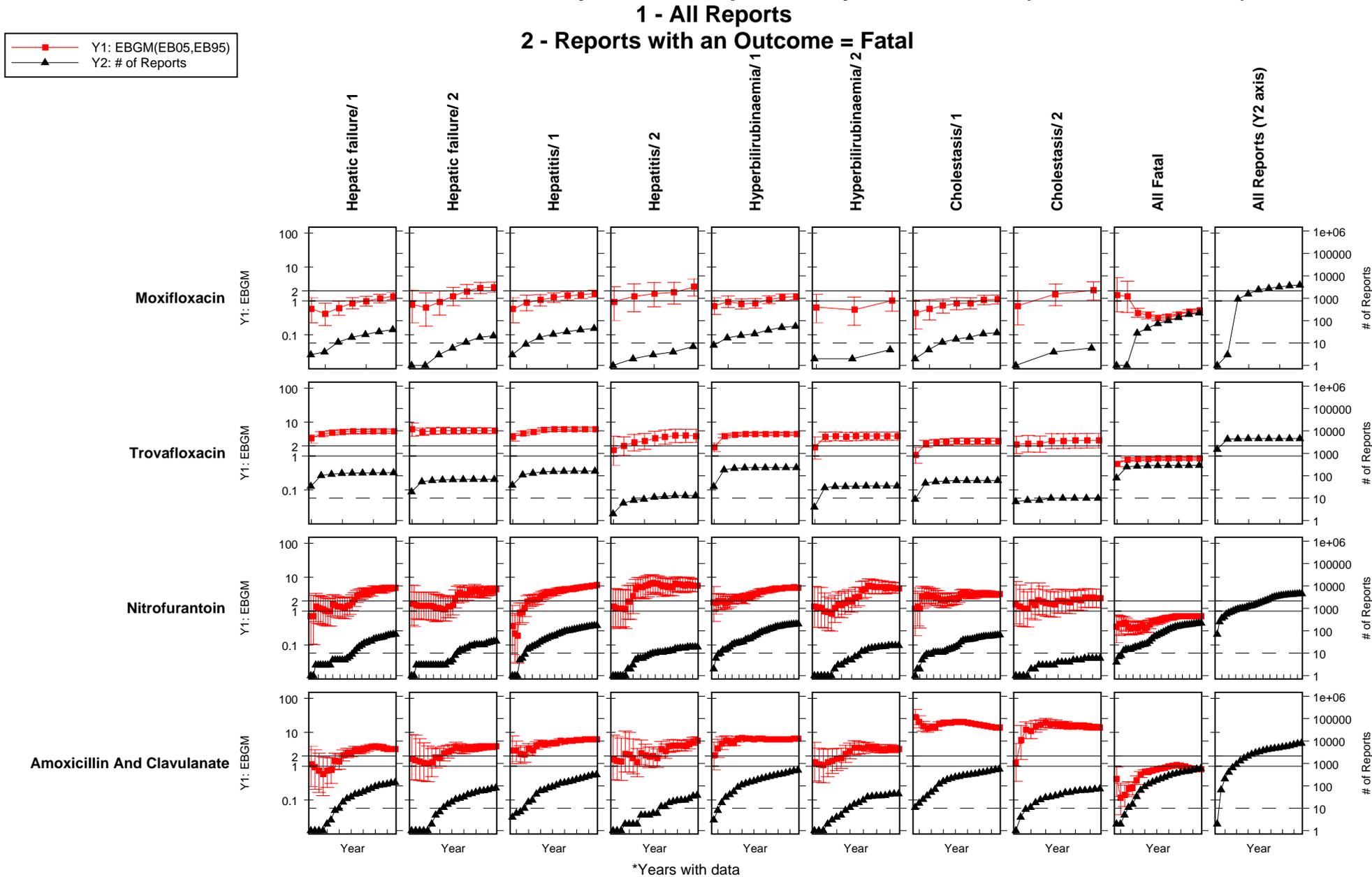
**Figure 9. Progression of EBGM values and Number of Reports Showing Selected Hepatotoxic Events and Fatal Outcome with Telithromycin and Comparators by Calendar Year (data 1968-2006M05)**

**1 - All Reports**

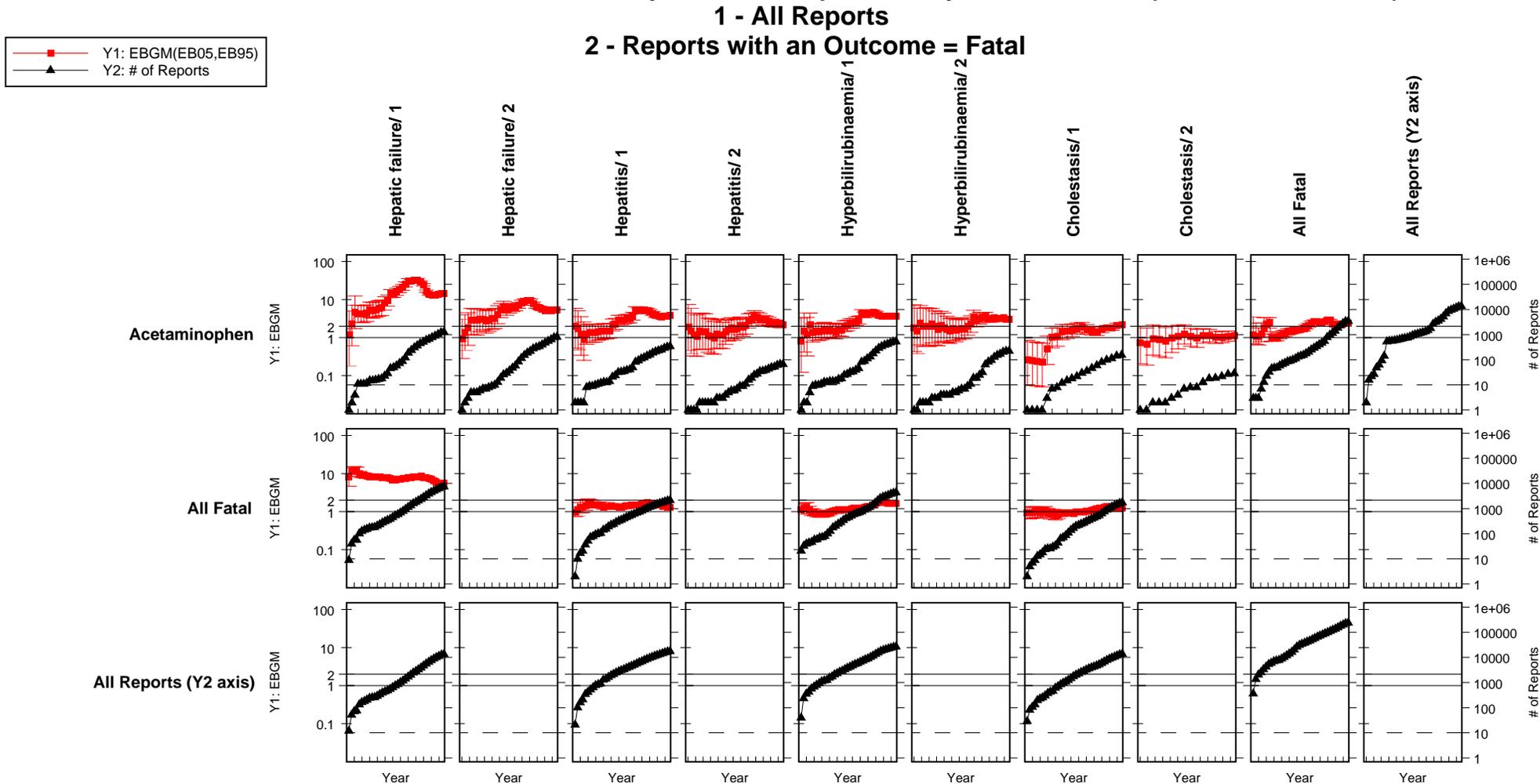
**2 - Reports with an Outcome = Fatal**



**Figure 9. Progression of EBGM values and Number of Reports Showing Selected Hepatotoxic Events and Fatal Outcome with Telithromycin and Comparators by Calendar Year (data 1968-2006M05)**



**Figure 9. Progression of EBGm values and Number of Reports Showing Selected Hepatotoxic Events and Fatal Outcome with Telithromycin and Comparators by Calendar Year (data 1968-2006M05)**



\*Years with data

## **6. Appendix: Data Mining at the FDA**

### **6.1. General Information**

#### **6.1.1. What is Data Mining?**

- *Definition:* a systematic analysis method used to simultaneously extract new and useful information hidden in large, complex databases.
- *Impact:* once meaningful patterns identified, information can be evaluated to forecast future trends and/or intervene as appropriate.
- Goal of Data Mining at the FDA:

to detect “higher than expected” drug-event combinations in post marketing reports.

to help monitor the safety of drugs, biologics, and vaccines after they have been approved for use.

- *Method implemented by the FDA:* a Bayesian data mining system called the Multi-item Gamma Poisson Shrinker (MGPS) (REF)

#### **6.1.2. What Opportunities Does MGPS Provide?**

Even when specific questions are not asked

- MGPS provides a large collection of positive and negative controls
- Provides reminders of what other experts know that serve to assess biologic plausibility of results
- Provides clues to complex safety issues quickly
- Signals important information that might be missed if the question is not asked
- Aids in predicting future trends or behaviors (e.g., of drugs in same class)
- Enables decision-makers to make proactive, knowledge driven decisions

## 6.2. *What is MGPS?*

- *MGPS* calculates adjusted reporting ratios.
- *Independence Assumption*: drug-event combinations are reported with no greater relative frequency for drug X than for any other drug. Example: if 3% of all reports contain acetaminophen as a drug, and 7% of all reports contain “rash” as an event, then the expected count for “acetaminophen-rash” as a drug-event combination would be 0.21% ( $0.03 * 0.07$ ) of the total number of reports.
- Adjustments:
  - *MGPS* systematically stratifies a huge database by more than 1,300 categories (9 for age, 3 for sex [male, female, unknown]), and 39 for year of report) to help adjust for background differences in relative reporting ratio by these variables.
  - *MGPS* fits all interaction model for stratification variables.
  - *MGPS* systematically “shrinks” observed-expected ratios that cannot be precisely estimated because of small counts. This process guards against generating multiple false-positive signals due to multiple independent comparisons.
- For every drug and event in AERS, *MGPS* evaluates all drug-event pairs.
- Calculations are limited to AERS data.

### 6.2.1. *Definitions*

- *EBGM* (Empirical Bayes Geometric Mean): adjusted estimate for the relative reporting ratio. Example: if *EBGM*=3.9 for acetaminophen-hepatic failure, then this drug-event combination occurred in the data 3.9 times more frequently than expected under the assumption of no association between the drug and the event.
- *EB05* and *EB95* are the lower and upper bounds of the 2-sided 90% confidence interval around *EBGM*.
- Comparing (*EB05*, *EB95*) intervals for the same event code or outcome between two or more drugs:

If the (EB05, EB95) intervals, it means the independence assumption is questionable for both. In other words, there may be an association between an adverse event and the drug in question.

Non-overlapping (EB05, EB95) intervals for a specific event code or outcome for two different drugs can be explained by considering that the proportional frequency of reported drug events is higher for one drug than for the other drug, displaying more “lack of independence” for one drug than the other for that particular event code.

Non-overlapping (EB05, EB95) intervals between two or more drugs for the same event can provide some information about the degree of relative toxicity between these drugs, though the exact degree of this relationship is not yet known. However, a drug is not proven to be more or less toxic than another simply because of EBGM scores or overlapping or non-overlapping (EB05, EB95) intervals in these patient records.

Overlapping (EB05, EB95) intervals are “inseparable” in the sense that there is not enough information regarding one drug’s relative association with that particular event code versus another.

### **6.2.2. Limitations of MGPS**

- Data mining simply identifies adjusted disproportionality of drug-event reporting patterns in databases.
- The absence of a “signal” (higher-than-expected reporting relationship between a drug and event) does not rule out a safety problem.
- Potential for confounding due to multiple indications.
- Data mining cannot prove or refute causal associations between drugs and events.
- MGPS does not estimate incidence or prevalence.
- There is a potential for masking and leakage of signals in situations of polypharmacy. MGPS does not adjust for polypharmacy.
- No dosage and formulation information is incorporated in the MGPS analyses.

- To further study the adverse-event risk, the signals generated by MGPS can be evaluated by individual case review and compared with various analyses from other sources (e.g. clinical trials, general practice databases, literature reports).

### **6.2.3. Limitations of AERS**

- Passive reporting system. Reports to companies from patients or healthcare providers are still voluntarily submitted.
- No measure of exposure or background rate systematically linked to the AERS data.
- Potential for confounding due to multiple drugs being prescribed to individual patients.
- Reporter bias.
- No certainty that a reported event is causal.
- Incorrect reporting (missing fields, indications entered as adverse events, etc.)
- Under-reporting and waivers.

Waivers: Although pharmaceutical companies of marketed products are required to submit to the FDA reports of adverse events for their drugs, a company can request a waiver of this requirement for non-serious, expected adverse events for drugs and certain biologics.

- Over-reporting of specific drug-events due to publicity or litigation.
- Duplicate reporting of the same drug-event by different manufacturers for events associated with multiple drugs manufactured by various manufacturers.
- Inconsistencies and changes over time in reporting, naming, coding, and data processing practices.
- Coding errors and misspellings.
- Changes over time in prescribing paradigms.

## 7. Appendix: General experience with MGPS

The authors of this document have close to nine years of hands-on experience developing and using MGPS, and its precursor GPS.

The MGPS algorithm was originally applied to detect fraudulent use of calling cards at AT&T and to analyze multi-Item combinations of adverse drug events, drug-drug interactions, and event syndromes at the FDA in 2000.<sup>(2,3)</sup> The GPS, an earlier version of MGPS, was developed and started to be applied at the FDA in January 1998. Funds to support its development came from the Office of Women's Health, with Ana Szarfman as principal investigator. GPS analyzed simple drug-event pairs with an earlier version of the AERS database.<sup>(18, 19)</sup>

The utility of MGPS is not limited to FDA. Other organizations such as the National Cancer Institute (NCI) of the United States and the Medicines and Healthcare products Regulatory Agency (MHRA) of the UK and several PhRMA companies already benefit from this technology.

The MHRA of the UK started applying MGPS in 2005.<sup>(20)</sup>

The NCI is applying MGPS to the multidimensional National Cancer Surveillance database. In a recent presentation at the FDA the NCI scientists concluded that MGPS has a uniquely good outlier detection capability in searching relative to expected values, including a sensitivity that was superior to LISA and SatScan with large scan windows and a specificity that is superior to Getis-Ord GI\* and SatScan with small scan windows.<sup>(21, 22)</sup>

## 8. Appendix: Data Mining Configurations

### 8.1. Audit Trail Details

#### 8.1.1. All Reports

Run number 494 on the cdsdrugsafe server  
Configuration Description: CBAERS data; best representative cases; suspect drugs only; with duplicate removal  
Database Restriction: No  
Item Variables: Generic name, PT Collapsed Liver Plus, OutcomeNew  
Highest Dimension: 2  
Stratification: Gender, AgeGroup11, FDA Year  
Subset: Cumulative  
Variable Name: FDA Year  
Subset Categories: 1968, 1968-1969, 1968-1970, 1968-1971, 1968-1972, 1968-1973, 1968-1974, 1968-1975, 1968-1976, 1968-1977, 1968-1978, 1968-1979, 1968-1980, 1968-1981, 1968-1982, 1968-1983, 1968-1984, 1968-1985, 1968-1986, 1968-1987, 1968-1988, 1968-1989, 1968-1990, 1968-1991, 1968-1992, 1968-1993, 1968-1994, 1968-1995, 1968-1996, 1968-1997, 1968-1998, 1968-1999, 1968-2000, 1968-2001, 1968-2002, 1968-2003, 1968-2004, 1968-2005, 1968-2006  
Calculate PRR: No  
Calculate ROR: No  
Minimum Count: 1

Fill in Hierarchy Values: Yes  
 Exclude single itemtypes: No  
 Fit separate distributions: Yes  
 Save Intermediate Files: No  
 Created By: Szarfman Szarfman  
 Created On: 07/03/2006 15:43:11 EDT  
 As Of Date: 06/02/2006 00:00:00  
 Source Database: Source Data: CBAERS data from Extract provided by CBER as of 06/02/2006 00:00:00 loaded on 2006-06-12 14:03:53.0

### **8.1.2. Reports of Fatal Outcome**

Run number 495 on the cdsdrugsafe server  
 Same run as 494 but with Database Restriction: Yes, only fatal outcomes  
 And Item Variables: Generic name, PT Collapsed Liver Plus Only  
 Created On: 07/03/2006 15:50:09 EDT  
 Loaded on 2006-06-12 14:03:53.0

### **8.1.3. Reports of Disability Outcome**

Run number 496 on the cdsdrugsafe server  
 Same run as 494 but with Database Restriction: Yes, only disability outcomes  
 Created On: 07/04/2006 14:14:27 EDT  
 As Of Date: 06/02/2006 00:00:00  
 Loaded on 2006-06-12 14:03:53.0

## **9. Appendix: Interesting PTs, Outcomes, and Recoded Event Classes**

Table 8 List of Interesting MedDRA PTs, Outcomes, and Recoded Event Classes

<b>Original SOC</b>	<b>Recoded Event Class</b>	<b>MedDRA PT</b>	<b>Ran k</b>
Inv	Blood	Bleeding time abnormal	1
Blood	Blood	Coagulopathy	2
Blood	Blood	Haemolysis	3
Blood	Blood	Haemolytic anaemia	4
Blood	Blood	Anaemia haemolytic autoimmune	5
Blood	Blood	Intravascular haemolysis	6
Blood	Blood	Haemolytic uraemic syndrome	7
Card	Cardiac	Myocardial fibrosis	8
Card	Cardiac	Cardiotoxicity	9
Card	Cardiac	Torsade de pointes	10
Inv	Cardiac	Electrocardiogram QT prolonged	11
Inv	Cardiac	Electrocardiogram QT corrected interval prolonged	12
Genrl	Cardiac	Sudden cardiac death	13
Genrl	Drug ineffective	Drug ineffective	14
Genrl	Drug ineffective	Drug effect decreased	15
Genrl	Drug ineffective	Drug ineffective for unapproved indication	16
Genrl	Drug ineffective	Therapeutic response decreased	17
Genrl	Drug interaction	Drug interaction	18
Genrl	Drug interaction	Drug interaction potentiation	19
Inv	Drug interaction	Drug level increased	20
Inv	Drug interaction	Drug level above therapeutic	21

Inv	Drug interaction	Antidepressant drug level above therapeutic	22
Ear	Ear	Ototoxicity	23
Ear	Ear	Deafness	24
Ear	Ear	Deafness permanent	25
Ear	Ear	Deafness neurosensory	26
Ear	Ear	Deafness transitory	27
Ear	Ear	Deafness bilateral	28
Ear	Ear	Deafness unilateral	29
Ear	Ear	Hearing impaired	30
Ear	Ear	Hypoacusis	31
Ear	Ear	Tinnitus	32
Ear	Ear	Vertigo	33
Blood	Eosinophilia	Eosinophilia	34
Inv	Eosinophilia	Eosinophil count increased	35
Resp	Eosinophilia	Eosinophilic pneumonia	36
Immun	Eosinophilia	Drug rash with eosinophilia and systemic symptoms	37
Eye	Eye	Visual brightness	38
Eye	Eye	Visual disturbance	39
Eye	Eye	Vision blurred	40
Eye	Eye	Visual acuity reduced	41
Eye	Eye	Accommodation disorder	42
Eye	Eye	Strabismus	43
Eye	Eye	Diplopia	44
Eye	Eye	Blindness transient	45
Eye	Eye	Optic neuropathy	46
Nerv	Eye	Optic neuritis retrobulbar	47
Nerv	Eye	Tunnel vision	48
Nerv	Eye	Visual field defect	49
Eye	Eye	Retinopathy	50
Infec	Clostridial infection	Clostridial infection	51
Infec	Clostridial infection	Clostridium colitis	52
Inj&P	Drug toxicity	Drug toxicity	53
Inj&P	Drug toxicity	Therapeutic agent toxicity	54
Metab	Gout	Gout	55
Musc	Gout	Gouty arthritis	56
Hepat	Hepatotoxicity	Hepatotoxicity	57
Hepat	Hepatic failure	Hepatic failure	58
Hepat	Hepatitis	Hepatitis	59
Hepat	Hepatocellular damage	Hepatocellular damage	60
Hepat	Biopsy liver abnormal	Biopsy liver abnormal	61
Hepat	Hyperammonaemia	Hyperammonaemia	62
Hepat	Hyperbilirubinaemia	Hyperbilirubinaemia	63
Eye	Hyperbilirubinaemia	Ocular icterus	64
Hepat	Prothrombin level decreased	Prothrombin level decreased	65
Hepat	Chronic hepatitis	Chronic hepatitis	66
Hepat	Hepatic fibrosis	Hepatic cirrhosis	67
Hepat	Hepatic fibrosis	Hepatic fibrosis	68

Hepat	Hepatic fibrosis	Hepatic atrophy	69
Hepat	Lactic acidosis	Lactic acidosis	70
Inv	Lactic acidosis	Blood lactic acid increased	71
Hepat	Cholestasis	Cholangitis	72
Hepat	Cholestasis	Cholecystitis	73
Hepat	Cholestasis	Cholestasis	74
Hepat	Cholestasis	Gallbladder disorder	75
Hepat	Hepatic steatosis	Hepatic steatosis	76
Hepat	Ischaemic hepatitis	Ischaemic hepatitis	77
Immun	Hypersensitivity	Anaphylactic shock	78
Immun	Hypersensitivity	Anaphylactic reaction	79
Immun	Hypersensitivity	Anaphylactoid reaction	80
Skin	Hypersensitivity	Angioneurotic oedema	81
Resp	Hypersensitivity	Laryngospasm	82
Resp	Hypersensitivity	Pharyngeal oedema	83
Immun	Hypersensitivity	Drug hypersensitivity	84
Immun	Hypersensitivity	Hypersensitivity	85
Immun	Hypersensitivity	Serum sickness	86
Immun	Hypersensitivity	Jarisch-Herxheimer reaction	87
Infec	Meningitis aseptic	Meningitis aseptic	88
Infec	Pathogen resistance	Pathogen resistance	89
Inv	Carnitine decreased	Carnitine decreased	90
Nerv	Hypoglycaemia	Hypoglycaemic coma	91
Metab	Hypoglycaemia	Hypoglycaemia	92
Musc	Tendon disorder	Tendon disorder	93
Inj&P	Tendon disorder	Tendon rupture	94
Musc	Tendon disorder	Tendonitis	95
Musc	Tendon disorder	Tenosynovitis	96
Musc	Myopathy	Myopathy	97
Musc	Myopathy	Rhabdomyolysis	98
Nerv	Myasthenia	Myasthenia gravis	99
Nerv	Myasthenia	Myasthenic syndrome	100
Nerv	Myasthenia	Myasthenia gravis crisis	101
Nerv	Neuropathy	Neuropathy peripheral	102
Nerv	Neuropathy	Polyneuropathy	103
Nerv	Neuropathy	Guillain-Barre syndrome	104
Nerv	Convulsion	Clonic convulsion	105
Nerv	Convulsion	Epilepsy	106
Nerv	Convulsion	Petit mal epilepsy	107
Inj&P	Overdose	Overdose	108
Inj&P	Overdose	Multiple drug overdose	109
Inj&P	Overdose	Multiple drug overdose accidental	110
Inj&P	Overdose	Multiple drug overdose intentional	111
Inj&P	Overdose	Intentional overdose	112
Inj&P	Overdose	Accidental overdose	113
Gastr	Pancreatitis	Pancreatitis	114
Gastr	Pancreatitis	Pancreatitis acute	115

Gastr	Pancreatitis	Pancreatic necrosis	116
Gastr	Pancreatitis	Pancreatitis chronic	117
Gastr	Pancreatitis	Pancreatitis necrotizing	118
Psych	Psychiatric	Psychotic disorder	119
Psych	Psychiatric	Acute psychosis	120
Psych	Psychiatric	Delusion	121
Psych	Psychiatric	Hallucination	122
Psych	Psychiatric	Hallucination, auditory	123
Psych	Psychiatric	Hallucination, visual	124
Psych	Psychiatric	Depersonalisation	125
Psych	Psychiatric	Hostility	126
Psych	Psychiatric	Mania	127
Psych	Psychiatric	Thinking abnormal	128
Psych	Psychiatric	Personality disorder	129
Psych	Psychiatric	Panic attack	130
Psych	Psychiatric	Panic reaction	131
Psych	Psychiatric other	Intentional self-injury	132
Psych	Suicide	Suicide attempt	133
Psych	Suicide	Completed suicide	134
Blood	Purpura	Thrombocytopenic purpura	135
Blood	Purpura	Idiopathic thrombocytopenic purpura	136
Skin	Purpura	Henoch-Schonlein purpura	137
Skin	Purpura	Vascular purpura	138
Skin	Purpura	Purpura	139
Skin	Purpura	Petechiae	140
Renal	Renal	Nephritis	141
Renal	Renal	Nephropathy	142
Renal	Renal	Nephropathy toxic	143
Renal	Renal	Glomerulonephritis	144
Renal	Renal	Nephritis interstitial	145
Renal	Renal	Renal failure	146
Renal	Renal	Renal failure acute	147
Renal	Renal	Renal impairment	148
Renal	Renal	Renal papillary necrosis	149
Renal	Renal	Renal tubular necrosis	150
Renal	Renal	Nephrosclerosis	151
Renal	Renal	Nephrotic syndrome	152
Surg	Renal	Dialysis	153
Surg	Renal	Haemodialysis	154
Resp	Toxic lung	Pulmonary fibrosis	155
Resp	Toxic lung	Pulmonary toxicity	156
Skin	Toxic skin	Erythema multiforme	157
Skin	Toxic skin	Stevens-Johnson syndrome	158
Skin	Toxic skin	Toxic epidermal necrolysis	159
Skin	Toxic skin	Toxic skin eruption	160
Skin	Photosensitivity	Photosensitivity reaction	161
Nerv	Syncope	Syncope	162

Nerv	Syncope	Loss of consciousness	163
Nerv	Syncope	Syncope vasovagal	164
Nerv	Syncope	Dizziness	165
Vasc	Vascular	Vasculitis	166
Vasc	Vascular	Vasculitis necrotising	167
Skin	Vascular	Leukocytoclastic vasculitis	168
Outcome	Outcome	Died*	169
Outcome	Outcome	Life-threatening*	170
Outcome	Outcome	Disabled*	171
Outcome	Outcome	Hospitalized*	172
Outcome	Outcome	Congenital Anomaly*	173
Outcome	Outcome	Required Intervention to Prevent Permanent Damage*	174

## 10. Appendix: Reporting Rates

We calculated crude reporting rates by year for the period 1991 to May 2006 (for the years we received the number of estimated dispensed prescriptions from the Office of Surveillance and Epidemiology). This was done for selected aggregated event codes based on the number of reports received by FDA divided by **estimated** prescriptions dispensed by year.<sup>(23, 24)</sup>

The total number of reports being analyzed by using the selected aggregated PTS add up to a total of 11,945 reports.

Table 9. Estimated Crude Reporting Rate per Million Prescriptions Dispensed per Year

Table 9: Number of AERS Reports (Estimated Crude Reporting Rate per Million Rxs Dispensed per Year)

GENERIC	Year	Estimated Number of Rxs dispensed	Number of AERS Reports (Estimated Crude Reporting Rate Per Million Rxs)										
			Anaphylaxis	Cardiac	Cholestasis	Clostridial	Drug-Drug Interaction	Hearing	Hepatic failure	Hepatitis	Toxic Lung	Toxic Skin	All Rates
All Drugs	1991	61,945,000	32 (.52)	5 (.08)	35 (.57)	163 (2.63)	33 (.53)	18 (.29)	22 (.36)	36 (.58)	9 (.15)	37 (.6)	372 (6.01)
All Drugs	1992	61,261,000	43 (.7)	8 (.13)	28 (.46)	310 (5.06)	110 (1.8)	37 (.6)	27 (.44)	62 (1.01)	8 (.13)	39 (.64)	647 (10.56)
All Drugs	1993	69,814,000	48 (.69)	15 (.21)	22 (.32)	353 (5.06)	182 (2.61)	35 (.5)	53 (.76)	61 (.87)	13 (.19)	62 (.89)	813 (11.65)
All Drugs	1994	71,104,000	48 (.68)	32 (.45)	30 (.42)	293 (4.12)	206 (2.9)	44 (.62)	81 (1.14)	74 (1.04)	3 (.04)	76 (1.07)	845 (11.88)
All Drugs	1995	79,427,000	45 (.57)	47 (.59)	35 (.44)	115 (1.45)	228 (2.87)	30 (.38)	79 (.99)	64 (.81)	10 (.13)	63 (.79)	677 (8.52)
All Drugs	1996	84,023,000	45 (.54)	54 (.64)	29 (.35)	60 (.71)	216 (2.57)	35 (.42)	85 (1.01)	96 (1.14)	9 (.11)	68 (.81)	654 (7.78)
All Drugs	1997	88,005,000	51 (.58)	37 (.42)	27 (.31)	51 (.58)	286 (3.25)	81 (.92)	79 (.9)	69 (.78)	11 (.12)	86 (.98)	734 (8.34)
All Drugs	1998	88,887,000	46 (.52)	40 (.45)	40 (.45)	72 (.81)	262 (2.95)	62 (.7)	147 (1.65)	103 (1.16)	6 (.07)	98 (1.1)	816 (9.18)
All Drugs	1999	99,422,000	109 (1.1)	51 (.51)	68 (.68)	72 (.72)	376 (3.78)	45 (.45)	144 (1.45)	135 (1.36)	7 (.07)	118 (1.19)	1034 (10.4)
All Drugs	2000	95,923,000	80 (.83)	74 (.77)	53 (.55)	68 (.71)	235 (2.45)	49 (.51)	130 (1.36)	94 (.98)	13 (.14)	72 (.75)	787 (8.2)
All Drugs	2001	97,626,000	97 (.99)	43 (.44)	51 (.52)	45 (.46)	189 (1.94)	38 (.39)	112 (1.15)	112 (1.15)	10 (.1)	76 (.78)	709 (7.26)
All Drugs	2002	92,438,000	123 (1.33)	44 (.48)	46 (.5)	52 (.56)	177 (1.91)	30 (.32)	139 (1.5)	81 (.88)	9 (.1)	85 (.92)	728 (7.88)
All Drugs	2003	95,172,000	67 (.7)	55 (.58)	55 (.58)	56 (.59)	211 (2.22)	17 (.18)	147 (1.54)	74 (.78)	8 (.08)	95 (1)	716 (7.52)
All Drugs	2004	88,727,000	134 (1.51)	51 (.57)	55 (.62)	90 (1.01)	166 (1.87)	32 (.36)	175 (1.97)	89 (1)	20 (.23)	105 (1.18)	842 (9.49)
All Drugs	2005	99,021,000	173 (1.75)	68 (.69)	95 (.96)	78 (.79)	285 (2.88)	42 (.42)	232 (2.34)	95 (.96)	6 (.06)	117 (1.18)	1083 (10.94)
All Drugs	2006*	43,983,000	70 (1.59)	34 (.77)	41 (.93)	24 (.55)	122 (2.77)	16 (.36)	108 (2.46)	81 (1.84)	3 (.07)	52 (1.18)	488 (11.1)
All Drugs	All	1,316,778,000	1211 (.92)	658 (.5)	710 (.54)	1902 (1.44)	3284 (2.49)	611 (.46)	1760 (1.34)	1326 (1.01)	145 (.11)	1249 (.95)	11945 (9.07)
Acetaminophen	1991	2,418,000	0 (0)	0 (0)	0 (0)	0 (0)	3 (1.24)	0 (0)	13 (5.38)	4 (1.65)	0 (0)	2 (.83)	20 (8.27)
Acetaminophen	1992	2,956,000	0 (0)	0 (0)	1 (.34)	0 (0)	2 (.68)	0 (0)	13 (4.4)	2 (.68)	0 (0)	1 (.34)	18 (6.09)
Acetaminophen	1993	4,041,000	4 (.99)	1 (.25)	1 (.25)	0 (0)	9 (2.23)	0 (0)	31 (7.67)	9 (2.23)	1 (.25)	5 (1.24)	55 (13.61)
Acetaminophen	1994	4,396,000	3 (.68)	1 (.23)	3 (.68)	1 (.23)	17 (3.87)	1 (.23)	61 (13.88)	33 (7.51)	0 (0)	1 (.23)	107 (24.34)
Acetaminophen	1995	5,083,000	1 (.2)	0 (0)	3 (.59)	0 (0)	26 (5.12)	1 (.2)	54 (10.62)	11 (2.16)	0 (0)	7 (1.38)	93 (18.3)
Acetaminophen	1996	5,168,000	5 (.97)	0 (0)	1 (.19)	0 (0)	22 (4.26)	0 (0)	63 (12.19)	17 (3.29)	0 (0)	3 (.58)	102 (19.74)
Acetaminophen	1997	5,022,000	4 (.8)	3 (.6)	2 (.4)	0 (0)	24 (4.78)	1 (.2)	59 (11.75)	13 (2.59)	1 (.2)	15 (2.99)	112 (22.3)
Acetaminophen	1998	4,170,000	6 (1.44)	1 (.24)	6 (1.44)	0 (0)	48 (11.51)	0 (0)	84 (20.14)	19 (4.56)	0 (0)	20 (4.8)	171 (41.01)
Acetaminophen	1999	4,699,000	8 (1.7)	2 (.43)	3 (.64)	0 (0)	93 (19.79)	0 (0)	60 (12.77)	18 (3.83)	1 (.21)	29 (6.17)	195 (41.5)
Acetaminophen	2000	4,210,000	10 (2.38)	1 (.24)	8 (1.9)	0 (0)	86 (20.43)	1 (.24)	89 (21.14)	29 (6.89)	2 (.48)	23 (5.46)	222 (52.73)

Table 9: Number of AERS Reports (Estimated Crude Reporting Rate per Million Rx's Dispensed per Year)

GENERIC	Year	Estimated Number of Rx's dispensed	Number of AERS Reports (Estimated Crude Reporting Rate Per Million Rx's)										
			Anaphylaxis	Cardiac	Cholestasis	Clostridial	Drug-Drug Interaction	Hearing	Hepatic failure	Hepatitis	Toxic Lung	Toxic Skin	All Rates
Acetaminophen	2001	3,988,000	7 (1.76)	2 (.5)	10 (2.51)	0 (0)	62 (15.55)	1 (.25)	61 (15.3)	22 (5.52)	0 (0)	13 (3.26)	161 (40.37)
Acetaminophen	2002	2,856,000	10 (3.5)	2 (.7)	16 (5.6)	1 (.35)	51 (17.86)	4 (1.4)	99 (34.66)	20 (7)	1 (.35)	16 (5.6)	207 (72.48)
Acetaminophen	2003	2,670,000	13 (4.87)	6 (2.25)	14 (5.24)	0 (0)	63 (23.6)	2 (.75)	120 (44.94)	15 (5.62)	1 (.37)	21 (7.87)	231 (86.52)
Acetaminophen	2004	2,015,000	10 (4.96)	5 (2.48)	11 (5.46)	0 (0)	40 (19.85)	6 (2.98)	134 (66.5)	22 (10.92)	1 (.5)	15 (7.44)	227 (112.66)
Acetaminophen	2005	2,202,000	17 (7.72)	13 (5.9)	27 (12.26)	1 (.45)	49 (22.25)	5 (2.27)	178 (80.84)	25 (11.35)	0 (0)	41 (18.62)	318 (144.41)
Acetaminophen	2006*	880,000	7 (7.95)	1 (1.14)	9 (10.23)	0 (0)	41 (46.59)	4 (4.55)	63 (71.59)	17 (19.32)	2 (2.27)	13 (14.77)	124 (140.91)
Acetaminophen	All	56,774,000	105 (1.85)	38 (.67)	115 (2.03)	3 (.05)	636 (11.2)	26 (.46)	1182 (20.82)	276 (4.86)	10 (.18)	225 (3.96)	2363 (41.62)
Amoxicillin And Clavulanate	1991	11,546,000	11 (.95)	0 (0)	29 (2.51)	14 (1.21)	4 (.35)	0 (0)	5 (.43)	20 (1.73)	0 (0)	14 (1.21)	83 (7.19)
Amoxicillin And Clavulanate	1992	11,626,000	9 (.77)	0 (0)	18 (1.55)	19 (1.63)	3 (.26)	1 (.09)	2 (.17)	18 (1.55)	0 (0)	12 (1.03)	75 (6.45)
Amoxicillin And Clavulanate	1993	12,554,000	7 (.56)	0 (0)	12 (.96)	20 (1.59)	5 (.4)	0 (0)	8 (.64)	5 (.4)	0 (0)	5 (.4)	56 (4.46)
Amoxicillin And Clavulanate	1994	12,101,000	4 (.33)	0 (0)	19 (1.57)	13 (1.07)	3 (.25)	0 (0)	6 (.5)	16 (1.32)	0 (0)	23 (1.9)	76 (6.28)
Amoxicillin And Clavulanate	1995	12,234,000	1 (.08)	0 (0)	17 (1.39)	14 (1.14)	8 (.65)	2 (.16)	5 (.41)	9 (.74)	0 (0)	10 (.82)	60 (4.9)
Amoxicillin And Clavulanate	1996	12,642,000	8 (.63)	0 (0)	11 (.87)	5 (.4)	12 (.95)	1 (.08)	9 (.71)	17 (1.34)	0 (0)	11 (.87)	70 (5.54)
Amoxicillin And Clavulanate	1997	15,350,000	7 (.46)	0 (0)	15 (.98)	11 (.72)	11 (.72)	1 (.07)	4 (.26)	23 (1.5)	0 (0)	10 (.65)	72 (4.69)
Amoxicillin And Clavulanate	1998	16,375,000	0 (0)	0 (0)	10 (.61)	15 (.92)	6 (.37)	2 (.12)	5 (.31)	7 (.43)	0 (0)	7 (.43)	48 (2.93)
Amoxicillin And Clavulanate	1999	19,321,000	5 (.26)	0 (0)	17 (.88)	10 (.52)	11 (.57)	1 (.05)	11 (.57)	16 (.83)	0 (0)	22 (1.14)	79 (4.09)
Amoxicillin And Clavulanate	2000	20,744,000	4 (.19)	1 (.05)	12 (.58)	12 (.58)	4 (.19)	4 (.19)	11 (.53)	14 (.67)	0 (0)	6 (.29)	60 (2.89)
Amoxicillin And Clavulanate	2001	22,609,000	9 (.4)	1 (.04)	16 (.71)	8 (.35)	8 (.35)	1 (.04)	15 (.66)	25 (1.11)	2 (.09)	17 (.75)	93 (4.11)
Amoxicillin And Clavulanate	2002	22,507,000	7 (.31)	0 (0)	14 (.62)	11 (.49)	9 (.4)	1 (.04)	12 (.53)	18 (.8)	1 (.04)	9 (.4)	75 (3.33)
Amoxicillin And Clavulanate	2003	22,971,000	25 (1.09)	1 (.04)	22 (.96)	19 (.83)	20 (.87)	2 (.09)	4 (.17)	23 (1)	2 (.09)	13 (.57)	119 (5.18)
Amoxicillin And Clavulanate	2004	20,451,000	22 (1.08)	0 (0)	23 (1.12)	21 (1.03)	11 (.54)	0 (0)	7 (.34)	30 (1.47)	1 (.05)	22 (1.08)	120 (5.87)
Amoxicillin And Clavulanate	2005	21,382,000	49 (2.29)	1 (.05)	33 (1.54)	24 (1.12)	20 (.94)	0 (0)	12 (.56)	27 (1.26)	0 (0)	25 (1.17)	168 (7.86)
Amoxicillin And Clavulanate	2006*	9,422,000	27 (2.87)	0 (0)	20 (2.12)	5 (.53)	19 (2.02)	0 (0)	7 (.74)	17 (1.8)	0 (0)	11 (1.17)	96 (10.19)
Amoxicillin And Clavulanate	All	263,835,000	195 (.74)	4 (.02)	288 (1.09)	221 (.84)	154 (.58)	16 (.06)	123 (.47)	285 (1.08)	6 (.02)	217 (.82)	1350 (5.12)
Azithromycin	1992	718,000	5 (6.96)	0 (0)	2 (2.79)	2 (2.79)	3 (4.18)	1 (1.39)	0 (0)	3 (4.18)	1 (1.39)	4 (5.57)	21 (29.25)
Azithromycin	1993	1,807,000	3 (1.66)	1 (.55)	2 (1.11)	2 (1.11)	7 (3.87)	4 (2.21)	0 (0)	3 (1.66)	1 (.55)	3 (1.66)	26 (14.39)
Azithromycin	1994	2,933,000	1 (.34)	4 (1.36)	0 (0)	0 (0)	18 (6.14)	6 (2.05)	0 (0)	2 (.68)	0 (0)	2 (.68)	30 (10.23)

Table 9: Number of AERS Reports (Estimated Crude Reporting Rate per Million Rxs Dispensed per Year)

GENERIC	Year	Estimated Number of Rxs dispensed	Number of AERS Reports (Estimated Crude Reporting Rate Per Million Rxs)										
			Anaphylaxis	Cardiac	Cholestasis	Clostridial	Drug-Drug Interaction	Hearing	Hepatic failure	Hepatitis	Toxic Lung	Toxic Skin	All Rates
Azithromycin	1995	6,349,000	5 (.79)	4 (.63)	2 (.32)	0 (0)	17 (2.68)	4 (.63)	5 (.79)	5 (.79)	0 (0)	8 (1.26)	47 (7.4)
Azithromycin	1996	12,459,000	8 (.64)	1 (.08)	6 (.48)	2 (.16)	50 (4.01)	9 (.72)	7 (.56)	24 (1.93)	0 (0)	22 (1.77)	122 (9.79)
Azithromycin	1997	17,881,000	8 (.45)	7 (.39)	2 (.11)	6 (.34)	71 (3.97)	60 (3.36)	5 (.28)	9 (.5)	0 (0)	20 (1.12)	183 (10.23)
Azithromycin	1998	23,625,000	7 (.3)	6 (.25)	7 (.3)	6 (.25)	71 (3.01)	35 (1.48)	10 (.42)	13 (.55)	0 (0)	23 (.97)	166 (7.03)
Azithromycin	1999	32,502,000	13 (.4)	11 (.34)	5 (.15)	6 (.18)	59 (1.82)	23 (.71)	3 (.09)	11 (.34)	2 (.06)	19 (.58)	148 (4.55)
Azithromycin	2000	33,472,000	16 (.48)	14 (.42)	12 (.36)	11 (.33)	57 (1.7)	25 (.75)	6 (.18)	10 (.3)	0 (0)	22 (.66)	158 (4.72)
Azithromycin	2001	35,797,000	14 (.39)	9 (.25)	11 (.31)	5 (.14)	31 (.87)	24 (.67)	12 (.34)	23 (.64)	0 (0)	17 (.47)	132 (3.69)
Azithromycin	2002	35,715,000	18 (.5)	8 (.22)	7 (.2)	4 (.11)	20 (.56)	17 (.48)	6 (.17)	12 (.34)	0 (0)	22 (.62)	109 (3.05)
Azithromycin	2003	39,264,000	9 (.23)	15 (.38)	8 (.2)	4 (.1)	36 (.92)	6 (.15)	7 (.18)	8 (.2)	0 (0)	11 (.28)	99 (2.52)
Azithromycin	2004	37,040,000	22 (.59)	7 (.19)	5 (.13)	3 (.08)	22 (.59)	13 (.35)	12 (.32)	4 (.11)	0 (0)	24 (.65)	103 (2.78)
Azithromycin	2005	43,018,000	11 (.26)	8 (.19)	6 (.14)	2 (.05)	27 (.63)	21 (.49)	7 (.16)	6 (.14)	0 (0)	17 (.4)	97 (2.25)
Azithromycin	2006*	19,533,000	5 (.26)	8 (.41)	5 (.26)	4 (.2)	2 (.1)	7 (.36)	6 (.31)	5 (.26)	0 (0)	5 (.26)	42 (2.15)
Azithromycin	All	342,113,000	145 (.42)	103 (.3)	80 (.23)	57 (.17)	491 (1.44)	255 (.75)	86 (.25)	138 (.4)	4 (.01)	219 (.64)	1483 (4.33)
Cefditoren	2001	1,000	2 (2000)	0 (0)	1 (1000)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1000)	4 (4000)
Cefditoren	2002	30,000	2 (66.67)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (33.33)	0 (0)	5 (166.67)	8 (266.67)
Cefditoren	2003	37,000	1 (27.03)	0 (0)	0 (0)	0 (0)	1 (27.03)	0 (0)	0 (0)	1 (27.03)	1 (27.03)	7 (189.19)	11 (297.3)
Cefditoren	2004	292,000	8 (27.4)	0 (0)	1 (3.42)	42 (143.84)	0 (0)	0 (0)	1 (3.42)	0 (0)	0 (0)	8 (27.4)	60 (205.48)
Cefditoren	2005	204,000	2 (9.8)	0 (0)	2 (9.8)	20 (98.04)	0 (0)	0 (0)	1 (4.9)	1 (4.9)	0 (0)	7 (34.31)	31 (151.96)
Cefditoren	2006*	34,000	1 (29.41)	0 (0)	0 (0)	1 (29.41)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (29.41)	3 (88.24)
Cefditoren	All	598,000	16 (26.76)	0 (0)	4 (6.69)	63 (105.35)	1 (1.67)	0 (0)	2 (3.34)	3 (5.02)	1 (1.67)	30 (50.17)	118 (197.32)
Cefixime	1991	3,082,000	3 (.97)	0 (0)	3 (.97)	66 (21.41)	2 (.65)	0 (0)	0 (0)	0 (0)	0 (0)	9 (2.92)	83 (26.93)
Cefixime	1992	3,435,000	2 (.58)	0 (0)	0 (0)	66 (19.21)	1 (.29)	0 (0)	2 (.58)	0 (0)	1 (.29)	4 (1.16)	75 (21.83)
Cefixime	1993	4,245,000	0 (0)	0 (0)	0 (0)	75 (17.67)	1 (.24)	0 (0)	0 (0)	0 (0)	0 (0)	9 (2.12)	85 (20.02)
Cefixime	1994	4,077,000	3 (.74)	0 (0)	0 (0)	89 (21.83)	2 (.49)	0 (0)	0 (0)	0 (0)	0 (0)	4 (.98)	98 (24.04)
Cefixime	1995	3,437,000	0 (0)	0 (0)	1 (.29)	34 (9.89)	5 (1.45)	1 (.29)	0 (0)	3 (.87)	0 (0)	4 (1.16)	47 (13.67)
Cefixime	1996	2,877,000	1 (.35)	0 (0)	0 (0)	16 (5.56)	3 (1.04)	1 (.35)	0 (0)	1 (.35)	0 (0)	1 (.35)	22 (7.65)
Cefixime	1997	2,328,000	0 (0)	0 (0)	1 (.43)	7 (3.01)	2 (.86)	0 (0)	0 (0)	2 (.86)	0 (0)	3 (1.29)	15 (6.44)

Table 9: Number of AERS Reports (Estimated Crude Reporting Rate per Million Rxs Dispensed per Year)

GENERIC	Year	Estimated Number of Rxs dispensed	Number of AERS Reports (Estimated Crude Reporting Rate Per Million Rxs)										
			Anaphylaxis	Cardiac	Cholestasis	Clostridial	Drug-Drug Interaction	Hearing	Hepatic failure	Hepatitis	Toxic Lung	Toxic Skin	All Rates
Cefixime	1998	1,898,000	2 (1.05)	0 (0)	0 (0)	8 (4.21)	1 (.53)	1 (.53)	1 (.53)	1 (.53)	0 (0)	0 (0)	14 (7.38)
Cefixime	1999	1,485,000	0 (0)	0 (0)	1 (.67)	7 (4.71)	1 (.67)	0 (0)	0 (0)	1 (.67)	0 (0)	2 (1.35)	12 (8.08)
Cefixime	2000	1,159,000	2 (1.73)	0 (0)	0 (0)	6 (5.18)	3 (2.59)	0 (0)	0 (0)	0 (0)	0 (0)	2 (1.73)	13 (11.22)
Cefixime	2001	1,000,000	0 (0)	0 (0)	0 (0)	3 (3)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	5 (5)
Cefixime	2002	818,000	1 (1.22)	0 (0)	1 (1.22)	6 (7.33)	0 (0)	0 (0)	0 (0)	1 (1.22)	0 (0)	3 (3.67)	11 (13.45)
Cefixime	2003	250,000	0 (0)	0 (0)	1 (4)	2 (8)	0 (0)	1 (4)	1 (4)	2 (8)	0 (0)	1 (4)	7 (28)
Cefixime	2004	45,000	0 (0)	0 (0)	1 (22.22)	2 (44.44)	0 (0)	0 (0)	1 (22.22)	1 (22.22)	0 (0)	2 (44.44)	6 (133.33)
Cefixime	2005	139,000	0 (0)	0 (0)	2 (14.39)	1 (7.19)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (21.58)
Cefixime	2006*	82,000	0 (0)	0 (0)	0 (0)	4 (48.78)	4 (48.78)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	8 (97.56)
Cefixime	All	30,357,000	14 (.46)	0 (0)	11 (.36)	392 (12.91)	26 (.86)	4 (.13)	5 (.16)	12 (.4)	1 (.03)	45 (1.48)	504 (16.6)
Cefpodoxime	1992	110,000	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (9.09)	1 (9.09)
Cefpodoxime	1993	1,240,000	1 (.81)	0 (0)	0 (0)	59 (47.58)	2 (1.61)	1 (.81)	0 (0)	1 (.81)	0 (0)	6 (4.84)	70 (56.45)
Cefpodoxime	1994	1,860,000	2 (1.08)	0 (0)	0 (0)	67 (36.02)	6 (3.23)	1 (.54)	1 (.54)	0 (0)	0 (0)	19 (10.22)	96 (51.61)
Cefpodoxime	1995	2,077,000	1 (.48)	0 (0)	1 (.48)	30 (14.44)	4 (1.93)	0 (0)	2 (.96)	2 (.96)	0 (0)	6 (2.89)	44 (21.18)
Cefpodoxime	1996	1,757,000	3 (1.71)	0 (0)	0 (0)	18 (10.24)	2 (1.14)	0 (0)	0 (0)	0 (0)	0 (0)	5 (2.85)	28 (15.94)
Cefpodoxime	1997	1,666,000	3 (1.8)	0 (0)	0 (0)	7 (4.2)	1 (.6)	0 (0)	0 (0)	1 (.6)	0 (0)	2 (1.2)	14 (8.4)
Cefpodoxime	1998	1,325,000	0 (0)	0 (0)	1 (.75)	4 (3.02)	0 (0)	1 (.75)	0 (0)	2 (1.51)	0 (0)	4 (3.02)	12 (9.06)
Cefpodoxime	1999	1,135,000	1 (.88)	0 (0)	0 (0)	2 (1.76)	3 (2.64)	0 (0)	1 (.88)	3 (2.64)	0 (0)	2 (1.76)	10 (8.81)
Cefpodoxime	2000	875,000	0 (0)	1 (1.14)	0 (0)	5 (5.71)	2 (2.29)	0 (0)	1 (1.14)	2 (2.29)	0 (0)	1 (1.14)	12 (13.71)
Cefpodoxime	2001	581,000	0 (0)	0 (0)	0 (0)	1 (1.72)	0 (0)	0 (0)	1 (1.72)	1 (1.72)	0 (0)	2 (3.44)	5 (8.61)
Cefpodoxime	2002	456,000	0 (0)	0 (0)	1 (2.19)	4 (8.77)	1 (2.19)	0 (0)	1 (2.19)	3 (6.58)	0 (0)	3 (6.58)	10 (21.93)
Cefpodoxime	2003	400,000	0 (0)	0 (0)	0 (0)	1 (2.5)	1 (2.5)	0 (0)	0 (0)	2 (5)	0 (0)	3 (7.5)	7 (17.5)
Cefpodoxime	2004	287,000	0 (0)	0 (0)	0 (0)	3 (10.45)	0 (0)	1 (3.48)	0 (0)	1 (3.48)	0 (0)	4 (13.94)	9 (31.36)
Cefpodoxime	2005	254,000	0 (0)	0 (0)	1 (3.94)	1 (3.94)	1 (3.94)	0 (0)	0 (0)	1 (3.94)	0 (0)	2 (7.87)	6 (23.62)
Cefpodoxime	2006*	109,000	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (18.35)	0 (0)	1 (9.17)	3 (27.52)
Cefpodoxime	All	14,132,000	11 (.78)	1 (.07)	4 (.28)	202 (14.29)	23 (1.63)	4 (.28)	7 (.5)	21 (1.49)	0 (0)	61 (4.32)	327 (23.14)
Ceftibuten**	1996	<1,000	0 (0)	0 (0)	0 (0)	5 (>5,000)	2 (>2,000)	0 (0)	0 (0)	1 (>1,000)	0 (0)	3 (>3,000)	11 (>11,000)

Table 9: Number of AERS Reports (Estimated Crude Reporting Rate per Million Rxs Dispensed per Year)

GENERIC	Year	Estimated Number of Rxs dispensed	Number of AERS Reports (Estimated Crude Reporting Rate Per Million Rxs)										
			Anaphylaxis	Cardiac	Cholestasis	Clostridial	Drug-Drug Interaction	Hearing	Hepatic failure	Hepatitis	Toxic Lung	Toxic Skin	All Rates
Ceftibuten**	1997	<1,000	1 (>1,000)	0 (0)	0 (0)	6 (>6,000)	2 (>2,000)	1 (>1,000)	0 (0)	0 (0)	0 (0)	8 (>8,000)	18 (>18,000)
Ceftibuten**	1998	<1,000	1 (>1,000)	0 (0)	0 (0)	6 (>6,000)	0 (0)	2 (>2,000)	0 (0)	0 (0)	0 (0)	1 (>1,000)	10 (>10,000)
Ceftibuten**	1999	<1,000	0 (0)	0 (0)	1 (>1,000)	0 (0)	1 (>1,000)	0 (0)	0 (0)	2 (>2,000)	0 (0)	0 (0)	3 (>3,000)
Ceftibuten**	2000	<1,000	0 (0)	0 (0)	0 (0)	1 (>1,000)	0 (0)	1 (>1,000)	0 (0)	0 (0)	0 (0)	1 (>1,000)	3 (>3,000)
Ceftibuten**	2001	<1,000	0 (0)	0 (0)	1 (>1,000)	2 (>2,000)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (>1,000)	4 (>4,000)
Ceftibuten**	2002	<1,000	0 (0)	0 (0)	0 (0)	0 (0)	1 (>1,000)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (>1,000)
Ceftibuten**	2003	<1,000	0 (0)	0 (0)	0 (0)	1 (>1,000)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (>1,000)	2 (>2,000)
Ceftibuten**	2004	23,000	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Ceftibuten**	2005	62,000	0 (0)	0 (0)	0 (0)	1 (16.13)	0 (0)	1 (16.13)	0 (0)	0 (0)	0 (0)	0 (0)	2 (32.26)
Ceftibuten**	2006*	23,000	1 (43.48)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (43.48)
Ceftibuten**	All	108,000	3 (27.78)	0 (0)	2 (18.52)	22 (203.7)	6 (55.56)	5 (46.3)	0 (0)	3 (27.78)	0 (0)	15 (138.89)	55 (509.26)
Cefuroxime	1991	4,880,000	14 (2.87)	0 (0)	0 (0)	81 (16.6)	3 (.61)	0 (0)	0 (0)	0 (0)	0 (0)	7 (1.43)	105 (21.52)
Cefuroxime	1992	4,907,000	12 (2.45)	0 (0)	2 (.41)	213 (43.41)	8 (1.63)	3 (.61)	3 (.61)	2 (.41)	0 (0)	9 (1.83)	248 (50.54)
Cefuroxime	1993	5,400,000	24 (4.44)	0 (0)	0 (0)	178 (32.96)	12 (2.22)	2 (.37)	4 (.74)	8 (1.48)	0 (0)	14 (2.59)	239 (44.26)
Cefuroxime	1994	5,273,000	24 (4.55)	0 (0)	0 (0)	102 (19.34)	8 (1.52)	0 (0)	0 (0)	2 (.38)	0 (0)	8 (1.52)	144 (27.31)
Cefuroxime	1995	5,621,000	29 (5.16)	0 (0)	1 (.18)	27 (4.8)	5 (.89)	1 (.18)	0 (0)	2 (.36)	0 (0)	6 (1.07)	71 (12.63)
Cefuroxime	1996	5,492,000	11 (2)	0 (0)	1 (.18)	6 (1.09)	2 (.36)	0 (0)	0 (0)	5 (.91)	0 (0)	3 (.55)	28 (5.1)
Cefuroxime	1997	5,577,000	21 (3.77)	1 (.18)	1 (.18)	12 (2.15)	5 (.9)	0 (0)	1 (.18)	1 (.18)	0 (0)	12 (2.15)	52 (9.32)
Cefuroxime	1998	5,244,000	14 (2.67)	0 (0)	1 (.19)	23 (4.39)	11 (2.1)	1 (.19)	0 (0)	3 (.57)	0 (0)	17 (3.24)	68 (12.97)
Cefuroxime	1999	6,019,000	13 (2.16)	0 (0)	2 (.33)	18 (2.99)	7 (1.16)	2 (.33)	0 (0)	2 (.33)	0 (0)	8 (1.33)	51 (8.47)
Cefuroxime	2000	5,244,000	8 (1.53)	0 (0)	5 (.95)	13 (2.48)	1 (.19)	1 (.19)	0 (0)	3 (.57)	0 (0)	4 (.76)	34 (6.48)
Cefuroxime	2001	4,948,000	15 (3.03)	0 (0)	1 (.2)	5 (1.01)	4 (.81)	1 (.2)	2 (.4)	3 (.61)	0 (0)	5 (1.01)	34 (6.87)
Cefuroxime	2002	3,845,000	18 (4.68)	0 (0)	2 (.52)	7 (1.82)	1 (.26)	0 (0)	1 (.26)	2 (.52)	0 (0)	1 (.26)	31 (8.06)
Cefuroxime	2003	3,337,000	7 (2.1)	1 (.3)	2 (.6)	6 (1.8)	4 (1.2)	0 (0)	3 (.9)	2 (.6)	0 (0)	7 (2.1)	28 (8.39)
Cefuroxime	2004	2,681,000	12 (4.48)	0 (0)	1 (.37)	2 (.75)	4 (1.49)	3 (1.12)	1 (.37)	2 (.75)	0 (0)	4 (1.49)	29 (10.82)
Cefuroxime	2005	2,780,000	15 (5.4)	0 (0)	5 (1.8)	5 (1.8)	3 (1.08)	0 (0)	2 (.72)	4 (1.44)	0 (0)	3 (1.08)	35 (12.59)
Cefuroxime	2006*	1,289,000	9 (6.98)	0 (0)	0 (0)	3 (2.33)	2 (1.55)	0 (0)	0 (0)	1 (.78)	0 (0)	3 (2.33)	18 (13.96)

Table 9: Number of AERS Reports (Estimated Crude Reporting Rate per Million Rxs Dispensed per Year)

GENERIC	Year	Estimated Number of Rxs dispensed	Number of AERS Reports (Estimated Crude Reporting Rate Per Million Rxs)										
			Anaphylaxis	Cardiac	Cholestasis	Clostridial	Drug-Drug Interaction	Hearing	Hepatic failure	Hepatitis	Toxic Lung	Toxic Skin	All Rates
Cefuroxime	All	72,537,000	246 (3.39)	2 (.03)	24 (.33)	701 (9.66)	80 (1.1)	14 (.19)	17 (.23)	42 (.58)	0 (0)	111 (1.53)	1215 (16.75)
Clarithromycin	1991	140,000	1 (7.14)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (7.14)	0 (0)	0 (0)	2 (14.29)
Clarithromycin	1992	2,997,000	5 (1.67)	2 (.67)	3 (1)	4 (1.33)	46 (15.35)	11 (3.67)	4 (1.33)	18 (6.01)	1 (.33)	5 (1.67)	93 (31.03)
Clarithromycin	1993	5,607,000	4 (.71)	5 (.89)	4 (.71)	8 (1.43)	104 (18.55)	10 (1.78)	3 (.54)	20 (3.57)	0 (0)	12 (2.14)	164 (29.25)
Clarithromycin	1994	8,255,000	6 (.73)	13 (1.57)	8 (.97)	13 (1.57)	97 (11.75)	18 (2.18)	9 (1.09)	14 (1.7)	0 (0)	15 (1.82)	188 (22.77)
Clarithromycin	1995	13,055,000	5 (.38)	20 (1.53)	7 (.54)	7 (.54)	109 (8.35)	12 (.92)	9 (.69)	21 (1.61)	0 (0)	13 (1)	197 (15.09)
Clarithromycin	1996	15,135,000	5 (.33)	23 (1.52)	7 (.46)	4 (.26)	94 (6.21)	14 (.93)	7 (.46)	16 (1.06)	1 (.07)	15 (.99)	174 (11.5)
Clarithromycin	1997	14,898,000	6 (.4)	12 (.81)	4 (.27)	3 (.2)	128 (8.59)	9 (.6)	3 (.2)	9 (.6)	0 (0)	12 (.81)	179 (12.02)
Clarithromycin	1998	13,233,000	5 (.38)	16 (1.21)	8 (.6)	7 (.53)	71 (5.37)	16 (1.21)	10 (.76)	8 (.6)	0 (0)	8 (.6)	137 (10.35)
Clarithromycin	1999	12,887,000	5 (.39)	19 (1.47)	5 (.39)	6 (.47)	81 (6.29)	6 (.47)	8 (.62)	11 (.85)	0 (0)	20 (1.55)	151 (11.72)
Clarithromycin	2000	10,986,000	5 (.46)	19 (1.73)	6 (.55)	4 (.36)	46 (4.19)	1 (.09)	5 (.46)	8 (.73)	1 (.09)	6 (.55)	93 (8.47)
Clarithromycin	2001	9,890,000	2 (.2)	15 (1.52)	3 (.3)	9 (.91)	57 (5.76)	6 (.61)	9 (.91)	5 (.51)	2 (.2)	9 (.91)	110 (11.12)
Clarithromycin	2002	8,458,000	6 (.71)	8 (.95)	2 (.24)	5 (.59)	50 (5.91)	1 (.12)	5 (.59)	3 (.35)	0 (0)	17 (2.01)	91 (10.76)
Clarithromycin	2003	8,429,000	3 (.36)	7 (.83)	8 (.95)	13 (1.54)	58 (6.88)	2 (.24)	4 (.47)	5 (.59)	1 (.12)	20 (2.37)	112 (13.29)
Clarithromycin	2004	6,497,000	1 (.15)	8 (1.23)	4 (.62)	6 (.92)	47 (7.23)	2 (.31)	6 (.92)	8 (1.23)	0 (0)	11 (1.69)	84 (12.93)
Clarithromycin	2005	6,318,000	4 (.63)	11 (1.74)	13 (2.06)	8 (1.27)	102 (16.14)	2 (.32)	10 (1.58)	10 (1.58)	0 (0)	7 (1.11)	149 (23.58)
Clarithromycin	2006*	2,680,000	4 (1.49)	5 (1.87)	5 (1.87)	3 (1.12)	33 (12.31)	0 (0)	2 (.75)	3 (1.12)	0 (0)	13 (4.85)	63 (23.51)
Clarithromycin	All	139,465,000	67 (.48)	183 (1.31)	87 (.62)	100 (.72)	1123 (8.05)	110 (.79)	94 (.67)	160 (1.15)	6 (.04)	183 (1.31)	1987 (14.25)
Dirithromycin	1995	65,000	0 (0)	1 (15.38)	0 (0)	0 (0)	0 (0)	1 (15.38)	0 (0)	0 (0)	0 (0)	0 (0)	2 (30.77)
Dirithromycin	1996	484,000	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.07)	0 (0)	0 (0)	4 (8.26)	0 (0)	0 (0)	5 (10.33)
Dirithromycin	1997	534,000	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.87)	0 (0)	0 (0)	1 (1.87)
Dirithromycin	1998	453,000	0 (0)	0 (0)	1 (2.21)	0 (0)	1 (2.21)	0 (0)	0 (0)	1 (2.21)	0 (0)	0 (0)	2 (4.42)
Dirithromycin	1999	353,000	0 (0)	0 (0)	0 (0)	0 (0)	2 (5.67)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (5.67)
Dirithromycin	2000	424,000	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.36)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.36)
Dirithromycin	2001	532,000	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Dirithromycin	2002	499,000	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)
Dirithromycin	2003	183,000	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Table 9: Number of AERS Reports (Estimated Crude Reporting Rate per Million Rxs Dispensed per Year)

GENERIC	Year	Estimated Number of Rxs dispensed	Number of AERS Reports (Estimated Crude Reporting Rate Per Million Rxs)											
			Anaphylaxis	Cardiac	Cholestasis	Clostridial	Drug-Drug Interaction	Hearing	Hepatic failure	Hepatitis	Toxic Lung	Toxic Skin	All Rates	
Dirithromycin	2004	9,000	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Dirithromycin	2005	<1,000	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Dirithromycin	2006*	<1,000	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Dirithromycin	All	3,536,000	1 (.28)	1 (.28)	1 (.28)	0 (0)	5 (1.41)	1 (.28)	0 (0)	6 (1.7)	0 (0)	0 (0)	14 (3.96)	
Erythromycin	1991	35,699,000	2 (.06)	5 (.14)	2 (.06)	2 (.06)	21 (.59)	17 (.48)	0 (0)	4 (.11)	1 (.03)	2 (.06)	54 (1.51)	
Erythromycin	1992	30,093,000	5 (.17)	6 (.2)	1 (.03)	6 (.2)	45 (1.5)	22 (.73)	0 (0)	13 (.43)	0 (0)	3 (.1)	95 (3.16)	
Erythromycin	1993	30,108,000	2 (.07)	8 (.27)	3 (.1)	7 (.23)	40 (1.33)	19 (.63)	2 (.07)	5 (.17)	0 (0)	3 (.1)	80 (2.66)	
Erythromycin	1994	27,012,000	2 (.07)	15 (.56)	0 (0)	20 (.74)	53 (1.96)	17 (.63)	2 (.07)	2 (.07)	0 (0)	4 (.15)	103 (3.81)	
Erythromycin	1995	26,117,000	2 (.08)	22 (.84)	4 (.15)	3 (.11)	52 (1.99)	7 (.27)	0 (0)	9 (.34)	0 (0)	11 (.42)	101 (3.87)	
Erythromycin	1996	22,439,000	2 (.09)	31 (1.38)	0 (0)	5 (.22)	28 (1.25)	10 (.45)	0 (0)	7 (.31)	0 (0)	4 (.18)	80 (3.57)	
Erythromycin	1997	19,181,000	1 (.05)	16 (.83)	1 (.05)	0 (0)	44 (2.29)	9 (.47)	1 (.05)	4 (.21)	0 (0)	3 (.16)	70 (3.65)	
Erythromycin	1998	15,655,000	0 (0)	17 (1.09)	1 (.06)	3 (.19)	19 (1.21)	3 (.19)	4 (.26)	6 (.38)	0 (0)	7 (.45)	56 (3.58)	
Erythromycin	1999	14,046,000	4 (.28)	17 (1.21)	2 (.14)	3 (.21)	30 (2.14)	2 (.14)	0 (0)	2 (.14)	0 (0)	8 (.57)	65 (4.63)	
Erythromycin	2000	11,704,000	1 (.09)	22 (1.88)	6 (.51)	3 (.26)	20 (1.71)	5 (.43)	2 (.17)	5 (.43)	0 (0)	8 (.68)	63 (5.38)	
Erythromycin	2001	10,087,000	2 (.2)	7 (.69)	6 (.59)	4 (.4)	11 (1.09)	0 (0)	3 (.3)	6 (.59)	0 (0)	9 (.89)	42 (4.16)	
Erythromycin	2002	8,526,000	0 (0)	15 (1.76)	0 (0)	2 (.23)	25 (2.93)	4 (.47)	1 (.12)	1 (.12)	0 (0)	2 (.23)	41 (4.81)	
Erythromycin	2003	7,694,000	1 (.13)	8 (1.04)	2 (.26)	4 (.52)	22 (2.86)	1 (.13)	0 (0)	2 (.26)	0 (0)	6 (.78)	40 (5.2)	
Erythromycin	2004	6,675,000	0 (0)	2 (.3)	4 (.6)	4 (.6)	11 (1.65)	2 (.3)	1 (.15)	2 (.3)	0 (0)	8 (1.2)	28 (4.19)	
Erythromycin	2005	6,271,000	2 (.32)	7 (1.12)	4 (.64)	1 (.16)	20 (3.19)	3 (.48)	1 (.16)	2 (.32)	0 (0)	4 (.64)	39 (6.22)	
Erythromycin	2006*	2,488,000	0 (0)	1 (.4)	0 (0)	0 (0)	10 (4.02)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	11 (4.42)	
Erythromycin	All	273,795,000	26 (.09)	199 (.73)	36 (.13)	67 (.24)	451 (1.65)	121 (.44)	17 (.06)	70 (.26)	1 (0)	82 (.3)	968 (3.54)	
Gemifloxacin	2004	20,000	2 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (50)	3 (150)	
Gemifloxacin	2005	193,000	4 (20.73)	0 (0)	2 (10.36)	7 (36.27)	6 (31.09)	0 (0)	2 (10.36)	0 (0)	0 (0)	3 (15.54)	22 (113.99)	
Gemifloxacin	2006*	150,000	2 (13.33)	0 (0)	0 (0)	1 (6.67)	0 (0)	0 (0)	0 (0)	1 (6.67)	0 (0)	1 (6.67)	5 (33.33)	
Gemifloxacin	All	363,000	8 (22.04)	0 (0)	2 (5.51)	8 (22.04)	6 (16.53)	0 (0)	2 (5.51)	1 (2.75)	0 (0)	5 (13.77)	30 (82.64)	
Moxifloxacin	1998	<1,000	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (>1,000)	1 (>1,000)	
Moxifloxacin	1999	<1,000	1 (>1,000)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (>1,000)	

Table 9: Number of AERS Reports (Estimated Crude Reporting Rate per Million Rx's Dispensed per Year)

GENERIC	Year	Estimated Number of Rx's dispensed	Number of AERS Reports (Estimated Crude Reporting Rate Per Million Rx's)										
			Anaphylaxis	Cardiac	Cholestasis	Clostridial	Drug-Drug Interaction	Hearing	Hepatic failure	Hepatitis	Toxic Lung	Toxic Skin	All Rates
Moxifloxacin	2000	885,000	33 (37.29)	15 (16.95)	1 (1.13)	14 (15.82)	11 (12.43)	9 (10.17)	2 (2.26)	3 (3.39)	1 (1.13)	2 (2.26)	89 (100.56)
Moxifloxacin	2001	1,917,000	43 (22.43)	10 (5.22)	2 (1.04)	6 (3.13)	12 (6.26)	2 (1.04)	1 (.52)	6 (3.13)	1 (.52)	6 (3.13)	88 (45.91)
Moxifloxacin	2002	2,584,000	59 (22.83)	11 (4.26)	2 (.77)	15 (5.8)	16 (6.19)	3 (1.16)	7 (2.71)	9 (3.48)	3 (1.16)	8 (3.1)	127 (49.15)
Moxifloxacin	2003	3,646,000	8 (2.19)	18 (4.94)	3 (.82)	8 (2.19)	9 (2.47)	3 (.82)	6 (1.65)	7 (1.92)	0 (0)	8 (2.19)	61 (16.73)
Moxifloxacin	2004	5,109,000	51 (9.98)	25 (4.89)	2 (.39)	6 (1.17)	17 (3.33)	4 (.78)	6 (1.17)	7 (1.37)	1 (.2)	9 (1.76)	119 (23.29)
Moxifloxacin	2005	5,867,000	54 (9.2)	25 (4.26)	6 (1.02)	10 (1.7)	25 (4.26)	6 (1.02)	7 (1.19)	7 (1.19)	2 (.34)	9 (1.53)	141 (24.03)
Moxifloxacin	2006*	3,085,000	14 (4.54)	15 (4.86)	2 (.65)	3 (.97)	8 (2.59)	4 (1.3)	8 (2.59)	6 (1.94)	0 (0)	5 (1.62)	59 (19.12)
Moxifloxacin	All	23,093,000	263 (11.39)	119 (5.15)	18 (.78)	62 (2.68)	98 (4.24)	31 (1.34)	37 (1.6)	45 (1.95)	8 (.35)	48 (2.08)	686 (29.71)
Nitrofurantoin	1991	4,180,000	1 (.24)	0 (0)	1 (.24)	1 (.24)	0 (0)	1 (.24)	4 (.96)	7 (1.67)	8 (1.91)	3 (.72)	26 (6.22)
Nitrofurantoin	1992	4,419,000	5 (1.13)	0 (0)	1 (.23)	1 (.23)	2 (.45)	0 (0)	3 (.68)	8 (1.81)	5 (1.13)	1 (.23)	25 (5.66)
Nitrofurantoin	1993	4,812,000	3 (.62)	0 (0)	0 (0)	5 (1.04)	3 (.62)	0 (0)	5 (1.04)	10 (2.08)	11 (2.29)	6 (1.25)	42 (8.73)
Nitrofurantoin	1994	5,197,000	3 (.58)	0 (0)	0 (0)	1 (.19)	2 (.38)	1 (.19)	2 (.38)	5 (.96)	3 (.58)	1 (.19)	18 (3.46)
Nitrofurantoin	1995	5,389,000	1 (.19)	0 (0)	1 (.19)	1 (.19)	2 (.37)	2 (.37)	4 (.74)	3 (.56)	10 (1.86)	1 (.19)	23 (4.27)
Nitrofurantoin	1996	5,570,000	2 (.36)	0 (0)	4 (.72)	0 (0)	2 (.36)	0 (0)	1 (.18)	7 (1.26)	8 (1.44)	2 (.36)	23 (4.13)
Nitrofurantoin	1997	5,568,000	0 (0)	0 (0)	1 (.18)	0 (0)	2 (.36)	0 (0)	8 (1.44)	7 (1.26)	10 (1.8)	3 (.54)	28 (5.03)
Nitrofurantoin	1998	5,605,000	1 (.18)	0 (0)	2 (.36)	0 (0)	0 (0)	1 (.18)	3 (.54)	6 (1.07)	6 (1.07)	6 (1.07)	22 (3.93)
Nitrofurantoin	1999	5,873,000	1 (.17)	0 (0)	2 (.34)	0 (0)	3 (.51)	0 (0)	2 (.34)	7 (1.19)	1 (.17)	2 (.34)	15 (2.55)
Nitrofurantoin	2000	6,218,000	0 (0)	1 (.16)	1 (.16)	0 (0)	5 (.8)	2 (.32)	2 (.32)	8 (1.29)	9 (1.45)	1 (.16)	25 (4.02)
Nitrofurantoin	2001	6,275,000	3 (.48)	0 (0)	0 (0)	1 (.16)	7 (1.12)	0 (0)	1 (.16)	4 (.64)	5 (.8)	1 (.16)	21 (3.35)
Nitrofurantoin	2002	6,144,000	0 (0)	0 (0)	1 (.16)	0 (0)	4 (.65)	0 (0)	7 (1.14)	9 (1.46)	5 (.81)	2 (.33)	23 (3.74)
Nitrofurantoin	2003	6,291,000	1 (.16)	0 (0)	0 (0)	1 (.16)	2 (.32)	0 (0)	4 (.64)	5 (.79)	3 (.48)	4 (.64)	20 (3.18)
Nitrofurantoin	2004	6,740,000	0 (0)	1 (.15)	1 (.15)	0 (0)	3 (.45)	0 (0)	2 (.3)	9 (1.34)	17 (2.52)	0 (0)	30 (4.45)
Nitrofurantoin	2005	7,091,000	0 (0)	0 (0)	1 (.14)	0 (0)	7 (.99)	0 (0)	3 (.42)	3 (.42)	4 (.56)	4 (.56)	20 (2.82)
Nitrofurantoin	2006*	2,951,000	0 (0)	0 (0)	1 (.34)	0 (0)	0 (0)	0 (0)	2 (.68)	2 (.68)	1 (.34)	0 (0)	6 (2.03)
Nitrofurantoin	All	88,323,000	21 (.24)	2 (.02)	17 (.19)	11 (.12)	44 (.5)	7 (.08)	53 (.6)	100 (1.13)	106 (1.2)	37 (.42)	367 (4.16)
Telithromycin	2003	<1,000	0 (0)	0 (0)	0 (0)	0 (0)	3 (>3,000)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (>3,000)
Telithromycin	2004	843,000	6 (7.12)	5 (5.93)	3 (3.56)	1 (1.19)	18 (21.35)	4 (4.74)	3 (3.56)	6 (7.12)	0 (0)	5 (5.93)	46 (54.57)

Table 9: Number of AERS Reports (Estimated Crude Reporting Rate per Million Rx's Dispensed per Year)

GENERIC	Year	Estimated Number of Rx's dispensed	Number of AERS Reports (Estimated Crude Reporting Rate Per Million Rx's)										
			Anaphylaxis	Cardiac	Cholestasis	Clostridial	Drug-Drug Interaction	Hearing	Hepatic failure	Hepatitis	Toxic Lung	Toxic Skin	All Rates
Telithromycin	2005	3,240,000	17 (5.25)	7 (2.16)	4 (1.23)	2 (.62)	27 (8.33)	4 (1.23)	13 (4.01)	15 (4.63)	0 (0)	1 (.31)	85 (26.23)
Telithromycin	2006*	1,257,000	2 (1.59)	5 (3.98)	3 (2.39)	1 (.8)	5 (3.98)	1 (.8)	23 (18.3)	35 (27.84)	0 (0)	3 (2.39)	70 (55.69)
Telithromycin	All	5,340,000	25 (4.68)	17 (3.18)	10 (1.87)	4 (.75)	53 (9.93)	9 (1.69)	39 (7.3)	56 (10.49)	0 (0)	9 (1.69)	204 (38.2)
Trovafloracin	1998	1,304,000	10 (7.67)	1 (.77)	6 (4.6)	2 (1.53)	39 (29.91)	3 (2.3)	31 (23.77)	38 (29.14)	0 (0)	8 (6.13)	127 (97.39)
Trovafloracin	1999	1,102,000	58 (52.63)	2 (1.81)	31 (28.13)	22 (19.96)	90 (81.67)	12 (10.89)	64 (58.08)	72 (65.34)	3 (2.72)	13 (11.8)	329 (298.55)
Trovafloracin	2000	2,000	2 (1000)	0 (0)	7 (3500)	2 (1000)	1 (500)	0 (0)	14 (7000)	19 (9500)	0 (0)	0 (0)	33 (16500)
Trovafloracin	2001	1,000	1 (1000)	0 (0)	4 (4000)	2 (2000)	0 (0)	3 (3000)	11 (11000)	21 (21000)	0 (0)	1 (1000)	33 (33000)
Trovafloracin	2002	<1,000	1 (>1,000)	0 (0)	3 (>3,000)	0 (0)	0 (0)	0 (0)	3 (>3,000)	4 (>4,000)	0 (0)	0 (0)	7 (>7,000)
Trovafloracin	2003	<1,000	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (>1,000)	4 (>4,000)	0 (0)	1 (>1,000)	5 (>5,000)
Trovafloracin	2004	<1,000	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (>4,000)	2 (>2,000)	0 (0)	0 (0)	4 (>4,000)
Trovafloracin	2005	<1,000	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Trovafloracin	2006*	<1,000	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Trovafloracin	All	2,409,000	72 (29.89)	3 (1.25)	51 (21.17)	28 (11.62)	130 (53.96)	18 (7.47)	128 (53.13)	160 (66.42)	3 (1.25)	23 (9.55)	538 (223.33)

\*As of May 2006

\*\*Ceftibuten received marketing approval in December 1995

	Reporting rate between 1 - 10 per Million RX's
	Reporting rate between 10 - 20 per Million RX's
	Reporting rate between 20 - 30 per Million RX's
	Reporting rate between 30 - 80 per Million RX's
	Reporting rate > 80 per Million RX's
	Less than 1,000 reports

## 11. Notes and References

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1 The CBAERS database is a reformatted, integrated (de-normalized) version of the AERS database containing wider tables with more complete data in each table, facilitating systematic retrieval and analyses.

2 DuMouchel W, Pregibon D. Empirical bayes screening for multi-item associations. Proceedings of the conference on knowledge discovery and data; 2001 Aug 26-29; San Diego (CA): ACM Press: 67-76.

3 Szarfman A, Machado SG, O'Neill RT. Use of Screening Algorithms and Computer Systems to Efficiently Signal Higher-Than-Expected Combinations of Drugs and Events in the US FDA's Spontaneous Reports Database. Drug Safety 2002; 25:381-392.

4 For example, renal failure is more prevalent in the elderly (even among those not taking medication); thus, increased reporting of an adverse event may occur for a drug for renal failure even though such event may not truly be caused by the drug, but rather, may be related to the underlying diseases common in the elderly. Without stratification, it is difficult to assess whether such events are reported more frequently in a particular group (age, gender, time period, etc.)

5 These are technically Bayesian *credible regions*, but are referred to as confidence intervals in order to simplify the presentation of results.

6 A "configuration" defines a mapping between "variables" used in the data mining analysis and CBAERS specific database tables and columns, including specification of the roles for the variables in a data mining run (e.g., a generic name or a trade name version of the drug name, an event name, an attribute suitable for use in stratification or subsetting, etc.) Different configurations are defined and used to support access to several different versions of the same database (e.g., different chronological snapshots, or versions that include or exclude so-called "concomitant" medications). See more details in the Appendix on 80.

7 To produce the "All Reports" configuration (described in more detail in the Appendix on page 80) we selected to use the best representative cases; suspect drugs only, duplicate removal, and no database restriction.

For Item Variables we selected Generic name as the drug variable, MedDRA PT (preferred term) as the event variable, and Outcome as the generalized Item variable. The PT variable consisted of the Recoded Hepatotoxic Event Codes described in Table 2 and any other PT in CBAERS. The Highest Dimension we

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selected was 2. The stratification variables that we selected in this configuration resulted in 1,287 distinct stratification categories: 3 (Gender) x 11 (Age Group) x 39 (FDA Year). We also selected to generate a Cumulative sub setting by FDA Year (see Appendix on page 80 for more details.)

8 The “Fatal Outcome” configuration for this output table was like the first configuration without Outcome as the generalized Item and with a database restriction of Outcome = Fatal.

9 The “Disabled Outcome” configuration for this output table was like the second configuration but with a database restriction of Outcome = Disabled

10 Topping, JM, Doraiswamy, PM. Pharmacovigilance in the 21st Century: New Systematic Tools for an Old Problem. *Pharmacotherapy*.2004.24:1099-104

11 van der Heijden PG, van Puijenbroek EP, van Buuren S, van der Hofstede JW. On the assessment of adverse drug reactions from spontaneous reporting systems: the influence of under-reporting on odds ratios. *Stat Med*. 2002. 21:2027-44

12 Refer to Section 2.5.3 on page 8 for details

13 Because reporting of adverse events for a drug changes over time, an analysis was made for telithromycin and each comparator drug according to the calendar year the report was received by the FDA.

14 When exploring severe adverse events (such as fatal outcomes), we use the whole range of EBM estimates ( $EBM > 0$ ) and confidence limits to assess the relative reporting ratio of a drug and appropriate surrogate control drugs. Szafrman, A, Topping, JM, Doraiswamy, PM. Pharmacovigilance in the 21st Century: New Systematic Tools for an Old Problem. *Pharmacotherapy*.2004.24:1099-104

15 With 3-dimensional runs of MGPS (not shown in this review) we are seeing drug-drug interactions between macrolides and some HMG-CoA Reductase Inhibitors, azoles, Selective Serotonin Reuptake Inhibitors, and carbamazepine, theophylline, disopyramide, warfarin, digoxin, glyburide, verapamil, phenytoin, colchicine, and other drugs. These drug-drug interactions could lead to toxic drug levels that may induce serious outcomes including delirium, convulsions, bleeding, rhabdomyolysis, or sudden death due to torsades de pointes.

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16 Because reporting of adverse events for a drug changes over time, analyses were made for telithromycin and each comparator drug according to their Max EBMG in any given year.

17 When drilling down at the reports coded as “Gout” with Clarithromycin, we identified that this event code was a surrogate for a serious, frequently fatal drug-drug interaction with colchicine.

18 DuMouchel W. Bayesian data mining in large frequency tables, with an application to the FDA Spontaneous Reporting System (with discussion). *The American Statistician* 1999; 53: 177-202

19 O’Neill RT, Szarfman A. Discussion: Bayesian data mining in large frequency tables, with an application to the FDA spontaneous reporting system. *The American Statistician* 1999; 53: 190-6

20 Press Release by the Medicines and Healthcare products Regulatory Agency: Innovative software to analyse adverse drug reaction data. [http://www.mhra.gov.uk/home/idcplg?IdcService=SS\\_GET\\_PAGE&useSecondary=true&ssDocName=CON2023221&ssTargetNodeId=389](http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&useSecondary=true&ssDocName=CON2023221&ssTargetNodeId=389) accessed July 2006.

21 Stinchcomb, D, Pickle L, Stephens A. Outlier detection as a Spatial data mining tool for National Cancer Surveillance. Presentation of June 8, 2006 at the FDA. The presentation is available within FDA at [http://cdernet/ob\\_apps/ob/edocs/eDocs\\_Main\\_Single.cfm?id=650](http://cdernet/ob_apps/ob/edocs/eDocs_Main_Single.cfm?id=650) accessed July 2006.

22 Rolka H, Bracy D, Russell C, Fram D, Ball R. Using simulation to assess the sensitivity and specificity of a signal detection tool for multidimensional public health surveillance data. *Stat Med.* 2005;24:551-62

23 Outpatient prescription use was measured by audits from Verispan, LLC, Vector One®: National (VONA). Vector One®: National (VONA) is a nationally projected database which measures the retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. The Vector One® database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over 2.0 billion prescription claims, representing over 160 million unique patients. The number of dispensed prescriptions is obtained from a sample of virtually all retail pharmacies throughout the U.S and represents approximately half of the retail prescriptions dispensed nationwide. Verispan receives all prescriptions from approximately

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one-third of the stores and a significant sample of prescriptions from the remaining stores. Mail order prescriptions are not included in the sample at this time.

24 Labels in  
Table 9 aggregate the following PTs:

Label="Cardiac": Electrocardiogram QT corrected interval prolonged, Electrocardiogram QT prolonged, Torsade de pointes.

Label="Drug-drug interaction": Antipsychotic drug level above therapeutic, Drug interaction, Drug interaction inhibition, Drug interaction potentiation, Drug level above therapeutic, Drug level increased.

Label="Hearing": Conductive deafness, Deafness, Deafness bilateral, Deafness congenital, Deafness neurosensory, Deafness permanent, Deafness transitory, Deafness unilateral, Hearing disability, Hearing impaired, Hypoacusis, Ototoxicity, Sudden hearing loss.

Label="Clostridial": Clostridial infection, Clostridium bacteraemia, Clostridium colitis, Clostridium difficile sepsis, Clostridium difficile toxin test positive, Gastroenteritis clostridial.

Label="Hepatic failure": Coma hepatic, Hepatic encephalopathy, Hepatic failure, Hepatic necrosis, Hepatitis fulminant, Liver transplant.

Label="Hepatitis": Autoimmune hepatitis, Cytolytic hepatitis, Hepatitis, Hepatitis acute.

Label="Cholestasis": Cholelithiasis, Cholestasis, Hepatitis cholestatic, Jaundice cholestatic.

Label="Anaphylaxis": Anaphylactic reaction, Anaphylactic shock, Anaphylactoid reaction, Anaphylactoid shock.

Label="Toxic skin": Erythema multiforme, Stevens-Johnson syndrome, Toxic epidermal necrolysis.

Label="Toxic lung": Pulmonary fibrosis, Pulmonary toxicity.

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Ana Szarfman  
9/21/2006 11:49:53 AM  
MEDICAL OFFICER

Norman Stockbridge  
9/21/2006 03:20:29 PM  
MEDICAL OFFICER