

## **APPENDIX H: EPIDEMIOLOGY TABLES**

**Disproportionality analysis of the FDA FOI database for selected over the counter medications**

**Disproportionality analysis of the FDA FOI database for selected antibiotics**

**MedDRA terms used in the evaluation of each AESI**

**Study report: PHARMetrics Integrated Outcome Database**

## **APPENDIX I-1: DISPROPORTIONALITY ANALYSIS OF THE FDA FOI DATABASE FOR SELECTED OVER-THE-COUNTER MEDICATIONS**

Results of the relative disproportionality analysis of spontaneous reports for selected over-the-counter medications (OTC) in the FDA FOI database are presented in this appendix. The selected OTC medications used in the analyses include 1) first-generation antihistamines: diphenhydramine, doxylamine, clemastine, chlorpheniramine, dexchlorpheniramine, brompheniramine, dexbrompheniramine, pheniramine, triprolidine, pyrilamine, chlorcyclizine, phenindamine, and thonzylamine; 2) motion sickness drugs: dramamine, cyclizine, and meclizine; 3) and acetaminophen. Two types of background comparators were used in the analyses: the full FDA FOI background and the full FDA FOI cases with fatal outcomes only. Details of the disproportionality results on the HLT and PT levels against the full FDA FOI background are shown in Appendix I-1 [Table 1](#) and Appendix I-1 [Table 2](#), for HLT and PT respectively. Details of the disproportionality results for reports with fatal outcomes against the full FDA FOI cases with fatal outcomes are shown in Appendix I-1 [Table 3](#) and Appendix I-1 [Table 4](#), for HLT and PT respectively. Only those HLT or PT terms that were detected as signals (i.e. EBGM05  $\geq 2$ ) are presented in the tables. The primary findings are addressed below.

Disproportionalities were found in following selected OTC drugs: the first generation of antihistamines, acetaminophen, and medications for motion sickness (Appendix I-1 [Table 1](#) and Appendix I-1 [Table 3](#)). Not surprisingly, hepatic AEs were found to be disproportionate, fatal and non-fatal outcomes combined (Appendix I-1 [Table 1](#)) and fatal outcomes only (Appendix I-1 [Table 3](#)) for acetaminophen. “Myocardial disorders”, “Ocular disorders NEC”, and “Pupil disorders” were disproportionate for antihistamines (Appendix I-1 [Table 1](#)). On a PT level, “myocardial fibrosis”, “ventricular hypertrophy”, and “dilatation atrial” were disproportionate within the HLT “Myocardial disorders”; “Eye pain” was disproportionate within the HLT “Ocular disorders NEC”, and “Mydriasis” was disproportionate within the HLT “Pupil disorders” (Appendix I-1 [Table 1](#)). The HLT “Aneurysms and dissections non-site specific” and “Central nervous system aneurysms” were disproportionate for antihistamines (Appendix I-1 [Table 1](#)). On the PT level, “Aneurysm” and “Aneurysm ruptured” were disproportionate within the HLT “Aneurysms and dissections non-site specific”, and “Intracranial aneurysm” and “Carotid artery aneurysm” within the HLT “Central nervous system aneurysms” (Appendix I-1 [Table 2](#)). “Bullous conditions” with a fatal outcome was disproportionate for motion sickness medications (Appendix I-1 [Table 3](#)). On a PT level, however, no disproportionality was found within the HLT “bullous conditions” for motion sickness medications (Appendix I-1 [Table 4](#)).

**TABLE 1 - Disproportionality of HLTs detected in various OTC medications using the full FDA FOI database as a background: FDA FOI database through March 31, 2006**

HLT	Antihistamines		Motion sickness drugs		Acetaminophen	
	N	EBGM05	N	EBGM05	N	EBGM05
abdominal injuries nec	-	-	-	-	26	2.60
abnormal behaviour nec	-	-	16	2.01	-	-
adrenal disorders congenital	-	-	-	-	7	9.04
aneurysms and dissections non-site specific	108	13.42	-	-	-	-
anxiety symptoms	1565	2.25	-	-	-	-
blood and blood product treatment	-	-	-	-	156	2.08
Blood gas and acid base analyses	-	-	-	-	437	4.03
cardiac disorders congenital nec	38	3.65	-	-	-	-
cardiac hypertensive complications	-	-	-	-	15	2.96
central nervous system aneurysms	86	11.27	-	-	-	-
central nervous system haemorrhages and cerebrovascular accidents	3978	9.07	-	-	-	-
central nervous system vascular disorders nec	234	7.29	-	-	-	-
cholestasis and jaundice	-	-	-	-	320	2.05
coagulation and bleeding analyses	-	-	-	-	823	4.41
coagulopathies	-	-	-	-	217	2.90
coma states	-	-	-	-	590	3.74
congenital disorders nec	1064	7.84	-	-	-	-
crime victims	17	2.97	-	-	-	-
disturbances in consciousness nec	1855	2.05	165	3.23	-	-
dyspeptic signs and symptoms	-	-	-	-	228	2.08
emotional and mood disturbances nec	569	2.88	-	-	-	-
encephalopathies nec	-	-	-	-	182	3.52
encephalopathies toxic and metabolic	-	-	-	-	85	4.77
facial cranial nerve disorders	82	2.51	-	-	-	-
fear symptoms	235	7.17	-	-	-	-
hepatic enzymes and function abnormalities	-	-	-	-	364	3.41
hepatic failure and associated disorders	-	-	-	-	860	12.23

HLT	Antihistamines		Motion sickness drugs		Acetaminophen	
	N	EBGM05	N	EBGM05	N	EBGM05
hepatic fibrosis and cirrhosis	-	-	-	-	88	2.95
hepatic therapeutic procedures	-	-	-	-	42	5.56
hepatobiliary signs and symptoms	-	-	-	-	125	2.28
hepatocellular damage and hepatitis nec	-	-	-	-	992	4.53
hydrocephalic conditions	53	4.88	-	-	-	-
increased intracranial pressure disorders	-	-	-	-	149	3.15
inner ear disorders nec	-	-	4	2.32	-	-
inner ear signs and symptoms	-	-	29	2.41	-	-
ischaemic coronary artery disorders	885	2.47	-	-	-	-
liver function analyses	-	-	-	-	1808	3.33
medication errors nec	-	-	51	3.14	471	2.16
memory loss (excl dementia)	388	2.18	-	-	-	-
mental disorders nec	176	2.52	-	-	-	-
mental impairment (excl dementia and memory loss)	229	2.13	-	-	-	-
metabolic acidoses (excl diabetic acidoses)	-	-	-	-	188	2.54
mineral and electrolyte analyses	-	-	-	-	297	2.21
mixed acid-base disorders	-	-	-	-	149	6.57
mood alterations with depressive symptoms	346	6.71	-	-	-	-
musculoskeletal and connective tissue disorders of limbs congenital	123	5.02	-	-	-	-
musculoskeletal disorders congenital nec	49	5.87	-	-	-	-
myocardial disorders nec	202	2.06	-	-	-	-
neonatal hepatobiliary disorders	-	-	3	3.70	-	-
nervous system disorders nec	757	6.64	-	-	-	-
neurological signs and symptoms nec	-	-	123	3.03	-	-
non-site specific injuries nec	2050	4.67	-	-	-	-
non-site specific necrosis and vascular insufficiency nec	152	2.52	-	-	-	-
ocular disorders nec	541	3.25	-	-	-	-
overdoses	1562	2.44	141	5.12	3260	5.74
paralysis and paresis (excl cranial	341	2.66	-	-	-	-

EBGM05 < 2;	2 ≤ EBGM05 < 5;	5 ≤ EBGM05 < 10;	EBGM05 ≥ 10.
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**Table 2 - Disproportionality of PTs detected in various OTC medications using the full FDA FOI database as a background: FDA FOI database through March 31, 2006**

Drug	PT	N	EBGM	EBGM05	EBGM95
Antihistamines	accelerated hypertension	6	8.52	4.00	18.14
Antihistamines	accidental overdose	290	2.41	2.14	2.70
Antihistamines	analgesic drug level increased	8	5.02	2.58	9.77
Antihistamines	aneurysm	90	16.62	13.48	20.50
Antihistamines	aneurysm ruptured	16	21.28	13.10	34.56
Antihistamines	anhedonia	337	15.09	13.54	16.83
Antihistamines	anticholinergic syndrome	25	5.07	3.43	7.51
Antihistamines	anxiety	961	3.09	2.90	3.30
Antihistamines	application site pain	25	3.84	2.60	5.69
Antihistamines	arcus lipoides	2	6.96	2.19	22.08
Antihistamines	arrhythmia supraventricular	496	21.39	19.55	23.39
Antihistamines	arterial stenosis	8	3.97	2.04	7.72
Antihistamines	arteriogram carotid abnormal	3	14.60	5.37	39.69
Antihistamines	arteriovenous malformation	18	11.01	6.96	17.42
Antihistamines	blood pressure increased	684	5.50	5.10	5.94
Antihistamines	brain compression	5	7.80	3.45	17.65
Antihistamines	brain death	24	3.16	2.12	4.72
Antihistamines	brain herniation	22	3.72	2.45	5.65
Antihistamines	brain oedema	85	2.72	2.19	3.37
Antihistamines	brain stem haemorrhage	7	12.11	5.97	24.56
Antihistamines	brain stem infarction	13	4.67	2.74	7.97
Antihistamines	carbon monoxide poisoning	8	5.04	2.59	9.83
Antihistamines	carotid artery aneurysm	8	10.85	5.57	21.13
Antihistamines	carotid artery atheroma	5	7.68	3.39	17.37
Antihistamines	carotid artery stenosis	49	8.30	6.26	11.02
Antihistamines	cerebellar infarction	26	11.71	7.97	17.21
Antihistamines	cerebral arteriovenous malformation haemorrhagic	6	22.27	10.46	47.43
Antihistamines	cerebral artery occlusion	38	11.92	8.65	16.41
Antihistamines	cerebral atrophy	25	3.34	2.26	4.94
Antihistamines	cerebral haematoma	16	15.11	9.30	24.54
Antihistamines	cerebral haemorrhage	139	3.92	3.31	4.64
Antihistamines	cerebral infarction	146	4.88	4.14	5.76
Antihistamines	cerebrovascular accident	2648	11.31	10.88	11.76

Drug	PT	N	EBGM	EBGM05	EBGM95
Antihistamines	cerebrovascular arteriovenous malformation	3	10.94	4.02	29.73
Antihistamines	cerebrovascular disorder	116	9.50	7.90	11.43
Antihistamines	cerebrovascular spasm	7	7.99	3.94	16.21
Antihistamines	cleft palate	17	3.26	2.04	5.23
Antihistamines	cognitive disorder	50	2.84	2.15	3.76
Antihistamines	congenital anomaly	1008	8.77	8.23	9.34
Antihistamines	congenital musculoskeletal anomaly	49	8.60	6.48	11.41
Antihistamines	dilatation atrial	23	3.97	2.64	5.97
Antihistamines	drug effect decreased	359	4.02	3.62	4.46
Antihistamines	drug screen positive	55	2.79	2.14	3.65
Antihistamines	dysarthria	138	2.98	2.52	3.54
Antihistamines	electrocardiogram t wave abnormal	25	6.14	4.15	9.09
Antihistamines	embolic stroke	10	5.54	3.03	10.12
Antihistamines	emotional distress	380	9.89	8.93	10.96
Antihistamines	encephalomalacia	20	18.04	11.66	27.91
Antihistamines	eye pain	456	5.75	5.23	6.31
Antihistamines	eye rolling	29	4.46	3.10	6.43
Antihistamines	facial palsy	64	2.76	2.15	3.53
Antihistamines	facial paresis	15	5.90	3.58	9.73
Antihistamines	fear	120	5.95	4.96	7.14
Antihistamines	fear of disease	115	14.09	11.70	16.96
Antihistamines	febrile convulsion	15	5.18	3.14	8.54
Antihistamines	fibrosis tendinous	7	6.28	3.10	12.73
Antihistamines	haematuria traumatic	2	7.25	2.28	22.99
Antihistamines	haemorrhagic cerebral infarction	8	8.31	4.27	16.19
Antihistamines	haemorrhagic stroke	446	17.08	15.53	18.77
Antihistamines	hallucination	295	2.38	2.12	2.67
Antihistamines	hangover	55	14.47	11.08	18.90
Antihistamines	heart disease congenital	38	5.05	3.66	6.95
Antihistamines	hemianopia homonymous	11	5.62	3.16	10.01
Antihistamines	hemiparesis	150	6.69	5.68	7.87
Antihistamines	hemiplegia	93	3.73	3.03	4.58
Antihistamines	hydrocephalus	53	6.49	4.95	8.52
Antihistamines	hyperkinesia	89	3.20	2.59	3.95
Antihistamines	hypertension	730	2.68	2.49	2.89

Drug	PT	N	EBGM	EBGM05	EBGM95
Antihistamines	injury	1701	9.38	8.94	9.85
Antihistamines	intentional drug misuse	140	4.41	3.73	5.22
Antihistamines	intentional overdose	463	2.76	2.52	3.03
Antihistamines	intracranial aneurysm	76	14.44	11.49	18.13
Antihistamines	intraventricular haemorrhage	38	12.85	9.33	17.71
Antihistamines	ischaemic stroke	65	9.93	7.77	12.70
Antihistamines	lacunar infarction	33	11.00	7.81	15.50
Antihistamines	limb reduction defect	91	18.35	14.90	22.61
Antihistamines	malformation venous	3	11.49	4.23	31.24
Antihistamines	memory impairment	204	3.41	2.97	3.92
Antihistamines	mental disorder	119	3.90	3.25	4.69
Antihistamines	mental impairment	125	4.65	3.89	5.55
Antihistamines	multiple congenital abnormalities	55	4.83	3.70	6.32
Antihistamines	multiple drug overdose	184	3.06	2.64	3.55
Antihistamines	multiple drug overdose accidental	13	7.31	4.28	12.47
Antihistamines	mydriasis	803	18.89	17.60	20.27
Antihistamines	myocardial fibrosis	14	4.38	2.62	7.35
Antihistamines	myocardial infarction	813	3.46	3.23	3.71
Antihistamines	nervous system disorder	741	9.21	8.56	9.91
Antihistamines	nervousness	353	2.28	2.05	2.54
Antihistamines	overdose	579	2.37	2.18	2.58
Antihistamines	pain	1264	2.23	2.11	2.36
Antihistamines	polytraumatism	75	5.91	4.70	7.44
Antihistamines	protein c deficiency	4	9.98	4.08	24.42
Antihistamines	reaction to colouring	5	12.45	5.50	28.16
Antihistamines	red blood cells csf positive	7	6.18	3.05	12.53
Antihistamines	ruptured cerebral aneurysm	35	20.03	14.35	27.95
Antihistamines	somnolence	988	3.42	3.21	3.64
Antihistamines	subarachnoid haemorrhage	175	12.06	10.37	14.03
Antihistamines	syndactyly	14	6.55	3.91	10.97
Antihistamines	thrombotic stroke	9	6.21	3.30	11.69
Antihistamines	toxicologic test abnormal	76	3.65	2.91	4.59
Antihistamines	transient ischaemic attack	136	4.35	3.67	5.16
Antihistamines	vasospasm	59	9.15	7.07	11.85
Antihistamines	ventricular hypertrophy	59	3.29	2.54	4.26



Drug	PT	N	EBGM	EBGM05	EBGM95
Antihistamines	victim of homicide	9	7.09	3.77	13.35
Antihistamines	walking aid user	8	6.92	3.55	13.48
Motion sickness drugs	actinic keratosis	2	10.87	3.43	34.50
Motion sickness drugs	arterial stenosis	2	7.71	2.43	24.46
Motion sickness drugs	delusion	8	4.14	2.13	8.06
Motion sickness drugs	dizziness	120	3.82	3.18	4.58
Motion sickness drugs	euphoric mood	11	11.02	6.19	19.63
Motion sickness drugs	feeling abnormal	25	3.69	2.49	5.46
Motion sickness drugs	hallucination	87	11.49	9.28	14.22
Motion sickness drugs	hallucination, visual	12	14.74	8.46	25.67
Motion sickness drugs	incoherent	4	5.33	2.18	13.03
Motion sickness drugs	inner ear disorder	2	10.67	3.36	33.86
Motion sickness drugs	intentional drug misuse	27	12.98	8.89	18.94
Motion sickness drugs	intentional overdose	59	8.69	6.72	11.25
Motion sickness drugs	jaundice neonatal	3	9.54	3.51	25.95
Motion sickness drugs	meniere's disease	2	7.37	2.32	23.39
Motion sickness drugs	overdose	69	6.34	4.99	8.05
Motion sickness drugs	radial nerve palsy	2	10.61	3.34	33.66
Motion sickness drugs	reaction to drug excipients	2	7.73	2.44	24.54
Motion sickness drugs	sedation	23	5.58	3.71	8.39
Motion sickness drugs	somnolence	91	6.05	4.91	7.45
Motion sickness drugs	vertigo	20	5.02	3.25	7.77
Acetaminophen	accidental overdose	567	6.47	5.95	7.03
Acetaminophen	acidosis	149	7.76	6.59	9.14
Acetaminophen	activated partial thromboplastin time prolonged	86	4.90	3.96	6.07
Acetaminophen	acute fatty liver of pregnancy	2	6.71	2.11	21.28
Acetaminophen	acute respiratory distress syndrome	69	2.54	2.00	3.22
Acetaminophen	adrenogenital syndrome	7	48.94	24.13	99.26
Acetaminophen	alanine aminotransferase increased	498	3.97	3.63	4.35
Acetaminophen	alcohol interaction	20	7.75	5.01	11.99
Acetaminophen	alcohol poisoning	21	3.91	2.55	5.99
Acetaminophen	ammonia increased	98	13.81	11.29	16.88
Acetaminophen	analgesic drug level above therapeutic	38	39.89	28.96	54.95

Drug	PT	N	EBGM	EBGM05	EBGM95
Acetaminophen	analgesic drug level decreased	3	27.80	10.23	75.57
Acetaminophen	analgesic drug level increased	89	67.31	54.52	83.11
Acetaminophen	anion gap	4	15.75	6.44	38.51
Acetaminophen	anion gap increased	41	16.27	11.95	22.15
Acetaminophen	aortic dissection	14	10.56	6.30	17.70
Acetaminophen	arteriosclerosis	41	2.81	2.06	3.82
Acetaminophen	arteriosclerosis coronary artery	44	4.84	3.59	6.52
Acetaminophen	aspartate aminotransferase increased	561	4.25	3.90	4.62
Acetaminophen	asterixis	7	5.62	2.77	11.41
Acetaminophen	blood alcohol increased	16	3.36	2.07	5.45
Acetaminophen	blood bicarbonate decreased	101	12.45	10.21	15.17
Acetaminophen	blood bilirubin increased	191	3.50	3.03	4.04
Acetaminophen	blood creatine increased	31	3.72	2.61	5.30
Acetaminophen	blood ethanol	3	5.51	2.03	14.98
Acetaminophen	blood ethanol increased	13	10.22	5.99	17.45
Acetaminophen	blood glucose decreased	76	2.95	2.35	3.71
Acetaminophen	blood methaemoglobin present	5	4.63	2.05	10.48
Acetaminophen	blood osmolarity increased	6	4.46	2.09	9.50
Acetaminophen	blood ph decreased	159	15.24	13.01	17.85
Acetaminophen	blood ph increased	17	5.25	3.28	8.41
Acetaminophen	blood pressure systolic decreased	29	3.60	2.50	5.18
Acetaminophen	body temperature decreased	36	3.82	2.75	5.30
Acetaminophen	brain death	33	6.71	4.76	9.45
Acetaminophen	brain herniation	29	6.95	4.82	10.01
Acetaminophen	brain oedema	118	5.03	4.19	6.04
Acetaminophen	bronchopneumonia	33	2.87	2.03	4.04
Acetaminophen	carbon dioxide decreased	28	4.81	3.32	6.97
Acetaminophen	cirrhosis alcoholic	5	5.93	2.62	13.42
Acetaminophen	coagulopathy	161	6.06	5.18	7.09
Acetaminophen	colitis microscopic	2	7.28	2.30	23.11
Acetaminophen	coma	545	4.06	3.73	4.42
Acetaminophen	coma acidotic	3	14.12	5.19	38.38
Acetaminophen	coma hepatic	42	16.44	12.12	22.30
Acetaminophen	completed suicide	790	4.09	3.81	4.39
Acetaminophen	cytolytic hepatitis	39	4.06	2.96	5.57

Drug	PT	N	EBGM	EBGM05	EBGM95
Acetaminophen	drug ineffective	1357	2.26	2.14	2.39
Acetaminophen	drug level above therapeutic	237	6.82	5.99	7.77
Acetaminophen	drug screen positive	97	6.16	5.03	7.54
Acetaminophen	drug toxicity	353	4.50	4.04	5.00
Acetaminophen	dyspepsia	215	2.53	2.21	2.90
Acetaminophen	electrocardiogram qrs complex prolonged	30	4.70	3.29	6.74
Acetaminophen	encephalopathy	171	4.96	4.26	5.78
Acetaminophen	fibrosis tendinous	6	13.51	6.34	28.77
Acetaminophen	haemodialysis	93	2.86	2.32	3.51
Acetaminophen	haemophilus sepsis	2	7.50	2.36	23.78
Acetaminophen	hepatic cirrhosis	68	4.07	3.20	5.18
Acetaminophen	hepatic encephalopathy	82	7.67	6.16	9.56
Acetaminophen	hepatic failure	795	13.34	12.43	14.32
Acetaminophen	hepatic function abnormal	364	3.78	3.41	4.20
Acetaminophen	hepatic haematoma	5	6.00	2.65	13.56
Acetaminophen	hepatic necrosis	256	13.92	12.29	15.77
Acetaminophen	hepatic steatosis	90	3.06	2.48	3.77
Acetaminophen	hepatitis	212	2.98	2.60	3.42
Acetaminophen	hepatitis alcoholic	6	9.91	4.65	21.10
Acetaminophen	hepatocellular damage	208	5.12	4.46	5.88
Acetaminophen	hepatorenal failure	23	14.06	9.35	21.15
Acetaminophen	hepatorenal syndrome	42	9.17	6.76	12.45
Acetaminophen	hepatotoxicity	115	8.54	7.09	10.28
Acetaminophen	hiv antibody positive	2	6.44	2.03	20.43
Acetaminophen	hyperbilirubinaemia	85	3.10	2.50	3.85
Acetaminophen	hypertensive heart disease	14	4.34	2.59	7.27
Acetaminophen	incorrect drug dosage form administered	12	22.51	12.93	39.20
Acetaminophen	intentional drug misuse	256	6.27	5.54	7.11
Acetaminophen	intentional overdose	989	6.41	6.02	6.83
Acetaminophen	international normalised ratio decreased	28	3.02	2.08	4.38
Acetaminophen	international normalised ratio increased	318	7.10	6.35	7.94
Acetaminophen	liver function test abnormal	244	2.49	2.19	2.83
Acetaminophen	liver tenderness	10	4.33	2.37	7.92
Acetaminophen	liver transplant	41	7.59	5.57	10.33
Acetaminophen	mental status changes	89	4.41	3.57	5.44

Drug	PT	N	EBGM	EBGM05	EBGM95
Acetaminophen	metabolic acidosis	147	5.31	4.51	6.26
Acetaminophen	multi-organ failure	108	2.79	2.30	3.38
Acetaminophen	multiple drug overdose	400	5.14	4.65	5.68
Acetaminophen	multiple drug overdose accidental	24	10.76	7.21	16.05
Acetaminophen	myocardial fibrosis	17	9.34	5.83	14.97
Acetaminophen	opiates positive	4	6.69	2.73	16.35
Acetaminophen	overdose	1217	6.28	5.93	6.65
Acetaminophen	pco2 decreased	36	10.21	7.35	14.18
Acetaminophen	peritoneal effusion	5	14.58	6.45	32.99
Acetaminophen	po2 increased	37	12.91	9.33	17.85
Acetaminophen	posturing	13	5.79	3.40	9.89
Acetaminophen	prothrombin level decreased	67	2.92	2.29	3.72
Acetaminophen	prothrombin level increased	50	9.69	7.32	12.82
Acetaminophen	prothrombin time prolonged	211	7.49	6.53	8.59
Acetaminophen	prothrombin time ratio abnormal	3	6.71	2.47	18.23
Acetaminophen	pulmonary congestion	64	3.30	2.57	4.23
Acetaminophen	pupil fixed	60	7.66	5.93	9.90
Acetaminophen	pyelonephritis chronic	4	5.81	2.37	14.20
Acetaminophen	renal failure	326	3.03	2.71	3.39
Acetaminophen	renal papillary necrosis	14	20.84	12.43	34.92
Acetaminophen	renal tubular necrosis	42	2.76	2.04	3.75
Acetaminophen	respiratory rate increased	66	3.37	2.64	4.31
Acetaminophen	reye's syndrome	18	11.60	7.33	18.36
Acetaminophen	suicide attempt	291	3.48	3.09	3.91
Acetaminophen	toxicologic test abnormal	143	10.03	8.49	11.85
Acetaminophen	transaminases increased	62	3.01	2.34	3.87
Acetaminophen	urine output decreased	23	3.59	2.39	5.40
Acetaminophen	vater syndrome	3	58.97	21.69	160.30

  :  $2 \leq \text{EBGM05} < 5$ ; 
   :  $5 \leq \text{EBGM05} < 10$ ; 
   :  $\text{EBGM05} \geq 10$ .

**Table 3 - Disproportionality of HLTS for FATAL OUTCOMES detected in otc medications using full FDA FOI cases with fatal outcomes as a background: FDA FOI database through March 31, 2006**

HLT	Antihistamines		Motion sickness drugs		Acetaminophen	
	N	EBGM05	N	EBGM05	N	EBGM05
aneurysms and dissections non-site specific	9	2.15	-	-	-	-
anxiety symptoms	87	2.10	-	-	-	-
blood gas and acid base analyses	-	-	-	-	557	3.71
bullous conditions	-	-	4	2.92	-	-
central nervous system haemorrhages and cerebrovascular accidents	224	2.34	-	-	-	-
coagulation and bleeding analyses	-	-	-	-	992	3.60
congenital disorders nec	103	5.88	-	-	-	-
decreased physical activity levels	13	2.88	-	-	-	-
digestive enzymes	-	-	-	-	583	3.48
hepatic enzymes and function abnormalities	-	-	-	-	372	2.84
hepatic failure and associated disorders	-	-	-	-	122	2.63
hepatocellular damage and hepatitis nec	-	-	-	-	97	2.46
liver function analyses	-	-	-	-	42	2.39
mental disorders nec	-	-	-	-	373	2.39
mineral and electrolyte analyses	-	-	-	-	404	2.32
mixed acid-base disorders	-	-	-	-	232	2.08
mood alterations with depressive symptoms	17	2.47	-	-	-	-
renal function analyses	-	-	-	-	258	2.06
therapeutic drug monitoring analyses	-	-	-	-	80	2.01
toxicology laboratory analyses	-	-	5	3.03	-	-
tympanic membrane disorders (excl infections)	3	2.63	-	-	-	-

 : 2 ≤ EBGM05 < 5; 
  : 5 ≤ EBGM05 < 10; 
  : EBGM05 ≥ 10.

**Table 4 - Disproportionality of PTs for fatal outcomes detected in OTC medications using full FDA FOI cases with fatal outcomes as a background: FDA FOI database through March 31, 2006**

Drug	PT	N	EBGM	EBGM05	EBGM95
Antihistamines	accidental overdose	174	2.60	2.24	3.03
Antihistamines	aneurysm	8	4.43	2.27	8.63
Antihistamines	anhedonia	16	10.75	6.62	17.46
Antihistamines	anxiety	68	4.38	3.44	5.57
Antihistamines	arrhythmia supraventricular	14	14.15	8.44	23.71
Antihistamines	blood pressure increased	27	3.19	2.19	4.66
Antihistamines	cerebrovascular accident	106	4.54	3.74	5.51
Antihistamines	congenital anomaly	88	7.09	5.74	8.76
Antihistamines	decreased activity	12	6.39	3.67	11.13
Antihistamines	haemorrhagic stroke	33	3.88	2.76	5.47
Antihistamines	injury	90	4.77	3.87	5.89
Antihistamines	lacunar infarction	3	6.66	2.45	18.09
Antihistamines	multiple congenital abnormalities	15	8.28	5.02	13.65
Antihistamines	myocardial fibrosis	14	5.54	3.31	9.29
Antihistamines	pain	81	3.56	2.85	4.44
Antihistamines	pseudarthrosis	2	12.19	3.84	38.68
Antihistamines	toxicologic test abnormal	57	2.62	2.01	3.41
Antihistamines	vasospasm	6	8.41	3.95	17.91
Motion sickness drugs	drug screen positive	3	7.84	2.89	21.32
Acetaminophen	acidosis	122	3.16	2.64	3.79
Acetaminophen	activated partial thromboplastin time prolonged	75	3.21	2.55	4.03
Acetaminophen	alanine aminotransferase increased	280	4.78	4.24	5.39
Acetaminophen	ammonia increased	82	5.13	4.12	6.39
Acetaminophen	analgesic drug level above therapeutic	30	6.79	4.74	9.72
Acetaminophen	analgesic drug level increased	71	8.87	7.01	11.23
Acetaminophen	anion gap decreased	2	6.81	2.15	21.61
Acetaminophen	anion gap increased	38	4.76	3.45	6.55
Acetaminophen	aortic dissection	14	4.51	2.69	7.56
Acetaminophen	aspartate aminotransferase increased	312	4.65	4.15	5.20
Acetaminophen	blood bicarbonate decreased	94	5.03	4.10	6.18

Drug	PT	N	EBGM	EBGM05	EBGM95
Acetaminophen	blood bilirubin increased	134	2.98	2.51	3.54
Acetaminophen	blood creatine increased	29	3.87	2.69	5.58
Acetaminophen	blood creatinine increased	155	2.52	2.14	2.95
Acetaminophen	blood glucose decreased	64	4.10	3.20	5.26
Acetaminophen	blood ph decreased	143	4.89	4.14	5.78
Acetaminophen	blood ph increased	14	3.77	2.25	6.32
Acetaminophen	blood pressure systolic decreased	27	3.15	2.16	4.59
Acetaminophen	coagulopathy	126	3.06	2.56	3.66
Acetaminophen	coma hepatic	17	3.40	2.12	5.45
Acetaminophen	drug level above therapeutic	203	3.20	2.78	3.68
Acetaminophen	hepatic encephalopathy	54	2.79	2.13	3.65
Acetaminophen	hepatic failure	535	3.88	3.56	4.23
Acetaminophen	hepatic function abnormal	97	3.02	2.47	3.70
Acetaminophen	hepatic necrosis	179	4.45	3.84	5.17
Acetaminophen	hepatorenal failure	19	3.89	2.49	6.09
Acetaminophen	hepatotoxicity	46	3.68	2.75	4.93
Acetaminophen	intentional drug misuse	186	2.75	2.38	3.18
Acetaminophen	international normalised ratio increased	250	5.44	4.79	6.17
Acetaminophen	lipase increased	19	3.20	2.04	5.00
Acetaminophen	liver function test abnormal	107	2.60	2.15	3.16
Acetaminophen	mental status changes	75	2.89	2.30	3.64
Acetaminophen	metabolic acidosis	118	2.74	2.28	3.29
Acetaminophen	pco2 decreased	33	4.07	2.89	5.73
Acetaminophen	po2 increased	35	4.40	3.15	6.14
Acetaminophen	prothrombin time prolonged	169	4.48	3.84	5.22
Acetaminophen	transaminases increased	33	3.70	2.63	5.22
Acetaminophen	vater syndrome	2	22.37	7.05	70.99

2 ≤ EBGM05 < 5;
5 ≤ EBGM05 < 10;
EBGM05 ≥ 10.

**APPENDIX I-2: DISPROPORTIONALITY ANALYSIS OF THE FDA FOI DATABASE FOR SELECTED ANTIBIOTICS**

Results of the relative disproportionality analysis of spontaneous reports for various antibiotics in the FDA FOI database are presented in this appendix. Two types of background comparators were used in the analyses: the full FDA FOI background and the full FDA FOI cases with fatal outcomes only. Details of the disproportionality results on the HLT and PT levels against the full FDA FOI background are shown in Appendix I-2 [Table 1](#) and Appendix I-2 [Table 2](#), for HLT and PT respectively. Details of the disproportionality results for reports with fatal outcomes against the full FDA FOI cases with fatal outcomes are shown in Appendix I-2 [Table 3](#) and Appendix I-2 [Table 4](#), for HLT and PT respectively.

The numbers presented in the cells of Appendix I-2 [Table 1](#) and Appendix I-2 [Table 3](#) are the numbers of adverse event reports found in the FDA FOI database for the specific antibiotic. Only those HLT or PT terms that were detected as signals (i.e.  $EBGM05 \geq 2$ ) are presented in the tables.



**Table 1 - Disproportionality of HLTs detected in various antibiotics using the full FDA FOI database as a background: FDA FOI database through March 31, 2006**

HLT	Number of cases detected							
	Tel	Aug	Cef	Cla	Ery	Azi	Mox	Lev
allergic conditions nec	-	314	179	-	-	294	181	-
allergies to foods, food additives, drugs and other chemicals	-	69	-	-	-	70	-	-
amblyopic vision impairment	-	-	-	-	-	-	9	-
anaemias haemolytic nec	-	-	-	-	-	-	-	33
anal and rectal signs and symptoms	-	-	8	-	13	-	-	-
anaphylactic responses	-	181	156	-	-	-	242	228
angioedemas	-	101	-	-	-	-	-	-
anxiety symptoms	-	-	-	-	-	-	244	-
arthropathies nec	-	-	-	-	-	-	-	89
atypical mycobacterial infections	-	-	-	19	-	-	-	-
auditory nerve disorders	-	-	-	-	2	-	-	-
bacterial infections nec	-	-	-	-	-	-	-	-
borreliac infections	-	-	-	-	-	7	-	-
bullous conditions	-	324	-	-	-	-	-	182
candida infections	-	79	-	203	-	81	-	-
cardiac signs and symptoms nec	-	-	-	-	-	-	107	-
cholestasis and jaundice	47	806	-	285	636	-	-	-
clostridia infections	-	274	938	-	-	-	32	130
coagulation and bleeding analyses	-	-	-	-	-	-	-	264
colitis (excl infective)	-	96	54	-	-	-	-	-
conjunctival infections, irritations and inflammations	-	-	-	-	129	-	-	-
coughing and associated symptoms	-	-	-	-	-	300	-	-
dental surface disorders	-	156	-	60	-	37	-	-
dermatitis and eczema	-	-	-	-	-	487	-	-
dermatitis ascribed to specific agent	-	98	-	-	-	-	-	-
diaphragmatic disorders congenital	-	-	-	-	2	-	-	-
diarrhoea (excl infective)	-	993	574	664	361	753	-	-
disability issues	-	-	-	-	-	-	-	65
dissociative states	-	-	-	74	-	-	22	-

HLT	Number of cases detected							
	Tel	Aug	Cef	Cla	Ery	Azi	Mox	Lev
dyspeptic signs and symptoms	-	-	-	437	230	-	-	-
ear disorders nec	-	-	-	-	-	162	-	-
ear infections	-	-	-	35	-	59	-	-
ecg investigations	-	-	-	156	106	-	80	-
eosinophilic disorders	-	81.00	-	-	-	-	-	-
erythemas	-	288	45	-	-	-	-	-
exfoliative conditions	-	134	-	-	-	-	-	-
faecal abnormalities nec	-	89	23	-	-	-	-	-
gait disturbances	-	-	-	-	-	-	-	239
gastric and pyloric stenosis and obstruction	-	-	-	-	16	-	-	-
gastric disorders congenital	-	-	-	-	35	-	-	-
gastritis (excl infective)	-	-	-	-	62	-	-	-
gastrointestinal and abdominal pains (excl oral and throat)	-	-	257	-	791	656	-	-
gastrointestinal disorders nec	-	-	40	-	141	-	-	-
genetic mitochondrial abnormalities nec	-	-	-	-	2	-	-	-
hearing losses	-	-	-	103	148	226	-	-
helicobacter infections	-	-	-	17	-	-	-	-
hepatic and hepatobiliary disorders nec	-	-	-	-	-	-	-	-
hepatic enzymes and function abnormalities	-	-	-	-	452	-	-	-
hepatic failure and associated disorders	27	-	-	-	-	-	-	-
hepatobiliary signs and symptoms	-	-	-	-	41	-	-	-
hepatocellular damage and hepatitis nec	91	430	-	-	277	-	-	-
hypoglycaemic conditions nec	-	-	-	-	-	-	-	-
immunology skin tests nec	-	13	-	-	-	-	-	-
infections nec	-	-	-	-	-	191	-	-
inner ear signs and symptoms	-	-	-	-	-	156	-	-
interactions	-	-	-	835	349	416	-	-
joint related disorders nec	-	-	-	-	-	-	-	23
joint related signs and symptoms	-	-	-	-	-	-	-	668
lid, lash and lacrimal infections, irritations and inflammations	-	35	-	-	-	-	-	-
ligament disorders	-	-	-	-	-	-	-	13

HLT	Number of cases detected							
	Tel	Aug	Cef	Cla	Ery	Azi	Mox	Lev
liver function analyses	192	791	-	-	-	-	-	-
lower respiratory tract and lung infections	-	-	-	-	-	297	-	-
mood alterations with manic symptoms	-	-	-	73	-	-	-	-
muscle pains	-	-	-	-	-	-	-	299
muscle, tendon and ligament injuries	-	-	-	-	-	-	33	298
mycoplasma infections	-	-	-	-	-	11	-	-
myopathies	-	-	-	129	-	-	-	-
nausea and vomiting symptoms	-	-	-	-	1081	-	-	-
nephritis nec	-	45	-	-	-	-	-	55
neurological signs and symptoms nec	156	-	-	-	-	-	323	-
neuromuscular junction dysfunction	20	-	-	-	-	-	-	-
ocular disorders congenital nec	11	-	-	-	-	-	-	-
olfactory nerve disorders	18	-	21	213	-	128	24	31
oral soft tissue signs and symptoms	-	-	-	-	-	-	25	-
paraesthesias and dysaesthesias	-	-	-	-	-	-	176	404
partial vision loss	23	-	-	-	-	-	-	-
perception disturbances	-	-	-	-	-	-	-	-
pharyngeal disorders (excl infections and neoplasms)	-	-	-	-	-	46	34	45
poisoning and toxicity	-	-	-	157	-	-	-	-
pruritus nec	-	565	-	-	-	-	165	-
psychotic disorder nec	-	-	-	-	-	-	-	65
pupil disorders	23	-	-	-	-	-	-	-
purpura and related conditions	-	186	-	-	-	-	-	-
pustular conditions	-	31	-	-	-	-	-	-
rashes, eruptions and exanthems nec	-	980	-	-	-	-	174	-
refractive and accommodative disorders	16	-	-	-	-	-	-	-
respiratory signs and symptoms nec	-	-	5	-	-	-	-	-
scleral structural change, deposit and degeneration	-	-	3	-	-	-	-	-
sensory abnormalities nec	-	-	-	1712	-	264	-	-
skin structures and soft tissue infections	-	74	-	-	-	-	-	-
skin vasculitides	-	38	-	-	-	-	-	-

HLT	Number of cases detected							
	Tel	Aug	Cef	Cla	Ery	Azi	Mox	Lev
skin vasomotor conditions	-	-	-	-	6	-	-	-
speech and language usage disturbances	-	-	-	9	-	-	-	-
stomatitis and ulceration	-	-	-	258	-	-	-	-
streptococcal infections	-	-	-	-	-	63	-	-
synovial disorders	-	-	-	-	-	-	-	-
tendon disorders	-	-	-	-	-	-	49	646
therapeutic drug monitoring analyses	-	-	-	280	-	-	-	-
tissue enzyme analyses nec	-	212	-	-	-	-	-	-
tongue disorders	-	-	-	256	-	81	23	-
tongue signs and symptoms	35	-	-	287	-	109	55	81
tremor (excl congenital)	-	-	-	-	-	-	104	-
tympanic membrane disorders (excl infections)	-	-	-	-	-	10	-	-
upper respiratory tract infections	-	-	-	-	-	501	-	-
urinalysis nec	-	-	-	-	53	-	-	-
urticarias	50	-	-	-	-	-	144	-
vasculitides nec	-	49	-	-	-	-	-	-
ventricular arrhythmias and cardiac arrest	-	-	-	-	-	-	162	-
viiiith cranial nerve disorders	-	-	2	-	-	-	-	-
visual disorders nec	454	-	-	-	-	-	-	-

 :  $2 \leq \text{EBGM05} < 5$ ; 
  :  $5 \leq \text{EBGM05} < 10$ ; 
  :  $\text{EBGM05} \geq 10$ . Tel=telithromycin; Aug=Augmentin; Cef=cefuroxime; Cla=clarithromycin; Ery=erythromycin; Azi=azithromycin; Mox=moxifloxacin; and Lev=levofloxacin.

**Table 2 – Disproportionality of PTs detected in various antibiotics using the full FDA FOI database as a background: FDA FOI database through March 31, 2006**

Antibiotics	PT	N	EBGM	EBGM05	EBGM95
Telithromycin	abdominal discomfort	23	4.94	3.29	7.44
Telithromycin	accommodation disorder	14	47.60	28.40	79.77
Telithromycin	angioneurotic oedema	22	3.05	2.01	4.63
Telithromycin	aspartate aminotransferase increased	49	2.71	2.05	3.60
Telithromycin	asthenopia	4	6.23	2.55	15.24
Telithromycin	bilirubinuria	2	12.11	3.81	38.41
Telithromycin	chromaturia	19	5.62	3.60	8.80
Telithromycin	colour blindness	11	42.75	24.00	76.15
Telithromycin	critical liver terms	36	3.36	2.42	4.66
Telithromycin	cytomegalovirus hepatitis	2	6.57	2.07	20.85
Telithromycin	diplopia	72	20.47	16.20	25.87
Telithromycin	dizziness	149	2.68	2.27	3.15
Telithromycin	dysgeusia	50	3.21	2.42	4.24
Telithromycin	eosinophil count increased	8	3.98	2.04	7.75
Telithromycin	eye pain	18	5.03	3.18	7.95
Telithromycin	hepatic enzyme increased	30	3.39	2.37	4.86
Telithromycin	hepatic failure	27	3.16	2.17	4.62
Telithromycin	hepatitis	33	5.86	4.16	8.25
Telithromycin	international normalised ratio increased	33	3.37	2.39	4.75
Telithromycin	jaundice	36	5.57	4.01	7.74
Telithromycin	monoparesis	3	5.89	2.16	16.00
Telithromycin	myasthenia gravis	16	34.84	21.45	56.59
Telithromycin	myasthenia gravis crisis	3	53.12	19.54	144.40
Telithromycin	mydriasis	16	5.98	3.68	9.72
Telithromycin	myelitis	3	6.76	2.49	18.38
Telithromycin	palpitations	41	2.82	2.07	3.83
Telithromycin	parosmia	7	4.85	2.39	9.84
Telithromycin	photopsia	14	16.96	10.12	28.42
Telithromycin	pre-existing condition improved	3	20.05	7.38	54.50
Telithromycin	strabismus	4	7.24	2.96	17.70
Telithromycin	swelling face	28	2.90	2.00	4.20
Telithromycin	tongue black hairy	6	30.56	14.35	65.09
Telithromycin	urticaria generalised	11	6.76	3.80	12.05

Antibiotics	PT	N	EBGM	EBGM05	EBGM95
Telithromycin	vision blurred	247	17.16	15.11	19.49
Telithromycin	visual acuity reduced	23	3.09	2.06	4.65
Telithromycin	visual brightness	16	135.86	83.64	220.67
Telithromycin	visual disturbance	103	12.25	10.07	14.90
Telithromycin	vith nerve paralysis	4	14.63	5.98	35.79
Telithromycin	yellow skin	4	14.90	6.09	36.45
Augmentin	abnormal faeces	35	4.36	3.12	6.08
Augmentin	acute generalised exanthematous pustulosis	31	20.99	14.74	29.90
Augmentin	anal abscess	3	13.23	4.87	35.97
Augmentin	anaphylactic shock	91	7.76	6.30	9.55
Augmentin	angioneurotic oedema	91	2.52	2.04	3.10
Augmentin	bilirubin conjugated increased	15	6.12	3.71	10.09
Augmentin	blood alkaline phosphatase increased	178	4.21	3.62	4.88
Augmentin	blood bilirubin increased	104	3.71	3.05	4.51
Augmentin	bronchospasm	56	3.49	2.68	4.55
Augmentin	cholestasis	97	9.29	7.59	11.36
Augmentin	choriomeningitis lymphocytic	2	10.76	3.39	34.14
Augmentin	chromaturia	62	5.35	4.16	6.88
Augmentin	clostridial infection	15	6.01	3.64	9.90
Augmentin	clostridium colitis	60	12.04	9.32	15.55
Augmentin	clostridium difficile colitis	6	19.99	9.39	42.58
Augmentin	coagulation factor v level decreased	10	11.87	6.50	21.70
Augmentin	colitis	70	5.06	3.99	6.42
Augmentin	colitis pseudomembranous	192	11.30	9.78	13.05
Augmentin	congenital acrochordon	3	29.59	10.89	80.44
Augmentin	congenital hearing disorder	3	5.65	2.08	15.36
Augmentin	cytolytic hepatitis	42	8.15	6.01	11.06
Augmentin	dermatitis bullous	77	2.75	2.20	3.45
Augmentin	dermatitis diaper	4	10.09	4.13	24.68
Augmentin	dermatitis exfoliative	79	2.54	2.03	3.18
Augmentin	diarrhoea	934	4.58	4.29	4.89
Augmentin	diarrhoea haemorrhagic	59	8.77	6.78	11.36
Augmentin	drug hypersensitivity	57	2.81	2.16	3.65
Augmentin	drug rash with eosinophilia and systemic	11	15.04	8.45	26.80

Antibiotics	PT	N	EBGM	EBGM05	EBGM95
	symptoms				
Augmentin	enantherma	5	5.24	2.31	11.85
Augmentin	enterocolitis haemorrhagic	13	4.85	2.84	8.28
Augmentin	eosinophilia	80	3.98	3.19	4.97
Augmentin	erythema	142	4.28	3.62	5.06
Augmentin	eyelid oedema	34	4.20	2.99	5.89
Augmentin	factor v deficiency	3	15.21	5.59	41.33
Augmentin	faeces discoloured	38	3.32	2.41	4.57
Augmentin	faeces pale	15	12.62	7.65	20.81
Augmentin	gamma-glutamyltransferase increased	144	5.14	4.36	6.07
Augmentin	generalised erythema	23	10.89	7.24	16.39
Augmentin	haemodynamic instability	13	3.82	2.24	6.51
Augmentin	haemodynamic test abnormal	2	12.59	3.97	39.96
Augmentin	henoch-schonlein purpura	15	9.03	5.48	14.89
Augmentin	hepatic enzyme increased	36	3.00	2.16	4.16
Augmentin	hepatic trauma	8	4.86	2.50	9.47
Augmentin	hepatitis	214	5.28	4.61	6.05
Augmentin	hepatitis cholestatic	93	17.00	13.83	20.89
Augmentin	hepatitis fulminant	18	4.90	3.09	7.75
Augmentin	hepatocellular damage	68	2.93	2.30	3.73
Augmentin	histamine level	2	26.70	8.42	84.73
Augmentin	hyperbilirubinaemia	112	5.34	4.43	6.45
Augmentin	hypersensitivity	246	2.51	2.21	2.85
Augmentin	hyperthermia	13	4.88	2.86	8.32
Augmentin	inflammation	52	3.32	2.53	4.37
Augmentin	jaundice	280	7.19	6.38	8.10
Augmentin	jaundice cholestatic	223	19.91	17.42	22.76
Augmentin	laryngeal discomfort	2	7.12	2.24	22.59
Augmentin	leukocytoclastic vasculitis	30	7.75	5.41	11.11
Augmentin	lipase increased	25	3.08	2.08	4.55
Augmentin	liver function test abnormal	119	2.53	2.11	3.04
Augmentin	lymphopenia	16	3.57	2.20	5.80
Augmentin	mucosal erosion	12	6.54	3.76	11.39
Augmentin	nephritis interstitial	26	3.56	2.42	5.23
Augmentin	nikolsky's sign	10	30.60	16.74	55.93
Augmentin	ocular icterus	9	5.22	2.77	9.82

Antibiotics	PT	N	EBGM	EBGM05	EBGM95
Augmentin	oedema genital	15	3.40	2.06	5.60
Augmentin	palatal disorder	4	7.23	2.96	17.68
Augmentin	palpable purpura	2	6.35	2.00	20.14
Augmentin	peripheral sensorimotor neuropathy	5	17.96	7.94	40.65
Augmentin	peritoneal effusion	7	27.01	13.32	54.77
Augmentin	prothrombin time shortened	16	5.45	3.35	8.85
Augmentin	prurigo	10	10.92	5.98	19.96
Augmentin	pruritus	506	2.54	2.32	2.77
Augmentin	purpura	95	5.53	4.51	6.78
Augmentin	pustular psoriasis	4	9.11	3.73	22.29
Augmentin	rash erythematous	121	4.41	3.68	5.29
Augmentin	rash generalised	54	3.35	2.56	4.39
Augmentin	rash macular	39	5.20	3.79	7.13
Augmentin	rash maculo-papular	188	4.20	3.63	4.86
Augmentin	rash morbilliform	11	5.69	3.20	10.14
Augmentin	rash pruritic	45	2.87	2.14	3.85
Augmentin	rash pustular	66	10.52	8.24	13.43
Augmentin	rash scarlatiniform	11	33.94	19.05	60.46
Augmentin	rash vesicular	14	5.08	3.03	8.52
Augmentin	retinal vasculitis	3	7.54	2.77	20.49
Augmentin	rib hypoplasia	2	13.42	4.23	42.59
Augmentin	skin candida	12	24.28	13.94	42.28
Augmentin	skin exfoliation	39	4.40	3.21	6.03
Augmentin	skin test positive	13	5.88	3.44	10.03
Augmentin	spinal myelogram abnormal	5	9.38	4.15	21.23
Augmentin	stevens-johnson syndrome	83	3.03	2.43	3.77
Augmentin	superinfection	16	4.45	2.74	7.23
Augmentin	tongue discolouration	22	3.80	2.51	5.77
Augmentin	tooth decalcification	4	14.90	6.09	36.44
Augmentin	tooth discolouration	155	12.58	10.72	14.76
Augmentin	toxic epidermal necrolysis	62	4.03	3.14	5.19
Augmentin	toxic skin eruption	83	13.79	11.08	17.15
Augmentin	transaminases increased	50	5.24	3.96	6.93
Augmentin	tryptase	2	19.42	6.12	61.62
Augmentin	tryptase increased	4	31.74	12.98	77.63



Antibiotics	PT	N	EBGM	EBGM05	EBGM95
Augmentin	urticaria generalised	21	9.06	5.92	13.88
Augmentin	vascular purpura	23	9.62	6.40	14.47
Augmentin	vasculitis	46	3.03	2.26	4.05
Cefuroxime	abdominal pain	242	2.91	2.56	3.30
Cefuroxime	abnormal faeces	16	3.78	2.33	6.14
Cefuroxime	ageusia	19	3.17	2.03	4.96
Cefuroxime	anaphylactic reaction	124	4.92	4.11	5.88
Cefuroxime	anaphylactic shock	31	12.95	9.09	18.44
Cefuroxime	bronchospasm	17	4.02	2.51	6.44
Cefuroxime	clostridium colitis	7	7.27	3.58	14.74
Cefuroxime	clostridium difficile colitis	3	26.75	9.84	72.71
Cefuroxime	colitis	51	8.45	6.40	11.15
Cefuroxime	colitis pseudomembranous	925	64.08	60.00	68.43
Cefuroxime	diarrhoea	520	6.36	5.83	6.95
Cefuroxime	diarrhoea haemorrhagic	54	19.19	14.66	25.13
Cefuroxime	gastrointestinal disorder	38	2.95	2.14	4.07
Cefuroxime	generalised erythema	4	5.81	2.37	14.20
Cefuroxime	hypersensitivity	142	2.66	2.25	3.14
Cefuroxime	nasal flaring	2	7.59	2.39	24.10
Cefuroxime	nikolsky's sign	3	39.57	14.56	107.57
Cefuroxime	pharyngeal oedema	8	4.44	2.28	8.64
Cefuroxime	prothrombin time ratio abnormal	2	19.38	6.11	61.49
Cefuroxime	prurigo	3	9.19	3.38	24.97
Cefuroxime	rash generalised	14	3.65	2.18	6.12
Cefuroxime	rectal tenesmus	7	5.91	2.91	11.99
Cefuroxime	stevens-johnson syndrome	33	3.10	2.20	4.37
Cefuroxime	swelling	16	3.64	2.24	5.92
Cefuroxime	tongue oedema	35	3.09	2.22	4.32
Cefuroxime	tooth decalcification	5	69.15	30.56	156.46
Cefuroxime	urticaria generalised	5	8.22	3.63	18.61
Cefuroxime	vestibular neuronitis	2	11.85	3.74	37.61
Clarithromycin	abdominal pain	628	2.27	2.10	2.46
Clarithromycin	acute psychosis	7	5.80	2.86	11.76

Antibiotics		PT	N	EBGM	EBGM05	EBGM95
Clarithromycin	ageusia		213	13.16	11.48	15.09
Clarithromycin	anosmia		28	10.24	7.06	14.84
Clarithromycin	atypical mycobacterial infection		4	8.39	3.43	20.51
Clarithromycin	clostridium colitis		17	6.96	4.34	11.15
Clarithromycin	cytomegalovirus chorioretinitis		7	11.76	5.80	23.86
Clarithromycin	deafness		83	2.96	2.38	3.68
Clarithromycin	delusional disorder, grandiose type		2	29.20	9.20	92.67
Clarithromycin	depersonalisation		72	3.63	2.87	4.59
Clarithromycin	diarrhoea		645	2.33	2.15	2.52
Clarithromycin	drug interaction		829	5.15	4.81	5.52
Clarithromycin	drug level		2	6.37	2.01	20.22
Clarithromycin	drug level increased		205	2.95	2.56	3.39
Clarithromycin	dysgeusia		1487	16.10	15.28	16.95
Clarithromycin	dyspepsia		412	3.81	3.45	4.20
Clarithromycin	electrocardiogram qt prolonged		106	5.94	4.89	7.20
Clarithromycin	generalised erythema		7	4.78	2.36	9.70
Clarithromycin	glossitis		201	8.88	7.71	10.22
Clarithromycin	glossoptosis		2	9.96	3.14	31.59
Clarithromycin	helicobacter gastritis		10	4.12	2.25	7.53
Clarithromycin	helicobacter infection		7	7.13	3.52	14.46
Clarithromycin	hepatitis acute		9	5.14	2.73	9.68
Clarithromycin	hiccups		29	4.19	2.91	6.03
Clarithromycin	hypopyon		4	19.36	7.91	47.35
Clarithromycin	infusion site phlebitis		2	21.21	6.69	67.31
Clarithromycin	jaundice		126	2.43	2.03	2.90
Clarithromycin	jaundice cholestatic		57	2.85	2.19	3.70
Clarithromycin	logorrhoea		9	5.91	3.14	11.13
Clarithromycin	long qt syndrome		6	44.50	20.90	94.77
Clarithromycin	mania		72	3.81	3.02	4.82
Clarithromycin	mouth ulceration		76	3.11	2.48	3.91
Clarithromycin	mycobacterial infection		6	8.57	4.02	18.24
Clarithromycin	mycobacterium avium complex infection		7	5.62	2.77	11.39
Clarithromycin	oral candidiasis		154	13.93	11.87	16.36
Clarithromycin	otitis media		31	6.56	4.61	9.34
Clarithromycin	parosmia		182	11.95	10.31	13.86

Antibiotics	PT	N	EBGM	EBGM05	EBGM95
Clarithromycin	pathogen resistance	10	4.28	2.34	7.83
Clarithromycin	radial pulse abnormal	2	11.75	3.70	37.27
Clarithromycin	rhabdomyolysis	90	2.68	2.17	3.30
Clarithromycin	schizotypal personality disorder	2	23.59	7.44	74.86
Clarithromycin	stomatitis	170	4.06	3.49	4.73
Clarithromycin	tangentiality	3	30.65	11.28	83.31
Clarithromycin	therapeutic agent toxicity	107	4.78	3.94	5.79
Clarithromycin	tongue discolouration	172	21.75	18.68	25.32
Clarithromycin	tongue disorder	52	4.76	3.62	6.27
Clarithromycin	tongue oedema	94	2.69	2.19	3.31
Clarithromycin	tooth discolouration	60	6.04	4.68	7.80
Clarithromycin	torsade de pointes	57	4.61	3.55	6.00
Clarithromycin	ventricular tachycardia	89	2.78	2.25	3.43
Clarithromycin	vomiting	801	2.21	2.06	2.38
Erythromycin	abdominal pain	773	5.19	4.83	5.58
Erythromycin	abnormal faeces	19	3.76	2.40	5.88
Erythromycin	anticonvulsant drug level increased	3	17.71	6.52	48.15
Erythromycin	biliary colic	5	5.03	2.22	11.38
Erythromycin	bilirubinuria	14	9.80	5.85	16.42
Erythromycin	congenital diaphragmatic hernia	2	7.35	2.32	23.34
Erythromycin	conjunctivitis	125	2.95	2.47	3.52
Erythromycin	deafness	99	5.00	4.09	6.11
Erythromycin	deafness transitory	38	11.12	8.08	15.32
Erythromycin	diarrhoea	348	2.39	2.15	2.66
Erythromycin	drug interaction	346	6.17	5.54	6.87
Erythromycin	drug level increased	99	3.16	2.58	3.85
Erythromycin	dyspepsia	222	4.59	4.02	5.25
Erythromycin	electrocardiogram qt corrected interval prolonged	8	8.13	4.18	15.84
Erythromycin	electrocardiogram qt prolonged	73	11.95	9.47	15.08
Erythromycin	feeding disorder	4	5.92	2.42	14.47
Erythromycin	gastritis	58	4.54	3.50	5.88
Erythromycin	gastrointestinal disorder	140	5.06	4.27	5.98
Erythromycin	hepatic function abnormal	452	4.26	3.88	4.68
Erythromycin	hepatitis	214	3.85	3.36	4.41

Antibiotics	PT	N	EBGM	EBGM05	EBGM95
Erythromycin	hyperbilirubinaemia	103	3.97	3.26	4.83
Erythromycin	jaundice	271	5.80	5.13	6.54
Erythromycin	jaundice cholestatic	258	11.29	9.97	12.79
Erythromycin	livedo reticularis	5	8.37	3.70	18.94
Erythromycin	liver tenderness	12	11.68	6.70	20.33
Erythromycin	obstruction gastric	16	117.43	72.29	190.73
Erythromycin	ototoxicity	3	7.79	2.87	21.18
Erythromycin	ovarian abscess	2	26.93	8.49	85.45
Erythromycin	pulmonary arterial wedge pressure increased	2	6.69	2.11	21.23
Erythromycin	pyloric stenosis	35	48.27	34.59	67.37
Erythromycin	pylorospasm	2	27.64	8.71	87.71
Erythromycin	rectal tenesmus	12	4.67	2.68	8.13
Erythromycin	scleral disorder	2	7.49	2.36	23.78
Erythromycin	sinus polyp	2	14.25	4.49	45.21
Erythromycin	sudden cardiac death	10	47.75	26.13	87.28
Erythromycin	systemic candida	3	6.49	2.39	17.63
Erythromycin	torsade de pointes	68	24.44	19.21	31.09
Erythromycin	urine analysis abnormal	52	3.34	2.54	4.40
Erythromycin	vein discolouration	2	8.80	2.77	27.92
Erythromycin	venous injury	2	14.27	4.50	45.29
Erythromycin	ventricular flutter	4	36.27	14.83	88.71
Erythromycin	ventricular tachycardia	66	4.57	3.58	5.83
Erythromycin	viiiith nerve lesion	2	17.77	5.60	56.40
Erythromycin	vomiting	695	3.13	2.90	3.37
Erythromycin	vomiting projectile	5	20.05	8.86	45.37
Azithromycin	abdominal pain	561	2.61	2.40	2.84
Azithromycin	ageusia	124	10.94	9.15	13.09
Azithromycin	albumin globulin ratio increased	2	12.39	3.90	39.31
Azithromycin	angioneurotic oedema	84	2.54	2.05	3.16
Azithromycin	anosmia	65	18.84	14.72	24.09
Azithromycin	antineutrophil cytoplasmic antibody positive	3	6.14	2.26	16.69
Azithromycin	application site pain	57	13.40	10.31	17.42
Azithromycin	bacterial infection	68	4.92	3.87	6.27

Antibiotics	PT	N	EBGM	EBGM05	EBGM95
Azithromycin	bronchitis	101	5.19	4.26	6.32
Azithromycin	cerebral toxoplasmosis	3	11.35	4.17	30.85
Azithromycin	cough	225	2.38	2.08	2.72
Azithromycin	deafness	183	9.20	7.94	10.66
Azithromycin	dermatitis	469	2.82	2.57	3.10
Azithromycin	diarrhoea	738	3.17	2.95	3.41
Azithromycin	drug hypersensitivity	64	3.00	2.34	3.85
Azithromycin	drug interaction	408	3.40	3.08	3.76
Azithromycin	ear discomfort	10	4.61	2.52	8.42
Azithromycin	ear disorder	103	13.99	11.50	17.02
Azithromycin	ear operation	2	14.99	4.72	47.55
Azithromycin	ear pain	38	4.45	3.23	6.14
Azithromycin	hypermobility syndrome	2	12.63	3.98	40.08
Azithromycin	hypersensitivity	256	2.62	2.31	2.97
Azithromycin	impaired work ability	10	4.55	2.49	8.31
Azithromycin	implant site reaction	18	5.22	3.30	8.25
Azithromycin	infrequent bowel movements	3	5.91	2.17	16.06
Azithromycin	injection site infection	14	4.39	2.62	7.35
Azithromycin	injection site irritation	26	3.29	2.24	4.83
Azithromycin	injection site pain	138	3.28	2.77	3.89
Azithromycin	international normalised ratio increased	96	3.27	2.67	4.01
Azithromycin	jarisch-herxheimer reaction	3	6.96	2.56	18.93
Azithromycin	jaundice cholestatic	40	4.52	3.30	6.17
Azithromycin	ligament laxity	2	8.19	2.58	25.99
Azithromycin	lyme disease	7	8.78	4.33	17.82
Azithromycin	meningitis pneumococcal	7	15.29	7.54	31.00
Azithromycin	myoglobinaemia	2	6.94	2.19	22.03
Azithromycin	nephritis	24	4.48	3.00	6.68
Azithromycin	oral candidiasis	50	5.68	4.29	7.51
Azithromycin	otitis media	42	7.09	5.23	9.62
Azithromycin	parosmia	63	6.88	5.36	8.83
Azithromycin	pathogen resistance	20	10.17	6.57	15.73
Azithromycin	pharyngitis	129	3.59	3.02	4.28
Azithromycin	pneumococcal infection	6	6.57	3.08	13.98
Azithromycin	pneumonia mycoplasmal	8	11.32	5.81	22.04

Antibiotics	PT	N	EBGM	EBGM05	EBGM95
Azithromycin	pneumonia streptococcal	11	10.57	5.93	18.83
Azithromycin	productive cough	51	4.22	3.20	5.57
Azithromycin	rash maculo-papular	93	2.61	2.12	3.21
Azithromycin	respiratory tract infection	10	5.06	2.77	9.25
Azithromycin	rheumatic fever	4	19.62	8.02	47.99
Azithromycin	sinusitis	160	6.75	5.77	7.90
Azithromycin	starvation	3	7.38	2.71	20.05
Azithromycin	stevens-johnson syndrome	98	3.45	2.82	4.22
Azithromycin	streptococcal infection	21	4.07	2.66	6.23
Azithromycin	teratogenicity	2	26.70	8.41	84.72
Azithromycin	tinnitus	119	3.69	3.08	4.43
Azithromycin	tongue discolouration	43	7.71	5.70	10.43
Azithromycin	tongue disorder	44	4.46	3.31	6.01
Azithromycin	tooth discolouration	36	4.30	3.09	5.97
Azithromycin	tooth infection	4	5.26	2.15	12.87
Azithromycin	torsade de pointes	42	3.95	2.91	5.36
Azithromycin	tympanic membrane perforation	6	17.17	8.06	36.56
Azithromycin	upper respiratory tract infection	96	4.19	3.42	5.13
Azithromycin	white blood cell morphology abnormal	2	25.22	7.95	80.03
Moxifloxacin	abdominal haematoma	12	34.68	19.91	60.39
Moxifloxacin	ageusia	22	5.37	3.54	8.15
Moxifloxacin	amblyopia	9	4.52	2.40	8.51
Moxifloxacin	anaphylactic reaction	145	14.20	12.04	16.76
Moxifloxacin	anaphylactic shock	39	4.73	3.45	6.49
Moxifloxacin	anaphylactoid reaction	58	12.90	9.94	16.74
Moxifloxacin	anosmia	16	6.78	4.18	11.02
Moxifloxacin	anoxic encephalopathy	10	12.34	6.75	22.56
Moxifloxacin	colitis pseudomembranous	19	7.10	4.54	11.10
Moxifloxacin	depersonalisation	21	11.84	7.73	18.13
Moxifloxacin	dizziness	316	3.29	2.94	3.68
Moxifloxacin	dyspnoea	239	2.28	2.01	2.60
Moxifloxacin	electrocardiogram qt corrected interval prolonged	16	5.19	3.20	8.43
Moxifloxacin	electrocardiogram qt prolonged	42	4.20	3.09	5.69
Moxifloxacin	eye swelling	18	6.93	4.38	10.97

Antibiotics	PT	N	EBGM	EBGM05	EBGM95
Moxifloxacin	face oedema	78	3.89	3.11	4.87
Moxifloxacin	glossitis	14	9.78	5.83	16.39
Moxifloxacin	hallucination	42	2.73	2.01	3.71
Moxifloxacin	hypersensitivity	175	5.83	5.01	6.77
Moxifloxacin	hypoesthesia	75	2.66	2.12	3.35
Moxifloxacin	hypoesthesia oral	12	3.64	2.09	6.34
Moxifloxacin	laryngospasm	11	6.99	3.92	12.45
Moxifloxacin	nervousness	90	5.96	4.83	7.35
Moxifloxacin	oropharyngeal swelling	11	6.09	3.42	10.84
Moxifloxacin	palpitations	91	2.99	2.42	3.68
Moxifloxacin	pharyngeal oedema	18	3.58	2.26	5.66
Moxifloxacin	pruritus	140	3.00	2.53	3.55
Moxifloxacin	rash	128	3.67	3.07	4.37
Moxifloxacin	respiratory rate	2	22.60	7.12	71.71
Moxifloxacin	swelling face	34	5.26	3.75	7.37
Moxifloxacin	swollen tongue	14	3.91	2.33	6.55
Moxifloxacin	syncope	80	2.74	2.20	3.42
Moxifloxacin	tachycardia	88	2.78	2.25	3.43
Moxifloxacin	tendon disorder	28	10.85	7.48	15.73
Moxifloxacin	tendon rupture	25	12.88	8.70	19.06
Moxifloxacin	tendonitis	21	7.75	5.06	11.87
Moxifloxacin	throat tightness	43	7.20	5.32	9.73
Moxifloxacin	tongue oedema	32	4.85	3.43	6.87
Moxifloxacin	torsade de pointes	38	9.39	6.82	12.93
Moxifloxacin	tremor	104	2.94	2.42	3.57
Moxifloxacin	urine bilirubin increased	2	15.54	4.90	49.29
Moxifloxacin	urticaria	140	4.72	3.99	5.58
Moxifloxacin	vasodilatation	34	7.21	5.14	10.11
Levofloxacin	activities of daily living impaired	24	4.35	2.92	6.49
Levofloxacin	anaphylactic reaction	109	5.11	4.22	6.18
Levofloxacin	anaphylactoid reaction	80	9.69	7.76	12.10
Levofloxacin	anosmia	19	3.36	2.15	5.25
Levofloxacin	arthralgia	547	5.93	5.44	6.46
Levofloxacin	arthropathy	41	3.21	2.36	4.37

Antibiotics	PT	N	EBGM	EBGM05	EBGM95
Levofloxacin	balanoposthitis	2	9.10	2.87	28.88
Levofloxacin	burning sensation	87	3.58	2.89	4.43
Levofloxacin	cartilage injury	10	8.78	4.80	16.04
Levofloxacin	clostridial infection	26	11.15	7.59	16.38
Levofloxacin	clostridium colitis	46	9.75	7.28	13.05
Levofloxacin	colitis pseudomembranous	52	8.96	6.81	11.80
Levofloxacin	difficulty in walking	176	4.31	3.71	5.01
Levofloxacin	electrocardiogram qt corrected interval prolonged	26	4.53	3.09	6.66
Levofloxacin	electrocardiogram qt prolonged	74	4.88	3.87	6.15
Levofloxacin	empyema	8	4.10	2.11	7.99
Levofloxacin	epiphyses premature fusion	2	8.12	2.56	25.76
Levofloxacin	feeling hot and cold	11	4.46	2.50	7.94
Levofloxacin	haemolytic anaemia	33	3.17	2.25	4.47
Levofloxacin	herpetic stomatitis	3	12.06	4.44	32.79
Levofloxacin	impaired work ability	18	3.39	2.14	5.37
Levofloxacin	infective exacerbation of chronic obstructive airways disease	3	15.10	5.55	41.04
Levofloxacin	injection site erythema	59	2.90	2.24	3.75
Levofloxacin	injection site pruritus	40	7.11	5.20	9.72
Levofloxacin	international normalised ratio increased	147	3.81	3.24	4.50
Levofloxacin	joint effusion	14	4.73	2.82	7.92
Levofloxacin	joint stiffness	31	3.45	2.42	4.91
Levofloxacin	joint swelling	67	3.91	3.07	4.99
Levofloxacin	ligament injury	9	13.78	7.32	25.94
Levofloxacin	ligament rupture	5	28.21	12.47	63.83
Levofloxacin	meniscus lesion	9	6.32	3.36	11.89
Levofloxacin	muscle rupture	14	17.03	10.16	28.54
Levofloxacin	muscle twitching	47	3.47	2.60	4.63
Levofloxacin	myalgia	285	3.06	2.72	3.45
Levofloxacin	nephritis interstitial	52	6.67	5.07	8.78
Levofloxacin	nightmare	41	2.99	2.20	4.08
Levofloxacin	pain in extremity	259	3.37	2.98	3.82
Levofloxacin	paraesthesia	183	2.32	2.00	2.68
Levofloxacin	pathogen resistance	15	5.67	3.44	9.35
Levofloxacin	pharyngeal oedema	34	4.07	2.91	5.71



Antibiotics	PT	N	EBGM	EBGM05	EBGM95
Levofloxacin	plantar fasciitis	9	13.90	7.39	26.17
Levofloxacin	post-traumatic osteoporosis	2	10.50	3.31	33.30
Levofloxacin	prostate infection	3	6.41	2.36	17.41
Levofloxacin	prothrombin level decreased	53	7.05	5.37	9.26
Levofloxacin	psychotic disorder	63	2.97	2.31	3.81
Levofloxacin	red blood cells csf positive	4	5.40	2.21	13.21
Levofloxacin	shoulder pain	21	5.34	3.49	8.19
Levofloxacin	stevens-johnson syndrome	74	3.69	2.93	4.65
Levofloxacin	streptococcal bacteraemia	5	12.57	5.56	28.45
Levofloxacin	swelling	65	2.77	2.17	3.55
Levofloxacin	tenderness	22	3.27	2.16	4.97
Levofloxacin	tendon disorder	387	85.51	77.25	94.65
Levofloxacin	tendon injury	16	19.19	11.81	31.17
Levofloxacin	tendon rupture	238	57.01	50.09	64.89
Levofloxacin	tendonitis	257	46.23	40.82	52.36
Levofloxacin	tongue oedema	44	3.37	2.50	4.54
Levofloxacin	torsade de pointes	115	12.98	10.78	15.63
Levofloxacin	toxic epidermal necrolysis	43	3.39	2.51	4.59
Levofloxacin	ventricular tachycardia	60	2.87	2.22	3.70
<div> <div></div> <div></div> <div></div> </div> : 2 ≤ EBGM05 < 5;  : 5 ≤ EBGM05 < 10;  EBGM05 ≥ 10					

**Table 3 – Disproportionality of HLTs for fatal outcomes detected in various antibiotics using full FDA FOI cases with fatal outcomes as a background: FDA FOI database through March 31, 2006**

HLT	Number of cases detected							
	Tel	Aug	Cef	Cla	Ery	Azi	Mox	Lev
allergic conditions nec	-	-	-	-	-	10	-	-
anaemias haemolytic nec	-	8	-	-	-	-	-	7
anaphylactic responses	-	26	9	-	-	-	-	-
aortic valvular disorders	-	-	3	-	-	-	-	-
atypical mycobacterial infections	-	-	-	4	-	-	-	-
autoimmunity analyses	-	-	-	-	-	-	-	-
breast signs and symptoms	-	-	3	-	3	-	-	-
bullous conditions	-	66	18	-	-	-	-	43
cardiac infections	3	-	-	-	-	-	-	-
central nervous system and spinal infections	-	-	-	-	-	5	-	-
cholestasis and jaundice	6	63	-	-	-	-	-	-
clostridia infections	-	33	20	-	-	-	-	15
coagulation disorders congenital	-	-	3	-	-	-	-	-
dermatitis ascribed to specific agent	-	11	-	-	-	-	-	-
diarrhoea (excl infective)	-	-	9	-	-	-	-	-
ecg investigations	-	-	-	-	-	-	-	20
exfoliative conditions	-	14	-	-	-	-	-	-
eye and eyelid infections	-	-	-	-	-	2	-	-
hearing disorders congenital	-	3	-	-	-	-	-	-
hearing losses	-	-	-	-	3	-	-	-
hepatic failure and associated disorders	-	54	-	-	-	-	-	-
hepatic therapeutic procedures	-	-	-	-	-	-	5	-
hepatobiliary histopathology procedures	-	-	-	-	-	-	-	3
hepatocellular damage and hepatitis nec	12	83	-	-	-	-	-	-
interactions	-	-	-	71	32	36	-	-
lid, lash and lacrimal infections, irritations and inflammations	-	3	-	-	-	-	-	-
muscle infections and inflammations	-	-	-	4	-	-	-	-
musculoskeletal and connective tissue disorders of face, neck and jaw congenital	-	4	-	-	-	-	-	-
musculoskeletal and connective tissue disorders of trunk congenital (excl spine)	-	2	-	-	-	-	-	-
mycoplasma infections	-	-	-	-	-	2	-	-

HLT	Number of cases detected							
	Tel	Aug	Cef	Cla	Ery	Azi	Mox	Lev
myopathies	-	-	-	-	8	-	-	-
nasal disorders nec	-	-	5	-	-	-	-	-
purine metabolism disorders nec	-	-	-	8	-	-	-	-
purpuras (excl thrombocytopenic)	-	2	-	-	-	-	-	-
rashes, eruptions and exanthems nec	-	23	-	-	-	-	-	-
renal neoplasms	-	-	-	-	2	-	-	-
retroviral infections	-	-	-	-	-	-	4	-
stillbirth and foetal death	-	-	-	-	9	-	-	-
streptococcal infections	-	-	-	-	-	12	-	-
telangiectasia and related conditions	-	-	-	-	-	-	2	-
tongue signs and symptoms	-	-	4	-	-	-	-	-

 :  $2 \leq \text{EBGM05} < 5$ ; 
  :  $5 \leq \text{EBGM05} < 10$ ; 
  :  $\text{EBGM05} \geq 10$ . 
 Tel=telithromycin; Aug=Augmentin; Cef=cefuroxime; Cla=clarithromycin; Ery=erythromycin; <sup>a</sup>zi=azithromycin; Mox=moxifloxacin; and Lev=levofloxacin.

**Table 4 – Disproportionality of PTs for fatal outcomes detected in various antibiotics using full FDA FOI cases with fatal outcomes as a background: FDA FOI database through March 31, 2006**

Antibiotics	PT	N	EBGM	EBGM05	EBGM95
Telithromycin	brain abscess	2	8.78	2.77	27.86
Telithromycin	critical liver terms	8	4.38	2.25	8.53
Telithromycin	duodenal ulcer perforation	2	8.78	2.77	27.85
Telithromycin	endocarditis	3	14.33	5.27	38.97
Telithromycin	jaundice	5	7.25	3.21	16.41
Telithromycin	mydriasis	4	19.74	8.07	48.27
Augmentin	anaphylactic shock	17	14.28	8.91	22.88
Augmentin	cholestasis	15	9.10	5.52	15.01
Augmentin	clostridium colitis	17	15.11	9.43	24.21
Augmentin	coagulation factor v level decreased	5	13.66	6.04	30.91
Augmentin	colitis pseudomembranous	13	13.91	8.15	23.75
Augmentin	congenital acrochordon	3	30.21	11.11	82.12
Augmentin	congenital hearing disorder	3	30.21	11.11	82.12
Augmentin	cytolytic hepatitis	10	10.64	5.82	19.45
Augmentin	dermatitis bullous	9	10.46	5.56	19.68
Augmentin	dermatitis exfoliative	10	6.35	3.47	11.61
Augmentin	diarrhoea	35	2.80	2.01	3.91
Augmentin	eyelid oedema	3	6.44	2.37	17.52
Augmentin	facial dysmorphism	3	10.26	3.77	27.88
Augmentin	foetal distress syndrome	4	12.55	5.13	30.70
Augmentin	haemodynamic test abnormal	2	24.70	7.78	78.36
Augmentin	hepatic pain	3	8.57	3.15	23.31
Augmentin	hepatitis	16	3.26	2.01	5.29
Augmentin	hepatitis acute	4	4.99	2.04	12.21
Augmentin	hepatitis cholestatic	9	8.06	4.28	15.17
Augmentin	hepatitis fulminant	11	5.28	2.97	9.41
Augmentin	hepatitis neonatal	2	7.91	2.49	25.11
Augmentin	hepatocellular damage	13	3.65	2.14	6.23
Augmentin	jaundice	26	3.74	2.55	5.50
Augmentin	jaundice cholestatic	10	11.79	6.45	21.54
Augmentin	melaena	10	3.97	2.17	7.25

Antibiotics		PT	N	EBGM	EBGM05	EBGM95
Augmentin	pancreatic insufficiency		2	6.51	2.05	20.67
Augmentin	peripheral sensorimotor neuropathy		2	19.60	6.18	62.20
Augmentin	purpura		7	4.89	2.41	9.93
Augmentin	purpura non-thrombocytopenic		2	7.05	2.22	22.38
Augmentin	rash scarlatiniform		2	34.80	10.97	110.43
Augmentin	renal vasculitis		2	19.77	6.23	62.72
Augmentin	reye's syndrome		4	6.08	2.48	14.86
Augmentin	rib hypoplasia		2	26.18	8.25	83.08
Augmentin	skin disorder		6	8.47	3.98	18.03
Augmentin	small intestinal haemorrhage		4	12.30	5.03	30.09
Augmentin	spider naevus		2	7.08	2.23	22.48
Augmentin	stevens-johnson syndrome		15	4.87	2.95	8.02
Augmentin	superinfection		4	5.20	2.13	12.71
Augmentin	toxic epidermal necrolysis		34	9.63	6.87	13.50
Augmentin	toxic skin eruption		11	31.97	17.95	56.95
Augmentin	tryptase increased		3	41.46	15.25	112.71
Augmentin	wegener's granulomatosis		2	11.35	3.58	36.03
Cefuroxime	anaphylactic reaction		7	4.09	2.02	8.29
Cefuroxime	breast pain		2	16.29	5.13	51.69
Cefuroxime	clostridium colitis		3	13.54	4.98	36.81
Cefuroxime	clostridium difficile colitis		2	20.59	6.49	65.32
Cefuroxime	colitis pseudomembranous		15	31.13	18.88	51.32
Cefuroxime	diarrhoea		9	4.00	2.12	7.52
Cefuroxime	epistaxis		5	9.14	4.04	20.68
Cefuroxime	face oedema		3	6.27	2.31	17.05
Cefuroxime	premature labour		2	8.68	2.74	27.54
Cefuroxime	stevens-johnson syndrome		10	15.45	8.46	28.24
Cefuroxime	tongue oedema		4	34.91	14.27	85.38
Clarithromycin	antineutrophil cytoplasmic antibody positive		2	15.99	5.04	50.75
Clarithromycin	bronchial carcinoma		3	17.89	6.58	48.64
Clarithromycin	cardiotoxicity		2	6.67	2.10	21.17
Clarithromycin	drug interaction		70	7.97	6.28	10.10
Clarithromycin	electrocardiogram qt prolonged		11	6.81	3.82	12.12

Antibiotics	PT	N	EBGM	EBGM05	EBGM95
Clarithromycin	gout	7	24.80	12.23	50.29
Clarithromycin	lower respiratory tract infection	6	5.24	2.46	11.15
Clarithromycin	mycobacterial infection	3	5.91	2.17	16.06
Clarithromycin	myositis	4	7.04	2.88	17.22
Clarithromycin	oesophagitis ulcerative	2	12.60	3.97	39.97
Clarithromycin	post herpetic neuralgia	2	11.23	3.54	35.63
Erythromycin	blood magnesium increased	2	7.44	2.35	23.62
Erythromycin	breast pain	2	16.92	5.33	53.69
Erythromycin	clostridium colitis	3	20.76	7.64	56.42
Erythromycin	drug interaction	32	8.54	6.03	12.10
Erythromycin	electrocardiogram qt prolonged	5	10.78	4.76	24.38
Erythromycin	myopathy	5	7.07	3.12	15.99
Erythromycin	oligohydramnios	2	7.29	2.30	23.12
Erythromycin	renal cyst	2	7.21	2.27	22.88
Erythromycin	stillbirth	7	5.31	2.62	10.76
Erythromycin	sudden cardiac death	10	50.15	27.44	91.66
Erythromycin	torsade de pointes	7	15.71	7.74	31.85
Erythromycin	ventricular fibrillation	14	3.68	2.20	6.17
Erythromycin	ventricular tachycardia	12	4.75	2.73	8.27
Azithromycin	blood creatinine decreased	2	6.73	2.12	21.36
Azithromycin	drug interaction	36	6.83	4.92	9.49
Azithromycin	hypersensitivity	10	7.59	4.15	13.88
Azithromycin	injection site irritation	2	17.70	5.58	56.16
Azithromycin	ischaemic cardiomyopathy	3	21.24	7.81	57.74
Azithromycin	meningitis	5	7.77	3.43	17.57
Azithromycin	pneumonia mycoplasmal	2	16.81	5.30	53.33
Azithromycin	pneumonia streptococcal	5	18.64	8.24	42.17
Moxifloxacin	acute pulmonary oedema	5	14.31	6.32	32.37
Moxifloxacin	bacteria urine identified	2	9.72	3.06	30.84
Moxifloxacin	chronic hepatitis	2	7.19	2.27	22.81
Moxifloxacin	electrocardiogram qt prolonged	4	8.03	3.28	19.63
Moxifloxacin	electromechanical dissociation	5	7.63	3.37	17.26

Antibiotics		PT	N	EBGM	EBGM05	EBGM95
Moxifloxacin	faecal incontinence		3	11.11	4.09	30.19
Moxifloxacin	haemoptysis		6	5.45	2.56	11.61
Moxifloxacin	liver transplant		5	40.47	17.89	91.57
Moxifloxacin	pancreatic insufficiency		2	9.85	3.10	31.25
Moxifloxacin	spider naevus		2	11.61	3.66	36.85
Moxifloxacin	torsade de pointes		6	21.89	10.28	46.61
Levofloxacin	biopsy liver abnormal		3	6.33	2.33	17.21
Levofloxacin	clostridium colitis		8	10.39	5.33	20.23
Levofloxacin	creatine phosphokinase decreased		2	7.52	2.37	23.87
Levofloxacin	electrocardiogram qt prolonged		12	12.98	7.45	22.60
Levofloxacin	haemolytic anaemia		7	6.88	3.39	13.96
Levofloxacin	infective exacerbation of chronic obstructive airways disease		3	25.06	9.22	68.11
Levofloxacin	nephritis interstitial		4	7.13	2.91	17.44
Levofloxacin	stevens-johnson syndrome		19	14.00	8.95	21.89
Levofloxacin	tendon rupture		2	12.32	3.88	39.09
Levofloxacin	torsade de pointes		22	25.97	17.12	39.41
Levofloxacin	toxic epidermal necrolysis		18	8.28	5.23	13.10

  :  $2 \leq \text{EBGM05} < 5$ ; 
   :  $5 \leq \text{EBGM05} < 10$ ; 
   :  $\text{EBGM05} \geq 10$ .

**APPENDIX I-3: THE MEDDRA TERMS USED IN THE EVALUATION OF EACH AESI**

All hepatic events were defined using a comprehensive list of MedDRA (version 9.0) HLT and PT from the Hepatobiliary, Nervous System, and Investigations SOCs.

- Broadly-defined hepatic injury is defined by using the HGLTs hepatic and hepatobiliary disorders and hepatobiliary investigations. In addition it included HLT hepatic therapeutic procedures, and the following PTs: blood alkaline phosphatase increased, blood lactate dehydrogenase increased, coma hepatic, and hepatic encephalopathy. These terms are very broad and non-specific and likely to yield more hepatic cases than those truly reflective of the disease or of interest.
- Critical hepatic events is defined by the following MedDRA PTs: coma hepatic, hepatic encephalopathy, liver transplant, hepatic necrosis, hepatitis fulminant, and hepatic failure.
- Myasthenia gravis is defined by the HLT neuromuscular junction dysfunction, which includes the following PTs: Eaton-Lambert syndrome, myasthenia gravis crisis, myasthenia gravis neonatal, myasthenia gravis, myasthenic syndrome, neuromuscular block prolonged, neuromuscular blockade, ocular myasthenia.
- Syncope is defined by the following PTs: Syncope, syncope vasovagal, loss of consciousness, depressed level of consciousness.
- Visual events is defined by using the following PTs: vision blurred, visual disturbance, diplopia, accommodation disorder, visual acuity reduced, photopsia, visual brightness, color blindness, hallucination, photophobia, visual field defect, visual hallucination, blindness, amaurosis fugax, blindness transient, vitreous floaters, glare, tunnel vision, altered visual depth perception, chromatopsia, hypermetropia, retinal disorder, retinal oedema, scotoma, halo vision, myopia, papilloedema, presbyopia, amaurosis, anisometropia, astigmatism, blindness unilateral, cataract, colour vision tests abnormal, corrective lens user, cycloplegia, hemianopia, iritis, macular degeneration, macular oedema, ophthalmological examination abnormal, optic neuritis retrobulbar, retinal vein occlusion, retinopathy, staring, uveitis.



# **Anti-infective Drug Use and the Risk of Severe Liver Injury Requiring Hospitalization**

**Global Pharmacovigilance and Epidemiology**

**sanofi-aventis**

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## BACKGROUND

Telithromycin (Ketek<sup>®</sup>) is a ketolide antibiotic for the treatment of acute bacterial exacerbation of chronic bronchitis, acute bacterial sinusitis, and community-acquired pneumonia. It was first marketed in Germany in 2001 and since then has been marketed in more than 50 countries worldwide. In the U.S., telithromycin was approved by the FDA in April 2004. During the clinical development program of Ketek, asymptomatic and reversible transaminase elevations were seen. Clinical overt hepatitis, with or without jaundice, was very rarely observed and reversible.

In the Summary of Product Characteristics (SPC) it was mentioned that an increase in liver enzymes was common, cholestatic jaundice was rare and hepatitis was very rare. The SPC also recommended discontinuation of telithromycin use in the case of cholestatic jaundice and hepatitis.

In the revised risk management plan submitted to the Food and Drug Administration (FDA) in March 2004, sanofi-aventis proposed to continue monitoring unlisted serious adverse events (SAE) through the post-marketing spontaneous reporting system. If there were an emergent issue of a rare SAE, sanofi-aventis would perform further analysis using a population-based claims database (e.g. PHARMetrics) to evaluate the risk of the rare SAE among telithromycin users in comparison with users of comparable anti-infective agents. In April 2005, sanofi-aventis received 3 alleged reports of hepatic failure occurring in North Carolina. Therefore, a preliminary evaluation of severe liver injury using the PHARMetrics database was conducted one year after the launch

of telithromycin. The preliminary investigation showed that the risk of severe liver injury in 35 days following telithromycin use was comparable with that of macrolides. However, there were only about 21,000 telithromycin users identified in the database at that time which was insufficient to evaluate the risk of a rare event. Following the publication of the three severe liver toxicity cases mentioned above in early 2006 (Clay, 2006), regulatory agencies requested a labeling change for the drug and asked sanofi-aventis to provide additional data on hepatic safety. Thus sanofi-aventis conducted the current study.

It is important to put the risk of identified or potential hepatic adverse events into context. Because liver enzyme elevations following telithromycin treatment were observed in clinical trials and are a known adverse event, we focused our investigation on cases of severe hepatic injury requiring hospitalization. To the best of our knowledge, a published population-based study evaluating this risk associated with telithromycin use compared to other anti-infective agents is not available. The current study was designed to compare the risk of severe hepatic injury requiring hospitalization among users of telithromycin compared to users of other marketed anti-infective agents for similar indication.

## **METHODS**

### **Study design**

This was a retrospective cohort study conducted using the PHARMetrics Integral Outcomes Database (PIOD). The PIOD contains medical and

pharmaceutical insurance claims from managed health care organizations across the United States.

During the period from July 2004 to December 2005, users of telithromycin and other comparator anti-infective agents were identified. Patients exposed to the selected anti-infective agents were followed for subsequent occurrences of a hospitalization for severe hepatic injury. Comparators included drugs in the class of macrolide, penicillin, and quinolone anti-infective agents. These particular agents were chosen because they are expected being used for similar indications.

#### **Data source**

The population for this study consisted of PIOD enrollees. As of July 2006, the database consisted of over 50 million patients enrolled from over 89 health plans. Patients from these plans are located in the West, South, East and Midwestern United States. Both inpatient and outpatient diagnosis data are included in the database and recorded in the form of International Classification of Disease, Ninth Revision (ICD-9) diagnosis codes. Medical procedures are recorded with ICD-9 procedure codes, Current Procedural Terminology (CPT) codes or Healthcare Common Procedure Coding System (HCPCS) codes. Pharmacy claims contain information on drug name, dosage form, drug strength, fill date, supply days, and quantity dispensed. Prescription drugs can be identified and selected by the National Drug Code (NDC). Demographic data,

such as patient age and gender, as well as enrollment and service data are also available.

### **Study population and eligibility criteria**

Patients to whom telithromycin, Augmentin (amoxicillin and clavulanic acid), clarithromycin, and moxifloxacin were dispensed during the study period were identified. All patients were required to be 18 years of age or older and have at least one year of claims history prior to dispensing to be eligible for the study. Patient with a diagnosis of cancer in the one-year period prior to an eligible anti-infective claim were excluded. A list of ICD-9 codes for cancer is presented in Appendix I. The spontaneous reports showed that a great majority of serious hepatic events, including liver failure, occurred during or shortly following telithromycin treatment. Therefore, a 40-day risk window was used for case identification in order to cover the 5-10 days of therapy and a sufficient time to capture hepatic events that might evolve to result in hospitalization following discontinuation of telithromycin use. Enrollment files were also required to indicate that there were at least 40 days of follow-up subsequent to an anti-infective claim.

### **Outcome definition**

The outcome of interest was an occurrence of severe hepatic injury requiring hospitalization, with or without a prior history of liver disease or disorder, following use of an anti-infective. For any hospitalization occurring

during the risk period, the medical claims of the hospitalization were searched. A hospitalization with a claim of a primary diagnosis code or a procedure code listed in Appendix II was identified as a study outcome of interest.

**Exposure definition**

Once a patient had a claim for an anti-infective agent, telithromycin or other anti-infective agent, the claims from the patient were reviewed to evaluate the eligibility of this patient on the start date of the claim. The risk window for identifying severe hepatic injury requiring hospitalization was defined as the start date of the anti-infective claim and continued for a period of 40 days. If a second claim for the same anti-infective agent was identified during the risk window, it would be considered to be part of the same risk period and counted as the same prescription in the prescription level analysis (e.g. number of prescriptions for the crude risk estimates), with the effect that the time frame for the first claim's risk window would be extended and encompass the period from the date of the first anti-infective claim until 40 days following the start date of the claim for the second anti-infective agent. If a second, but different, anti-infective agent was identified, the risk window for the first anti-infective remained the same and a second exposure period was created for the new anti-infective. Claims for anti-infective agents that occurred outside of the 40-day risk window of earlier dispensed anti-infective agents were treated as new exposures.

**Covariate or potential confounders**

A number of factors that might influence the risk of severe hepatic injury were captured for stratified analysis. These covariates included age, gender, concomitant medication use during the risk window, and a prior history of liver disease during the one-year baseline period. The concomitant medications used during the risk window were identified based on the NDC. Diagnoses associated with claims 14 days prior to and including the start date of each anti-infective dispensing were captured to identify the indication for the drug. The number and seriousness of comorbid diseases within 6 month prior to the start date of each anti-infective dispensing were measured by the Charlson index (Charlson,1987). The ICD-9 codes for identifying prior liver disease are listed in Appendix III.

**DATA ANALYSIS**

Characteristics of each drug cohort are expressed as counts (N) and fractions (%). The 40-day risk was calculated by summing the number of severe hepatic injury cases requiring hospitalization identified within the risk window for each anti-infective agent divided by the total number of prescriptions or patients for the corresponding anti-infective. The crude risk of severe hepatic injury requiring hospitalization associated with use of telithromycin or comparable anti-infective agent was estimated on the prescription-level. The crude risk of severe hepatic injury was also stratified by each covariate. The risk ratio of hepatic injury requiring hospitalization was calculated using the antibiotic group that has the lowest crude risk as the reference. Because each patient could have more

than one prescription for an anti-infective, the generalized estimating equations (GEE) method was used to estimate the risk ratio in order to take into account any possible within subject correlation (Hanley, 2003). Both crude and adjusted risk ratios were calculated. The 95% confidence interval associated with each crude risk or risk ratio estimate was also presented.

## RESULTS

During the study period, between July 2004 and December 2005, there were 124,413, 93,871, 202,456, and 111,336 patients who met the pre-specified study criteria and had had at least 1 claim for telithromycin, Augmentin, clarithromycin, and moxifloxacin respectively. The corresponding numbers of prescriptions for each drug cohort were 137,299, 102,853, 223,095, and 124,078 respectively. The ratio of prescriptions to patients was the same (1.1) for all four drug cohorts. For each corresponding drug cohort, 11, 6, 26, and 21 cases were identified having one or more discharge diagnoses or procedure codes for severe hepatic injury requiring hospitalization.

Table 1 displays the characteristics of the study subjects for each drug cohort. The telithromycin cohort contained fewer males (37%) while the Augmentin cohort had the greatest proportion of male subjects (43%). The average age was 44, 43, 45, and 48 for users of telithromycin, Augmentin, clarithromycin, and moxifloxacin, respectively. Moxifloxacin had the highest composition (11%) of users 65 years of age or older. For the four drug groups, over 97% of the users had no prior history of liver disease or disorder. The



majority (over 80%) of the patients in the study were healthy with a Charlson score of zero for the telithromycin, Augmentin and clarithromycin drug cohorts. About 75% of moxifloxacin users had a Charlson score of zero. The higher the Charlson score the more substantial the morbidity. For telithromycin, Augmentin, and clarithromycin cohorts, about 15% of the users had a Charlson score of 1 or 2, and less than 3% of the users had a Charlson score 3 or over. Over 20% of moxifloxacin cohort had a Charlson score of 1 or 2, and about 5% of the cohort having a Charlson score of 3 or over. Therefore, on average the moxifloxacin cohort was sicker.

The average number of concomitant medication used during the risk window was 4 to 5 drugs among four drug cohorts. More than 90 percent of every drug cohort had been dispensed with concomitant medications other than the study medications. Table 2 describes the most frequent diagnosis associated with claims 14 days prior to and including the start date of each anti-infective dispensing. The percent of patients who did not have a diagnosis during the 14 days period ranged from 16% (moxifloxacin users) to 19% (clarithromycin users) for the four drug cohorts. The most common diagnosis was unspecified acute sinusitis (ICD-9 461.9) for users of telithromycin (21%), Augmentin (20%), and moxifloxacin (17%). For clarithromycin users, acute bronchitis and bronchiolitis (ICD-9 466.0) was the most frequent diagnosis (18%).

Table 3 shows that toxic hepatitis was the most frequent outcome event for the four drug cohorts. The next frequent diagnosis was acute and subacute liver necrosis including acute liver failure for telithromycin, clarithromycin, and

moxifloxacin. Following moxifloxacin use, one patient had a diagnosis of liver failure and also had a liver transplant based on the pre-specified CPT codes.

Table 4 presents the crude risk estimates for severe hepatic injury requiring hospitalization per 100,000 prescriptions and their corresponding 95% confidence intervals for each drug cohort during the study period. The point estimate of the crude risk was the highest for the moxifloxacin cohort and the lowest for the Augmentin cohort. The crude risks were 8.01 (95% CI: 3.28 – 12.75), 5.83 (95% CI: 1.17 – 10.50), 11.65 (95% CI: 7.17 – 16.13), and 16.93 (95% CI: 9.69 – 24.16) cases per 100,000 prescriptions following use of telithromycin, Augmentin, clarithromycin, and moxifloxacin, respectively.

Table 5 displays the crude risk estimates of severe hepatic injury requiring hospitalization per 100,000 prescriptions stratified by gender and age groups for each drug cohort. Male users had higher point estimates compared to female users for the four drug cohorts. The crude risks following telithromycin use were 10.01 (95% CI: 1.24 – 18.78) and 6.87 (95% CI: 1.37 – 12.37) cases per 100,000 prescriptions for male users and for female users respectively. The risk in different age groups was also evaluated. Because of the small numbers of outcome events in each age group, we categorized patients into two age categories: age 18 to 44 years old, and 45 years or older. We chose 45 years old as the cut off based on the age distribution of the four drug cohorts (e.g. the average age of patients ranged from 43 to 48 years old). The age was categorized only in the stratification analysis. In the GEE model described below, age was kept as a continuous variable. The risk of severe hepatic injury varies in

each age group among the four drug cohorts. The risks for the age group 18 to 44 years old were 9.10 (95% CI: 1.82 – 16.38), 5.58 (95% CI: 0 – 11.90), 7.45 (95% CI: 2.29 – 12.61), and 10.41 (95% CI: 1.28 – 19.35) cases per 100,000 prescriptions following the use of telithromycin, Augmentin, clarithromycin, and moxifloxacin, respectively. The corresponding crude risks for the age group 45 years or older were 7.02 (95% CI: 0.87 – 13.17), 6.14 (95% CI: 0 – 13.09), 15.61 (95% CI: 8.40 – 22.82), and 21.06 (95% CI: 10.74 – 31.37) cases per 100,000 prescriptions for these same drugs, respectively.

Table 6 presents the crude risk estimates of severe hepatic injury requiring hospitalization stratified by prior history of liver disease or disorder for each drug cohort. The point estimates for the risk of severe hepatic injury with a prior history of liver disease were consistently higher for the four drug cohorts. The risks of severe hepatic injury with no prior history of liver disease were 5.94 (95% CI: 1.82 – 10.06), 4.96 (95% CI: 0.61 – 9.31), 8.25 (95% CI: 4.44 – 12.07), and 13.24 (95% CI: 6.75 – 19.72) cases per 100,000 prescriptions following the use of telithromycin, Augmentin, clarithromycin, and moxifloxacin, respectively.

Table 7 presents the crude risk estimates of severe hepatic injury requiring hospitalization stratified by the Charlson Index. Among the healthy users (Charlson Index = 0), the crude risk of severe hepatic injury was the highest (9.85 cases per 100,000 prescriptions, 95% CI: 3.41-16.28) among moxifloxacin users, and followed by users of clarithromycin (9.38 cases per 100,000 prescriptions, 95% CI: 4.92 – 13.84), Augment (4.72 cases per 100,000 prescriptions, 95% CI: 0.09 – 9.35), and telithromycin (4.49 cases per 100,000

prescriptions, 95% CI: 0.55 – 8.43). Among the users with comorbid diseases (Charlson Index > 0), the crude risk of severe hepatic injury was the highest among moxifloxacin users (36.72 cases per 100,000 prescriptions, 95% CI: 15.94 – 57.50), and the second highest among telithromycin users (23.06 cases per 100,000 prescriptions, 95% CI: 4.61 – 41.50). Augmentin users with comorbidity had the lowest risk of severe hepatic injury (11.0 cases per 100,000 prescriptions, 95% CI: 0 – 26.24).

Risk estimates stratified by concomitant medication use were not done because all patients with severe hepatic injuries had been dispensed with other medication during the exposure period. Table 8 displays the crude risk estimates stratified by the number of study antibiotic prescriptions during the 40-day risk window each patient had been dispensed. The percentage of patients who had more than one prescription ranged from 12.2% to 14.8% for the four drug cohorts. The point estimates for the risk were higher for patients with more than 1 prescription. The risks with one prescription were 6.45 cases (95% CI: 1.67 – 11.23), 4.88 cases (95% CI: 0.10 – 9.66), 12.94 cases (95% CI: 7.65 – 18.23), and 17.93 cases (95% CI: 9.41 – 26.45) per 100,000 prescriptions associated with use of telithromycin, Augment, clarithromycin, and moxifloxacin respectively.

Table 9 presents the crude and adjusted risk ratios of severe hepatic injury requiring hospitalization following the use of telithromycin, clarithromycin and moxifloxacin using the GEE model. Augmentin was used as the reference group because its crude risk estimate of severe hepatic injury was the lowest

among the four drug cohorts. Compared to the Augmentin cohort, telithromycin cohort had a point estimate of 1.37 (95% C.I., 0.51-3.71) for the crude risk for severe hepatic injury. The point estimate for the clarithromycin cohort was 2.00 (95% CI, 0.82-4.85), which is not statistically significant. However, moxifloxacin cohort had a nearly threefold (2.9, 95% CI, 1.17-7.19) increase in the risk. After adjustment for age, sex, prior history of liver disease, and Charlson index, the risk ratios remained stable except the point estimate in the moxifloxacin cohort was reduced almost 30%, but still maintained its statistical significance. Concomitant medication use was not included in the GEE models because all cases of severe hepatic injury had at least one concomitant medication use during the exposure period.

## **DISCUSSION**

The current study, a retrospective cohort design, evaluated the risk of severe hepatic injury requiring hospitalization among users of telithromycin and other anti-infective agents during the period July 2004 to December 2005 using the PHARMetrics Integrated Outcomes Database. Potential covariates or confounders for the outcome of interest were explored and adjusted for in the risk estimation. The demographic characteristics of the four drug cohorts were similar. The exception was that the moxifloxacin cohort was older and sicker (e.g. more users had comorbid diseases or prior history of liver disorder). The current analysis shows the crude risks of severe hepatic injury requiring hospitalization were in the range from 5.83 to 16.93 per 100,000 prescriptions among users of

the four drug cohorts. The highest risk was among users of moxifloxacin followed by users of clarithromycin, telithromycin, and Augmentin. Only the risk of severe hepatic injury in the moxifloxacin cohort was statistically different from the risk of the reference group (Augmentin cohort). Male gender, prior history of liver disease, users with comorbid diseases, and having more than one prescription of each study anti-infective during the exposure time seems to put one at a higher risk, though small numbers precluded statistical confidence in those estimates.

As known, many drug-induced liver diseases may be asymptomatic and only related to minor liver enzyme abnormalities. These patients are likely to be treated in an outpatient facility and are therefore not included in the current study population. We focused only on the severe liver injuries that required hospitalization because it was important to assess the relative risk across comparable drugs in these rare but severe and medically important outcomes.

In our study drug exposure data were based on pharmacy billing records. Studies (Carson, 1993) have demonstrated that pharmacy billing data are highly accurate and are not subject to recall or interview bias, although compliance with drug use, as with most records-based observation study, cannot be assessed or documented.

A study by Maddrey et al (Maddrey, 2005) showed that factors affecting susceptibility to drug-induced injury include age, gender, concomitant use of other medications, and genetic polymorphism in metabolic pathways involved in activation or disposition of therapeutic drugs. We adjusted for age, sex, a prior

history of liver disease, and Charlson Index in the GEE model. Genetic information was not adjusted in the GEE model because this type of data are not available in the claims database.

The current findings demonstrate that the risks of severe hepatic injury are higher among patients with a prior history of liver disease compared with those without a prior history. Studies (Pan, 2005; Lee, 2005) have shown that drug-induced hepatotoxicity during anti-tuberculosis treatment occurred more frequently in hepatitis B surface antigen (HBsAg) carriers than in non-carriers. The result for the HBsAg test is not recorded in the claims database. In the current analysis, some of the patients with no prior history of liver disorder might be the HBsAg carriers. The carrier status was not taken into account because this information was not recognized or documented in this claims database. Therefore the effect of this condition on the development of severe hepatic injury in antibiotic-exposed persons remains unknown.

Drug-induced hepatic injury (DIHI) is an important clinical problem. Several studies were conducted to evaluate the incidence of DIHI in different population. Studies in Spain and France (Ibanez, 2002; Sgro, 2002) showed that the estimated incidence of DIHI in the general population was 7.4 and 13.9 per 100,000 inhabitants in Spain and France, respectively. De Abajo et al. (de Abajo, 2004) conducted a population –based case-control study using the General Practice Research Database in the U.K. to provide quantitative information about the absolute and relative risks of acute and clinically relevant drug-induced liver injury. Potential cases were identified by computer search and

then validated by medical record review. Only patients with idiopathic liver injury that serious enough to be referred to hospital or a consultant were considered as cases. This study showed that the crude incidence rate for Augmentin was 5.8 per 100,000 prescriptions (95% CI, 1.6 – 9.9). Rodriguez et al. (Rodriguez, 1996) reported that the estimated risk of hepatotoxicity was 17 per 100,000 prescriptions associated with Augmentin use presumably due to the clavulanate component. The injury was mostly cholestatic. Rodriguez et al. (Rodriguez, 1997) also reviewed published epidemiologic studies in order to identify and quantify the risk of acute liver injury associated with individual drugs. Three categories were created: drugs with a risk of acute liver injury greater than 100 per 100,000 users, drugs with a lesser risk but greater than 10 per 100,000 users, and drugs with a risk of less than 10 per 100,000 users. The last group was considered very rare adverse drug reactions according to the classification scheme from the Council for International Organizations of Medical Sciences III Working Party in 1995. Gutthann et al (Gutthann, 1993) conducted a nested case-control study based on a computerized database in Switzerland that contains a large amount of medical care information. The potential cases of liver injury were validated by medical record review. The study reported that the crude risks of acute liver injury resulting in hospitalization was 14 cases per 100,000 prescriptions in current users of erythromycin estolate. The variance observed in these risk or rate estimates are partially due to differences in outcome definitions, study population, and the nature of the data sources. Identifying a potential association between the use of an anti-infective and severe hepatic injury is



difficult mostly because this adverse event is very rare. Of note, the risk of severe hepatic injury following antibiotic use found in the current study is comparable with those reported in the studies mentioned above.

Our current analysis is the first study to investigate the risk of severe hepatic injury requiring hospitalization among users of telithromycin compared to users of anti-infective agents from other classes, including  $\beta$ -lactams, macrolides, and quinolones, using the largest U.S. claims database. The various health insurance plans represented in this study population, including private health maintenance organizations, and preferred provider organizations, maximize the generalizability of the study results.

This study was conducted using the data from a health insurance claims data system PHARMetrics Integrated Outcomes Database that has well-recognized limitations. To establish a diagnosis of DILI requires a careful exclusion of competing causes and an awareness of the hepatotoxicity profile of the suspect agent (Fontana, 2005). This ascertainment is difficult to conduct within a claims database without reviewing the medical record of the patients. The identified cases of severe hepatic injury from the current analysis could not be validated through medical record review because the link between the claims records and medical records is not available with this database. Potential misclassification of the cases is likely. If medical record review was possible, many of the cases identified from the claims database might not be valid which would result in a decrease in the number of cases. This is a common occurrence in claims database research. If there were reasons to believe that the rates of

positive validation were expected to be different across the chosen study drugs, the ranking seen with the non-validated risk could be changes. However, if the validation rates were similar across the four drugs, the ranking would hold. We have no reason to expect differential validation across these drugs. Therefore, we believe that the non-validated risks found in this study, while likely an overestimate of the true risk, represents a defensible ranking. The study shows that with the possible exception of moxifloxacin, these anti-infective agents present a similar risk of severe hepatic injury following exposure. A separate and large epidemiological study with the capability of accessing medical charts for the identified cases based upon the diagnosis codes is needed to complement this study.

Other potential risk factors such as the use of potentially hepatotoxic agents including over-the-counter medication (e.g. acetaminophen), alcohol consumption, body mass index, etc. were not available in the database and therefore were not included in the current analysis. Carson et al (Carson, 1992) conducted a feasibility study of drug-induced acute hepatitis with use of Medicaid data. The study showed that a large proportion of this outcome was due to alcoholism. While that proportion may be lower in the claims database population than the Medicaid population, it remains the leading cause of liver disease as well as one of the leading cause for liver failure. However this information was not systematically captured in the claims database. Therefore its distribution across four drug cohorts as well as its potential role in developing severe hepatic injury could not be evaluated. As shown in the study by Lazerow

et al. (Lazerow, 2005), acetaminophen was reported to be the leading cause of drug induced acute liver failure, accounting for nearly 50% of cases in the US. In the current study, the most frequent indications associated with claims 14 days prior to the index date for the four drug cohorts were upper respiratory infection including acute sinusitis, acute bronchitis and bronchiolitis, acute pharyngitis, acute upper respiratory infections of unspecified site, cough, etc. Use of acetaminophen among these patients is likely to be common. Therefore the estimated risks of severe hepatic injury following antibiotic exposure may include a component that is due to drugs such as acetaminophen. However we cannot see a reason why they would be differential across drug cohorts.

In the current study, moxifloxacin cohort had a higher representation of the elderly.. A study (Thomson, 1995) showed that elderly male had a higher risk of Augmentin associated hepatotoxicity. However, the Acute Liver Failure Study showed no association of increased age with worse outcomes for drug induced liver injury (Lee, 2005). The PIOD population is proportionately younger than the US national data, and it did not provide sufficient numbers of elderly (age 65 years or older) for a rigorous separate analysis of age as a risk factor.

Another known limitation of claims database is that vital status is not routinely recorded. Death information such as cause of death is on file in the State vital statistics office, which is part of the National Death Index. The identified cases with severe hepatic injury can't be linked to the National Death Index without providing the patient's identifier such as name, social security number, birth date, etc. The inability to link this data is due to compliance

requirements set forth by The Health Insurance Portability and Accountability Act (HIPAA) that each database vendor is committed to follow. Therefore the current study could not provide further information for identified cases with fatal outcome.

It is estimated that genetics can account for 20 to 95 percent of variability in drug disposition and effects (Evans, 2003). Although the current study showed that some factors such as prior history of liver disease increase the risk of severe hepatic injury, it was reported (Larrey, 1997) that the most important susceptibility factor for hepatotoxicity is genetic variability. Genetic data were not evaluated in this analysis because testing of biomarkers or single nucleotide polymorphisms that have a known effect on the risk of drug adverse reactions have not been incorporated into regular clinical practice yet. However, the role of pharmacogenomic testing in predicting hepatotoxicity remains important but challenging, for both the preclinical and clinical setting.

## **CONCLUSION**

The current results, although with limitations, provide some evidence that the risk of severe hepatic injury requiring hospitalization following telithromycin use is within the range of other anti-infective agents used for similar indications. The observed non-validated risks of severe hepatic injury following use of any of the four anti-infective agents could be attributed to factors such as the underlying medical conditions, the use of other prescription medications, the use of OTC analgesics, alcohol consumption, the exposure to the antibiotic of interest, or due to misclassification.

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Table 1 - Patient characteristics for each drug cohort

	Telithromycin	Augmentin	Clarithromycin	Moxifloxacin
All	N=124,413	N=93,871	N=202,456	N=111,336
Gender (%)				
Male	36.93	43.14	40.73	39.25
Female	63.03	56.80	59.21	60.72
Mean Age (yr)	44.67	43.13	44.65	48.33
Mean age by gender (yr)				
Male	44.50	43.39	44.52	48.22
Female	44.77	42.95	44.76	48.50
Age (%)				
18 – 24	7.49	10.58	8.89	4.85
25 - 34	15.48	16.96	15.05	11.88
35 - 44	25.53	25.22	24.66	22.54
45 - 54	27.26	25.62	26.51	27.87
55 - 64	19.18	16.72	18.40	22.19
65 - 74	3.88	3.43	4.56	6.52
75- 84	0.90	0.93	1.45	2.93
85 +	0.20	0.30	0.31	1.18
Prior History of liver disease (%)				
Yes	1.93	2.00	2.24	2.54
No	98.07	98.00	97.76	97.46
Charlson index (%)				
0	81.84	82.93	81.83	74.60
1	10.94	8.90	10.36	14.13
2	4.88	5.64	5.19	6.56
3	2.20	2.29	2.38	4.38
4	0.09	0.15	0.16	0.20
5	0.02	0.04	0.03	0.04
6	0.03	0.05	0.05	0.07



Table 2 The three most frequent diagnoses associated with claims 14 days prior to the index date for each drug cohort

	Telithromycin		Augmentin		Clarithromycin		Moxifloxacin	
	ICD-9	N (%)	ICD-9	N (%)	ICD-9	N (%)	ICD-9	N (%)
1st most freq Dx	Acute sinusitis	28300 (20.6)	Acute sinusitis	20583 (20.3)	Acute bronchitis & bronchiolitis	39599 (17.7)	Acute sinusitis	21431 (17.3)
2 <sup>nd</sup> most freq Dx	Acute bronchitis & bronchiolitis	22907 (16.7)	Acute pharyngitis	7952 (7.7)	Acute sinusitis	32492 (14.6)	Acute bronchitis & bronchiolitis	19964 (16.1)
3 <sup>rd</sup> most freq Dx	Acute URI, unspecified site	13709 (10.0)	Acute bronchitis & bronchiolitis	6616 (6.4)	Acute URI, unspecified site	18314 (8.2)	Cough	11562 (9.3)

Table 3 Distribution of severe hepatic injury events for each drug cohort

Outcome event	Telithromycin	Augmentin	Clarithromycin	Moxifloxacin
Liver necrosis, including acute hepatic failure	4	1	11	8
Hepatic coma	1	2	2	4
Toxic hepatitis	7	4	17	11
Liver transplant	0	0	0	2**
Total number of cases*	11	6	26	21

\* One case could be diagnosed with more than one event.

\*\* This represents one patient who was recorded for liver transplant anesthesia and liver transplant as two events with two different CPT codes.

Table 4      Crude risk estimates of severe hepatic injury for each drug cohort – per 100,000 prescriptions (Rxs)

	Telithromycin	Augmentin	Clarithromycin	Moxifloxacin
Number of cases	11	6	26	21
Number of Rxs	137,299	102,853	223,095	124,078
Crude risk per 100,000 Rxs (95% C.I.)	8.01 (3.28-12.75)	5.83 (1.17-10.50)	11.65 (7.17-16.13)	16.93 (9.69-24.16)

Table 5 Crude risk estimates of severe hepatic injury by age and sex for each drug cohort – per 100,000 Rxs

	Telithromycin		Augmentin		Clarithromycin		Moxifloxacin	
Gender	# of cases	Risk (95% CI)	# of cases	Risk (95% CI)	# of cases	Risk (95% CI)	# of cases	Risk (95% CI)
Male	5	10.01 (1.24-18.78)	3	6.81 (0-14.51)	16	17.78 (9.07-26.50)	11	22.85 (9.35-36.36)
Female	6	6.87(1.37-12.37)	3	5.11 (0-10.89)	10	7.52 (2.86-12.18)	10	13.17 (5.01-21.34)
Age								
18 – 44	6	9.10 (1.82-16.38)	3	5.58 (0-11.90)	8	7.45 (2.29-12.61)	5	10.41 (1.28-19.35)
45 +	5	7.02 (0.87-13.17)	3	6.14 (0-13.09)	18	15.61 (8.40-22.82)	16	21.06 (10.74-31.37)

Table 6 Crude risk estimates of severe hepatic injury by prior history of liver disease for each drug cohort -  
Per 100,000 Rxs

	Telithromycin	Augmentin	Clarithromycin	Moxifloxacin
Without a prior History of liver disease				
Number of cases	8	5	18	16
Number of Rxs	134613	100737	218063	120882
Crude risk per 100,000 Rxs (95% C.I.)	5.94 (1.82-10.06)	4.96 (0.61-9.31)	8.25 (4.44-12.07)	13.24 (6.75 –19.72)
With a prior History of liver disease				
Number of cases	3	1	8	5
Number of Rxs	2686	2116	5032	3196
Crude risk per 100,000 Rxs (95% C.I.)	111.69 (0-238.08)	47.26 (0-139.89)	158.98 (48.81-269.15)	156.45 (19.31-293.58)

Table 7 Crude risk estimates of severe hepatic injury by Charlson Index for each drug cohort - per 100,000 Rxs

	Telithromycin	Augmentin	Clarithromycin	moxifloxacin
Charlson Index = 0				
No. of cases	5	4	17	9
No. of Rxs	111274	84665	181228	91399
Crude risk per 100,000 Rx (95% C.I.)	4.49 (0.55-8.43)	4.72 (0.09-9.35)	9.38 (4.92-13.84)	9.85 (3.41 –16.28)
Charlson Index > 0				
No. of cases	6	2	9	12
No. of Rxs	26,025	18,188	41,867	32,679
Crude risk per 100,000 Rx (95% C.I.)	23.06 (4.61-41.50)	11.00 (0.00-26.24)	21.50 (7.45-35.54)	36.72 (15.94-57.50)

Table 8 Crude risk estimates of severe hepatic injury by number of Rx's for each drug cohort - per 100,000 users

Drug/ No. of Rx	No. of users	No. of cases	Risk per 100,000 users (95% C.I.)
Telithromycin			
1 Rx	108500	7	6.45 (1.67-11.23)
>1 Rx	15913	4	25.14 (0.50-49.77)
Augmentin			
1 Rx	82002	4	4.88 (0.10-9.66)
>1 Rx	11869	2	16.85 (0-40.20)
Clarithromycin			
1 Rx	177696	23	12.94 (7.65-18.23)
>1 Rx	24760	3	12.12 (0-25.83)
Moxifloxacin			
1 Rx	94814	17	17.93 (9.41-26.45)
>1 Rx	16522	4	24.21 (0.48-47.94)

Table 9 Crude and adjusted\* risk ratio estimates using Augmentin as a reference group - per 100,000 Rxs

	Crude risk ratio	95% C.I.	Adjusted risk ratio	95% CI
Telithromycin	1.37	0.51 – 3.71	1.44	0.53 – 3.89
Clarithromycin	2.00	0.82 – 4.85	1.95	0.80 – 4.73
Moxifloxacin	2.90	1.17 – 7.19	2.58	1.04 – 6.43
Augmentin	1.00	N/A	1.00	N/A

\* Covariates age, sex, prior history of liver disease, and Charlson Index were adjusted in the GEE model.



## Appendix I

### ICD-9 Codes for Cancer Diagnoses

ICD-9 140.x-149.x	Malignant neoplasm of the lip, oral cavity, and pharynx
ICD-9 150.x-159.x	Malignant neoplasm of the digestive organs and peritoneum
ICD-9 160.x-165.x	Malignant neoplasm of the respiratory and intrathoracic organs
ICD-9 170.x-176.x	Malignant neoplasm of the bone, connective tissue, skin, and breast
ICD-9 179.x-189.x	Malignant neoplasm of the genitourinary organs
ICD-9 190.x-199.x	Malignant neoplasm of other and unspecified sites
ICD-9 200.x-208.x	Malignant neoplasm of the lymphatic and hematopoietic tissue
ICD-9 230.x-234.x	Carcinoma in-situ
ICD-9 235.x-238.x	Neoplasm of uncertain behavior
ICD-9 239.x	Neoplasm of unspecified nature

## Appendix II

### **ICD-9 and CPT Codes for Severe Hepatic Injury (Code must be present as a primary diagnosis for a hospitalization)**

#### Primary diagnosis

ICD-9 570.x	Acute and subacute necrosis of liver
ICD-9 572.2	Hepatic coma
ICD-9 573.3	Toxic (non-infectious) hepatitis

#### Procedure

CPT 47135	Liver transplant
CPT 47136	Liver transplant
CPT 47140	Liver transplant
CPT 47141	Liver transplant
CPT 47142	Liver transplant
CPT 00796	Anesthesia - liver transplant

## Appendix III

### **ICD-9 and CPT Codes for Prior Liver Disease (Code could be either an inpatient or outpatient code during the one-year baseline period)**

#### Diagnosis

ICD-9 070.x	Viral hepatitis
ICD-9 570.x	Acute and subacute necrosis of liver
ICD-9 571.x	Chronic liver disease and cirrhosis
ICD-9 572.x	Liver abscess and sequelae of chronic liver disease
ICD-9 573.x	Other disorders of liver
ICD-9 782.4	Jaundice unspecified, not of newborn

#### Procedure

CPT 47135	Liver transplant
CPT 47136	Liver transplant
CPT 47140	Liver transplant
CPT 47141	Liver transplant
CPT 47142	Liver transplant
CPT 00796	Anesthesia - liver transplant