

FDA Advisory Committee

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KETEK[®] (telithromycin)

sanofi-aventis US

Epidemiology

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Global Pharmacovigilance and Epidemiology

Investigation with FDA FOI Database

- Spontaneous adverse event reports to detect drug safety signals
 - disproportionality analysis
 - reporting rate analysis
- Severe hepatic injury was observed in spontaneous reports and warranted further investigation by epidemiological studies.

Epidemiological Investigation of Hepatic Injury

- 1) PHARMetrics Integrated Outcome Database
- 2) Ingenix Proprietary Research Database

Final study protocols were submitted to both FDA and EMEA in August 2006.

Epidemiological Investigation of Hepatic injury

PHARMetrics Integrated Outcome Database

PHARMetrics Integrated Outcome Database

- Integrated enrollment, medical, and prescription claims data
- Members in all 50 states and the District of Columbia
 - includes data from 1995 to 2006
 - currently includes 89 healthcare plans
 - approximately 12 million active enrollees in June 2005

Study Design

- Objective: To evaluate risk of severe hepatic injury among telithromycin users in comparison with other oral anti-infectives of similar indications (Augmentin, clarithromycin, and moxifloxacin)
- Study Design: Retrospective cohort study
- Study population: 18-yr or older with at least 1-yr enrollment; cancer patients were excluded from the study

Study Design (2)

- Exposure: use of telithromycin (TEL), Augmentin (AUG), clarithromycin (CLA), or moxifloxacin (MOX)
- Risk window: 40 days following dispensing of an antibiotic
- Outcome: Severe hepatic injury
- Study period: Jul 2004 - Feb 2006

Definition of Severe Hepatic Injury

- Severe hepatic injury is captured by inpatient diagnosis and procedure codes:
 - ICD-9 code 570 (Acute or subacute necrosis of liver, including acute hepatic failure, acute or subacute hepatitis not specified as infective, acute or subacute necrosis of liver, etc)
 - ICD-9 code 572.2 (Hepatic coma)
 - ICD-9 code 573.3 (Hepatitis unspecified, i.e. toxic, noninfectious, hepatitis)
 - CPT codes 47135, 47136, 47140, 47141, and 47142 (Liver transplant)
 - CPT code 00796 (Anesthesia - liver transplant)

Patient Characteristics

	TEL	AUG	CLA	MOX
No. of Patients	N=124,413	N=93,871	N=202,456	N=111,336
No. of Rxs	137,299	102,853	223,095	124,078
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
Prior Hx 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	18.16	17.07	18.17	25.40

Distribution of Severe Hepatic Injury Events

Event	TEL (N=124,413)	AUG (N=93,871)	CLA (N=202,456)	MOX (N=111,336)
Liver necrosis	4	1	11	8
Hepatic coma	1	2	2	4
Hepatitis unspecified	7	4	17	11
Liver transplant	0	0	0	1
Total*	11	6	26	21

* One patient may have >1 event.

Crude Risk Estimates of Severe Hepatic Injury

	TEL	AUG	CLA	MOX
No. of events	11	6	26	21
No. 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)

Crude Risk Estimates of Severe Hepatic Injury by History of Liver Disorders

	TEL	AUG	CLA	MOX
Without a prior history of liver disorder				
No. of events	8	5	18	16
No. of Rxs	134,613	100,737	218,063	120,882
Crude risk per	5.94	4.96	8.25	13.24
100,000 Rxs (95% C.I.)	(1.82 – 10.06)	(0.61 – 9.31)	(4.44 – 12.07)	(6.75 – 19.72)

Crude Risk Estimates of Severe Hepatic Injury by History of Liver Disorders

	TEL	AUG	CLA	MOX
Without a prior history of liver disorder				
No. of events	8	5	18	16
No. of Rxs	134,613	100,737	218,063	120,882
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 disorder				
No. of events	3	1	8	5
No. of Rxs	2,686	2,116	5,032	3,196
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)

Crude Risk Estimates of Severe Hepatic Injury by Charlson Index

	TEL	AUG	CLA	MOX
Charlson Index = 0				
No. of events	5	4	17	9
No. of Rxs	111,274	84,665	181,228	91,399
Crude risk per 100,000	4.49	4.72	9.38	9.85
Rxs (95% C.I.)	(0.55 – 8.43)	(0.09 – 9.35)	(4.92 – 13.84)	(3.41 – 16.28)

Crude Risk Estimates of Severe Hepatic Injury by Charlson Index

	TEL	AUG	CLA	MOX
Charlson Index = 0				
No. of events	5	4	17	9
No. of Rxs	111,274	84,665	181,228	91,399
Crude risk per 100,000 Rxs (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 ≥ 1				
No. of events	6	2	9	12
No. of Rxs	26,025	18,188	41,867	32,697
Crude risk per 100,000 Rxs (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)

Crude and Adjusted Risk Ratios of Severe Hepatic Injury

	Crude		Adjusted*	
	Risk ratio	95% C.I.	Risk ratio	95% C.I.
AUG **	1.00	N/A	1.00	N/A
CLA	2.00	0.82 – 4.85	1.95	0.80 – 4.73
MOX	2.90	1.17 – 7.19	2.58	1.04 – 6.43
TEL	1.37	0.51 – 3.71	1.44	0.53 – 3.89

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

** Augmentin was used as a reference group in the GEE model

Summary of Epidemiological Investigation of Hepatic Injury by sanofi-aventis

- Data from a retrospective cohort study using PHARMetrics database shows that:
 - risk of severe hepatic injury following telithromycin use falls within the range demonstrated by other oral antibiotics

Epidemiological Investigation of Hepatic Injury

Ingenix Proprietary Research Database

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