

## **APPENDIX C: POSTMARKETING SAFETY METHODS**

**PMS Methodology**

**AESI checklist for visual adverse events**

**AESI form for hepatic events**

**AESI form for cardiac adverse events**

## 1.1 SAFETY DATA COLLECTION

Spontaneous adverse event reports may be received from health care professionals, consumers, Health Authorities, or via published literature and may take various forms (eg, letters, telephone contacts, or brief contact reports from field sales representatives after in-office contacts). Within 48 hours of receipt by any sanofi-aventis employee, these reports are forwarded to the local pharmacovigilance unit for review, to ensure adequate data collection for reporting.

The safety information is consolidated by the local safety officer, and a “Suspected Adverse Drug Reaction (ADR)” form is completed. For all serious cases, a full narrative of all relevant case details is required. In general, no narrative is required for nonserious and listed AE reports. For these cases<sup>1</sup>, the narrative contains any additional information not otherwise captured in the database fields and addresses any aspects which may otherwise be difficult to understand. The information captured on the Suspected ADR form may not always be a verbatim translation of all written documents (where available), but is intended to capture all of the medically salient items from the report.

These forms are then forwarded for entry into a single worldwide clinical safety database (ClinTrace), which serves as the repository for all adverse events occurring with telithromycin. (sanofi-aventis entry sites include 2 global sites located in Bridgewater, New Jersey, USA, and Chilly-Mazarin, France, as well as 4 non-global data entry sites in Germany, France, the United States, and Japan.) Forms are transmitted within 24 hours for serious cases and within 10 days for nonserious cases.

## 1.2 MEDICAL EVALUATION AND FOLLOW-UP

At the global site, sanofi-aventis corporate safety officers review all cases entered into the safety database. These safety officers all have medical training, with either medical (MD) or Pharmacy (PharmD) doctoral degrees.

Their medical review includes an evaluation of the correctness, completeness and consistency of the clinical information, especially with respect to seriousness, labeling and the determination of additional necessary follow-up information. All spontaneous report cases are considered to have an implied causality by the reporter. Nevertheless, the safety officers take other factors into consideration when reviewing the case, such as the adequacy of available information, the temporal relationship between drug administration and the onset of the event, dechallenge/rechallenge results, and possible alternative explanations for the reported event(s).

The local safety officer is responsible for pursuing standard follow-up information (eg, event outcome, lot/batch number for the suspect drug, concomitant medications, co-morbid diseases) as well as the additional information requested by the corporate officer who has reviewed the case.

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<sup>1</sup> Unlisted refers to those adverse events not identified in the labeling for the drug.

Requests for additional follow-up information on spontaneous reports are generally made in writing to the reporting health care provider or regulatory authority. In some instances, telephone calls are made to expedite the receipt of information or to clarify a particular point.

Special emphasis is placed on requesting follow-up information in serious unlisted cases, and in cases involving death, life-threatening events, or “special interest” events (for telithromycin, these AESI including hepatic, cardiac and visual AEs). For the latter telithromycin AESIs, augmented pharmacovigilance activities implemented since May 2003 include additional questionnaires designed to collect consistent specific detailed information for these cases. These forms are sent to reporters at time of case receipt in an attempt to enhance the clinical detailed information for these events of interest. Copies of these AESI forms are included in the appendices to this document.

sanofi-aventis makes its best efforts to rigorously follow-up spontaneous reports, particularly those designated serious and AESI reports; operating procedures require that a minimum of 2 attempts be made to collect relevant follow-up information. It should be noted, however, that the receipt of follow-up information depends upon the willingness or ability of the reporting health care provider to locate, collect and submit the data. Follow-up information is entered, along with the date of receipt, as an identified addendum to the original case narrative.

As part of the ongoing close surveillance of hepatic reports, sanofi-aventis began submitting all hepatic SAE reports received from outside of the US to the FDA, although the reporting of these events (as expected/listed events) are not required by regulations and have not, to our knowledge, been routinely submitted for other antibiotics with hepatitis included in their labeling.

#### Aggregate safety review

The corporate safety physicians are not only responsible for individual case review of serious, unlisted and associated cases, but also for aggregate safety analysis, management of global safety issues, and safety signal detection. For this purpose, ClinTrace is utilized to monitor and report safety information, as well as to detect and analyze potential safety signals.

It should be noted that adverse events are described in terms of diagnoses and symptoms, with each case requiring at least 1 diagnosis. For spontaneous reports, all reporter-designated diagnoses are entered into the database as ‘diagnoses,’ linked to their respective symptoms. Symptoms are assumed to have the same characteristics (ie, seriousness, outcome) as the diagnoses to which they are linked. If a reporter fails to designate terms as either ‘diagnoses’ or ‘symptoms,’ sanofi-aventis will enter each of the reported terms in a ‘diagnoses’ database field.

Adverse event data tables include MedDRA coded terms from both the ‘diagnoses’ and ‘symptoms’ database fields, eg, all terms provided by the reporter, not just the term considered to be the diagnosis. In some cases, this merging of diagnoses and symptoms will result in redundancy of individual reports. For example, a single case report with a ‘diagnosis’ of hepatic injury and ‘symptoms’ of alanine transaminase (ALT) elevation and aspartate transaminase (AST) elevation will be counted 3 times within the hepatic event totals, ie, an individual case report will have 3 events associated with it.

For telithromycin, aggregate postmarketing safety analyses have been performed at frequent intervals, particularly for the designated events of interest. In addition to the required IND reports and NDA annual and periodic reports, cumulative analyses of hepatic, visual, and cardiac (including syncope) events were performed at 6-month intervals in Periodic Safety Update Reports (PSURs), covering the period from January 2002 through September 2006. While these PSURs are submitted in Europe as part of the International Conference on Harmonization (ICH) guidance for safety reporting, these reports were also submitted to the US FDA (where they are not required) to maintain complete safety reporting between worldwide agencies.

In addition, a separate analysis for syncope was performed in February 2005; hepatic analyses were also performed in June 2005, February 2006, June 2006, July 2006, and August 2006; and a detailed cumulative postmarketing visual analysis, performed as a postmarketing commitment, was completed in October 2006.



## Visual Events of Interest for Ketek (telithromycin) Follow-up Questions

<b>Case Number:</b>		<b>Country:</b>	
<b>Adverse Reaction(s):</b>			
<b>Onset:</b> DD/MM/YY	<b>As reported:</b>	<b>As coded:</b>	<b>Outcome:</b> (recovered, ongoing, unknown, death)

Does the patient have any history of visual abnormalities?  No  Yes

If yes, please specify:

Mark any of the symptoms patient complains of:

**a. blurred vision?**  No  Yes\*

\*If yes  Distance vision only  Near vision only  Both distance and near vision

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**b. abnormalities of color vision**  No  Yes\*

\*If yes  Colors appear darker  Colors appear lighter  Color tinges around objects

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**c. abnormalities of light perception?**  No  Yes\*

\*If yes  Increased brightness  Flashing lights when blinking

**Visual Episode: (complete separate form for each visual episode described)**

**Onset of episode relative to dose:** Date: \_\_/\_\_/\_\_ and Day of treatment:

DD/MM/YY

Timing after dose:

Reporting Date: \_\_/\_\_/\_\_ DD/MM/YY

Minutes:   or Hour(s):   .  Unknown:

Duration of episode: Minutes:   or Hour(s):   .  Unknown:

**Visual Event:**

**Description of event:**

<input type="checkbox"/>	Continuous, lasting several days	
<input type="checkbox"/>	Episodic, occurring with each dose	Number of episodes: <input style="width: 40px;" type="text"/>
<input type="checkbox"/>	Other, describe:	

.....

.....



**Case Number:**

**Impact on activity:**  No  Yes  Unknown

**If "Yes", indicate all that apply:**

General impairment/ not specified	<input type="checkbox"/>	Reading	<input type="checkbox"/>	Writing	<input type="checkbox"/>	Driving	<input type="checkbox"/>
Working	<input type="checkbox"/>	Walking	<input type="checkbox"/>	Watching TV	<input type="checkbox"/>	Eating	<input type="checkbox"/>
Other (specify):	<input type="checkbox"/>						

**Does the patient complain of any of the following associated symptoms:**

Nausea	<input type="checkbox"/>	Vomiting	<input type="checkbox"/>	Headache	<input type="checkbox"/>
Dizziness	<input type="checkbox"/>	Vertigo	<input type="checkbox"/>	Lightheadedness	<input type="checkbox"/>
Incoordination or loss of balance	<input type="checkbox"/>	Other (specify):	<input type="checkbox"/>		

**Discontinued treatment:**  No  Yes, date:   /  /    
DD/MM/YY

**Was the patient seen by an optometrist or ophthalmologist?**  No  Yes\*

\*If yes, please attach report for any evaluations performed.

**Exam/tests performed:**  No  Yes  Unknown

If "Yes", date:   /  /    
DD/MM/YY

If date not available, was exam performed

During Event  After event  Unknown

**If "Yes", indicate all that apply:**

Physical	<input type="checkbox"/>	Ophthalmologic	<input type="checkbox"/>	Fundoscopy	<input type="checkbox"/>
Visual fields	<input type="checkbox"/>	Visual acuity	<input type="checkbox"/>	CT scan	<input type="checkbox"/>
Other (specify):	<input type="checkbox"/>			MRI	<input type="checkbox"/>



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**Case Number:**

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**Describe examination findings:**

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## Hepatic Events of Interest for Ketek (telithromycin) Follow-up Questions

**History**

Associated signs/symptoms:

- |                                  |                                   |  |
|----------------------------------|-----------------------------------|--|
| <input type="checkbox"/> Fatigue | <input type="checkbox"/> Jaundice | <input type="checkbox"/> Abdominal pain            |
| <input type="checkbox"/> Nausea  | <input type="checkbox"/> Rash     | <input type="checkbox"/> Right upper quadrant pain |
| <input type="checkbox"/> Fever   | <input type="checkbox"/> Pruritis | <input type="checkbox"/> Dark urine                |

Any history of

alcohol use? **Yes / No** Please quantify:

acetaminophen use? **Yes / No** Please quantify:

corticosteroid use? **Yes / No** Please quantify:

Any history of herbal, homeopathic, or over-the-counter drug use? **Yes / No**

List all medications taken

Drug	Route	Daily Dose	Duration	Start Date	Stop Date	Indication

Any history of viral hepatitis, other previous liver disease, or abnormal liver tests?

**Yes / No**

Any contacts with similar symptoms in the same time period? **Yes / No**

Any evidence of uncontrolled heart failure at the time of the event? **Yes / No**

Any history of cancer? **Yes / No** Type:

Known metastases? **Yes / No** Location:

Any suspected sepsis associated with the underlying infection? **Yes / No**

Any suspected hypotension associated with the underlying infection? **Yes / No**

Any clinical suspicion of acute gallstones? **Yes / No**

**Laboratory evaluations**

Provide dates and results of any tests performed (baseline, event, and recovery)

*Use additional sheets as necessary*

- Transaminases
- Alkaline phosphatase
- Bilirubin (total and fractionated)
- Hepatitis A, B, and C titers
- Anti nuclear antibodies
- Anti-mitochondrial antibodies
- Anti-smooth muscle antibodies
- Anti-DNA antibodies
- WBC count with differential
- Prothrombin Time
- Ultrasound scan
- CT scan
- Liver biopsy



## Cardiac Events of Interest for Ketek (telithromycin) Follow-up Questions

**History**

Was an electrocardiogram done? **Yes / No** Findings:

Provide ECG and previous ECG for comparison

Were any of the following symptoms associated with the event:

- Chest pain                       Nausea             Lightheadedness
- Shortness of breath       Palpitations

How was the onset of symptoms? **Sudden / Progressive**  
Duration?

Any Loss of Consciousness? **Yes / No**

Was this witnessed? **Yes / No**

Any history of Cardiac Disease, particularly

Coronary artery disease **Yes / No**

Heart failure (known EF or NYHA classification) **Yes / No**

Ventricular arrhythmia **Yes / No**

Loss of consciousness **Yes / No**

List all medications taken

Drug	Route	Daily Dose	Duration	Start Date	Stop Date	Indication

Does the patient have an Implantable Cardioverter Defibrillator? **Yes / No**

Does the patient have a pacemaker? **Yes / No**

Was the patient evaluated by a cardiac specialist? **Yes / No**

Provide medical records

Was the patient hospitalized? **Yes / No**

Provide medical records

Was the patient diagnosed with an acute myocardial infarction within 1 week of the event? **Yes / No**

Provide work-up results (cardiac enzymes, ECGs, cardiac catheterization, etc)

**Laboratory evaluations**

Provide dates and results of any tests performed (baseline, event, and recovery)

*Use additional sheets as necessary*

- Serial cardiac enzymes (CPK with isoenzymes, troponin)
- Echocardiogram
- Nuclear scan
- Coronary angiogram
- Holter monitor
- Potassium
- Magnesium