Southwest
Oncology Group
A National Clinical Research Group

January 15, 2001

TO: ALL SOUTHWEST ONCOLOGY GROUP, CCOP, AFFILIATE AND UCOP MEDICAL ONCOLOGISTS, RADIATION ONCOLOGISTS AND PATHOLOGISTS

FROM: Southwest Oncology Group Operations Office

RE: Adverse Event Possibly Associated with Gemzar (Gemcitabine Hydrochloride)

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## MEMORANDUM

Attached is a memorandum from Eli Lily and Company regarding serious adverse events (SAEs) that occurred in association with the drug Gemzar (Gemcitabine Hydrachloride). These events DID NOT occur on a Southwest Oncology Group protocol, and we have no information regarding the protocols on which the events occurred. The following Southwest Oncology Group and Intergroup protocols may have patients enrolled who are receiving gemticabine.

## ACTIVE PROTOCOLS

**R9704**

## CLOSED PROTOCOLS

**S9810** **S9708** **S9801**

**S9803** **S9718** **S9802** **S9806**

Protocol amendments are not necessary at this point, but your consent form may be revised to include the information provided in this letter if it is deemed necessary by your institution. Please forward this memorandum and letter to your Institutional Review Board (IRB) immediately for review. Should any further information regarding these SAEs be made available, it will be forwarded to you.

**A copy of this correspondence should be attached to the front of each of the above-noted protocols and kept in your files for future reference**.

cc: Southwest Oncology Group Statistical Center
Nickey McCasland, R.N.
Elaine Pakuris - RTOG
Dana Nordbeck, R.N., M.S. - Lilly Oncology
Joseph Ashland - Lilly Oncology
Michael Proctor - OTN

www.lilly.com

Lilly Research Laboratories
A Division of Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285 U.S.A.

Phone 317 276 2000

# Notice to Investigators
## Expedited Safety Report of an Adverse Drug Reaction

Dear Investigator; Sehr geehrte(r) Kollegin(e); Estimado Investigador; 治験責任医師の皆様へ

Please find the enclosed expedited safety report(s). This report describes an event that is serious, unexpected, and may have a reasonable possibility of being caused by the study drug. This report is being submitted to the appropriate regulatory authorities by the sponsor.
We believe this report may be helpful to you. Please share this information with any co-investigators who are assisting you in the care of your patients and pursuit of your protocol. It is your responsibility to promptly forward this report to your Ethical or Institutional Review Board (ERB/IRB). In addition, please keep this report and any correspondence to the ERB/IRB in your files for this study.

Anbei erhalten sie eine(mehrere) unverzügliche Meldung(en) unerwünschter Arzneimittelwirkung(en). Diese Meldungen beschreiben Ereignisse, die schwerwiegend und unerwartet sind und möglicherweise in Zusammenhang mit der Gabe der Studienmedikation stehen. Als Sponsor der Studie unterrichten wir unverzüglich auch die zuständigen Behörden, sofern dies erforderlich ist.
Wir sind der Auffassung, daß diese Berichte für Sie in der Betreuung Ihrer Patienten nützlich sein können. Wir möchten Sie bitten, die Informationen ggf. auch weiteren Prüfärzten Ihres Zentrums mitzuteilen, die an der Betreuung der Patienten und der Durchführung der Studie beteiligt sind.
Es obliegt Ihrer Verantwortung, die Ethikkommission über alle schwerwiegenden oder unerwarteten unerwünschten Ereignisse, die während der Studie auftreten und die Sicherheit der Studienteilnehmer oder die Durchführung der Studie beeinträchtigen können zu unterrichten. Bitte berücksichtigen Sie hierbei auch die Empfehlungen Ihrer zuständigen Ethikkommission. Weiterhin empfehlen wir, diese Meldungen sowie die gesamte Korrespondenz mit der Ethikkommission in Ihren Prüfunterlagen aufzuheben.

Sirvase revisar el(los) reporte(s) de seguridad urgente(s) adjunto(s). Este reporte corresponde a un Evento Adverso que puede ser Serio, Inesperado, y puede tener alguna razonable posibilidad de haber sido causado por la droga en estudio. Este reporte esta siendo sometido a las Autoridades Regulatorias correspondientes por el patrocinante del estudio.
Consideramos que éste reporte será de su utilidad. Por favor comparta esta información con cada uno de los co-investigadores quienes lo asistan en el cuidado de sus pacientes y en la completación de su protocolo. El pronto envío del presente reporte al Comite de Etica / Comision Revisora Institucional (CE/CRI) de su respectivo centro, forma parte de sus responsabilidades. Así mismo, agradecemos que mantenga el presente reporte así como cualquier otra correspondencia dirigida al CE/CRI en los archivos del presente estudio.

緊急安全性報告を同封致します。本報告は、「予期しない重篤な事象」で、治験薬との関連が疑われる事象について報告したもので、本邦における治験依頼者により、国内規制に照らし合わせた後に、必要であれば厚生省に提出される予定でございます。

本報告は必ずや先生方のお役に立つものと存じます。つきましては、治験に参加されている患者様の治療及びプロトコールの遂行を補佐されているすべての治験分担医師の方々にも本情報をご伝達賜ります様お願い申し上げます。
なお、英文中には「施設内治験（倫理）審査委員会に本報告を提出する必要がある」との記載がございますが、本邦においては不要でございます。ただし、別に本邦における治験依頼者より送付される日本語の治験薬に関する安全性情報につきましては、施設内審査委員会での審議の必要性について別途ご検討賜ります様お願い申し上げます。

***Please refer to the back side of this letter for instructions on how to read the Medwatch form.***

The following information may help you interpret the Medwatch form, which is used for expedited safety mailings to investigators.

- The research and study codes may be found at the beginning of the text in Section B, Box 5, as well as Section G, Box 6.
- Section G, Box 7 will state whether this is a new case or follow-up to a previously reported case. If it is follow-up, there will be a brief statement(s) at the end of the narrative summary describing what was added or changed in the report.
- Section C, Box 4 lists the indication for use (IFU). If an * is there instead, please refer to the last page for the IFU; it was too long to print in the box on page 1.
- In most clinical trials, the suspect drug will be named in Section C, Box 1. However, in some clinical trials, the suspect drug will be reported as "Blinded Therapy", which means the suspect drug could be either the actual study drug, placebo, or the comparator.

# MEDWATCH
THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Eli Lilly and Company

Page 1 of 2

Domain Facsimile — Approved by FDA on 3/22/94

Mfr report # EWC001208804

UF/Dist report #

FDA Use Only

## A. Patient information

| 1. Patient identifier | 2. Age at time of event: | 3. Sex | 4. Weight |
|---|---|---|---|
| in confidence | 48 yrs or Date of birth: * | ☐ female ☒ male | 132 lbs or 60 kgs |

## B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)
- ☒ death 11/01/1999 (mo/day/yr)
- ☐ life-threatening
- ☐ hospitalization - initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other:

3. Date of event (mo/day/yr): 19/AUG/1999

4. Date of this report (mo/day/yr): 13/DEC/2000

5. Describe event or problem

Investigator Copy to B9E

THIS CLINICAL TRIAL CASE NOT FOR REGISTRATION, CONCERNS A 49 YEAR OLD MALE WHO EXPERIENCED HEPATITIS B AND HEPATITIS C AND DIED. HE WAS RECEIVING GEMCITABINE AND CISPLATIN (INDICATION UNKNOWN). THERE WAS NO RELEVANT HISTORY. CONCOMITANT MEDICATIONS WERE UNKNOWN.

HE FIRST RECEIVED GEMCITABINE (2018MG ON DAY 1 AND 8 OF A 21 DAY CYCLE) AND CISPLATIN (129MG ON DAY 1 OF THE CYCLE) ON 10-JUN-1999 AND LAST RECEIVED A DOSE OF STUDY DRUGS ON 12-AUG-1999 (CUMULATIVE DOSE OF GEMCITABINE GIVEN WAS 14090MG AND CISPLATIN WAS 515MG). ON 19-AUG-1999, ON DAY 8 OF CYCLE 4, HE *

6. Relevant tests/laboratory data, including dates

Lab data:
Lab test or Procedure / Result Units / Date and Time / Reference to normal range

1) BILIRUBIN, TOTAL/12.8 MILLIGRAM/DECILITER/19-AUG-1999/UNK *

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

Relevant history / Concurrent conditions:
NONE

## C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
- #1 GEMCITABINE HYDROCHLORIDE
- #2 CISPLATIN

2. Dose, frequency & route used
- #1
- #2

3. Therapy dates (if unknown, give duration) from/to (or best estimate)
- #1 10-JUN-1999 to 12-AUG-1999
- #2 10-JUN-1999 to 12-AUG-1999

4. Diagnosis for use (indication)
- #1 NSCLC
- #2 NSCLC

5. Event abated after use stopped or dose reduced
- #1 ☐ yes ☐ no ☒ doesn't apply
- #2 ☐ yes ☐ no ☒ doesn't apply

6. Lot # (if known)
- #1 NI
- #2 NI

7. Exp. date (if known)
- #1 NI
- #2 NI

8. Event reappeared after reintroduction
- #1 ☐ yes ☐ no ☐ doesn't apply
- #2 ☐ yes ☐ no ☐ doesn't apply

9. NDC # - for product problems only (if known)
- #1
- #2

10. Concomitant medical products and therapy dates (exclude treatment of event)

1) Unknown

## G. All manufacturers

1. Contact office - name/address (& mfring site for devices)

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

2. Phone number: NI

3. Report source (check all that apply)
- ☒ foreign
- ☒ study
- ☐ literature
- ☐ consumer
- ☒ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other:

EG

4. Date received by manufacturer (mo/day/yr): 11/DEC/2000

5. (A)NDA # ____ IND # 29,653 PLA # ____ pre-1938 ☐ yes OTC product ☐ yes

6. If IND, protocol #: S005

7. Type of report (check all that apply) WS 13DEC00
- ☐ 5-day ☒ 15-day
- ☒ 10-day ☐ periodic
- ☒ Initial ☐ follow-up #____

8. Adverse event term(s)

HEPATITIS B POSITIVE SA

HEPATITIS C VIRUS

9. Mfr. report number: EWC001208804

## E. Initial reporter

1. Name, address & phone #

2. Health professional? ☐ yes ☐ no

3. Occupation

4. Initial reporter also sent report to FDA ☐ yes ☐ no ☐ unk

FDA

Domain Facsimile of FDA Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

* Item completed on continuation pages.

| MEDWATCH | A.1. Patient Identifier | G.9. Mfr. report number<br>EWC001208804 | Page 2 of 2 |
|---|---|---|---|

A.2. Date of birth(mo/day/yr)

48 years 6 weeks 4 days
05/JUL/1951

B.5. Describe event or problem

[continuation:] EXPERIENCED GRADE III JAUNDICE (TOTAL BILIRUBIN=12.8MG/DL, ASPARTATE AMINOTRANSFERASE=196 IU/L, ALANINE AMINOTRANSFERASE=339 IU/L ON 19-AUG-2000). INVESTIGATIONS PROVED POSITIVE FOR HEPATITIS B AND HEPATITIS C. STUDY DRUGS WERE STOPPED AND HE WAS GIVEN UNSPECIFIED SYMPTOMATIC TREATMENT. HE SUBSEQUENTLY EXPERIENCED DISEASE PROGRESSION AND THE CONDITION OF HIS LIVER DETERIORATED. HE DIED ON 1-NOV-1999, 78 DAYS AFTER STOPPING TREATMENT, FROM PROGRESSIVE DISEASE AND HEPATITIS. THE EVENTS WERE UNASSESSED BY THE INVESTIGATOR FOR RELATEDNESS TO STUDY DRUGS. FURTHER INFORMATION HAS BEEN REQUESTED.
LILLY ANALYSIS STATEMENT: HEPATITIS B AND C ARE VIRAL CONDITIONS UNLIKELY TO BE RELATED TO TREATMENT.

UPDATE 12-DEC-2000: ADDITIONAL INFORMATION RECEIVED 11-DEC-2000: STUDY DRUG DOSAGES AND CYCLE DETAILS ADDED. TIME TO ONSET CLARIFIED.
Cause of Death: DISEASE PROGRESSION AND HEPATITIS

B.6. Relevant tests/laboratory data ,including dates

[continuation:] 2) ALT/SGPT, ALANINE AMINOTRANSFERASE/339 INT'L UNITS/LITER/19-AUG-1999/UNK
3) AST/SGOT, ASPARTATE AMINOTRANSFERASE /196 INT'L UNITS/LITER/19-AUG-1999/UNK

# MEDWATCH
THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Eli Lilly and Company

Page 1 of 5

Domain Facsimile — Approved by FDA on 3/22/94
Mfr report # US_000134623
UF/Diet report #
FDA Use Only

## A. Patient information

| 1. Patient identifier | 2. Age at time of event: / or Date of birth: | 3. Sex | 4. Weight |
|---|---|---|---|
| in confidence | 55 yrs | ☒ female ☐ male | NI lbs or ____ kgs |

## B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)
- ☐ death (mo/day/yr)
- ☐ life-threatening
- ☐ hospitalization - initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☒ other: NI

3. Date of event (mo/day/yr): 13/JAN/2000

4. Date of this report (mo/day/yr): 15/DEC/2000

5. Describe event or problem

Investigator Copy to H3E-MC-JMCD

THIS CLINICAL TRIAL CASE REGARDS A 55-YEAR OLD CAUCASIAN FEMALE PATIENT WHO EXPERIENCED ELEVATED BILIRUBIN, SERUM GLUTAMATE OXALOACETATE (SGOT) AND SERUM GLUTAMATE PYRUVATE TRANSAMINASE (SGPT) LEVELS. THE PATIENT RECEIVED THE STUDY DRUG COMBINATION LY231514 AND GEMCITABINE HYDROCHLORIDE FOR TREATMENT OF NON-SMALL CELL LUNG CARCINOMA (NSCLC). SHE HAD A HISTORY OF HEPATITIS (EITHER A OR C) IN 1979. SHE WAS DIAGNOSED WITH POORLY DIFFERENTIATED, STAGE IV NSCLC ON 28OCT99. SHE HAD RECEIVED NO PREVIOUS CHEMOTHERAPY OR RADIOTHERAPY FOR HER NSCLC. WHEN SHE ENTERED INTO THE STUDY, HER THE STAGING OF HER NSCLC WAS: PRIMARY TUMOR 4, *

6. Relevant tests/laboratory data, including dates

Lab data:
Lab test or Procedure / Result Units / Date and Time / Reference to normal range

1) ALCOHOL LEVEL/19.0 /06-JAN-2000/UNK
2) HEMOGLOBIN/15 *

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

Relevant history / Concurrent conditions:
HEPATITIS (HEPATITIS NOS)

NON-SMALL CELL LUNG CANCER. HISTORY OF HEPATITIS (EITHER A OR C) IN 1979.
*

## C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
#1 GEMCITABINE HYDROCHLORIDE
#2 MULTI-TARGETED ANTIFOLATE (LY231514)

2. Dose, frequency & route used
#1
#2

3. Therapy dates (if unknown, give duration) (from/to (or best estimate))
#1 11-NOV-1999, not continuing
#2 19-NOV-1999, not continuing

4. Diagnosis for use (indication)
#1 NSCLC
#2 NSCLC

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☒ doesn't apply
#2 ☐ yes ☐ no ☒ doesn't apply

6. Lot # (if known)
#1 NI
#2 NI

7. Exp. date (if known)
#1 NI
#2 NI

8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☐ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

9. NDC # - for product problems only (if known)
#1 #2

10. Concomitant medical products and therapy dates (exclude treatment of event)

1) MULTIVITAMINS
Dose: UNK, Dates: ??-DEC-1999 Continuing, Route: POIndication: PROPHYLAXIS
2) VITAMIN B12 *

## G. All manufacturers

1. Contact office - name/address (& mfring site for devices)
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

2. Phone number: NI

3. Report source (check all that apply)
- ☐ foreign
- ☒ study
- ☐ literature
- ☐ consumer
- ☒ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other:

4. Date received by manufacturer (mo/day/yr): 30/NOV/2000

5. (A)NDA # ____
IND # 40,061
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #: JMCD

7. Type of report (check all that apply) WS
☐ 5-day ☒ 15-day 15DEC00
☒ 10-day ☐ periodic
☐ Initial ☒ follow-up # 1

8. Adverse event term(s)
SGOT INCREASED
SGPT INCREASED
BILIRUBINEMIA *

9. Mfr. report number: US_000134623

## E. Initial reporter

1. Name, address & phone #

2. Health professional? ☐ yes ☐ no

3. Occupation

4. Initial reporter also sent report to FDA ☐ yes ☐ no ☐ unk

FDA

Domain Facsimile of FDA Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

Item completed on continuation pages.

| MEDWATCH | A.1. Patient Identifier | G.9. Mfr. report number<br>US_000134623 | Page 2 of 5 |
|---|---|---|---|

A.2. Date of birth(mo/day/yr)

55 years 48 weeks 4 days
08/FEB/1944

B.5. Describe event or problem

[continuation:] REGIONAL LYMPH NODES 3, DISTANT METASTASIS 1 (METASTASIS TO THE BONE AND LYMPH NODES). HER TRANSAMINASE AND ALKALINE PHOSPHATASE LEVELS WERE SLIGHTLY ELEVATED AT BASELINE. BASELINE LABS (04NOV00) INCLUDED: TOTAL BILIRUBIN 0.7MG/DL, ALBUMIN 2.9G/DL, ASPARTATE AMINOTRANSFERASE (AST) 46U/L, ALANINE AMINOTRANSFERASE (ALT) 37U/L, ALKALINE PHOSPHATASE (ALK PHOS) 164U/L. THE PATIENT RECEIVED CONCOMITANT MULTIVITAMINS (CONTAINING 400UG OF FOLIC ACID), CYANOCOBALAMIN, IPRATROPIUM BROMIDE, ALBUTEROL AND PROCHLORPERAZINE.

THE PATIENT FIRST RECEIVED LY231514 (500MG/M2 ON DAY 8 EVERY 3 WEEKS) ON 19NOV99 AND LAST RECEIVED A DOSE ON 16DEC99. SHE FIRST RECEIVED GEMCITABINE (1250MG/M2 ON DAYS 1 AND 8 EVERY 3 WEEKS) ON 11NOV99 AND LAST RECEIVED A DOSE (2313MG) ON 30DEC99 (CYCLE 3/DAY 1). THE PATIENT'S TRANSAMINASE AND ALK PHOS LEVELS CONTINUED TO RISE DURING STUDY TREATMENT. ALK PHOS LEVELS INCLUDED: 224U/L (18NOV99), 393U/L (09DEC99), 279U/L (16DEC99), 223U/L (22DEC99), 400U/L (06JAN00). CYCLE 3/DAY 8 THERAPY WAS HELD BECAUSE THE PATIENT HAD A BLOOD ALCOHOL LEVEL OF 19.0. THE FOLLOWING WEEK, ON 13JAN00, THE PATIENT'S TOTAL BILIRUBIN WAS 6.6MG/DL (10:25AM) AND 7.0MG/DL, HER ALK PHOS WAS 480U/L (10:25AM) AND 508U/L, AND HER AST WAS 340U/L. THE PATIENT WAS NEGATIVE FOR HEPATITIS B CORE ANTIGEN AND HEPATITIS C VIRUS ANTIGEN ON 14JAN00. ON 19JAN00, THE PATIENT'S TOTAL BILIRUBIN WAS 11.2MG/DL. AT THE TIME OF THE INITIAL REPORT, THE EVENTS WERE CONTINUING. THE PATIENT ENDED STUDY PARTICIPATION ON 27JAN00 DUE TO THE ELEVATED BILIRUBIN; SHE DID NOT HAVE PROGRESSIVE DISEASE PRESENT AT THE TIME SHE DISCONTINUED THE STUDY. IN THE OPINION OF THE INVESTIGATOR, THE ELEVATED SGOT, SGPT AND BILIRUBIN LEVELS WERE RELATED TO THE STUDY DRUGS BUT NOT TO THE PROTOCOL PROCEDURES. THE INVESTIGATOR FURTHER STATED THAT THE STUDY DRUGS COULD POSSIBLY HAVE EXACERBATED THE LIVER DYSFUNCTION.

THE PATIENT LEFT THE STATE TO BE WITH FAMILY. THROUGH A SEARCH ON THE SOCIAL SECURITY DATABASE, THE INVESTIGATOR FOUND THAT THE PATIENT DIED ON 18FEB00. THE INVESTIGATOR LISTED THE DEATH AS DUE TO OTHER CAUSES (NOT STUDY DISEASE RELATED OR STUDY DRUG RELATED), BUT THE CAUSE OF DEATH WAS NOT REPORTED.
FOLLOW-UP HAS BEEN ATTEMPTED.

LILLY ANALYSIS STATEMENT 20NOV00: THIS PATIENT EXPERIENCED SIGNIFICANT ELEVATION OF LIVER ENZYMES (SGOT, SGPT AND ALK PHOS) AND VERY SIGNIFICANT ELEVATION OF SERUM BILIRUBIN WHILST RECEIVING LY231514 AND GEMCITABINE FOR NSCLC. ELEVATIONS OF LIVER ENZYMES ARE WELL RECOGNIZED WITH BOTH LY231514 AND GEMCITABINE. HOWEVER, ALTHOUGH MINOR ASSOCIATED ELEVATIONS OF BILIRUBIN MIGHT BE "EXPECTED", I WOULD CONSIDER THE LEVEL OF BILIRUBIN ELEVATION REPORTED HERE TO BE "UNEXPECTED" FOR EITHER LY231514 OR GEMCITABINE. IT IS VERY IMPORTANT TO NOTE THAT THIS PATIENT HAD A PAST HISTORY OF HEPATITIS (A OR C) AND THAT, FROM THE NARRATIVE, THERE IS ALSO A SUGGESTION THAT THERE MAY HAVE BEEN CONCERNS ABOUT THE LEVEL OF ALCOHOL INTAKE. WHILST IT IS CLEARLY NOT POSSIBLE TO REFUTE CAUSALITY FOR LY231514 AND/OR GEMCITABINE, BOTH OF THESE ADDITIONAL FACTORS COULD EASILY HAVE CONTRIBUTED TO THE ABNORMALITIES OF LIVER FUNCTION THAT HAVE BEEN REPORTED. MOREOVER, IT IS NOT YET CLEAR WHETHER THE PATIENT HAD LIVER METASTASES FROM THEIR NSCLC OR WHETHER THERE WAS ANY DEFINITIVE EVIDENCE OF OTHER CO-EXISTING, NON-MALIGNANT LIVER PATHOLOGY (EG: GALL STONES, CIRRHOSIS OR CHRONIC HEPATITIS). FURTHER FOLLOW-UP INFORMATION HAS BEEN REQUESTED, AND THIS MAY PERMIT A CLEARER *

| MEDWATCH | A.1. Patient Identifier | G.9. Mfr. report number<br>US_000134623 | Page 3 of 5 |
|---|---|---|---|

B.5. Describe event or problem

[continuation:] ASSESSMENT TO BE MADE OF THE EXACT CAUSE OF THE ELEVATED LIVER ENZYMES AND SERUM BILIRUBIN REPORTED IN THIS CASE.

UPDATE 15NOV00: INFO RECEIVED 13NOV00: DELETED THE EVENT "ELEVATED LIVER FUNCTION TESTS" AND ADDED THE EVENTS "ELEVATED SGPT", "ELEVATED SGOT" AND "ELEVATED BILIRUBIN"; UPDATED NARRATIVE.
UPDATE 21NOV00: CHANGED THE EVENT OF ELEVATED BILIRUBIN FROM EXPECTED TO UNEXPECTED PER LILLY PHYSICIAN REVIEW; ADDED ANALYSIS STATEMENT.
UPDATE 30NOV00: INFO RECEIVED 30NOV00: ADDED BASELINE AND PRE-SAE LABS; ADDED CONCOMITANT MEDS; ADDED DEATH INFORMATION; UPDATED NARRATIVE.
UPDATE 05DEC00: ADDED ADDITIONAL LABS.

B.6. Relevant tests/laboratory data ,including dates

[continuation:] GRAM/DECILITER/06-JAN-2000/UNK
3) HEMOGLOBIN/17 GRAM/DECILITER/04-NOV-1999/UNK
4) HEMOGLOBIN/14.4 GRAM/DECILITER/13-JAN-2000/UNK
5) ERYTHROCYTE COUNT/5.32 MILLION/MICROLITER/04-NOV-1999/UNK
6) NEUTROPHILS /1.9 THOUSAND/MICROLITER/06-JAN-2000/UNK
7) NEUTROPHILS /10.5 THOUSAND/MICROLITER/13-JAN-2000/UNK
8) EOSINOPHILS/0 THOUSAND/MICROLITER/06-JAN-2000/UNK
9) EOSINOPHILS/0 THOUSAND/MICROLITER/13-JAN-2000/UNK
10) PLATELET COUNT/280 THOUSAND/MICROLITER/04-NOV-1999/UNK
11) PLATELET COUNT/70 THOUSAND/MICROLITER/06-JAN-2000/UNK
12) PLATELET COUNT/128 THOUSAND/MICROLITER/13-JAN-2000/UNK
13) PROTHROMBIN ACTIVITY/17.8 SECOND/04-FEB-2000 08:00:00/ABOVE
14) PROTHROMBIN ACTIVITY/18.4 SECOND/03-FEB-2000 06:00:00/ABOVE
15) PROTHROMBIN ACTIVITY/18.9 SECOND/01-FEB-2000 06:00:00/ABOVE
16) PROTHROMBIN ACTIVITY/17.1 SECOND/31-JAN-2000 17:50:00/ABOVE
17) AST/SGOT, ASPARTATE AMINOTRANSFERASE /109 UNITS/LITER/04-FEB-2000 08:00:00/ABOVE
18) AST/SGOT, ASPARTATE AMINOTRANSFERASE /120 UNITS/LITER/01-FEB-2000 06:00:00/ABOVE
19) AST/SGOT, ASPARTATE AMINOTRANSFERASE /158 UNITS/LITER/31-JAN-2000 17:50:00/ABOVE
20) AST/SGOT, ASPARTATE AMINOTRANSFERASE /128 UNITS/LITER/19-JAN-2000 14:13:00/ABOVE
21) AST/SGOT, ASPARTATE AMINOTRANSFERASE /46 UNITS/LITER/04-NOV-1999/WITHIN
22) AST/SGOT, ASPARTATE AMINOTRANSFERASE /340 UNITS/LITER/13-JAN-2000/UNK
23) ALT/SGPT, ALANINE AMINOTRANSFERASE/37 UNITS/LITER/04-NOV-1999/WITHIN
24) ALT/SGPT, ALANINE AMINOTRANSFERASE/54.0 UNITS/LITER/31-JAN-2000 17:50:00/ABOVE
25) ALT/SGPT, ALANINE AMINOTRANSFERASE/61.0 UNITS/LITER/19-FEB-2000 14:13:00/ABOVE
26) ALP ISOENZYME - LIVER/287.0 UNITS/LITER/04-FEB-2000 08:00:00/ABOVE
27) ALP ISOENZYME - LIVER/270 UNITS/LITER/01-FEB-2000 06:00:00/ABOVE
28) ALP ISOENZYME - LIVER/426 UNITS/LITER/19-JAN-2000 14:13:00/ABOVE
29) ALP ISOENZYME - LIVER/373 UNITS/LITER/31-JAN-2000 17:50:00/ABOVE
30) ALKALINE PHOSPHATASE/164 UNITS/LITER/04-NOV-1999/ABOVE
31) ALKALINE PHOSPHATASE/224 UNITS/LITER/19-NOV-1999/ABOVE
32) ALKALINE PHOSPHATASE/393 UNITS/LITER/09-DEC-1999/ABOVE
33) ALKALINE PHOSPHATASE/279 UNITS/LITER/16-DEC-1999/ABOVE
34) ALKALINE PHOSPHATASE/223 UNITS/LITER/22-DEC-1999/ABOVE *

B.6. Relevant tests/laboratory data ,including dates

[continuation:] 35) ALKALINE PHOSPHATASE/400 UNITS/LITER/06-JAN-2000/ABOVE
36) ALKALINE PHOSPHATASE/480 UNITS/LITER/13-JAN-2000 10:25:00/ABOVE
37) ALKALINE PHOSPHATASE/508 UNITS/LITER/13-JAN-2000/ABOVE
38) ALBUMIN/2.9 GRAM/DECILITER/04-NOV-1999/BELOW
39) ALBUMIN/1.8 GRAM/DECILITER/04-FEB-2000 08:00:00/BELOW
40) ALBUMIN/2.0 GRAM/DECILITER/31-JAN-2000 17:50:00/BELOW
41) ALBUMIN/1.5 GRAM/DECILITER/01-FEB-2000 06:00:00/BELOW
42) ALBUMIN/2.1 GRAM/DECILITER/19-JAN-2000 14:13:00/BELOW
43) BILIRUBIN, TOTAL/0.7 MILLIGRAM/DECILITER/04-NOV-1999/WITHIN
44) BILIRUBIN, TOTAL/20.5 MILLIGRAM/DECILITER/31-JAN-2000/ABOVE
45) BILIRUBIN, TOTAL/16.0 MILLIGRAM/DECILITER/01-FEB-2000/ABOVE
46) BILIRUBIN, TOTAL/21.5 MILLIGRAM/DECILITER/04-FEB-2000/ABOVE
47) BILIRUBIN, TOTAL/7.0 MILLIGRAM/DECILITER/13-JAN-2000/ABOVE
48) BILIRUBIN, TOTAL/6.6 MILLIGRAM/DECILITER/13-JAN-2000 10:25:00/ABOVE
49) BILIRUBIN, TOTAL/11.2 MILLIGRAM/DECILITER/19-JAN-2000/ABOVE
50) BILIRUBIN, INDIRECT/2.2 MILLIGRAM/DECILITER/19-JAN-2000 14:13:00/ABOVE
51) BILIRUBIN, INDIRECT/3.0 MILLIGRAM/DECILITER/31-JAN-2000 17:50:00/ABOVE
52) BILIRUBIN, INDIRECT/1.6 MILLIGRAM/DECILITER/01-FEB-2000 06:00:00/ABOVE
53) BILIRUBIN, INDIRECT/4.4 MILLIGRAM/DECILITER/04-FEB-2000 08:00:00/ABOVE
54) BILIRUBIN, DIRECT/17.5 MILLIGRAM/DECILITER/31-JAN-2000 17:50:00/ABOVE
55) BILIRUBIN, DIRECT/9.0 MILLIGRAM/DECILITER/19-JAN-2000 14:13:00/ABOVE
56) BILIRUBIN, DIRECT/14.4 MILLIGRAM/DECILITER/01-FEB-2000 06:00:00/ABOVE
57) BILIRUBIN, DIRECT/17.1 MILLIGRAM/DECILITER/04-FEB-2000 08:00:00/ABOVE
58) CREATININE CLEARANCE/83.9 MILLITER/MINUTE/04-NOV-1999/UNK
59) WBC COUNT/7.7 THOUSAND/MICROLITER/04-NOV-1999/UNK
60) WBC COUNT/3.9 THOUSAND/MICROLITER/06-JAN-2000/UNK
61) WBC COUNT/12.6 THOUSAND/MICROLITER/13-JAN-2000/UNK
62) BACTERIAL CULTURE, BLOOD/NEGATIVE /04-FEB-2000 15:45:00/UNK
63) BACTERIAL CULTURE, BLOOD/NEGATIVE /31-JAN-2000 17:30:00/UNK
64) EXAM/NO VIRUS ISOLATED /14-JAN-2000 15:01:00/UNK

B.7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

[continuation:] Origin: CAUCASIAN

C.10. Concomitant medical products and therapy dates (exclude treatment of event)

[continuation:] Dose: 1000 ug, Dates: 06-JAN-2000 Continuing, Route: SCIndication: PROPHYLAXIS
3) ATROVENT(IPRATROPIUM BROMIDE)
Dose: UNK, Dates: ??-???-1999 Continuing, Route: IH4) ALBUTEROL
Dose: UNK, Dates: ??-???-1999 Continuing, Route: IH5) COMPAZINE(PROCHLORPERAZINE EDISYLATE)
Dose: UNK, Dates: 11-NOV-1999 to 27-JAN-2000, Route: PO Duration: 11 weeks 1 day

| MEDWATCH | A.1. Patient identifier | G.9. Mfr. report number<br>US_000134623 | Page 5 of 5 |
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G.8. Adverse event term(s)

[continuation:]