



National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

DATE: September 28, 2011
FROM: Helen Chen, M.D., Investigational Drug Branch, CTEP, DCTD, NCI
SUBJECT: Bevacizumab (rhuMAb VEGF) Investigator Notification: **Ataxia**
Genentech Manufacturer Report # 797273
TO: Investigators using Bevacizumab (NSC 704865)

The U.S. Food and Drug Administration (FDA) regulations require sponsors of clinical studies conducted under a U.S. IND to notify the FDA and all participating investigators of any serious and unexpected adverse experiences that are possibly related to the investigational agent. A CIOMS form, which describes fatal ataxia in a patient participating in a Genentech-sponsored clinical trial utilizing the investigational agent bevacizumab, was recently distributed to investigators.

The following must be completed by all investigators using bevacizumab under NCI INDs 7921 and 11460:

- Send a copy of this letter to your Institutional Review Board (IRB) of record according to your policies and procedures.
- File a copy of this letter in your protocol file.

If your study is not covered under INDs 7921 or 11460, it is strongly recommended that you follow the instructions above.

Please note that for Cooperative Group studies, the Cooperative Group Operations Office will provide instructions for IRB submissions, any patient notifications, etc.

Based on CTEP's assessment of the current information in light of previous experience with bevacizumab, there does not appear to be a change in the risk-benefit ratio for bevacizumab studies; therefore, CTEP is not requiring a protocol amendment at this time.

Please continue to report events according to the adverse event reporting guidelines in your protocol(s).

The Dear Investigator Letter and CIOMS Form that describe the following adverse event are attached:

A 37-year-old Caucasian female with breast cancer experienced **ataxia and subsequently expired**, while participating in a clinical study utilizing the agent bevacizumab in combination with paclitaxel, in patients with advanced triple negative breast cancer.

Attachments: Dear Investigator Letter
CIOMS Form



Welwyn Garden City, UK, 07 September 2011

Dear Investigator/Independent Ethics Committee:

Re: Fatal ataxia in a patient enrolled in Protocol ML22780 , randomized to Bevacizumab . MCN #: 797273.

Enclosed please find a summary of **Fatal ataxia** in a 37 year old Caucasian female patient who was enrolled in the **Phase IV ML22780** protocol. A regulatory reporting form (MedWatch and/or CIOMS I) is attached along with an Analysis of Similar Events, where appropriate.

Please forward a copy of this letter and the attachments to your Investigational Review Board/Independent Ethics Committee.

Note: In European Economic Area (EEA) Roche will directly inform the Institutional Review Boards unless communication with them is only accepted via the investigator.

- This information applies to all ongoing protocols with Bevacizumab at your site.
- This 15 day Expedited Safety Report must be filed with your IB for information only. If this report has been made available to you via the Secure Document Exchange website, the Secure Document Exchange website can serve as the temporary archive for this information until the time of site close-down. This expedited report is not an addendum to your safety reference document.

At this time there is no sponsor recommendation to change the Informed Consent.

For Non-EEA countries:

Irrespective of the Roche recommendation, addition of this information to the informed consent form is at the discretion of individual investigators together with the local Institutional Review Board or Independent Ethics Committee. Should you decide to revise the informed consent form, please contact the study monitor and provide Roche (via the study monitor) with a copy of the revision.

Should you have any questions or concerns, please do not hesitate to contact your local Roche Representative.

Yours truly,

Fraser McCallum
PDS Operations – Head, Regional Centre Europe
Roche Products Limited
6 Falcon Way
Shire Park
Welwyn Garden City AL7 1TW
Registered in England No. 100674

MCN: 797273

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Welwyn Garden City, UK, 07 september 2011

Dear Investigator/Independent Ethics Committee:

Re: Fatal possible paraneoplastic syndrome in a patient enrolled in Protocol ML22780 , randomized to Bevacizumab . MCN #: 797273.

Enclosed please find a summary of **Fatal possible paraneoplastic syndrome** in a **37** year old Caucasian female patient who was enrolled in the **Phase IV ML22780** protocol. A regulatory reporting form (MedWatch and/or CIOMS I) is attached along with an Analysis of Similar Events, where appropriate.

Please forward a copy of this letter and the attachments to your Investigational Review Board/Independent Ethics Committee.

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- **This information applies to all ongoing protocols with Bevacizumab at your site.**
- **This 15 day Expedited Safety Report must be filed with your IB for information only. If this report has been made available to you via the Secure Document Exchange website, the Secure Document Exchange website can serve as the temporary archive for this information until the time of site close-down. This expedited report is not an addendum to your safety reference document.**

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7. DESCRIBE REACTIONS INCLUDING RELEVANT TESTS/LAB DATA - continued

(RESULT NOT REPORTED). ON 02 AUGUST 2011, THE PATIENT COMPLAINED OF GENERALISED WEAKNESS (AND NEEDING A WHEELCHAIR FOR DISTANCES), HENCE A BRAIN MRI WAS REQUESTED. CHEST, ABDOMEN AND PELVIC MRI WERE DONE (RESULT NOT PROVIDED). TREATMENT WITH BEVACIZUMAB AND PACLITAXEL WAS DEFERRED. ON 10 AUGUST 2011, PATIENT WAS UNABLE TO BLINK THE LEFT EYELID. SHE ALSO BECAME ATAXIC AND WAS TREATED WITH PREGABALIN 100 MG. TREATMENT WITH BEVACIZUMAB AND PACLITAXEL WAS FURTHER DELAYED. ON 17 AUGUST 2011, SHE WAS UNABLE TO ATTEND CLINIC AND WAS HOSPITALISED. TREATMENT WITH BEVACIZUMAB AND PACLITAXEL WAS PERMANENTLY DISCONTINUED.

AT THE TIME OF THE REPORT, THE EVENT ATAXIA HAD WORSENERD.

IN ADDITION TO HOSPITALISATION, THE INVESTIGATOR ASSESSED THE EVENT ATAXIA AS RESULTING IN DISABILITY AND CONSIDERED THE EVENT TO BE RELATED TO BEVACIZUMAB AND PACLITAXEL, AND PRE-EXISTING/UNDERLYING DISEASE (UNSPECIFIED).

NO FURTHER INFORMATION WAS PROVIDED.

FOLLOWING REVIEW ON 25 AUGUST 2011, THE INITIAL INFORMATION RECEIVED ON 17 AUGUST 2011 WAS CORRECTED: THIS CASE WAS IDENTIFIED AS A SUSAR AND THE ASIME WAS EMBEDDED WITHIN THE NARRATIVE.

ADDITIONAL INFORMATION WAS RECEIVED ON 30 AUGUST 2011.

THE PATIENT PREVIOUSLY RECEIVED TREATMENT WITH CYCLOPHOSPHAMIDE, DEXAMETHASONE, DOCETAXEL, EPIRUBICIN HYDROCHLORIDE, FLUOROURACIL AND ONDANSETRON.

THE PATIENT ALSO RECEIVED CALCICHEW D3 FORT, CHLORPHENIRAMINE, DEXAMETHASONE, METOCLOPRAMIDE (INJECTION AND TABLET), RANITIDINE (INJECTION) AND ZOLEDRONIC ACID (INFUSION).

ON 2 AUGUST 2011, A THORAX, ABDOMEN AND PELVIS CT SCAN ALSO SHOWED A GOOD RESPONSE TO THE TREATMENT. THERE WERE NO SIGNIFICANTLY ENLARGED PULMONARY HILAR NODES AND ONLY A SMALL RESIDUAL SUBCARINAL NODE WAS NOTED IN THE MEDIASTINUM. THE PLEURAL EFFUSION HAD REGRESSED. THE POSTSURGICAL LEFT AXILLARY SEROMA MEASURED 3 CM COMPARED TO 3-4 CM PREVIOUSLY. THERE WERE DIFFUSE SCLEROTIC CHANGES THROUGHOUT THE VISUALIZED SKELETON IN KEEPING WITH WIDESPREAD BONY DISEASE. KIDNEYS WERE NORMAL. TRACE OF PELVIC ASCITES WAS SEEN. BRAIN CT SCAN ON THE SAME DAY SHOWED 2 TINY BRIGHT FOCI, ONE IN THE RIGHT FRONTAL LOBE AND THE OTHER IN THE LEFT PARIETAL LOBE. APPEARANCES WERE NOT ENTIRELY TYPICAL FOR METASTASIS. THERE WAS NO SIGNIFICANT EDEMA OR HYDROCEPHALUS ON 06 AUG 2011. A BRAIN MR SCAN SUBCARINAL NODE REVEALED: NO OBVIOUS ACTIVE PARENCHYMAL ABNORMALITY WAS SEEN. A FEW CALCIFIC AREAS WERE SEEN WHICH DID NOT SUGGEST ANY ACTIVE LESIONS. ON 10 AUGUST 2011, THE PATIENT EXPERIENCED ATAXIA, POSSIBLE PARANEOPlastic SYNDROME AND POSSIBLE MENINGEAL METS. THESE EVENTS WERE FATAL AND THE PATIENT DIED ON 29 AUGUST 2011. TREATMENT WITH DEXAMETHASONE AND PREGABALIN WAS NOT DISCONTINUED.

THE INVESTIGATOR ASSESSED THE EVENTS OF ATAXIA, POSSIBLE PARANEOPlastic SYNDROME AND POSSIBLE MENINGEAL METS AS RELATED TO BEVACIZUMAB AND PACLITAXEL.

NO FURTHER INFORMATION WAS PROVIDED.

ANALYSIS OF SIMILAR EVENTS - FATAL ATAXIA

THE INDEX CASE (MCN 797273) CONCERNS A 37 YEAR OLD FEMALE PATIENT WHO DEVELOPED FATAL ATAXIA FOLLOWING TREATMENT WITH BEVACIZUMAB FOR BREAST CANCER. THE PATIENT ALSO HAD BLURRED VISION, HEADACHE AND GENERALIZED WEAKNESS. MRI SHOWED POSSIBLE MENINGEAL METASTASES. THERE IS NO SIGNIFICANT PAST MEDICAL HISTORY. THE PATIENT WAS ON CONCOMITANT PACLITAXEL TREATMENT.

ON 02 SEPTEMBER 2011, THE ROCHE SAFETY DATABASE WAS SEARCHED WITH A MEDDRA PREFERRED TERM (PT) OF ALL CASES OF BEVACIZUMAB LINKED WITH ATAXIA AND 49 PREVIOUS CASES WERE IDENTIFIED: (MCN NO. 368599, 381246, 393259, 403561, 434529, 462259, 466323, 478622, 500693, 512176, 529379, 533431, 537011, 537616, 548897, 561182, 562317, 567947, 578849, 584410, 595594, 596689, 600287, 620082, 628954, 633727, 636428, 661644, 677281, 684351, 684820, 689891, 714252, 715464, 718367, 718383, 723781, 726742, 731504, 752019, 767809, 776484, 782647, 785958, 793037, 794839, 796287, 797337, 798605)

THESE 50 CASES (INCLUDING THE INDEX CASE) CONSISTED OF ADVANCED TUMORS FROM A RANGE OF ORGAN SYSTEMS. MOST CASES UNDERWENT IMAGING OF THE BRAIN AND THE SPINAL CORD, WHICH REVEALED A RANGE OF ABNORMALITIES VARYING FROM ISCHEMIA, METASTASIS TO NO ABNORMALITY FOUND. THERE IS A WIDE VARIATION IN TERMS OF RESOLUTION OF THE ATAXIA (RANGING FROM COMPLETE RESOLUTION TO NO RESOLUTION). IN SOME CASES THE INVESTIGATOR CONSIDERED THE EVENT TO BE RELATED TO THE STUDY DRUG. AGE RANGE WAS 4 TO 86 YEARS. GENDER DISTRIBUTION WAS 23 MALES, 25 FEMALES, 3 NOT KNOWN LATENCY PERIOD RANGED FROM 1 TO 833 DAYS AFTER REVIEW OF THE CLINICAL DETAILS OF THE INDEX CASE AND SIMILAR PREVIOUS CASES, THE SPONSOR DOES NOT BELIEVE THAT CHANGES TO THE CONDUCT OF THE CLINICAL TRIAL ARE WARRANTED IN RESPONSE TO THIS CASE REPORT.

ANALYSIS OF SIMILAR EVENTS - FATAL PARANEOPlastic SYNDROME

THE INDEX CASE (MCN 797273) CONCERNS A 37 YEAR OLD FEMALE PATIENT WHO DEVELOPED FATAL PARANEOPlastic SYNDROME FOLLOWING TREATMENT WITH BEVACIZUMAB FOR BREAST CANCER. THE PATIENT ALSO HAD BLURRED VISION, HEADACHE, GENERALIZED WEAKNESS AND ATAXIA. MRI SHOWED POSSIBLE MENINGEAL METASTASES. THERE IS NO SIGNIFICANT PAST MEDICAL HISTORY. THE PATIENT

WAS ON CONCOMITANT PACLITAXEL TREATMENT.

ON 02 SEPTEMBER 2011, THE ROCHE SAFETY DATABASE WAS SEARCHED FOR ALL CASES OF BEVACIZUMAB LINKED WITH FATAL PARANEOPLASTIC SYNDROME AND 3 PREVIOUS WERE IDENTIFIED (MCN NO. 509930, 592811, 629805). ALL PATIENTS WERE ON MULTIPLE CHEMOTHERAPEUTIC DRUGS. MCN 509930 CONCERNS AN 82 YEAR OLD MALE WITH METASTATIC COLORECTAL CANCER WHO DEVELOPED DEHYDRATION, SEPSIS AND PARANEOPLASTIC SYNDROME FOLLOWING TREATMENT WITH BEVACIZUMAB. THERE WERE NO IMAGING STUDIES REPORTED. CAUSE OF DEATH WAS REPORTED AS SEPSIS

MCN 592811 CONCERNS A 43 YEAR OLD FEMALE WITH METASTATIC OVARIAN CANCER WHO DEVELOPED CEREBELLAR SYNDROME (DEGENERATION) AND PARANEOPLASTIC SYNDROME FOLLOWING TREATMENT WITH BEVACIZUMAB. MRI SHOWED NO SIGNIFICANT CHANGES. PARANEOPLASTIC EVALUATION WAS POSITIVE FOR PURKINJE ANTIBODIES. PATIENT WAS TREATED WITH STEROIDS. CAUSE OF DEATH WAS STATED AS OVARIAN CANCER.

MCN 629805 CONCERNS A 68 YEAR OLD MALE WITH METASTATIC LUNG CANCER WHO DEVELOPED PARANEOPLASTIC ENCEPHALITIS FOLLOWING TREATMENT WITH BEVACIZUMAB. PATIENT WAS TREATED WITH STEROIDS. CAUSE OF DEATH WAS REPORTED AS SUSPECTED PARANEOPLASTIC ENCEPHALOPATHY.

AFTER REVIEW OF THE CLINICAL DETAILS OF THE INDEX CASE AND SIMILAR PREVIOUS CASES, THE SPONSOR DOES NOT BELIEVE THAT CHANGES TO THE CONDUCT OF THE CLINICAL TRIAL ARE WARRANTED IN RESPONSE TO THIS CASE REPORT.

ADVERSE EVENT TERM(S):

ATAXIA/ATAXIA/MEDDRA 14.0 +++
 POSSIBLE PARANEOPLASTIC SYNDROME/PARANEOPLASTIC SYNDROME/MEDDRA 14.0
 POSSIBLE MENINGEAL METS/METASTASES TO MENINGES/MEDDRA 14.0

(+++ denotes adverse event that generated submission)

RELEVANT TEST(S)/LAB DATA:

Lab Test Name: CT SCAN
 Date (Day-Month-Year): 2-AUG-2011
 Lab Result (Low-High Unit): -
 Normal (Low-High): -
 Lab Result Text: CHEST CT SCAN

Lab Test Name: CT SCAN
 Date (Day-Month-Year): 2-AUG-2011
 Lab Result (Low-High Unit): -
 Normal (Low-High): -
 Lab Result Text: ABDOMEN CT SCAN

Lab Test Name: CT SCAN
 Date (Day-Month-Year): 2-AUG-2011
 Lab Result (Low-High Unit): -
 Normal (Low-High): -
 Lab Result Text: PELVIC CT SCAN

Lab Test Name: MRI
 Date (Day-Month-Year): 29-JUL-2011
 Lab Result (Low-High Unit): -
 Normal (Low-High): -
 Lab Result Text: SPINE

Lab Test Name: MRI
 Date (Day-Month-Year): 6-AUG-2011
 Lab Result (Low-High Unit): -
 Normal (Low-High): -
 Lab Result Text: BRAIN

2 AUGUST 2011:A THORAX, ABDOMEN AND PELVIS CT SCAN ALSO SHOWED A GOOD RESPONSE TO THE TREATMENT. THERE WERE NO SIGNIFICANTLY ENLARGED PULMONARY HILAR NODES AND ONLY A SMALL RESIDUAL SUBCARNIAL NODE IS NOTED IN THE MEDIASTINUM. THE PLURAL EFFUSION HAD REGRESSED. THE POSTSURGICAL LEFT AXILLARY SEROMA MEASURED 3 CM COMPARED TO 3-4 CM PREVIOUSLY. THERE ARE DIFFUSE SCLEROTIC CHANGES THROUGHOUT THE VISUALIZED SKELETON IN KEEPING WITH WIDESPREAD BONY DISEASE. KIDNEYS WERE NORMAL. TRACE OF PELVIC ASCITES WAS SEEN. BRAIN CT SCAN ON THE SAME DAY SHOWED 2 TINY BRIGHT FOCI, ONE IN THE RIGHT FRONTAL LOBE, THE OTHER IN THE LEFT PARIETAL LOBE. APPEARANCES WERE NOT ENTIRELY TYPICAL FOR METASTASIS. THERE WAS NO SIGNIFICANT EDEMA OR HYDROCEPHALUS.

MR SCAN BRAIN 6 AUGUST 2011: NO OBVIOUS ACTIVE PARENCHYMAL ABNORMALITY WAS SEEN. A FEW CALCIFIC AREAS WERE SEEN WHICH DID NOT SUGGEST ANY ACTIVE LESIONS

PAST PATIENT DRUGS AND REACTIONS:
CYCLOPHOSPHAMIDE (CYCLOPHOSPHAMIDE)
DEXAMETHASONE (DEXAMETHASONE)
DOCETAXEL (DOCETAXEL)
EPIRUBICIN HYDROCHLORIDE (EPIRUBICIN)
FLUOROURACIL (FLUOROURACIL)
ONDANSETRON (ONDANSETRON)

14-19. SUSPECT DRUGS - continued

Suspect Drug: PACLITAXEL
Generic Name: PACLITAXEL
Daily Dose(s)/Strength: 180 MG 1 X per 1 WEEK /
Route: INTRAVENOUS
Indication: BREAST CANCER/BREAST CANCER/MEDDRA 14.0
Therapy From Date: 17-JUN-2011
Therapy To Date: 17-AUG-2011
Therapy Duration: 62 DAYS

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION - continued

OXYNORM
(OXYCODONE)
21-JUL-2011 / 29-AUG-2011

LANSOPRAZOLE
(LANSOPRAZOLE)
21-JUL-2011 / 29-AUG-2011

CITALOPRAM
(CITALOPRAM)
6-AUG-2011 / 29-AUG-2011

DIFFLAM
(BENZYLAMINE HYDROCHLORIDE)
7-AUG-2011 / 29-AUG-2011

CIOMS TEXT

No CIOMS Text.

REPORTER INFORMATION

Reporter: 1
 Name: ELAINE YOUNG
 Organisation: ROYAL PRESTON HOSPITAL
 Address 1: SHAROE GREEN LANE
 Address 2: FULWOOD
 Address 3:
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 City: PRESTON LANCASHIRE PR2 9HT
 Country: UNITED KINGDOM
 Address Phone:
 Address Fax:
 Representative Phone: 177252136
 Representative Fax:
 Reporter Type: HEALTH PROFESSIONAL
 Occupation: DOCTOR OF MEDICINE

CLINICAL TRIAL INFORMATION

Clin. Study Id: ML22780
 Clin. CRTN 203680
 Design and Phase: OPEN IV
 Clin. Patient Id: 8004
 Clin. Investigator Id: 251145

DRUG-EVENT INFORMATION

Event: ATAXIA/ATAXIA/MEDDRA 14.0
 SOC: NERVOUS SYSTEM DISORDERS
 Outcome: OUTCOME DEATH
 Severity:
 Seriousness: DEATH, DISABILITY,
 NEW/PROLONGED HOSPITAL
 Onset Date: 10 AUG 2011
 Resolved Date:
 Duration Reported:

Relation To: BEVACIZUMAB
 Drug Continued: DISCONTINUED
 AE Abated: NO - EVENT DID NOT ABATE
 AE Reappeared: NOT APPLICABLE
 Labeled US: NO
 Labeled Local: NOT APPLICABLE - GB
 Labeled IB: NO
 Labeled SPC: NO
 Labeled Core: NO
 Drug Related(Comp): YES
 Drug Related(Rept): YES
 Latency Reported: (First Dose)
 Latency Reported (Last Dose):

Relation To: PACLITAXEL
 Drug Continued: DISCONTINUED
 AE Abated: NO - EVENT DID NOT ABATE
 AE Reappeared: NOT APPLICABLE
 Labeled US: NOT APPLICABLE
 Labeled Local: NOT APPLICABLE - GB
 Labeled IB: NOT APPLICABLE
 Labeled SPC: NOT APPLICABLE
 Labeled Core: NOT APPLICABLE
 Drug Related(Comp): YES
 Drug Related(Rept): YES
 Latency Reported: (First Dose)
 Latency Reported (Last Dose):

Event: POSSIBLE PARANEOPLASTIC SYNDROME/PARANEOPLASTIC
 SYNDROME/MEDDRA 14.0
 SOC: NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL

Outcome: CYSTS AND POLYPS)
 OUTCOME DEATH
 Severity:
 Seriousness: DEATH
 Onset Date: 10 AUG 2011
 Resolved Date:
 Duration Reported:

Relation To: BEVACIZUMAB
 Drug Continued: DISCONTINUED
 AE Abated: NO - EVENT DID NOT ABATE
 AE Reappeared: NOT APPLICABLE
 Labeled US: NO
 Labeled Local: NOT APPLICABLE - GB
 Labeled IB: NO
 Labeled SPC: NO
 Labeled Core: NO
 Drug Related(Comp): YES
 Drug Related(Rept): YES
 Latency Reported: (First Dose)
 Latency Reported (Last Dose):

Relation To: PACLITAXEL
 Drug Continued: DISCONTINUED
 AE Abated: NO - EVENT DID NOT ABATE
 AE Reappeared: NOT APPLICABLE
 Labeled US: NOT APPLICABLE
 Labeled Local: NOT APPLICABLE - GB
 Labeled IB: NOT APPLICABLE
 Labeled SPC: NOT APPLICABLE
 Labeled Core: NOT APPLICABLE
 Drug Related(Comp): YES
 Drug Related(Rept): YES
 Latency Reported: (First Dose)
 Latency Reported (Last Dose):

Event: POSSIBLE MENINGEAL METS/METASTASES TO
 MENINGES/MEDDRA 14.0
 SOC: NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL
 CYSTS AND POLYPS)
 Outcome: OUTCOME DEATH
 Severity:
 Seriousness: DEATH
 Onset Date: 10 AUG 2011
 Resolved Date:
 Duration Reported:

Relation To: BEVACIZUMAB
 Drug Continued: DISCONTINUED
 AE Abated: NO - EVENT DID NOT ABATE
 AE Reappeared: NOT APPLICABLE
 Labeled US: NO
 Labeled Local: NOT APPLICABLE - GB
 Labeled IB: YES
 Labeled SPC: NO
 Labeled Core: NO
 Drug Related(Comp): YES
 Drug Related(Rept): YES
 Latency Reported: (First Dose)
 Latency Reported (Last Dose):

Relation To: PACLITAXEL
 Drug Continued: DISCONTINUED
 AE Abated: NO - EVENT DID NOT ABATE
 AE Reappeared: NOT APPLICABLE
 Labeled US: NOT APPLICABLE
 Labeled Local: NOT APPLICABLE - GB
 Labeled IB: NOT APPLICABLE
 Labeled SPC: NOT APPLICABLE
 Labeled Core: NOT APPLICABLE

Drug Related(Comp): YES
Drug Related(Rept): YES
Latency Reported: (First Dose)
Latency Reported (Last Dose):