



National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

DATE: August 19, 2010

FROM: Helen Chen, M.D., Investigational Drug Branch, CTEP, DCTD, NCI *YJH*

SUBJECT: Bevacizumab (rhuMAb VEGF) Investigator Notification: **Microangiopathic Hemolytic Anemia**
Genentech Manufacturer Report # 718784

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. An investigator notification form, which describes microangiopathic hemolytic anemia 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) according to your local IRB's 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, MedWatch Report, and CIOMS Form that describe the following adverse event are attached:

A 67-year-old female with renal cell carcinoma experienced microangiopathic hemolytic anemia while participating in a multicenter phase 2 study utilizing the investigational agent bevacizumab in combination with sunitinib malate.

Attachments: Dear Investigator Letter
MedWatch Report
CIOMS Form

Genentech

A Member of the Roche Group

Date: 9 August 2010

RE: **IND Safety Report**

Investigational Product(s): **Bevacizumab**

MCN: **713959 FU #2**

Other Reference Number(s):

Helen Chen, MD
National Cancer Institute
6130 Executive Blvd.
Suite 7131
Bethesda, MD 20852

Dear Investigator,

Attached is an individual case safety report (ICSR) that meets criteria for expedited safety reporting to applicable regulatory authorities and investigators.

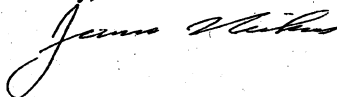
Genentech has evaluated this case in accordance with guidelines published by the U.S. Food and Drug Administration (FDA)⁹ and has concluded that this case *does not* represent an "unanticipated problem" involving risk to human subjects or others pursuant to 21 C.F.R. §§ 56.108(b)(1), 312.53(c)(1)(vii), and 312.66. If your site uses a local Institutional Review Board (IRB) or Independent Ethics Committee (IEC), please note that IRBs and IECs may choose to review only those ICSRs that represent "unanticipated problems" under the foregoing regulations. Accordingly, since Genentech has concluded that this ICSR is not an "unanticipated problem," you should refer to the policies and procedures of your local IRB or IEC to determine if you should submit a copy of this ICSR to them. In any event, this correspondence must be archived in your Study File so that it will be available for review during a sponsor monitoring visit, audit, or regulatory inspection.

In the European Economic Area, the sponsor or its designee will directly inform the IRB/IEC, as appropriate. In the United States, if your site uses a central or regional IRB or IEC, Genentech or its designee will directly transmit all required information to the IRB or IEC. This correspondence must be archived in your Study File so that it will be available for review during a sponsor monitoring visit, audit, or regulatory inspection.

Although this ICSR has been documented and reported to the applicable regulatory authorities, please note that this report does not necessarily reflect a conclusion by the sponsor that Bevacizumab contributed to the adverse event.

If questions arise, please contact the Medical Monitor for your study.

Sincerely,



James Nickas, PharmD
Head of Regional Centers America
Genentech Drug Safety

CC: AVF3303s, AVF3490s, AVF3892s, AVF4618s, AVF4228s, AVF4406s, AVF4587s, AVF460s, AVF3860s

⁹ FDA, Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting to IRBs – Improving Human Subject Protection (January 2009).

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For use by user-facilities,
distributors and manufacturers for
MANDATORY reporting.

Page 1 of 2

Mfr report #	718784
UF/Importer report #	
FDA Use only	

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at time of event: or 67 YEARS Date of birth:	3. Sex <input checked="" type="checkbox"/> female <input type="checkbox"/> male	4. Weight UNK lbs or kgs
-----------------------	---	---	-----------------------------------

In confidence

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. <input checked="" type="checkbox"/> Adverse event and/or	<input type="checkbox"/> Product problem (e.g., defects/malfunctions)
2. Outcomes attributed to adverse event (check all that apply)	
<input type="checkbox"/> death	<input type="checkbox"/> congenital anomaly/birth defect
<input type="checkbox"/> life threatening	<input type="checkbox"/> required intervention to prevent permanent impairment/damage (devices)
<input type="checkbox"/> hospitalization-initial or prolonged	<input checked="" type="checkbox"/> other serious (important medical events)
<input type="checkbox"/> disability or permanent damage	MEDICALLY SIGNIFICANT
3. Date of event (mm/dd/yyyy) UNK/ /	4. Date of this report (mm/dd/yyyy) 08 / 09 / 2010

5. Describe event or problem

INITIAL INFORMATION FOR THIS CLINICAL LITERATURE CASE WAS RECEIVED ON 28 JULY 2010 FROM A HEALTH PROFESSIONAL AND CONCERNS A 67-YEAR-OLD FEMALE PATIENT (PATIENT NO.) WHO EXPERIENCED MICROANGIOPATHIC HEMOLYTIC ANEMIA WHILST ENROLLED IN AVF4167G; A MULTICENTER, PHASE II, RANDOMIZED, BLINDED, PLACEBO-CONTROLLED TRIAL EVALUATING THE EFFICACY AND SAFETY OF SUTENT WITH OR WITHOUT BEVACIZUMAB IN FIRST-LINE PATIENTS WITH METASTATIC RENAL CELL CANCER.

THE PATIENT UNDERWENT NEPHRECTOMY IN THE PAST. NO CONCOMITANT MEDICATIONS OR PAST DRUGS WERE REPORTED.

ON AN UNSPECIFIED DATE, THE PATIENT COMMENCED TREATMENT WITH INTRAVENOUS BEVACIZUMAB AT A DOSE OF 10 MG/KG ONCE EVERY TWO WEEKS AND ORAL SUNITINIB AT A DOSE OF 50 MG ON 4/2 SCHEDULE. THE DURATION OF THE STUDY TREATMENT WAS REPORTED AS 74 DAYS. ON AN UNKNOWN DATE, HER LABORATORY EXAMINATION REVEALED THROMBOCYTOPENIA, ELEVATED LACTATE DEHYDROGENASE, ELEVATED CREATININE AND

CONTINUED

6. Relevant tests/laboratory data, including dates
CREATININE LAB RESULT: 1.4 mg/dL BASELINE VALUE: 1.0
HAPTOGLOBIN LAB RESULT: 8 mg/dL

CONTINUED

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)
Medical History Terms NEPHRECTOMY/NEPHRECTOMY/MEDDRA 13.0 RENAL CELL CARCINOMA/RENAL CELL CARCINOMA/MEDDRA 13.0

C. SUSPECT PRODUCT(S)

1. Name (give labeled strength & mfr/labeler)	
#1 BEVACIZUMAB (BEVACIZUMAB)	
#2 SUNITINIB (SUNITINIB)	
2. Dose, frequency & route	3. Therapy dates (If unk. give duration) from/to (or best estimate)
#1 10 MG/KG 1 per 2 WEEK INTRAVENOUS	#1 74 DAYS
#2 50 MG ORAL	#2 74 DAYS
4. Diagnosis for use (indication)	
#1 RENAL CELL CARCINOMA/RENAL CELL CARCINOMA/MEDDRA 13.0	
#2 RENAL CELL CARCINOMA/RENAL CELL CARCINOMA/MEDDRA 13.0	
5. Event abated after use stopped or dose reduced	
#1 <input type="checkbox"/> yes <input type="checkbox"/> no <input checked="" type="checkbox"/> doesn't apply	
#2 <input type="checkbox"/> yes <input type="checkbox"/> no <input checked="" type="checkbox"/> doesn't apply	
6. Lot #	
#1 UNK	7. Exp. date
#2 UNK	#1 UNK
#2 UNK	#2 UNK
8. Event reappeared after reintroduction	
#1 <input type="checkbox"/> yes <input type="checkbox"/> no <input checked="" type="checkbox"/> doesn't apply	
#2 <input type="checkbox"/> yes <input type="checkbox"/> no <input checked="" type="checkbox"/> doesn't apply	
9. NDC # or Unique ID	
#1 NA #2 NA	
10. Concomitant medical products and therapy dates (exclude treatment of event)	
UNK	

G. ALL MANUFACTURERS

1. Contact Office-name/address (& mfring site for devices)		2. Phone Number	
Genentech, Inc. James Nickas, PharmD 1 DNA Way South San Francisco 94080 USA		+1 650 225-5591	
4. Date received by manufacturer (mm/dd/yyyy)		3. Report source (check all that apply)	
07 / 28 / 2010		<input type="checkbox"/> foreign <input checked="" type="checkbox"/> study <input checked="" type="checkbox"/> literature <input type="checkbox"/> consumer <input checked="" type="checkbox"/> health professional <input type="checkbox"/> user-facility <input type="checkbox"/> company representative <input type="checkbox"/> distributor <input type="checkbox"/> other:	
5. (A)NDA#		IND # 7023	
6. If IND, protocol #		STN # 125085	
NA		PMA/510(k)#	
7. Type of report (check all that apply)		Combination product <input type="checkbox"/> yes pre-1938 <input type="checkbox"/> yes OTC product <input type="checkbox"/> yes	
<input type="checkbox"/> 5 - day <input checked="" type="checkbox"/> 15 - day <input type="checkbox"/> 7 - day <input type="checkbox"/> periodic <input type="checkbox"/> 10 - day <input type="checkbox"/> 30 - day <input checked="" type="checkbox"/> initial <input type="checkbox"/> follow-up #		8. Adverse event term(s) MICROANGIOPATHIC HEMOLYTIC ANEMIA/MICROANGIOPATHIC HAEMOLYTIC ANAEMIA/MEDDRA 13.0 +++	
9. MFR. report number		+++ adverse event that generated submission	
718784			

E. INITIAL REPORTER

1. Name, address		Phone #	
2. Health professional?		3. Occupation	
<input checked="" type="checkbox"/> yes <input type="checkbox"/> no		N/A	
4. Initial reporter also sent report to FDA			
<input type="checkbox"/> yes <input type="checkbox"/> no <input checked="" type="checkbox"/> unk.			



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

Where MedDRA is used the following format applies:
Reported term/ MedDRA PT/version number

00003

B.5. Describe event or problem - continued

ELEVATION OF THE RETICULOCYTE COUNT. HER PLATELET COUNT WAS 68 K/UL (BASELINE VALUE: 241), HEMOGLOBIN WAS 12.3 G/DL (BASELINE VALUE: 11), LACTATE DEHYDROGENASE WAS 351 U/L (BASELINE VALUE: 283), CREATININE LEVEL WAS 1.4 MG/DL (BASELINE VALUE: 1.0), RETICULOCYTE COUNT WAS 3.1 % (NORMAL RANGE UNSPECIFIED), PROTEIN TO CREATININE RATIO IN URINE WAS 0.15 (BASELINE VALUE: 0.06) AND HAPTOGLOBIN WAS 8 MG/DL (NORMAL RANGE UNSPECIFIED). SHE WAS DIAGNOSED WITH MICROANGIOPATHIC HEMOLYTIC ANEMIA. AN UNSPECIFIED TIME LATER, SHE DEVELOPED GRADE 2 EVENTS INCLUDING HYPOTHYROIDISM, FATIGUE, MUCOSITIS AND HAND-FOOT SKIN REACTION.

THE OUTCOME OF MICROANGIOPATHIC HEMOLYTIC ANEMIA WAS NOT REPORTED.

THE HEALTH PROFESSIONAL ASSESSED THE EVENT OF MICROANGIOPATHIC HEMOLYTIC ANEMIA AS RELATED TO THE USE OF BEVACIZUMAB AND SUNITINIB BUT DID NOT PROVIDE THE SERIOUSNESS CRITERIA.

THE COMPANY ASSESSED THE EVENT OF MICROANGIOPATHIC HEMOLYTIC ANEMIA AS MEDICALLY SIGNIFICANT.

NO FURTHER INFORMATION WAS PROVIDED.

FELDMAN D R, SCAPPATICCI F A AND MOTZER R J.
TOXICITY OF SUNITINIB PLUS BEVACIZUMAB IN RENAL CELL CARCINOMA REPLY
JOURNAL OF CLINICAL ONCOLOGY 2010; 28 (17): E286-7

THIS CASE IS CROSS-REFERENCED WITH MCN(S) 717661 (SAME LITERATURE ARTICLE).

B.6. Relevant tests/laboratory data - continued

HEMOGLOBIN
LAB RESULT: 12.3 g/dL
BASELINE VALUE: 11

INVESTIGATION
D-DIMER: POSITIVE

LDH
LAB RESULT: 351 U/L
BASELINE VALUE: 283

PLATELET COUNT
LAB RESULT: 68
BASELINE VALUE: 241; UNITS: K/UL

RETICULOCYTE COUNT
LAB RESULT: 3.1 %

URINE PROTEIN/CREATININE RATIO
LAB RESULT: 0.15
BASELINE VALUE: 0.06

SUSPECT ADVERSE EVENT REPORT

EVENT INFORMATION

PAGE 1 OF 4

1. PATIENT INITIALS (FIRST, LAST) (IN CONFIDENCE)	1A. COUNTRY USA	2. DATE OF BIRTH			2A. AGE (YRS) 67 YR	3. SEX F	4-6. EVENT ONSET			8-12. CHECK ALL APPROPRIATE
		DA	MO	YR			DA	MO	YR	

7. DESCRIBE REACTIONS INCLUDING RELEVANT TESTS/LAB DATA

INITIAL INFORMATION FOR THIS CLINICAL LITERATURE CASE WAS RECEIVED ON 28 JULY 2010 FROM A HEALTH PROFESSIONAL AND CONCERNS A 67-YEAR-OLD FEMALE PATIENT (PATIENT NO.) WHO EXPERIENCED MICROANGIOPATHIC HEMOLYTIC ANEMIA WHILST ENROLLED IN AVF4167G; A MULTICENTER, PHASE II, RANDOMIZED, BLINDED, PLACEBO-CONTROLLED TRIAL EVALUATING THE EFFICACY AND SAFETY OF SUTENT WITH OR WITHOUT BEVACIZUMAB IN FIRST-LINE PATIENTS WITH METASTATIC RENAL CELL CANCER.

THE PATIENT UNDERWENT NEPHRECTOMY IN THE PAST. NO CONCOMITANT MEDICATIONS OR PAST DRUGS WERE REPORTED.

ON AN UNSPECIFIED DATE, THE PATIENT COMMENCED TREATMENT WITH INTRAVENOUS BEVACIZUMAB AT A DOSE OF 10 MG/KG ONCE EVERY TWO WEEKS AND ORAL SUNITINIB AT A DOSE OF 50 MG ON 4/2 SCHEDULE. THE DURATION OF THE STUDY TREATMENT WAS REPORTED AS 74 DAYS. ON AN UNKNOWN DATE,

CONTINUED

SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUGS (INCLUDE GENERIC NAME) BEVACIZUMAB (BEVACIZUMAB)		20. DID EVENT ABATE AFTER STOPPING DRUGS? <input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> NA
15. DAILY DOSE(S) / STRENGTH 10 MG/KG 1 X per 2 WEEK /		
16. ROUTE(S) OF ADMINISTRATION INTRAVENOUS		21. DID EVENT REAPPEAR AFTER REINTRODUCTION? <input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> NA
17. INDICATION(S) FOR USE RENAL CELL CARCINOMA/RENAL CELL CARCINOMA/MEDDRA 13.0		
18. THERAPY DATES (FROM/TO) FROM TO	19. THERAPY DURATION 74 DAYS	

CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (EXCLUDE THOSE USED TO TREAT EVENT)

23. OTHER RELEVANT HISTORY (E.G. DIAGNOSES, ALLERGIES, PREGNANCY, WITH LMP, ETC.)
MEDICAL HISTORY TERM(S):
NEPHRECTOMY/NEPHRECTOMY/MEDDRA 13.0
RENAL CELL CARCINOMA/RENAL CELL CARCINOMA/MEDDRA 13.0

MANUFACTURER INFORMATION

24. NAME AND ADDRESS OF MANUFACTURER Genentech, Inc. James Nickas, PharmD 1 DNA Way South San Francisco 94080 USA		24b. MFR. CONTROL NO. 718784
24c. DATE RECEIVED BY MANUFACTURER 28-JUL-2010	24d. REPORT SOURCE <input checked="" type="checkbox"/> STUDY <input checked="" type="checkbox"/> LITERATURE <input checked="" type="checkbox"/> HEALTH PROFESSIONAL	
25a. REPORT TYPE <input checked="" type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOWUP		UNITED STATES OF AMERICA

CIOMS

Where MedDRA is used the following format applies: Reported term/ MedDRA LLT/version number

00005

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

HER LABORATORY EXAMINATION REVEALED THROMBOCYTOPENIA, ELEVATED LACTATE DEHYDROGENASE, ELEVATED CREATININE AND ELEVATION OF THE RETICULOCYTE COUNT. HER PLATELET COUNT WAS 68 K/UL (BASELINE VALUE: 241), HEMOGLOBIN WAS 12.3 G/DL (BASELINE VALUE: 11), LACTATE DEHYDROGENASE WAS 351 U/L (BASELINE VALUE: 283), CREATININE LEVEL WAS 1.4 MG/DL (BASELINE VALUE: 1.0), RETICULOCYTE COUNT WAS 3.1 % (NORMAL RANGE UNSPECIFIED), PROTEIN TO CREATININE RATIO IN URINE WAS 0.15 (BASELINE VALUE: 0.06) AND HAPTOGLOBIN WAS 8 MG/DL (NORMAL RANGE UNSPECIFIED). SHE WAS DIAGNOSED WITH MICROANGIOPATHIC HEMOLYTIC ANEMIA. AN UNSPECIFIED TIME LATER, SHE DEVELOPED GRADE 2 EVENTS INCLUDING HYPOTHYROIDISM, FATIGUE, MUCOSITIS AND HAND-FOOT SKIN REACTION.

THE OUTCOME OF MICROANGIOPATHIC HEMOLYTIC ANEMIA WAS NOT REPORTED.

THE HEALTH PROFESSIONAL ASSESSED THE EVENT OF MICROANGIOPATHIC HEMOLYTIC ANEMIA AS RELATED TO THE USE OF BEVACIZUMAB AND SUNITINIB BUT DID NOT PROVIDE THE SERIOUSNESS CRITERIA.

THE COMPANY ASSESSED THE EVENT OF MICROANGIOPATHIC HEMOLYTIC ANEMIA AS MEDICALLY SIGNIFICANT.

NO FURTHER INFORMATION WAS PROVIDED.

FELDMAN D R, SCAPPATICCI F A AND MOTZER R J.
TOXICITY OF SUNITINIB PLUS BEVACIZUMAB IN RENAL CELL CARCINOMA REPLY
JOURNAL OF CLINICAL ONCOLOGY 2010; 28 (17): E286-7

THIS CASE IS CROSS-REFERENCED WITH MCN(S) 717661 (SAME LITERATURE ARTICLE).

ADVERSE EVENT TERM(S):

MICROANGIOPATHIC HEMOLYTIC ANEMIA/MICROANGIOPATHIC HEMOLYTIC ANEMIA/MEDDRA 13.0 +++

(+++ denotes adverse event that generated submission)

RELEVANT TEST(S)/LAB DATA:

Lab Test Name: CREATININE
Date (Day-Month-Year): --
Lab Result (Low-High Unit): 1.4- mg/dL
Normal (Low-High): -
Lab Result Text: BASELINE VALUE: 1.0

Lab Test Name: HAPTOGLOBIN
Date (Day-Month-Year): --
Lab Result (Low-High Unit): 8- mg/dL
Normal (Low-High): -
Lab Result Text:

Lab Test Name: HEMOGLOBIN
Date (Day-Month-Year): --
Lab Result (Low-High Unit): 12.3- g/dL
Normal (Low-High): -
Lab Result Text: BASELINE VALUE: 11

Lab Test Name: INVESTIGATION
Date (Day-Month-Year): --
Lab Result (Low-High Unit): -
Normal (Low-High): -
Lab Result Text: D-DIMER: POSITIVE

Lab Test Name: LDH
Date (Day-Month-Year): --
Lab Result (Low-High Unit): 351- U/L
Normal (Low-High): -
Lab Result Text: BASELINE VALUE: 283

Lab Test Name: PLATELET COUNT
Date (Day-Month-Year): --
Lab Result (Low-High Unit): 68-
Normal (Low-High): -
Lab Result Text: BASELINE VALUE: 241; UNITS: K/UL

Lab Test Name: RETICULOCYTE COUNT
Date (Day-Month-Year): --
Lab Result (Low-High Unit): 3.1- %

Normal (Low-High): -
Lab Result Text:

Lab Test Name: URINE PROTEIN/CREATININE RATIO
Date (Day-Month-Year): --
Lab Result (Low-High Unit): 0.15-
Normal (Low-High): -
Lab Result Text: BASELINE VALUE: 0.06

14-19. SUSPECT DRUGS - continued

Suspect Drug: SUNITINIB
Generic Name: SUNITINIB
Daily Dose(s)/Strength: 50 MG /
Route: ORAL
Indication: RENAL CELL CARCINOMA/RENAL CELL CARCINOMA/MEDDRA 13.0
Therapy From Date:
Therapy To Date:
Therapy Duration: 74 DAYS

CIOMS TEXT

No CIOMS Text.

REPORTER INFORMATION

CLINICAL TRIAL INFORMATION

Clin. Study Id: AVF4167G
Clin. CRTN
Design and Phase: DOUBLE BLIND II
Clin. Patient Id:
Clin. Investigator Id:

DRUG-EVENT INFORMATION

Event: MICROANGIOPATHIC HEMOLYTIC ANEMIA/MICROANGIOPATHIC
HEMOLYTIC ANEMIA/MEDDRA 13.0
SOC: BLOOD AND LYMPHATIC SYSTEM DISORDERS
Outcome: INSUFFICIENT INFO
Severity:
Seriousness: MEDICALLY SIGNIFICANT
Onset Date:
Resolved Date:
Duration Reported:

Relation To: BEVACIZUMAB
Drug Continued: INSUFFICIENT INFO
AE Abated: NOT APPLICABLE
AE Reappeared: NOT APPLICABLE
Labeled US: NO
Labeled Local: NO - USA
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: SUNITINIB
Drug Continued: INSUFFICIENT INFO
AE Abated: NOT APPLICABLE
AE Reappeared: NOT APPLICABLE
Labeled US: NOT APPLICABLE
Labeled Local: NOT APPLICABLE - USA
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):