



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: November 03 2006

To: NCCTG Primary Clinical Research Associates

From: Janis Wobschall
Protocol Development Coordinator

Re: N0272, Phase II Trial of STI-571 in Treatment of Recurrent Oligodendroglioma and Mixed Oligoastrocytoma

The purpose of this memorandum is to provide investigators with a recent report of an adverse event that has occurred in association with STI-571 for a study where the Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI) is distributing this agent. You may have also received this communication directly from DCTD.

AE_PHHO2006CA15732

Please note that all risks currently cited in the NCCTG consent form can not be omitted; it is at the discretion of your local IRB as to whether they wish to add risks based on the enclosed information. If a determination has been made by the NCCTG Research Base that a protocol amendment is necessary, you will receive the NCI-approved protocol addendum at a later date; for purposes of cross-reference, this communication will cite the adverse event noted above.

Please submit this adverse event to your Institutional Review Board.

If you have any questions concerning this communication, please contact Janis Wobschall at wobschall.janis@mayo.edu or 507/284-4852

JW/dkf
enclosure



To: All Investigators in ST1571 (Glivec) Studies*

Date: 27 September 2006

Re: Investigator Notification for ST1571 (Glivec): Dilantin toxicity- PHHO2006CA15732

Dear Doctor,

In accordance with the Good Clinical Practice and specific national regulatory requirements we wish to inform you of a serious, unexpected, possibly related adverse report of Dilantin toxicity that occurred in a patient being treated with ST1571 (Glivec) during the course of a clinical study.

For the current case, details of the adverse event are provided in the attached CIOMS form, which contains the available information as reported to Novartis.

To summarize briefly,

Initial report received 15 Sep 2006: A 64 year-old patient was enrolled in study protocol CSTI571H2202, a phase II, open-label, multi-centre, single arm study, evaluating the efficacy of Glivec plus hydroxyurea (HU) in patients with progressive glioblastoma multiforme (GBM), receiving enzyme inducing anticonvulsant drugs (EIACDs). He received his first dose of the study medication on 25 August 2006. Medical history: myocardial infarction (1998), hypertension, hypercholesterolaemia, emphysema, CVA (2005), seizures and pancreatitis (2000). In September 2006, the patient complained of anxiety and confusion. On 08 Sep 2006, the patient was noted to have confusion, memory impairment, insomnia, mood alteration - agitation and anxiety. Treatment with Seroquel was started the same day. On 13 September 2006, the patient's symptoms appeared to have increased and the patient stopped taking study medication (the last dose was received on 10 Sep 2006). On 14 Sep 2006, the events had increased in severity and the patient was sent to hospital. The patient was admitted to hospital on 15 Sep 2006 for confusion and Dilantin toxicity (phenytoin level: 115 mcmol/ l - reference range: 40 - 80 mcmol/l). Between 08 Sep 2006 and 15 Sep 2006, the patient's condition had deteriorated and he was reported to be much weaker and was not ambulating independently. He was also drowsy and much more confused. The patient was also having delusions (of having killed his grand children) and was quite agitated. The dose of Seroquel was increased on 13 Sep 2006. It was suspected that other medication the patient was taking were possibly contributing to his condition (such as Decadron and Clobazam). Blood work on 15 September 2006 revealed thrombocytopenia (haemoglobin grade 2: 92 g/l - reference range: 140 - 180 g/l), leukocytopenia, anaemia, and neutropenia. On 16 September 2006, the patient had lunch (at 12:00) and went to bed. The patient then woke up at 14:00 with dyspnoea. Oxygen saturation was 93% on 5L. Lasix was administered and approximately 2L of urine was diuresed. At 18:15 the patient was de-saturated again (oxygen saturation 82% on 50% oxygen face mask). The patient was again given Lasix and placed on a 95% oxygen mask and he responded well. A chest x-ray on 16 September 2006 suggested aspiration pneumonia. On 17 September 2006, the patient went into respiratory arrest (oxygen saturation decreased to 78% despite bag-mask vent). Midazolam, Fentanyl and 'Propofel' were given and the patient was intubated. The patient's blood pressure dropped and was subsequently increased with Levophed, vasopressin and epinephrine. The patient's family decided to stop all aggressive medical intervention, including intravenous therapies/solutions and medication that day (18 September 2006). On 19 September 2006, the patient's family requested that the patient be taken off ventilation in the early morning and the patient was extubated in the late morning. A few hours after extubation on 19 September 2006, the patient died. Medical doctors stated that the cause of death was septic shock. An autopsy was not performed. The investigator suspected a relationship between the events and study medication.

A search of the Novartis Clinical Safety database for Glivec for MedDRA PTs drug toxicity, therapeutic agent toxicity, drug level increased, drug level above therapeutic, drug level altered revealed no similar reports of Dilantin toxicity that were considered to be related to study drug by the investigator.

We will keep you informed if further medically significant information becomes available. We ask that you please inform your Institutional Review Board or Ethics Review Board of this event, if you have such an

obligation. For clinical trials in the U.S. only, if you are utilizing the services of a central Institutional Review Board (IRB) that has been contracted through Novartis, Novartis will submit the Investigator Notification on your behalf to the central IRB.

Sincerely,

Sumita Rai, MD
PVL, Integrated Safety, Novartis Pharmaceuticals
One Health Plaza 419, Rm 1258
East Hanover NJ 07936, USA
862-778-6370 (phone)

Attachment: CIOMS case report

* Novartis Investigator Notification: International Guidelines for Good Clinical Practice as well as specific health authority regulations require that clinical investigators be informed of any adverse drug reaction which is serious (according to specific regulatory criteria), unexpected (i.e. not specifically mentioned in the Investigator's Brochure) and which has a 'reasonable possibility' (in the opinion of the reporter and/or the Company) of being related to the study medication. While Novartis tries to obtain all meaningful information as soon as possible, we are required to communicate all available information within a specified time of its receipt. Since initial data is frequently incomplete, further information must be sent in the form of follow-up reports. Where they have such an obligation, investigators are expected to inform institutional review boards/ethics committees, of each investigator notification. Should Novartis believe that a change in protocol or other action needs to be taken on the basis of clinical reports or other available data, the company will communicate such changes to involved investigators.

SUSPECT ADVERSE REACTION REPORT	

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH			2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET			8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
		Day	Month	Year	64 Years	Male	49.00 kg	Day	Month	Year	
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data) Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) Other Serious Criteria: Medically Significant Septic shock [Septic shock] Respiratory arrest [Respiratory arrest] Dilantin toxicity [Drug toxicity] Aspiration pneumonia [Pneumonia aspiration] ([Dyspnoea]) Neutropenia/neutrophils grade 3 [Neutropenia] Anaemia/Haemoglobin grade 2 [Anaemia] Thrombocytopenia/Platelets grade 2 [Thrombocytopenia] Leukocytopenia/Leukocytes grade 2 [Leukopenia] Memory impairment [Memory impairment] (continue)											<input checked="" type="checkbox"/> PATIENT DIED Date: 19-SEP-2006 <input checked="" type="checkbox"/> INVOLVED OR PROLONGED INPATIENT HOSPITALISATION <input type="checkbox"/> INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY <input type="checkbox"/> LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

(Continued on Additional Information Page)

14. SUSPECT DRUG(S) (include generic name)		20. DID REACTION ABATE AFTER STOPPING DRUG?
#1 GLIVEC(STI571/CGP57148B T35717+TAB)Tablet #2 HYDROXYUREA (HYDROXYCARBAMIDE)		
15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	<input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA
#1 500 mg, BID #2 500 mg, BID	#1 Oral #2 Oral	
17. INDICATION(S) FOR USE		21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
#1 Glioblastoma multiforme #2 Glioblastoma multiforme		
18. THERAPY DATES(from/to)	19. THERAPY DURATION	<input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA
#1 25-AUG-2006 00:00 / 10-SEP-2006 00:00 #2 25-AUG-2006 00:00 / 10-SEP-2006 00:00	#1 17 days #2 17 days	

III. CONCOMITANT DRUG(S) AND HISTORY

(Continued on Additional Information Page)

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)									
23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.) <table style="width: 100%; border-collapse: collapse;"> <tr> <th style="text-align: left;">From/To Dates</th> <th style="text-align: left;">Type of History / Notes</th> <th style="text-align: left;">Description</th> </tr> <tr> <td>1998 to Unknown</td> <td>Current Condition</td> <td>Myocardial infarction</td> </tr> <tr> <td>Unknown</td> <td></td> <td>Hypertension</td> </tr> </table>	From/To Dates	Type of History / Notes	Description	1998 to Unknown	Current Condition	Myocardial infarction	Unknown		Hypertension
From/To Dates	Type of History / Notes	Description							
1998 to Unknown	Current Condition	Myocardial infarction							
Unknown		Hypertension							

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER Investigator's Notification Copy Novartis Pharma Headquarter		26. REMARKS
24b. MFR CONTROL NO. PHHO2006CA15732		
24c. DATE RECEIVED BY MANUFACTURER 19-SEP-2006	24d. REPORT SOURCE <input checked="" type="checkbox"/> STUDY <input type="checkbox"/> LITERATURE <input checked="" type="checkbox"/> HEALTH PROFESSIONAL <input type="checkbox"/> OTHER:	25b. NAME AND ADDRESS OF REPORTER
DATE OF THIS REPORT 26-SEP-2006	25a. REPORT TYPE <input checked="" type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOWUP:	

ADDITIONAL INFORMATION**7+13. DESCRIBE REACTION(S) continued**

Confusion [Confusional state]

Anxiety [Anxiety]

Insomnia [Insomnia]

Mood alteration - Agitation [Agitation]

Drowsy [Somnolence]

Delusion [Delusion]

Condition deteriorated [General physical health deterioration] ([Abasia])

Weaker [Asthenia]

Blood pressure dropped [Blood pressure decreased]

Case Description: Initial report received 15 Sep 2006: This patient (centre number X, patient number X) was enrolled in study protocol CST1571H2202, a phase II, open-label, multi-centre, single arm study, evaluating the efficacy of Glivec plus hydroxyurea (HU) in patients with progressive glioblastoma multiforme (GBM), receiving enzyme inducing anticonvulsant drugs (EIACDs). He received his first dose of the study medication on 25 Aug 2006. Medical history: myocardial infarction (1998), hypertension, hypercholesterolaemia, emphysema, CVA (2005), seizures and pancreatitis (2000). In Sep 2006, the patient complained of anxiety and confusion. On 08 Sep 2006, the patient was noted to have confusion (grade 1), memory impairment (grade 1), insomnia (grade 1), mood alteration - agitation (grade 1) and anxiety (grade 1). Treatment with Seroquel was started the same day. On 13 Sep 2006, the patient's symptoms appeared to have increased and the patient stopped taking study medication (the last dose was received on 10 Sep 2006). On 14 Sep 2006, the events had increased in severity and the patient was sent to hospital. The patient was admitted to hospital on 15 Sep 2006 for confusion and Dilantin toxicity (phenytoin level: 115 mcmol/l - reference range: 40 - 80 mcmol/l). Between 08 Sep 2006 and 15 Sep 2006, the patient's condition had deteriorated and he was reported to be much weaker and was not ambulating independently. He was also drowsy and much more confused. The patient was also having delusions (of having killed his grand children) and was quite agitated. The dose of Seroquel was increased on 13 Sep 2006. It was suspected that other medication the patient was taking were possibly contributing to his condition (such as Decadron and Clobazam). Blood work on 15 Sep 2006 revealed thrombocytopenia (haemoglobin grade 2: 92 g/l - reference range: 140 - 180 g/l), leukocytopenia (leukocytes grade 2: $1.1 \times 10^9/l$ - reference range: $4 - 11 \times 10^9/l$), anaemia (platelets grade 2: $63 \times 10^9/L$ - reference range: $150 - 400 \times 10^9/L$), and neutropenia (neutrophils grade 3: $0.6 \times 10^9/L$ - reference range: $2 - 7.5 \times 10^9/L$). At the time of this report (15 Sep 2006), the patient's condition remained unchanged. The investigator did suspect a relationship between the event and the study medication.

Follow-up received on 19 Sep 2006: On 16 Sep 2006, the patient had lunch (at 12:00) and went to bed. The patient then woke up at 14:00 with dyspnoea. Oxygen saturation was 93% on 5L. Lasix was administered and approximately 2L of urine was diuresed. At 18:15 the patient was de-saturated again (oxygen saturation 82% on 50% oxygen face mask). The patient was again given Lasix and placed on a 95% oxygen mask and he responded well. A chest x-ray on 16 Sep 2006 suggested aspiration pneumonia. On 17 Sep 2006, the patient went into respiratory arrest (oxygen saturation decreased to 78% despite bag-mask vent). Midazolam, Fentanyl and 'Propofol' were given and the patient was intubated. The patient's blood pressure dropped and was subsequently increased with Levophed, vasopressin and epinephrine. On 18 Sep 2006, haemoglobin was 91 g/l, leukocytes were $1.5 \times 10^9/l$, platelets were $60 \times 10^9/l$ and neutrophils were $1.1 \times 10^9/l$. The patient's family decided to stop all aggressive medical intervention, including intravenous therapies/solutions and medication that day (18 Sep 2006). On 19 Sep 2006, the patient's family requested that the patient be taken off ventilation in the early morning and the patient was extubated in the late morning. A few hours after extubation on 19 Sep 2006, the patient died. Medical doctors stated that the cause of death was septic shock. An autopsy was not performed. The investigator suspected a relationship between the event and study medication.

Novartis Comment: Serious adverse event report "Drug toxicity (Dilantin toxicity)", (Hospitalisation), assessed as unexpected according to the Investigator's Brochure.

The information provided in this individual case does not warrant a change to the Investigator's Brochure text. The topic will be monitored closely. Investigator causality is suspected.

Serious adverse event report "Septic Shock, Respiratory Arrest, Aspiration Pneumonia, Blood Pressure Decreased, Neutropenia, Anaemia, Thrombocytopenia, Leukopenia, Memory impairment, Confusional state, Anxiety, Insomnia, Agitation, Somnolence, Delusion, General physical health deterioration & Asthenia", (Hospitalisation), assessed as expected according to the Investigator's Brochure. Investigator causality is suspected.

13. Relevant Tests

(15 Sep 2006) Phenytoin level (reference range: 40 - 80 mcmol/l): 115 mcmol/l

(15 Sep 2006) Haemoglobin (reference range: 140 - 180 g/l): 92 g/l

(18 Sep 2006) Haemoglobin: 91 g/l

(15 Sep 2006) Leukocytes (reference range: $4 - 11 \times 10^9/l$): $1.1 \times 10^9/l$

(18 Sep 2006) Leukocytes: $1.5 \times 10^9/l$

(15 Sep 2006) Platelets (reference range: $150 - 400 \times 10^9/L$): $63 \times 10^9/L$

ADDITIONAL INFORMATION**13. Relevant Tests**(18 Sep 2006) Platelets: $60 \times 10^9/l$ (15 Sep 2006) Neutrophils (reference range: $2 - 7.5 \times 10^9/L$): $0.6 \times 10^9/L$ (18 Sep 2006) Neutrophils: $1.1 \times 10^9/l$

(16 Sep 2006 - 14:00) Oxygen saturation: 93% on 5L

(16 Sep 2006 - 18:15) Oxygen saturation 82% on 50% oxygen face mask.

(17 Sep 2006) Oxygen saturation: 78% despite bag-mask vent.

(16 Sep 2006) Chest x-ray: Suggested aspiration pneumonia.

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#3 DILANTIN (PHENYTOIN SODIUM); Regimen #1	Unknown; Unknown	Unknown	Unknown / 15-SEP-2006 00:00; Unknown
#4 DECADRON (DEXAMETHASONE); Regimen #1	Unknown; Unknown	Brain oedema	Unknown; Unknown
#5 CLOBAZAM (CLOBAZAM); Regimen #1	Unknown; Unknown	Unknown	Unknown; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown		Hypercholesterolaemia
Unknown		Emphysema
2005 to Unknown	Historical Condition	Cerebrovascular accident
Unknown		Convulsion
Unknown		Pancreatitis