



National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

DATE: August 23, 2010

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

SUBJECT: Erlotinib (OSI-774, Tarceva™) Investigator Notification: **Optic Neuropathy**
OSI Pharmaceuticals Report # 2010002862

TO: Investigators of CTEP-sponsored Trials Using OSI-774 (NSC 718781)

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, which describes optic neuropathy in a patient participating in an OSI Pharmaceuticals-sponsored clinical study utilizing the investigational agent erlotinib, was recently distributed to investigators.

The following must be completed by all investigators using erlotinib under NCI IND 63383:

- 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 IND 63383, 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 erlotinib there does not appear to be a change in the risk-benefit ratio for erlotinib 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 MedWatch Report and Dear Investigator Letter that describe the following adverse event are attached:

A 66-year-old female with pancreatic cancer developed optic neuropathy while participating in a Phase 1B study utilizing the investigational agent erlotinib in combination with gemcitabine & nab-paclitaxel.

Attachments: Dear Investigator Letter
MedWatch Report

(osi)™ pharmaceuticals

Drug Safety Department

Tarceva (erlotinib)

Serious Adverse Event Report – 15 Day Investigator Notification

Report # 2010002862

Preferred Term: Optic Neuropathy

16-AUG-2010

Re: OSI-774-108 A Phase 1B Study of erlotinib in Combination with Gemcitabine and Nab-Paclitaxel in Patients with Previously Untreated Advanced Pancreatic Cancer.

«InvFirstName» «InvLastName» «Suffix»
«InvInstitution»
«InvStreetAddress»
«InvAddress1» «InvAddress2» «InvAddress3» «InvCountry»

Dear Dr. «InvLastName»:

This letter is to advise you that we have submitted a follow-up report to local regulatory authorities regarding a patient who was hospitalized due to optic neuropathy that was considered at least possibly related to erlotinib therapy. This patient was treated in study OSI-774-108. This report, originating from USA, was received at OSI Pharmaceuticals on 05-AUG-2010 and 09-AUG-2010. Please include a copy of this letter with your study records and forward a copy to your Institutional Review Board/Ethics Committee as required by local regulations.

Follow-up received 05 AUG 2010 and 09 AUG 2010.

The investigator clarified that rash was a non-serious event and updated the causality of the event.

Event Narrative

This 66-year-old Female patient was enrolled in Protocol OSI-774-108 A Phase 1B Study of erlotinib in Combination with Gemcitabine and Nab-Paclitaxel in Patients with Previously Untreated Advanced Pancreatic Cancer. The patient was diagnosed with pancreatic cancer on 01 JUN 2010. Sites of metastasis included liver. Significant medical history included hypertension and hyperlipidemia. Relevant concomitant medication included promethazine, prochlorperazine, metoclopramide, diclofenac, oxycodone, zolpidem, lorazepam, lovastatin, metoprolol, and amlodipine. The patient started erlotinib 100 mg PO QD; gemcitabine 1,000 mg IV on days 1, 8, and 15; and nab-paclitaxel 100 mg on days 1, 8, and 15 on 01 JUL 2010.

On 13 JUL 2010, the patient experienced OPTIC NEUROPATHY requiring hospitalization. She presented to the emergency department on 13 JUL 2010 with complaints of a 1-2 week history of progressive bilateral blurry vision and rash. The patient was an avid

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reader and had difficulty reading over the past week. Previously she was able to read a book in 1-2 days and was only able to read 1-2 pages per day recently. She could not distinguish print on the page and reported difficulty recognizing faces. She did not describe any blank areas in her vision, only diffuse blurriness. She denied tunnel vision or loss of peripheral vision. Denied floaters, blackouts, and headaches. On confrontation, both visual fields were full. She reported diffuse weakness but nothing focal. She did endorse mild nyctalopia. She had low grade temperatures and night sweats but nothing measurable. She reported feeling constantly cold. She had chronic nausea and abdominal pain that she attributed to the cancer. On examination, the optic nerve as pink and disk margin was sharp with temporal and nasal heme. Macula was flat. Retinal vessels were tortuous and mildly dilated with normal distribution. No retinal hemorrhages. Peripheral retina was flat and attached. Vitreous was clear. Optic nerve showed increased temp pallor compared to right. Peripheral retina was flat and attached. Vision was 20/100 both eyes (right eye 20/40, left eye 20/50). Optic nerve appearance suggested toxic neuropathy most likely from the chemotherapy. MRI of brain with and MRA of the head from 13 JUL 2010 showed focal mass in the left temporal lobe 1.7 x 2.2 cm concerning for malignancy although pancreatic tumors are unlikely to metastasize to the brain. No evidence of an acute stroke. No cerebral edema or mass effect. MRI of brain on 13 JUL 2010 additionally noted L postero-medial temporal enhancing lesion about 1.7 x 2.2 cm in size, no mass effect, no surrounding edema noted, appears to be dural-based mass, concerning for either meningioma or less likely dural-based metastasis. It was felt that the MRI finding of a left temporal mass did not correspond to the patient's symptoms and that this was an incidental finding of meningioma. Differential diagnoses included vitamin A deficiency and giant cell arteritis. The patient was admitted to the hospital on 14 JUL 2010 when a room became available. The patient's last dose of erlotinib prior to the event was on 14 JUL 2010. The patient's last dose of gemcitabine and nab-paclitaxel prior to the event was 08 JUL 2010. Therapy with erlotinib, gemcitabine, and nab-paclitaxel was permanently discontinued due to the event. The patient was discharged home on 15 JUL 2010. Erythrocyte sedimentation rate from 15 JUL 2010 was 31 mm/hr (reference range 0-30) which was considered at the upper limit of normal but not profoundly elevated as seen in giant cell arteritis. On 20 JUL 2010, serum vitamin A was 74 mcg/L (reference range 325-780). She reported on 22 JUL 2010 that her vision was improving but not fully recovered. The rash was slowly improving but the patient continued to have pruritis at the time of the report.

The event of optic neuropathy was serious, unlabelled in the erlotinib IB and considered by the investigator to be not related to erlotinib and gemcitabine but rather to nab-paclitaxel, and vitamin A deficiency.

Company Medical Assessment

Optic neuropathy was a serious adverse event as it resulted in hospitalization and was associated with a significant decrease in vision. This event is not expected/labelled in the erlotinib IB. However, rare reports of visual disturbance and blindness are listed in the IB. Erlotinib has been associated with peripheral neuropathy. Paclitaxel has been associated with optic nerve and/or visual disturbances including optic nerve damage as

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well as ototoxicity and peripheral neuropathy. It is more likely that this event was associated with chemotherapy treatment.

Similar Events

The OSI and Roche erlotinib clinical safety databases were searched for all reports with the preferred term of cranial nerve disorder, optic neuritis, ocular toxicity, optic ischaemic neuropathy and vision blurred. The search found three reports of cranial nerve disorder, three reports of ocular neuritis, two reports of ocular toxicity, one report of optic ischaemic neuropathy, and 68 reports of vision blurred. Of the three reports of optic neuritis, one was considered possibly related to erlotinib by the investigator. Possible alternative explanations for the event included concomitant use of quinine sulfate and Cordarone (amiodarone) and the patient's underlying condition of diabetes mellitus. In one of the two reports of ocular toxicity, investigator assessment was not provided; however, the reporter considered the event at least possibly related to erlotinib. No additional information or alternative explanations were provided. In the one report of optic ischaemic neuropathy, the event was considered by the investigator to be at least possibly related to erlotinib. This case was previously submitted as an IND Safety Report (OSI MCN- 2007000559). Eight of the 68 reports of vision blurred were considered at least possibly related to erlotinib by the investigator. However, of these eight cases, only one had mention of nerve damage. This was a case in which the patient with cerebral metastasis had pre-existing blurred vision which worsened after study treatment with erlotinib and bevacizumab. The patient was found to have optic nerve atrophy. Etiology was unknown, but the patient's neuro-ophthamologist noted possible multiple etiologies including cancer-associated retinopathy and/or radiation-associated atrophy, newly diagnosed low-tension glaucoma, and chemotherapeutic agents. This case was previously submitted as an IND Safety Report (OSI MCN-2008002000).

Conclusion

After review of the clinical details and investigator comments pertaining to this adverse event and based upon the experience of erlotinib to date, the sponsor does not believe that changes to the conduct of this clinical trial are warranted.

Please feel free to contact the OSI Drug Safety Department or your local clinical contact with any questions or concerns you may have in this regard. We appreciate your continuing efforts and cooperation in the conduct of our clinical trials.

Sincerely,

Drug Safety Department
OSI Pharmaceuticals, Inc.
Telephone: (303) 546-7869
e-mail: safetygroup@osip.com

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"A safety report or other information submitted by a sponsor under this section (and any release by FDA of that report or information) does not necessarily reflect a conclusion by the sponsor or FDA that the report or information constitutes an admission that the drug caused or contributed to an adverse experience. A sponsor need not admit, and may deny, that the drug caused or contributed to an adverse experience." [Code of Federal Regulations 312.32]

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0005

U.S. Department of Health and Human Services
Food and Drug AdministrationFor use by user-facilities,
importers, distributors and manufacturers
for MANDATORY reporting

Page 1 of 4

MEDWATCH

FORM FDA 3500A (10/05)

Mfr Report # 2010002862
UF/Importer Report #
FDA Use Only

A. PATIENT INFORMATION			
1. Patient Identifier SJM	2. Age at Time of Event: 66 Years or Date of Birth: 12/21/1943	3. Sex <input checked="" type="checkbox"/> Female <input type="checkbox"/> Male	4. Weight ____ lbs or 66.4 kgs
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: _____ (mm/dd/yyyy) <input type="checkbox"/> Disability or Permanent Damage <input type="checkbox"/> Life-threatening <input type="checkbox"/> Congenital Anomaly/Birth Defect <input checked="" type="checkbox"/> Hospitalization - initial or prolonged <input type="checkbox"/> Other serious (Important Medical Events) <input type="checkbox"/> Required Intervention to Prevent Permanent Impairment/Damage (Devices)			
3. Date of Event (mm/dd/yyyy) 07/13/2010	4. Date of This Report (mm/dd/yyyy) 08/16/2010		
5. Describe Event or Problem			
VERBATIM TERM (Preferred term) OPTIC NEUROPATHY (Optic neuropathy)			
This 66-year-old Female patient was enrolled in Protocol OSI-774-108 A Phase 1B Study of erlotinib in Combination with Gemcitabine and Nab-Paclitaxel in Patients with Previously Untreated Advanced Pancreatic Cancer. The patient was diagnosed with pancreatic cancer on 01 JUN 2010. Sites of metastasis included liver. Significant medical history included hypertension and hyperlipidemia. Relevant concomitant medication included promethazine, prochlorperazine, metoclopramide, diclofenac, oxycodone, zolpidem, lorazepam, lovastatin, metoprolol, and amlodipine. The patient started erlotinib 100 mg PO QD; gemcitabine 1,000 mg IV on days 1, 8, and 15; and nab-paclitaxel 100 mg on days 1, 8, and 15 on 01 JUL 2010.			
On 13 JUL 2010, the patient experienced OPTIC NEUROPATHY requiring hospitalization. She presented to the emergency department on 13 JUL 2010 with complaints of a 1-2 week history of progressive bilateral blurry			
6. Relevant Tests/Laboratory Data, Including Dates			
13 JUL 2010 CHEST X-RAY: Retrocardiac patchy opacities may reflect developing infiltrate or atelectasis.			
13 JUL 2010 MRI OF BRAIN WITH AND WITHOUT INTRAVENOUS CONTRAST AND MRA OF THE HEAD: Focal mass in the left temporal lobe 1.7 x 2.2 cm concerning for malignancy although pancreatic tumors are unlikely to metastasize to the brain. No evidence of an			
7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)			
Past Disease: Tubal ligation			
Concurrent Disease: Hypertension Hyperlipidemia Pain Constipation Insomnia Nausea			

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

3500A Facsimile

C. SUSPECT PRODUCT(S)			
1. Name (Give labeled strength & mfr/labeler)			
#1 Erlotinib (Erlotinib HCl) (Tablet) (Erlotinib HCl)			
#2 GEMCITABINE (GEMCITABINE) Cont...			
2. Dose, Frequency & Route Used		3. Therapy Dates (If unknown, give duration from/to (or best estimate))	
#1 (100 mg, QD), Oral		#1 07/01/2010 - 07/14/2010	
#2 (1000 mg, Days 1, 8, and		#2 07/01/2010 - 07/08/2010	
4. Diagnosis for Use (Indication)		5. Event Abated After Use Stopped or Dose Reduced?	
#1 Pancreatic cancer		#1 <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply	
#2 Pancreatic cancer		#2 <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply	
6. Lot #		7. Exp. Date	
#1		#1	
#2		#2	
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			
10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)			
1) METOPROLOL (METOPROLOL)			
2) LOVASTATIN (LOVASTATIN)			
3) DICLOFENAC (DICLOFENAC) Cont...			
G. ALL MANUFACTURERS			
1. Contact Office - Name/Address (and Manufacturing Site for Devices)		2. Phone Number	
OSI Pharmaceuticals Ardsley Drug Safety 420 Saw Mill River Road Ardsley, NY 10502 USA (Initial Unit)		303-546-7600	
3. Report Source (Check all that apply)			
<input type="checkbox"/> Foreign			
<input checked="" type="checkbox"/> Study			
<input 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			
4. Date Received by Manufacturer (mm/dd/yyyy) 08/05/2010		5. (A)NDA # IND # 53,728	
6. If IND, Give Protocol # OSI-774-108		STN #	
7. Type of Report (Check all that apply)		PMA/510(k) #	
<input type="checkbox"/> 5-day <input type="checkbox"/> 30-day		Combination Product <input type="checkbox"/> Yes	
<input type="checkbox"/> 7-day <input type="checkbox"/> Periodic		Pre-1938 <input type="checkbox"/> Yes	
<input type="checkbox"/> 10-day <input type="checkbox"/> Initial		OTC Product <input type="checkbox"/> Yes	
<input checked="" type="checkbox"/> 15-day <input checked="" type="checkbox"/> Follow-up # 2			
9. Manufacturer Report Number 2010002862		8. Adverse Event Term(s) 1) OPTIC NEUROPATHY (Optic Cont...	
E. INITIAL REPORTER			
1. Name and Address		Phone #	
Dr. Bert O'Neil UNC NC USA			
2. Health Professional? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No		3. Occupation Principal Cont...	
		4. Initial Reporter Also Sent Report to FDA <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Unk.	

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B. ADVERSE EVENT OR PRODUCT PROBLEM

B.5 Describe Event or Problem (Cont...)

vision and rash. The patient was an avid reader and had difficulty reading over the past week. Previously she was able to read a book in 1-2 days and was only able to read 1-2 pages per day recently. She could not distinguish print on the page and reported difficulty recognizing faces. She did not describe any blank areas in her vision, only diffuse blurriness. She denied tunnel vision or loss of peripheral vision. Denied floaters, blackouts, and headaches. On confrontation, both visual fields were full. She reported diffuse weakness but nothing focal. She did endorse mild nyctalopia. She had low grade temperatures and night sweats but nothing measurable. She reported feeling constantly cold. She had chronic nausea and abdominal pain that she attributed to the cancer. On examination, the optic nerve as pink and disk margin was sharp with temporal and nasal heme. Macula was flat. Retinal vessels were tortuous and mildly dilated with normal distribution. No retinal hemorrhages. Peripheral retina was flat and attached. Vitreous was clear. Optic nerve showed increased temp pallor compared to right. Peripheral retina was flat and attached. Vision was 20/100 both eyes (right eye 20/40, left eye 20/50). Optic nerve appearance suggested toxic neuropathy most likely from the chemotherapy. MRI of brain with and MRA of the head from 13 JUL 2010 showed focal mass in the left temporal lobe 1.7 x 2.2 cm concerning for malignancy although pancreatic tumors are unlikely to metastasize to the brain. No evidence of an acute stroke. No cerebral edema or mass effect. MRI of brain on 13 JUL 2010 additionally noted L postero-medial temporal enhancing lesion about 1.7 x 2.2 cm in size, no mass effect, no surrounding edema noted, appears to be dural-based mass, concerning for either meningioma or less likely dural-based metastasis. It was felt that the MRI finding of a left temporal mass did not correspond to the patient's symptoms and that this was an incidental finding of meningioma. Differential diagnoses included vitamin A deficiency and giant cell arteritis. The patient was admitted to the hospital on 14 JUL 2010 when a room became available. The patient's last dose of erlotinib prior to the event was on 14 JUL 2010. The patient's last dose of gemcitabine and nab-paclitaxel prior to the event was 08 JUL 2010. Therapy with erlotinib, gemcitabine, and nab-paclitaxel was permanently discontinued due to the event. The patient was discharged home on 15 JUL 2010. Erythrocyte sedimentation rate from 15 JUL 2010 was 31 mm/hr (reference range 0-30) which was considered at the upper limit of normal but not profoundly elevated as seen in giant cell arteritis. On 20 JUL 2010, serum vitamin A was 74 mcg/L (reference range 325-780). She reported on 22 JUL 2010 that her vision was improving but not fully recovered. The rash was slowly improving but the patient continued to have pruritis at the time of the report.

The event of optic neuropathy was serious, unlabelled in the erlotinib IB and considered by the investigator to be not related to erlotinib and gemcitabine but rather to nab-paclitaxel, and vitamin A deficiency.

Follow-up received 22 JUL 2010.

The investigator clarified the action taken with the study drugs in response to the event and the admit date. The investigator provided additional laboratory results, the stop date and outcome of the event and the discharge summary.

Follow-up received 05 AUG 2010 and 09 AUG 2010.

The investigator clarified that rash was a non-serious event and updated the causality of the event.

B.6 Relevant Tests/Laboratory Data, Including Dates (Cont...)

acute stroke. No cerebral edema or mass effect.

13 JUL 2010 MRI BRAIN: L postero-medial temporal enhancing lesion about 1.7 x 2.2 cm in size, no mass effect, no surrounding edema noted, appears to be dural-based mass, concerning for either meningioma or less likely dural-based metastasis.

13 JUL 2010 MRA OF THE NECK WITH INTRAVENOUS CONTRAST: Unremarkable MRA of the neck.

Lab Result :

Test name	Test date	Test result	Normal value
APTT	07/13/2010	27.6 sec	24.7 - 35.3
BLOOD CULTURE	07/15/2010	No growth at 2 days	
CREATININE	07/13/2010	0.53 mg/dL	0.60 - 1.00
	07/15/2010	0.48 mg/dL	0.60 - 1.00
ESR	07/15/2010	31 mm/hr	0 - 30
HCT	07/13/2010	29.5 %	36 - 46
	07/15/2010	27.4 %	36.0 - 46.0
HGB	07/13/2010	9.4 g/dL	12.0 - 16.0
	07/15/2010	8.8 g/dL	12.0 - 16.0
INR	07/13/2010	1.5	
PLATELET COUNT	07/13/2010	87 X10E9/L	150 - 440
	07/15/2010	58 X10E9/L	150 - 440
POTASSIUM	07/13/2010	3.8 mmol/L	3.5 - 5.0
	07/15/2010	3.5 mmol/L	3.5 - 5.0

OSI Pharmaceuticals
Ardsley Drug Safety
420 Saw Mill River Road
Ardsley, NY 10502
USA

Continuation Sheet for FDA-3500A Form

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Mfr. Report # : 2010002862

Date of This Report : 08/16/2010

PT	07/13/2010	16.8 sec	9.3 - 12.6
SODIUM	07/13/2010	138 mmol/L	135 - 145
	07/15/2010	137 mmol/L	135 - 145
UREA NITROGEN	07/13/2010	15 mg/dL	7 - 21
	07/15/2010	13 mg/dL	7 - 21
Vitamin A	07/20/2010	74 ug/L	325 - 780
WBC	07/13/2010	3.1 X10E9/L	4.5 - 11.0
	07/15/2010	3.8 X10E9/L	4.5 - 11.0

B.7 Other Relevant History, Including Preexisting Medical Conditions (Cont...)

Vomiting
Dry cough
Anxiety

C. SUSPECT PRODUCT(S) (Cont...)

Seq No.	: 2
C.1 Suspect Product	: GEMCITABINE (GEMCITABINE)
C.2 Dose, Frequency & Route Used	: 1) (1000 mg, Days 1, 8, and 15), Intravenous
Seq No.	: 3
C.1 Suspect Product	: NAB-PACLITAXEL
C.2 Dose, Frequency & Route Used	: 1) (100 mg, Days 1, 8, and 15), Intravenous

C.10 Concomitant Medical Products and Therapy Dates

Seq No.	: 3
Concomitant Medical Product	: DICLOFENAC (DICLOFENAC)
Seq No.	: 4
Concomitant Medical Product	: IBUPROFEN (IBUPROFEN)
Seq No.	: 5
Concomitant Medical Product	: MIRALAX (MACROGOL)
Seq No.	: 6
Concomitant Medical Product	: AMLODIPINE (AMLODIPINE)
Seq No.	: 7
Concomitant Medical Product	: AMBIEN (ZOLPIDEM TARTRATE)
Seq No.	: 8
Concomitant Medical Product	: OXYCODONE (OXYCODONE)
Seq No.	: 9
Concomitant Medical Product	: COMPAZINE (PROCHLORPERAZINE EDISYLATE)
Seq No.	: 10
Concomitant Medical Product	: ONDANSETRON (ONDANSETRON)
Seq No.	: 11
Concomitant Medical Product	: ROBITUSSIN DM (ROBITUSSIN-DM)
Seq No.	: 12
Concomitant Medical Product	: ATIVAN (LORAZEPAM)
Seq No.	: 13
Concomitant Medical Product	: METOCLOPRAMIDE (METOCLOPRAMIDE)

E. INITIAL REPORTER (Cont...)

Occupation: Principal Investigator

G. ALL MANUFACTURERS

G.8 Adverse Event Term(s)

1) OPTIC NEUROPATHY (Optic neuropathy)

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