



To: All Investigators in RAD001 Studies*

Date: Jan 26, 2009

Re: Investigator Notification for RAD001
Abdominal adhesion, small bowel thickness and diverticulum /PHHO2008US15235

Dear Doctor,

In accordance with the Good Clinical Practice and specific national regulatory requirements, we would like to inform you of serious, unexpected, possibly related adverse events of abdominal adhesion, small bowel thickness, and diverticulum that occurred in 74-year-old male patient who enrolled in the study CRAD001L2401, an open-label, multi-center, expanded access study of RAD001 in patients with metastatic carcinoma of the kidney that have progressed despite vascular endothelial growth factor receptor tyrosine kinase inhibitor therapy.

Details of the adverse events as reported to Novartis are provided in the attached CIOMS I form.

A search of the Novartis Clinical Safety Database for RAD001 was performed using MedDRA 11.0 Preferred Terms of Abdominal adhesion and Diverticulum and verbatims that contains small bowel thickness. Seven cases of abdominal adhesion and three cases of diverticulum were identified. No additional small bowel thickness case was identified. Only current case was suspected.

In the index case, the patient had left radical nephrectomy and currently has multiple tumor metastases in chest and abdomen. Histories of abdominal pain, ascites, thickening of cecum, colitis, and ileus were also reported. Given the available information, the relationship between the study drug and the events cannot be established.

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,

Holly Zhang, MD
Senior Pharmacovigilance Leader, Integrated Medical Safety
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey, 07936-1080
United States

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 United States	2. DATE OF BIRTH			2a. AGE 74 Years	3. SEX Male	3a. WEIGHT 88.50 kg	4-6 REACTION ONSET			8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
		Day 10	Month OCT	Year 1934			Day 17	Month DEC	Year 2008	<input type="checkbox"/> PATIENT DIED <input checked="" type="checkbox"/> INVOLVED OR PROLONGED INPATIENT HOSPITALISATION <input type="checkbox"/> INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY <input type="checkbox"/> LIFE THREATENING	
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data) Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) Abdominal adhesions [Abdominal adhesions] ([Laparotomy]) Thickening of small bowel/colon [Gastrointestinal disorder] Diverticulosis [Diverticulum] Ascites [Ascites] Nausea grade 3, vomiting grade 3 [Nausea] Nausea grade 3, vomiting grade 3 [Vomiting] ([Dehydration], [Asthenia]) Abdominal pain / cramping abdominal pains [Abdominal pain] Episodic diarrhoea [Diarrhoea] Mild chronic gastritis [Gastritis] Fever with rigors [Pyrexia] ([Chills])											

(Continued on Additional Information Page)

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name) #1) RAD001 (RAD001) Tablet		20. DID REACTION ABATE AFTER STOPPING DRUG? <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA <input type="checkbox"/> Unknown
(Continued on Additional Information Page)		
15. DAILY DOSE(S) #1) 10 mg daily	16. ROUTE(S) OF ADMINISTRATION #1) Oral	21. DID REACTION REAPPEAR AFTER REINTRODUCTION? <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA <input type="checkbox"/> Unknown
17. INDICATION(S) FOR USE #1) Metastatic kidney cancer (Renal cancer)	18. THERAPY DATES(from/to) #1) 20-SEP-2008 / 15-NOV-2008	
19. THERAPY DURATION #1) 57 days		

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction) #1) LISINOPRIL (LISINOPRIL) ; Unknown #2) ASPIRIN (ACETYLSALICYLIC ACID) ; Unknown #3) GLIPIZIDE (GLIPIZIDE) ; Unknown #4) LORATADINE (LORATADINE) ; Unknown #5) SIMVASTATIN (SIMVASTATIN) ; Unknown #6) PATANOL (OLOPATADINE HYDROCHLORIDE) ; Unknown	
(Continued on Additional Information Page)	
23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.) From/To Dates	Description
Unknown	Magnesium low (Blood magnesium decreased)
Unknown	Multiple allergies (Multiple allergies)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER Investigator's Notification Copy Novartis Pharma Headquarter		26. REMARKS
	24b. MFR CONTROL NO. PHHO2008US15235	25b. NAME AND ADDRESS OF REPORTER
24c. DATE RECEIVED BY MANUFACTURER 14-JAN-2009	24d. REPORT SOURCE <input checked="" type="checkbox"/> STUDY <input type="checkbox"/> LITERATURE <input checked="" type="checkbox"/> HEALTH PROFESSIONAL <input type="checkbox"/> OTHER:	
DATE OF THIS REPORT 26-JAN-2009	25a. REPORT TYPE <input checked="" type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOWUP:	

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

Hypotension [Hypotension]
Bilateral pleural effusion [Pleural effusion]
Fluid overload [Fluid overload]
Leukocytosis [Leukocytosis]

Case Description: Initial report received on 18 Dec 2008: This patient (centre no. xxx, patient no. xxx) was enrolled in the study CRAD001L2401, an open-label, multi-center, expanded access study of RAD001 in patients with metastatic carcinoma of the kidney that have progressed despite vascular endothelial growth factor receptor tyrosine kinase inhibitor therapy. The patient's medical history included high cholesterol, diabetes mellitus type II, metastatic kidney cancer to lung, hypertension and gout. The patient received his first dose of study medication on 20 Sep 2008. On 17 Dec 2008, the patient presented to the clinic for evaluation of grade 3 nausea and vomiting which resulted in hospitalization for further work-up. Treatment was not reported. The outcome of the event was reported as still present and unchanged. The investigator did not suspect a relationship between this event and the study medication. The investigator indicated that the event was not due to lack of efficacy or progression of underlying disease.

Follow up received on the 30 Dec 2008: On the 26 Dec 2008 the patient reported to the emergency room for the fourth time with grade three nausea and vomiting and grade two pain in the abdomen. The patient was treated with morphine which made him feel better. The patient was admitted to the hospital after receiving fluids, for further work up and evaluation. An abdominal x-ray showed a little extra stool in the right but was unremarkable. On the 28 Dec 2008, the patient underwent a laparotomy with lysis of adhesions. The surgeon removed one liter of ascites. Complete encasement of the small bowel, fibrous exudates and thickening of the entire small bowel throughout were noted. There was no evidence of obstruction or obstructing mass noted. It was noted that the thickening of the small bowel was from the ileocecal valve up to the ligament of treitz. It was also noted that there was thickening of the colon for the entire length but again no obstructing mass was noted. Cytology reports the ascitic fluid contains single nest of epithelium, low index of suspicion for carcinoma possibly associated with normal mucosa from the bowel. At the time of this report the patient's condition was still present and unchanged. The investigator suspected a relationship between the events and the study medication.

Following internal review of the data on 14 Jan 2009, the adhesions, ascites and thickening of the small bowel/colon have been reassessed by the Novartis medical safety expert as provisionally not suspected to be related to the study medication, based on current available information.

Follow-up received on 14 Jan 2009: The investigator stated that the patient was hospitalized due to vomiting and nausea and during hospitalization, the abdominal adhesions, ascites and thickening of the small bowel were discovered. The investigator suspected the events could be related to the study medication.

Follow-up received on 21 Jan 2009 (prior to circulation of previous follow): Additional medical history included allergies, pain, constipation, and low magnesium. Family history included cancer of the colon (1 of his brothers) and breast cancer (Mother) but no history of renal cancer. The patient's left kidney was resected in Nov 2006, the tumour invaded the vena cava. Lung masses were discovered in Oct 2007. The patient had failed 2 tyrosine kinase inhibitors prior to starting study medication. The patient's baseline cancer status on 8 Sep 2008 was hypernephroma metastatic to lung with progression. On 27 Oct 2008, the patient's wife reported that on 25 Oct 2008, the patient began vomiting and went to the emergency room (ER), where he was diagnosed with colitis and received 3 units of packed red blood cells (reported under PHHO2008US12963). On 3 Nov 2008, the patient's wife reported that the patient was nauseated on 1 Nov 2008 and 2 Nov 2008. The patient had Phenergan on 1 Nov 2008 that helped. On 10 Nov 2008, the patient's wife reported that the patient had a cold and diarrhoea with no cough or temperature. The patient also experienced nausea. Kytril helped. It was noted that the patient's blood sugar was not well controlled with Glipizide. On 14 Nov 2008, the patient's wife reported that the patient had vomited three times the previous day (13 Nov 2008) and once that morning. The patient had also experienced diarrhoea once only. On 17 Nov 2008, the patient's wife reported that the patient had presented to the ER on the weekend (15 Nov 2008 and 16 Nov 2008) with severe abdominal cramping, diarrhoea and vomiting. The patient stopped RAD001 as instructed by the doctor on 15 Nov 2008 and was considered to be much better. The patient restarted RAD001 on 17 Nov 2008. On 24 Nov 2008, physical examination showed abdomen to be mildly distended with sluggish bowel sounds with possible diagnosis of partial bowel obstruction. On 12 Dec 2008, the patient's wife reported that the patient had vomited twice that morning. The patient's blood sugars were noted to be good but a little low as the patient was not eating very well. The patient continued Reglan and Kytril. The patient vomited again on 12 Dec 2008 and was experiencing diarrhoea. The patient stopped RAD001 on 12 Dec 2008 (morning dose was taken). The patient was admitted on 12 Dec 2008 with weakness, dehydration, acute renal insufficiency likely secondary to chemotherapy for metastatic cancer (reported under PHHO2008US15255). He was initially thought to have pneumonia and colitis based on a non-contrast CT scan (showed pericolonic fat stranding and inflammatory stranding throughout the mesenteric), however this did not manifest itself clinically. The patient was placed on antibiotics and intravenous fluid. The patient was planned to be discharged on 15 Dec 2008 and was still not receiving RAD001. The patient received 2 units packed red blood cells on 15 Dec 2008 prior to discharge. The patient was admitted to hospital on 17 Dec 2008, with intractable nausea and vomiting (recurrent for a number of weeks). The vomiting was biliary in nature. The patient reported getting quite bloated sometimes and being unable to pass gas. The patient also had cramping abdominal pains, episodic diarrhoea, bilateral pleural effusion and fluid overload - possible connected with the large amount of fluid given to him during the last hospitalisation. CT scan (from previous hospital) showed ascites, some thickening of the cecum, prominent appendix, ascites, bilateral pleural effusion, more on the left than on the right, pulmonary metastases improved since Sep 2008 scan, contracted gallbladder and atrophic pancreas. The patient had additional history of recurrent anaemia. Stool occult blood was negative for blood. After treatment with fluid the patient improved. The patient underwent an oesophagogastroduodenoscopy (19 Dec 2008) which showed mild chronic gastritis and no evidence of

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

obstruction. Colonoscopy (19 Dec 2008) showed diverticulitis, no sign of colitis, ulceration of malignancy, most likely the patient could have chemotherapy related side effect versus viral enteritis. During hospitalisation, the patient's nausea and vomiting stopped and the diarrhoea improved. Gallbladder ultrasound showed gallstones. A conclusive diagnosis was not made, but the patient was discharged as he had improved and could keep food down. There was considered a remote possibility that the patient had a small bowel obstruction. Final diagnoses were intractable nausea and vomiting (exact aetiology unknown), possible gallbladder disease, possible intermittent small bowel obstruction (cancer related), gastritis, fluid overload and gallstones. The patient was discharged from hospital on 21 Dec 2008 and restart RAD001 on 22 Dec 2008. On 26 Dec 2008, the patient was admitted with nausea and vomiting all day, abdominal pain (mostly upper), acute dehydration and fever with rigors. He started feeling extremely weak and rated his pain at 8/10 in his upper abdomen and all the way across the top. Leukocytosis (possibly due to cancer) and hypotension were also noted. The patient was receiving "Eberal Limus" as part of his concomitant medication therapy. The patient was treated with fluids. The patient's symptoms improved with morphine, but he felt worse over time. The patient was also treated with Levaquin. Ultrasound obtained previously showed questionable evidence of gallstones versus calcified gallbladder. The patient was evaluated for possible acute cholecystitis. CT scan of abdomen and pelvis showed moderate ascites, mild intrahepatic ductal dilatation without extra hepatic ductal dilatation and without abnormality of the gallbladder. No calcification or cholelithiasis was seen. There was dilation of loops of proximal small bowel along with thickening of the wall of the small bowel in the left upper and mid left abdomen. Other findings suggested a partial small bowel obstruction with probable bowel ischaemia. The patient had taken last dose of RAD001 on 27 Dec 2008. The patient underwent an exploratory laparotomy with lysis of adhesions on 28 Dec 2008 which showed complete encasement of small bowel, fibrinous exudates and thickening of the entire bowel throughout, no evidence of obstruction or no obstructing mass noted. Cytology showed no malignancy with low index of suspicion. On 8 Jan 2009, the patient was discharged from hospital and was to stay off magnesium supplementation. On 8 Jan 2009, the patient experienced 4 loose stools and 2 on 9 Jan 2009. The investigator confirmed that the abdominal adhesions, ascites and thickening of small bowel were considered serious (involving / prolonging hospitalisation). The patient remained off study medication at the time of this report until further review. The investigator confirmed that the nausea and vomiting were suspected to be related study medication as RAD001 is associated with these symptoms. In the absence of an investigator causality the Novartis medical safety physician has provisionally assessed the diarrhea, diverticulosis, gastritis, fever and hypotension as suspected to the study medication and the pleural effusion, fluid overload and leukocytosis as not suspected to the study medication, based on the current available information.

Internal review on 26 Jan 2009: The colonoscopy on 19 Dec 2008 showed diverticulosis, and not diverticulitis as reported previously.

Novartis Comment: Serious adverse drug reaction, abdominal adhesions and thickening of the small bowel (hospitalisation), assessed as unexpected according to the Investigator Brochure for RAD001. The information provided in this individual case does not warrant a change to the Investigator Brochure text. The topic will be monitored closely. Investigator causality is suspected.

Serious adverse drug reaction, diverticulosis (hospitalisation), assessed as unexpected according to the Investigator Brochure for RAD001. The information provided in this individual case does not warrant a change to the Investigator Brochure text. The topic will be monitored closely. In the absence of an investigator causality the Novartis medical safety physician has provisionally assessed the event as suspected based on the current available information.

Serious adverse drug reaction, abdominal pain, nausea, vomiting and ascites (hospitalisation), assessed as expected according to the Investigator Brochure for RAD001. Investigator causality is suspected.

Serious adverse drug reaction, diarrhea, gastritis, fever, hypotension (hospitalisation), assessed as expected according to the Investigator Brochure for RAD001. In the absence of an investigator causality the Novartis medical safety physician has provisionally assessed the event as suspected based on the current available information.

All remaining reported leading events and associated symptoms were assessed as not suspected by the Novartis medical safety physician.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	DEC-2008	Abdominal X-ray	Showed a little extra stool.	
2	28-DEC-2008	Abdominal X-ray		
3	19-DEC-2008	Colonoscopy	Showed diverticulitis, no sign of colitis, ulceration of malignancy, most likely the patient could have chemotherapy related side effect versus viral enteritis	
4	12-DEC-2008	Computerised tomogram		

ADDITIONAL INFORMATION**13. Lab Data**

#	Date	Test / Assessment / Notes	Results	Normal High / Low
		Showed inflammatory pericolic fat stranding, especially on the left side and mesenteric fat stranding throughout. Suspected colitis.		
5	DEC-2008	Computerised tomogram		
		Showed ascites, some thickening of the cecum, prominent appendix, ascites bilateral pleural effusion, more on the left than on the right, pulmonary metastases improved since Sep 2008 scan, contracted gallbladder and atrophic pancreas		
6	26-DEC-2008	Computerised tomogram		
		Showed moderate ascites, mild intrahepatic ductal dilatation without extra hepatic ductal dilatation and without abnormality of the gallbladder. No calcification or cholelithiasis was seen. There was dilation of loops of proximal small bowel along with thickening of the wall of the small bowel in the left upper and mid left abdomen. Other findings suggested a partial small bowel obstruction with probable bowel ischaemia. dilatation without extra hepatic ductal dilatation and without abnormality of the gallbladder		
7	28-DEC-2008	Cytology		
		The ascitic fluid contains single nest of epithelium, low index of suspicion for carcinoma possibly associated with normal mucosa from the bowel.		
8	19-DEC-2008	Oesophagogastroduodenoscopy		
		Showed mild chronic gastritis and no evidence of obstruction		
9	DEC-2008	Ultrasound scan		
		Gallbladder ultrasound showed gallstones versus calcified gallbladder		
10	26-DEC-2008	White blood cell count	19,000	

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
#1) RAD001 (RAD001) Tablet; Regimen #2	10 mg daily; Oral	Metastatic kidney cancer (Renal cancer)	17-NOV-2008 / 12-DEC-2008; 26 days
#1) RAD001 (RAD001) Tablet; Regimen #3	10 mg daily; Unknown	Metastatic kidney cancer (Renal cancer)	22-DEC-2008 / 27-DEC-2008; 6 days

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION continued

- #7) B12 (CYANOCOBALAMIN-TANNIN COMPLEX) ; Unknown
- #8) ALLOPURINOL (ALLOPURINOL) ; Unknown
- #9) FISH OIL (FISH OIL) ; Unknown
- #10) MAGNESIUM OXIDE (MAGNESIUM OXIDE) ; Unknown
- #11) STOOL SOFTENER (DOCUSATE SODIUM) ; Unknown

ADDITIONAL INFORMATION**22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION continued**

- #12) SENOKOT (SENNA ALEXANDRINA FRUIT) ; Unknown
- #13) TYLENOL (PARACETAMOL) ; Unknown
- #14) ANTINEOPLASTIC AGENTS (NO INGREDIENTS/SUBSTANCES) ; Unknown
- #15) PAVATINE (PAPAVERINE HYDROCHLORIDE) ; Unknown
- #16) KYTRIL (GRANISETRON) ; Unknown
- #17) FLONASE (FLUTICASONE PROPIONATE) ; Unknown
- #18) INSULIN (INSULIN) ; Unknown
- #19) METOCLOPRAMIDE (METOCLOPRAMIDE) ; Unknown
- #20) IMODIUM (LOPERAMIDE HYDROCHLORIDE) ; Unknown
- #21) NEXIUM (ESOMEPRAZOLE MAGNESIUM) ; Unknown
- #22) CARTROL (CARTEOLOL HYDROCHLORIDE) ; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown		Constipation (Constipation);
Unknown		Pain (Pain);
Unknown		Gout (Gout);
Unknown		Hypertension (Hypertension);
Unknown	with progression	Kidney cancer stage IV (Renal cancer stage IV);
Unknown		Type 2 diabetes mellitus (Type 2 diabetes mellitus);
Unknown		High cholesterol (Blood cholesterol increased);