CIOMS FORM

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET
GV	GERMANY	Day Month Year 22 / 11 / 1948	Years 62	M	Day Month Year 19 12/ 2010

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)

PARALYTIC ILEUS (10033641): recovered/resolved with sequel
HYPOVOLEMIC SHOCK (10021140): recovered/resolved with sequel
ACUTE RENAL FAILURE (10001041): Ongoing

This report was received from an investigator participating in EORTC clinical trial study: 40054 (PETACC-6) and refers to a 62 years old male subject, with diagnosed Rectal cancer. The world wide case ID of this case is: DE-EORTC-40054-537-1. A 62 years old male subject with the following significant past medical history: No other relevant medical history besides diagnosed rectal cancer. On 15/12/2010, the patient experienced massive diarrhea. A co medication of Tinctura opii was established to stop therapy induced diarrhea. On 19/12/2010, the patient was admitted to the hospital with massive copremesis, hypovolemic shock and acute renal failure. Suspected diagnosis of obstructive ileus was invalidated by laparotomy. Instead of an obstruction, a paralytic ileus was See end of event in appendix

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

☐ PATIENT DIED

■ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION

☐ INVOLVED PERSISTENCE OR SIGNIFICANT DISABILITY OR INCAPACITY

■ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
See appendix

20 DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ■ NA

15. DAILY DOSE(S)
See appendix

ROUTE(S) OF ADMINISTRATION
See appendix I

17. INDICATION(S) FOR USE
See appendix

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ■ NA

18. THERAPY DATES (from/to)
See appendix

THERAPY DURATION
See Appendix

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
Tinctura opii
Dose: 15 DF (1 in 1 Days) / Route: Oral / Indication: DIARRHEA / Dates: 15/12/2010 to 19/12/2010 (5 Days)

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

Rectal cancer. No other relevant medical history.

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER

EORTC, Avenue E. Mounier 83, bte 11,
Brussels 1200 BELGIUM

EUDRACT No: 2006-006532-21
Study No: 40054
Center No: 501
Patient No: 537

24b. MFR CONTROL NO.
40054-537-1 (5)

24c. DATE RECEIVED BY MANUFACTURER
11/02/2011

24d. REPORT SOURCE
■ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL

DATE OF THIS REPORT
16/02/2011

25a. REPORT TYPE
■ INITIAL ☐ FOLLOWUP

APPENDIX

I. REACTION INFORMATION

found which was relieved intra-operatively. In consideration of the temporal relation, the newly established co medication of tinctura opii has to be suspected as most probable cause of paralytic ileus and the consecutive hypovolemic shock and acute renal failure. On the other hand both, Capecitabine and Oxaliplatin have a potential to cause obstipation and (seldom) paralytic ileus. Therefore a causative role of the study treatment cannot be excluded. Following examinations were performed: Blood creatinine: 19/12/2010 (3.5 mg/dl), Blood potassium: 19/12/2010 (2.67 mmol/l), Serum creatinine: 23/12/2010 (4.7 mg/dl), Serum creatinine: 03/01/2011 (2.4 mg/dl), Serum creatinine: 13/01/2011 (2.4 mg/dl), Serum creatinine: 14/01/2011 (2.4 mg/dl). The investigator considered this case as serious as the events PARALYTIC ILEUS, HYPOVOLEMIC SHOCK and ACUTE RENAL FAILURE met the seriousness criteria of 'life threatening' and 'inpatient hospitalization'. The subject was admitted to the hospital on 19/12/2010 and discharged on 14/01/2011. The subject received first administration of Xeloda on 22/11/2010, Eloxatin on 22/11/2010, Radiotherapy on 22/11/2010. The subject received the last administration prior to onset of SAE of Xeloda (2000 mg) on 13/12/2010, Eloxatin (100 mg) on 13/12/2010, Radiotherapy (1.8 Gy) on 17/12/2010. Summary of treatments given for the adverse events: Laparotomy, Bowel exhaustion, Electrolyte solutions, Intra-operative decompression. There is a reasonable possibility that PARALYTIC ILEUS was related to Xeloda, Eloxatin and this was expected for both. There is a reasonable possibility that HYPOVOLEMIC SHOCK was related to all of the study treatment. Due to the severity of the event, this was considered as unexpected for the study treatment. There is a reasonable possibility that ACUTE RENAL FAILURE was related to all of the study treatment and this was unexpected for all of them. Due to the severity of the event, this was considered as unexpected for the study treatment. The outcome at the time of this report: PARALYTIC ILEUS was recovered/resolved with sequel (ileostoma) on 23/12/2010. HYPOVOLEMIC SHOCK was recovered/resolved with sequel (renal insufficiency) on 14/01/2011. ACUTE RENAL FAILURE was ongoing on 14/01/2011.

Investigators' description of the SAE:

Patient 0537/GV gave his informed consent to participate in protocol PETACC-6 on 15NOV2010 and was randomized into investigational arm (Xeloda + Oxaliplatin + radiotherapy) on the same day. Start of neo adjuvant treatment was on 22NOV2010. On 13DEC2010 Xeloda treatment was discontinued due to hand-foot syndrome CTC grade 2. On 15DEC2010 patient had massive diarrhea and collapsed at home due to exsiccation and hypotonia. A co medication of Tinctura opii was established to stop therapy induced diarrhea. On 19DEC2010 patient was admitted to hospital with massive copremesis hypovolemic shock and acute renal failure (Lab values on admission: Creatinine of 3.5 mg/dl, Potassium of 2.67 mmol/l). Suspected diagnosis of obstructive ileus was invalidated by laparotomy. Instead of obstruction a paralytic ileus was found and relieved intraoperatively. Currently patient is in stable condition and monitored on ICU. In consideration of temporal relation the newly established co medication of Tinctura opii has to be suspected as most probable cause of paralytic ileus and consecutive hypovolemic shock and acute renal failure. On the other hand both Capecitabine and Oxaliplatin have a potential to cause obstipation and (seldom) paralytic ileus. Therefore a causative role of the study treatment can not be excluded. Possible other cause than trial medication: Tinctura opii. No exams/tests performed. Follow-up (27/12/2010): After short relief following initial intraoperative decompression of bowel, a further episode of ileus with sequestration of multiple liters of enteral fluid appeared, therefore, on 23DEC2010 patient had a relaparotomy and a collateral ileostoma was established, possibly this kind of ileus is at least partly obstructive, maybe through swelling of tumorous rectum section under radiotherapy, but this hypothesis could not be proven so far. Patient is till in a state of renal failure with current serum

creatinine of 4.7 mg/dl and further has to be monitored on ICU. Follow-up (05/01/2011): Renal failure persisted at that point of time where serum creatinine of 4.7 mg/dl and patient had to be monitored on ICU. On 03/01/2011 his status has stabilized and he left ICU with a decreased serum creatinine of 2.4 mg/dl. Currently he is still loosing a lot of fluid through his ileostoma and therefore has to be supported with infusions. Apart from that, recovery is on a good way and discharge from hospital could become possible within a weeks time. Presumably Petacc-6 neo-adjuvant treatment will not be resumed. Follow-up (13/01/2011): On 3/01/2011 his status stabilized. Since then he recovered clinically and was only supported with fluid infusions to balance losses of water and electrolytes through his ileostoma. Unfortunately renal insufficiency is persisting with an altered serum creatinine of 2.4 mg/dl and therefore discharge from hospital had to be delayed. Follow-up (21/01/2011): Although renal insufficiency is persisting with an altered serum creatinine of 2.4 mg/dl nephrology decided that no further inpatient monitoring was necessary. Patient 0537/GV was dismissed form hospital on 14/01/2011. Current status of SAE is: Resolved with sequelae:. Follow-up (11/02/2011): The events 'hand-foot syndrome', 'diarrhoea' and 'copremesis' did not meet any seriousness criteria. The event 'hypovolemic shock' met the seriousness criteria of 'life-threatening' and 'inpatient hospitalization'. The event 'acute renal failure' met the seriousness criterion of 'inpatient hospitalization'. The event 'hypovolemic shock' resolved with sequelae: renal insufficiency. The SAE 'hypovolemic shock' was possibly caused by rectal cancer and concomitant medication Tinctura opii. No detailed information is available on treatment for the SAE 'hypovolemic shock'; standard shock therapy with intravenous fluid infusion and electrolyte supplementation. Details on IV fluids are not documented by hospital. The SAE 'acute renal failure' was possible caused by the SAE 'hypovolemic shock'. The SAE 'Paralytic ileus' resolved with sequelae: ileostoma. The patient is not yet withdrawn from the study; neoadjuvant/preoperative radiochemotherapy had to be stopped for reason of SAE. Course of SAE sequelae renal impairment is currently unforeseeable and could prospectively become a reason to cancel adjuvant treatment. There were 16 fractions of radiotherapy given up to 17/12/2010. Besides creatinine and potassium, there were no other relevant lab tests performed regarding this SAE. There was no relevant diagnostic imaging performed regarding this SAE.

II. SUSPECT DRUG(S) INFORMATION

1. Xeloda [Capecitabine]

Therapy 1	Dose :	2000 mg (2 in 1 Days)
	Route of Admin :	Oral
	Indication for Use :	RECTAL CANCER
	Dates (Duration) :	22/11/2010 to 13/12/2010 (22 Days)
	Therapy ongoing :	

2. Eloxatin [Oxaliplatin]

Therapy 1	Dose :	100 mg
	Route of Admin :	Intravenous (not otherwise specified)
	Indication for Use :	RECTAL CANCER
	Dates (Duration) :	22/11/2010 to 13/12/2010 (22 Days)
	Therapy ongoing :	

III. 22 CONCOMITANT DRUG(S)

Tinctura opii

Therapy 1	Dose :	15 DF (1 in 1 Days)
	Route of Admin :	Oral
	Indication for Use :	DIARRHEA
	Dates (Duration) :	15/12/2010 to 19/12/2010 (5 Days)
	Therapy ongoing :	No

IV. 23 RELEVANT HISTORY

Rectal cancer
Comment :
No other relevant medical history.

V. ADDITIONAL INFORMATION

Lab Result(s):

Test	LLT (Lowest Level Term)	Date	Test Result	Unit
1. Serum creatinine	Serum creatinine	19/12/2010	3.5	mg/dl
2. Potassium	Blood potassium	19/12/2010	2.67	mmol/L
3. Serum creatinine	Serum creatinine	23/12/2010	4.7	mg/dl
4. Serum creatinine	Serum creatinine	03/01/2011	2.4	mg/dl
5. Serum creatinine	Serum creatinine	13/01/2011	2.4	mg/dl
6. Serum creatinine	Serum creatinine	14/01/2011	2.4	mg/dl
7. Laparotomy	Laparotomy	19/12/2010	Suspected diagnosis of obstructive ileus was invalidated. Instead of obstruction, a paralytic ileus was found and relieved intra-operatively.	