

I did not include eyelid edema, facial edema or periorbital edema since these terms could represent distinct processes. Excluding infections, which were discussed under the relevant body system, the sponsor reported that 1.7% (n=37) of oxcarbazepine exposed subjects experienced an SAE in the body as a whole category. These events included no adverse reaction (n=17), deterioration of concomitant underlying disease (n=9), non-specific complaints (n=4), and non-classifiable complaints. When viewing the risks from the controlled trials, there did not appear to be substantial evidence of difference in risk for SAEs in the *Body as a Whole* category when comparing oxcarbazepine and placebo/active control subjects. The sponsor reported that 3% (n=68) of oxcarbazepine exposed subjects discontinued for events in this category. The most commonly reported events leading to discontinuation in this category were fatigue (1.8%, n=39), asthenia (0.3%, n=7) and edema (0.3%, n=7 after collapsing the various edema terms). No other body as a whole event led to discontinuation of more than 5 subjects. In the adjunctive therapy/monotherapy substitution trials, there was an increased risk for discontinuation due to body as a whole events when comparing oxcarbazepine exposed (3.8%, n=48), to placebo (0.6%, n=2) or phenobarbital (0/52), but there was little difference when compared to carbamazepine (3%, n=4). For specific events leading to discontinuation the greatest difference in risk was for fatigue (2.4%, n=30; oxcarbazepine 0.3% n=1 placebo; 0 for carbamazepine and phenobarbital). In addition there were slight increases in risk for asthenia (0.4%, n=5 oxcarbazepine and 0 for the comparators) and edema (0.2%, n=3 oxcarbazepine and 0 placebo or phenobarbital, 0.7% n=1 carbamazepine). In the initiation of monotherapy trials there did not appear to be substantial evidence of increase risk of discontinuation for *Body as a Whole* events when comparing oxcarbazepine exposed subjects with placebo/active comparator exposed subjects. *Body as a Whole* AEs were commonly reported by oxcarbazepine exposed subjects in the clinical trials (36.5%, n=812). The most commonly reported events were fatigue (15%, n=334), fever (7.6%, n=170), injury (4.5%, n=101), weight increase (3.8%, n=84), edema combined 2.9% (n=66) and trauma (2%, n=44). In the adjunctive therapy/monotherapy substitution trials, the risk for fatigue in oxcarbazepine subjects was 13.4% (n=170) compared to 6.8% (n=24) for placebo, 4.5% (n=6) for carbamazepine and 1.9% (n=1) for phenobarbital. Also in these trials, the risk for an edema related AE for oxcarbazepine subjects was 2.6% (n=33) compared to 0.6% (n=2) for placebo and 2.2% (n=3) for carbamazepine. In the initiation of monotherapy trials there was no substantial evidence of increased risk of body as a whole events when comparing oxcarbazepine exposed subjects to placebo/active comparator subjects.

I reviewed the reports from the secondary databases to identify *Body as a Whole* events of interest. There were no serious *Body as a Whole* events in the pre-GCP database. The Named Patient Program database included a report of an allergic reaction that involved rash and transaminase elevations. I requested a narrative for this patient. This 43YO female developed a skin rash 9 days after starting oxcarbazepine that was associated with increased transaminases (neither described in detail). Concomitant medications were carbamazepine, morphine, and baclofen. The skin rash was treated with erythromycin ointment and oxcarbazepine was discontinued. Outcome was not provided. In reviewing the spontaneous reports, there were 10 serious events described as hypersensitivity. In general, the reports contained few details of these events. One report appeared to describe an acute hypersensitivity reaction (bronchospasm, hypotension, and angioedema) in a patient who had a similar reaction to carbamazepine. Two other reports described urticaria/angioedema/facial swelling. There were 5 reports that were suspicious for an anticonvulsant hypersensitivity syndrome. Three of these reports mentioned fever, 3 mentioned liver function abnormalities, 2 mentioned leukopenia, 2 rash and 1 lymphadenopathy.

6.0 Discussion

The sponsor has adequately described the safety experience for the oxcarbazepine-exposed subjects. The number of individuals exposed to oxcarbazepine in the NDA primary database exceeds the ICH guidelines. There is insufficient exposure in the oxcarbazepine database to accurately describe the occurrence of infrequent drug related adverse events. Although there did not appear to be differences in the types of adverse events for different age groups, there is insufficient exposure in the very young (<6 years old) or the elderly (≥ 65 years old) in controlled trials to allow meaningful comparisons of adverse event relative risks. The studies appear to have been adequately designed to capture adverse events. The coding of adverse events, with noted exceptions, appeared appropriate, although the use of different body systems to group events occasionally complicated the review of this NDA. The descriptions of deaths and serious events included in the narrative summaries were brief, but appeared no less detailed than the descriptions provided with other NDAs.

Exposure to oxcarbazepine did not appear to be associated with increased mortality risk. Oxcarbazepine use was associated with several commonly occurring adverse events (observed in at least 10% of exposed patients). These events included dizziness, nausea, vomiting, diplopia, ataxia, headache, somnolence, and blurred vision. Oxcarbazepine subjects experienced increased risks for these events compared to placebo subjects in controlled trials and there appeared to be dose response relationships, further supporting the suspicion that the drug is likely causative for these events. These events do not appear to be associated with substantial risk to patients and the symptoms generally improved with dose reductions or drug discontinuation. In proposed product labeling, the sponsor suggests a dose range of 600mg/day to 2,400mg/day. Experience in one controlled trial suggested that tolerability was poor at 2,400mg/day and patients experience a high dropout due to AE risk.

Oxcarbazepine use is associated with a relatively unusual adverse event, namely hyponatremia. The sponsor provided the results from a water balance study demonstrating that within the proposed dose range oxcarbazepine causes an alteration in the body's regulation of serum osmolality, which can result in hyponatremia. In the clinical trial database, 3% of patients experienced a serum sodium value <125 mmol/L. There were 16 discontinuations for hyponatremia and 14 hyponatremia events were considered SAEs. In most cases the subjects were without symptoms and these events resolved following dose reduction or discontinuation. There is a suggestion, from an analysis of clinical trial data, that the risk for some adverse events including convulsions was inversely related to serum sodium concentration. Although not observed in the primary database there was a death in the named patient program with the finding of cerebral edema on autopsy and a post marketing report of a death due to idiopathic brain edema. In neither case was the patient's serum sodium mentioned and therefore it is not certain if these findings were related to hyponatremia. There were two cases of sudden deaths associated with hyponatremia in oxcarbazepine treated patients reported in the literature. It is not known if hyponatremia causally contributed to either of these deaths or if it was merely a coincidental finding. From post marketing reports, there were hyponatremia events associated with serious outcomes including encephalopathy, coma and increased seizure frequency. The sponsor's consultant feels that the drug can be considered safe with regards to its effect on serum osmolality/sodium concentration. He cited the low percentage of patients in the clinical trials database who experienced a serum sodium concentration <125 mmol/L and the infrequent extreme low sodium values (1 below 118mmol/L). Although 3% may seem small, if the drug is prescribed on a large scale, the number of patients developing significant hyponatremia could be substantial. Also, despite the rather close monitoring during the studies, there were 2 additional subjects from the primary database with serum sodium values of 115mmol/L that were identified outside of clinical trial lab collection (during hospital evaluations). These results were not

identified during scheduled lab testing and therefore did not make it into the clinical trials lab listings, resulting in an underestimation of the risk for the most extreme decreases in serum sodium. The sponsor's expert points to the slow rate at which hyponatremia develops as another reason why oxcarbazepine should be considered safe. In general this is reassuring for most patients but as Dr. Wasserstein mentioned, there are circumstances in which there is at least the theoretical potential to decrease sodium abruptly (ex. situations associated with increased free water intake). Hyponatremia is not an effect unique to oxcarbazepine, it also occurs with at least 1 other AED, specifically carbamazepine. Although it is not completely clear if the risk of hyponatremia (% of patients effected, magnitude of decrease) differs for these two agents, there is some evidence to suggest that it may be higher with oxcarbazepine.

The sponsor described decreases in serum T₄ that appeared to occur commonly in oxcarbazepine exposed subjects. There did not appear to be associated increases in TSH, making the significance of decreased T₄ unclear. If approved, oxcarbazepine would not be the only anticonvulsant associated with decreases in serum T₄. Both carbamazepine and phenytoin are associated with decreases in serum T₄ and T₃. Patients experiencing these lab abnormalities while using these agents remain clinically euthyroid and have normal TSH concentrations. The finding of decreased T₄ and T₃ observed with carbamazepine and phenytoin may be related to protein binding and the method used for routine testing of T₄ and T₃*. It is not clear at this time if a similar phenomenon is being observed in patients taking oxcarbazepine.

This review of the safety data has raised questions about the association of oxcarbazepine and several rare and potentially serious adverse events. Those events include liver toxicity, serious skin reactions, hematological toxicity, hypersensitivity reactions and lupus like reactions. The evidence for the risk for these events will be discussed.

Although no glaring increased risk of elevated transaminases was observed in the analysis of controlled trial data, there was a numerical excess of outliers for ALT and AST in oxcarbazepine exposed subjects. Most patients who developed transaminase elevations did not develop increased bilirubin and the events resolved either on drug or following discontinuation. In the primary database there was a case of hepatocellular injury associated with elevated bilirubin although the case was confounded by the use of another suspected hepatotoxic drug (carbamazepine). A death identified from a post marketing report was suspicious for drug related hepatic necrosis although there were few details describing the event. These cases could potentially signal a relationship between exposure and hepatic injury.

The sponsor demonstrated that oxcarbazepine is associated with a risk of rash. A review of the primary database identified reports of rashes that were categorized as SAEs but none appeared to describe events of particular concern (e.g. toxic epidermal necrolysis, Stevens-Johnson syndrome, exfoliative dermatitis). Stevens-Johnson syndrome was diagnosed in an oxcarbazepine-exposed patient from the NPP, although the case was confounded by the use of other suspect medications. There have been reports of serious skin reactions in oxcarbazepine exposed patients from post marketing reports (TEN, exfoliative dermatitis, and Stevens-Johnson syndrome) although limited detail and suspect concomitant medications make it difficult to definitively determine that oxcarbazepine was causative in any of the cases.

*Surks M. I., DeFesi C., Normal Serum Free Thyroid Hormone Concentrations in Patients Treated With Phenytoin or Carbamazepine, *JAMA* 1996; 275: 1495-1498.

The sponsor described cases that were suspicious for anticonvulsant hypersensitivity syndrome. A healthy volunteer from the CP/PK trials developed fever, urticaria, hepatomegally, and lymphadenopathy, among other symptoms, that resolved following discontinuation of oxcarbazepine. A patient from the NPP developed skin rash and elevated transaminases and there were 5 reports from post marketing use suspicious for a hypersensitivity syndrome (symptoms including fever, rash, lymphadenopathy, liver function abnormalities, and hematologic abnormalities). The limited detail provided in the reports makes it difficult to conclude that any of these cases represent anticonvulsant hypersensitivity syndrome but they do raise concern that this could be a potential drug related effect.

There were cases of hematologic adverse events of concern in the oxcarbazepine database. In a clinical trial, an oxcarbazepine exposed subject developed pancytopenia with marrow depression, although the subject had an underlying illness and took other medications, which could have caused this event. The secondary database contained 2 cases of pancytopenia and one of the two had a bone marrow biopsy demonstrating decreased cell lines. Both patients recovered upon discontinuation of oxcarbazepine. There was one case of pancytopenia from post marketing use but the report but contained few details about the event. In addition to pancytopenia, there have been reports of leukopenia and granulocytopenia in oxcarbazepine exposed subjects. In the controlled trials, there was no marked difference in the occurrence of hematological AEs between treatment groups and the lab data analysis did not reveal any remarkable differences between treatments. These findings could either be compatible with no oxcarbazepine related increased hematological risk or with drug related risks too infrequent to be accurately compared based on the exposure in the database.

The sponsor provided several reports suspicious for drug induced lupus erythematosus. One event was from the primary database (pericardial effusion requiring drainage) but was confounded by the use of carbamazepine. There were additional reports from the post marketing database but these often contained insufficient detail to allow thorough assessment of the events.

7.0 Review of Labeling

Safety related descriptions are provided starting on p.14 of the sponsor's proposed labeling. Neither the warnings nor the precautions sections contain information about hyponatremia. The sponsor proposes including the information under Laboratory tests. Since this seems to be a potentially serious, physiological effect of the drug, I would recommend a description of this effect in the warnings section. The description should include information from the water load study as well as a description of severity and reversibility of the events. It may be helpful to provide a list of conditions and drugs, which could lead to increased risk for hyponatremia (similar to what the sponsor's consultant had done). The sponsor should also discuss the evidence for differences in risk for hyponatremia with oxcarbazepine and carbamazepine. Since the data seem to suggest that the hazard for hyponatremia may be greatest following initiation of therapy we should request Kaplan Meier curves for hyponatremia (ex. first sodium less than 135mEq/L and first sodium less than 125mEq/L) to further examine the hazard with time. If the hazard appears to be greatest early on, we may suggest increased monitoring of serum sodium during that period in addition to the monitoring recommended by the sponsor.

The sponsor appears to remain silent about the observation of decrease in T_4 . The laboratory section should provide descriptive information about this finding. The sponsor might also mention the observed decreases in uric acid.

I would recommend striking the following phrase: In vivo and in vitro studies demonstrate that Trileptal has a low potential for drug interactions. The sponsor could be more factual and describe which interactions were systematically studied and provide the results of such studies.

On page 20 of the proposed labeling, I would recommend striking the following sentence: As enzyme induction is not a feature of Trileptal therapy, liver toxicity is not a relevant safety issue for patients. This statement appears to suggest that we understand all mechanisms of drug related hepatic injury and that we can reliably identify which drugs will cause hepatic injury. In addition there are cases of hepatic injury in oxcarbazepine exposed individuals although that information is insufficient to determine causality.

On page 21 of the proposed labeling, I would recommend re-wording the pediatric use section to better define the exact exposure to pediatric patients and letting the reader come to their own conclusions about the adequacy of the safety evaluation in children. In my opinion, the exposure is insufficient to conclude that the safety profile is the same for adults and children. Again, on p.22 of the proposed labeling, in the Adverse Reactions section, I would recommend striking the first sentence, which suggests no difference in the adverse event profile between children and adults.

In the Treatment Emergent Adverse Events section, Table 4, which describes the experience in the initiation of monotherapy trials, may be irrelevant if the drug does not receive a monotherapy indication. It may be useful to provide adverse event risks by dose groups.

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/S/

Gerard Boehm MD, MPH

cc: NDA21-014/Boehm/Burkhart/Hershkowitz/Katz

8-23-99
my comments in
separate memo

/S/

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Appendices

Tables Summarizing Primary Database Trials

Study Design Summary Table

Exclusion Criteria Table

Safety Parameters Evaluated by Trial

Listing of Serious Adverse Events in Oxcarbazepine Subjects with Epilepsy

Pregnancy Outcome Tables

Serious Balance, Gait, and Coordination Adverse Events from Epilepsy Trials

Listing of Post Marketing Reports by Organ Class

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Tables of trials included in the primary database

Exhibit 2.1.1.-1. Completed, open-label, adjunctive therapy trials

Protocol	Study Type	Population	Study Design/ concomitant AEDs	subjects enrolled/ planned	OXC Regimen	Duration of therapy
Open-label						
001	safety and efficacy	patients > 18 years completing an inpatient presurgical evaluation	open-label, multicenter	13/12	OXC 2400 mg/day	11 days
FTRI02	safety and tolerability	patients 2-12 years	open-label, multicenter 1-3 AEDs	112/80	flexible dose (maximum=90 mg/kg/day)	236 days

Exhibit: 2.1.1.-2. Completed, clinical pharmacology trials in patients with epilepsy

Protocol	Study Type	Study Population	Study Design	subjects enrolled/ planned	OXC regimen	Duration of therapy
NGB90027	interaction study to evaluate the interactions of OXC, CBZ, VPA and PHT	male and female adult patients with epilepsy	double-blind, placebo-control, single-center, crossover	43/43	single dose 600mg, multiple dose 900mg	43 or 22 days
021	evaluate the effects of OXC and PHT on endocrine function	adult male and female patients with epilepsy	open-label, randomized, parallel-group, single-center	24/24	≥900 mg/day	6 mo
FTRI01	pharmacokinetics in children	epileptic children (2-12 yrs) on adjunctive therapy	open label, randomized, single-center, parallel group single dose	31/24	5 and 15 mg/kg	single dose
OT/F11	pharmacokinetics and safety in children	male and female newly diagnosed or untreated patients with epilepsy 3-15 yrs	open label, randomized, single center, crossover	14/24	20 mg/kg/day	8 weeks
OT/E26	evaluate enzyme induction using antipyrine as marker	adult male and female patients with newly diagnosed epilepsy	open-label, multicenter, crossover	12/12	titrate to max of OXC 2700 mg/day	5 weeks

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Exhibit: 2.1.4-1. Clinical pharmacology in healthy volunteers

Protocol	Study Type	Study Population	Study Design	subjects enrolled/ planned	OXC dosage	Duration of therapy
Healthy volunteers						
009	interaction with ethinylestradio/ levonorgestrel	healthy adult female patients	double-blind, randomized, placebo-control, crossover	22/16	1200 mg/day	21 days
013	bioequivalence/ bioavailability	healthy adult male patients	open-label, randomized, two-way crossover	12/12	300mgTab p.o. and 250mgMHD i.v.	single dose
022	comparative bioavailability of tablet formulations and oral suspension	healthy adult male and female patients	open-label, randomized, single-center, three-way crossover	12/12	300mgTab (formulation F4 and F8), and 6% oral suspension	single dose
027	comparative bioavailability of tablet formulations	healthy adult male patients	open-label, randomized, single center, three-way, crossover	12/12	300mgTab (formulation F8 and F9)	single dose
OT/E27	evaluate enzyme induction using antipyrine as marker	healthy adult male patients	open-label, single center	13/12	titrate to 1800 mg/day	5 weeks
OT/E28	evaluate enzyme induction using antipyrine and nifedipine as markers	healthy adult male patients	open-label, single center, placebo-control	13/24	titrate to 1800 mg/day	30 days

Exhibit: 2.1.5-1. Clinical pharmacology trial in subjects with hepatic impairment

Protocol	Study Type	Study Population	Study Design	# enrolled/ planned	oxcarbazepine dosage (formulation)	Duration of therapy
003	pharmacokinetics in special populations (hepatic impairment)	male healthy subjects and male subjects with hepatic impairment	open-label	26/18	900 mg	single dose

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Table of Trials: Controlled Trials

Project No. Report No. Publication	Country Start Date Status	Study Design	Dosage Strength/ Formulation No.	Treatment Duration	Treatment Doses	No. Pts. entered each Trt.	Sex Race (w/b/o)	Mean Age (years) (range)	Volume/Page report data listings* CRF's
Epilepsy, Monotherapy, Placebo-Controlled									
004 Schachter, SC et al. <i>Epilepsia</i> , 1996; 37(5), 153-202 and 1997; 38(3)30	USA 11-Aug-94 complete	DB, R, MC, PC, parallel-group	300 mg F8 600 mg F4	10 yrs	OXC 2400 mg/day PLB	51 51	31m/20f (41/0/10) 25m/26f (40/0/11)	33 (11-51) 34 (14-62)	145/8-1
004E	USA 06-Oct-94 ongoing	OL extension	300 mg F8 600 mg F4	long-term	no max dose of OXC defined	97	53m/44f (76/7/14)	33 (11-62)	148/8-1
026	USA 21-Mar-95 complete	DB, R, MC, PC, parallel-group	300 mg F8 600 mg F4	12 wks	OXC 1200 mg/d PLB	32 35	16m/16f (31/0/1) 17m/18f (30/0/5)	32.7 (8-63) 36.5 (10-69)	152/8-1
026E	USA 06-Jul-95 ongoing	OL extension	300 mg F8 600 mg F4	long-term	OXC max = 2400 mg/day	45	23m/22f (43/1/1)	36.3 (8-69)	155/8-1
006 Ehres RDC, et al BAU 1996; 297: 948-50.	D, S, H, NL 30-Jun-95 prematurely terminated due to slow enrollment	DB, R, MC, PC, parallel-group	150 mg F2 300 mg F8	18 wks	OXC 18-36 mg/kg/d PLB	9 13	4m/5f 6m/7f	11 (7-15) 8 (4-14)	157/8-1

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010 (OT/TE1)	RA, UK, AUS 20-Apr-95 prematurely terminated due to slow enrollment	DB, R, MC, PC, parallel-group	150 mg F2 300 mg F8	51 wks	OXC 1200 mg/d PLB	31 18	10m/21f 7m/11f	77 (65-88) 75 (65-85)	159/8-1
Epilepsy, Monotherapy, Dose-Controlled									
028 Sachdeo R. et al. <i>Neurology</i> 1995; (50)A200	USA 15-Apr-95 complete	DB, R, MC, dose- control, parallel-group	150 mg F2 300 mg F8 600 mg F4	210 days	OXC 300 mg/d OXC 2400 mg/d	45 51	24m/21f (39/0/6) 22m/27f (42/0/7)	35 (18-53) 38 (12-65)	162/8-1
026E	USA 12-Jun-95 ongoing	OL extension	150 mg F2 300 mg F8 600 mg F4	long-term	max = 3000 mg/day	115	53m/62f (100/9/6)	38 912-66)	167/8-1
028	USA 11-Sep-96 complete	DB, R, dose-control, parallel-group	150 mg F2 300 mg F8 600 mg F4	126 days	OXC 300 mg/day OXC 2400 mg/day	46 41	18m/27f (42/0/4) 15m/26f (38/0/3)	38 (11-66) 35 (13-59)	169/8-1
028E	USA 01-Nov-96 ongoing	OL extension	150 mg F2 300 mg F8 600 mg F4	long-term	max = 3000 mg/day	14	11m/3f (13/0/1)	39 (22-66)	172/8-1
OT/F 10 BPK 1995/017	D 20-Sep-91 complete	DB, regimen-control, parallel group	300 mg F4 600 mg F1	382 days	OXC max=2700 mg/day	106 OXC b.i.d. 51 OXC L.L.d.	55m/51f 31m/20f	35 38	173/8-1
OT/F 10E	D 01-Sep-93 complete	OL extension	300 mg F4 600 mg F1	long-term	OXC max = 2700 mg/day	28	16m/12f (28/0/0)	42.8 (19-62)	180/8-1

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Epilepsy, Monotherapy, Active-Controlled									
OT/F01 BPK 1996/048 Christie W, et al. Epi Res 1997; 26: 451-60	B, Br, NL, F, D, ZA, UK, E 22-Nov-95 complete	DB, R, MC, active- control, parallel-group	300 mg F5 300 mg F8 600 mg F1	56 wks	OXC max = 2400 mg/day VPA max = 2400 mg/day	128	60m/68f (125/21)	33 (15-65)	182/8-1
						121	67m/54f (120/01)	33 (15-65)	
OT/F01E	B, Br, NL, F, D, ZA, UK, E 11-Mar-91 complete	OL extension	300 mg F5 300 mg F8 600 mg F1	up to 4.5 years	OXC max = 2400 mg/day VPA max = 2400 mg/day	84	39m/45f (84/00)	32.9 (15-64)	195/8-1
						85	46m/39f (84/16)	32.4 (15-63)	
OT/F02 BPK 1996/125 Bill AP, et al. Epi Res 1997; 27: 195-204	Br, RA, Mex, ZA 26-Jun-91 complete	DB, R, MC, active- control, parallel-group	300 mg F4 600 mg F1	56 wks	OXC max = 2400 mg/d PT max = 800 mg/day	143	82m/61f (72/22/49)	27 (16-63)	201/8-1
						144	82m/52f (68/23/53)	27 (15-91)	
OT/F02E	Br, RA, Mex, ZA 24-Aug-92 complete	OL extension	300 mg F4 600 mg F1	up to 3.5 years	OXC max = 2400 mg/d PHT max = 800 mg/day	86	48m/37f (48/9/29)	28.3 (16-63)	214/8-1
						77	48m/29f (38/13/26)	27.1 (16-91)	

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OT/F04 BPK 1996/098 Guerreiro M, et al. Epi Res 1997; 27: 205- 213	RA, Br 04-Jul-91 Completed	DB, R, MC, active- control, parallel-group	300 mg F4 600 mg F1	56 wks	OXC max = 2400 mg/day PHT max = 800 mg/day	97	46m/51f (80/11/6)	10 (5-17)	220/8-1
						96	50m/46f (80/6/10)	11 (6-17)	
OT/F04E	RA, Br 14-Sep-92 complete	OL extension	300 mg F4 600 mg F1	up to 3 years	OXC max = 2400 mg/day PHT max = 800 mg/day	73	38/35 (59/9/5)	10.8 (5-17)	211/8-1
						58	28m/30f (47/4/7)	10.5 (6-17)	
OT/E26 BPK 1995/015	F 28-Mar-91 complete	DB, R, active-control, parallel-group	300 mg F4	336 days	OXC max = 2100 mg/day CBZ max = 1400 mg/day	127	64m/64f	38 (18-74)	235/8-1
						134	63m/71f	38 (18-81)	
OT/E25E	F 26-May-92 ongoing	OL extension	300 mg F4	long-term	OXC max = 2100 mg/day CBZ max = 1400 mg/day	63	35m/28f	36.5 (18-73)	243/8-1
						76	36m/4f	38.1 (17-77)	
NOC03	I 10-Feb-92 prematurely discontinued due to expiration of drug	DB, R, active-control, parallel-group	300 mg F4	413-422 days	OXC max = 2400 mg/day PB max = 90 mg/day	50	18m/32f	32 (18-59)	243/8-1
						53	23m/30f	34 (17-64)	

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Epilepsy, Adjunctive Therapy, Placebo-Controlled									
011	USA, CDN, AUS, RA, Israel 00-May-95 complete	DB, R, PC, add-on trial	150 mg F2 300 mg F8	112 days	OXC max = 1800 mg/d PLB	138	70m/68f (120/0/18)	11 (3-17)	250/8-1
						129	71m/58f (112/0/17)	11 (3-17)	
011E	USA, CDN, AUS, RA, Israel 24-Oct-95 ongoing	OL extension	150 mg F2 300 mg F8	long-term	no max dose of OXC defined	139	69m/70f (121/1/0/8)	11 (4-17)	256/8-1
OT/PE1	CH, UK, RA, ZA 04-Jun-94 complete	DB, R, MC, PC, 4- arm parallel-group trial	300 mg F8	252 days	OXC 800 mg/day OXC 1200 mg/day OXC 2400 mg/day PLB	158	80m/82f	35 (15-65)	260/8-1
						177	80m/97f	34 (16-64)	
						174	98m/78f	35 (15-66)	
						173	77m/96f	34 (15-66)	
OT/PE1E	CH, UK, RA, ZA 28-Jan-95 ongoing	OL extension	300 mg F8	long term	OXC max = 3000 mg/day	292	156m/136f	33.1 (15-65)	272/8-1

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Project No. Report No. Publication	Country Start Date Status	Study Design	Dosage Strength/ Formulation No.	Treatment Duration	Treatment Doses	No. Pts. entered each Trt.	Sex Race (w/b/o)	Mean Age (years) (range)	Volume/Page report data listings* CRF's
Mania, Placebo-Controlled									
002	USA 10-Aug-93 terminated due to slow enrollment	DB, PC, patients with mania	300 mg F8	21 days	OXC 900 mg/d OXC 1800 mg/d OXC 2700 mg/d PLB	9	8m	52 (37-63)	231/8-1
						7	8m (5/0/1)	34 (26-46)	
						10	8m/1f (9/0/1)	44 (23-59)	
						9	7m/1f (5/0/3)	39 (24-60)	

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Table of Trials: Uncontrolled Trials

Project No. Report No. Publication	Country Start Date Status	Study Design	Dosage Strength/ Formulation No.	Treatment Duration	Treatment Doses	No. Pts. entered each Trt.	Sex Race (w/b/o)	Mean Age (years) (range)	Volume/Page report data listings* CRFs*
001 BPX 1995/ 015 Fisher RS, et.al. Drug Dev Res 1996; 38: 43-49	USA 11-Jun-93 complete	OL	300 mg F6	11 days	OXC 2400 mg	13	8m/5f (12/0/1)	36 (19-50)	289/8-2
FTR102 Motte J et.al. Epilepsia 1995; 36 (suppl 3): S118	F 01-Feb-91 complete	OL	300 mg F4	236 day	OXC max = 90 mg/kg/day	112	54/60m	7 (2-12)	292/8-1
FTR102E	F 20-Jun-92 ongoing	open-label follow-up and extension	300 mg F4	ongoing extension	no max dose of OXC defined	67	38m/29f	7.8 (2-13)	297/8-1
030	USA 18-Oct-97 complete (report in preparation)	OL, single-center study to evaluate water balance	300 mg F8 600 mg F4	28 days + extension	titrate to 2400 mg/day	11 pts with epilepsy 10 healthy volunteers	4m/7f (2/0/2) 7m/3f (0/0/10)	31.7 (18-50)	N/A
031	USA 14-Apr-98 ongoing	OL, MC, extension of Protocol 477779-03	300 mg F8 600 mg F4	long term	OXC ≤3000 mg	18 planned	not yet available	not yet available	N/A
032	CDN, AUS, D, I, E, B Apr-98 ongoing	OL, MC, extension of Protocol 477779-02	300 mg F8 600 mg F4	long term	OXC ≤3000 mg	96 planned	not yet available	not yet available	N/A

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Oxcarbazepine study summary table

Exhibit 2.1.3.-1. Overview of Study Phases: Completed, double-blind trials¹

Study Interval	Planned Duration	Therapy	Purpose
Screening Phase	1-28 days	Recent history of therapy with AEDs if substitution monotherapy trial or adjunctive polytherapy trial. No chronic history of AEDs if monotherapy initiation trial.	Determine eligibility
Baseline Phase ²	Group A: 14-24 weeks Group B: 8-24 weeks Group C: 8 weeks	Standard AEDs ³	Observation period for subsequent comparison
Double-blind Phase			
Titration Period	Group A: 1-12 weeks Group B: 1 day-12 weeks Group C: 2 weeks	OXC increased at weekly intervals to the assigned (or maximum tolerated) dosage; concurrently, background AEDs were decreased	Achieve the assigned (or maximum tolerated) dosage of OXC and conduct efficacy and safety observations
Maintenance Period ⁴	Group A: 12-48 weeks Group B: 1-48 weeks Group C: 14-24 weeks	Maintenance on the assigned (or maximum tolerated, if less) dosage of trial drug.	Efficacy and safety observations
Tapering Period ⁵	6-10 days	Decreasing dosages of OXC.	Safe withdrawal of OXC therapy.
Long-term Extension Phase	ongoing	Maintenance on OXC; allowed to add-on additional AEDs	Long-term safety observations

¹ Group A (Protocols 006, 010, 025, OT/F01, OT/F02, OT/F04) = initiation of monotherapy, Group B (Protocols 004, 026, 028, OT/E25, OT/F10, NIOC03) = monotherapy substitution, Group C (011, OT/PE1) = adjunctive therapy

² Protocol 026 had a 4-week Open-label Conversion Phase before the Baseline Phase. Protocol 004 had a 48-hour Baseline Period

³ Standard AEDs included phenytoin, carbamazepine, phenobarbital, primidone, and valproic acid

⁴ Assigned daily doses of oxcarbazepine during the trial were 300-2400 mg/day in Group A, 300 mg-2700 mg/day in Group B and 600-2400 mg/day in Group C.

⁵ Patients who completed the Maintenance Period of these protocols were permitted to enter a Long-term Extension Phase at the discretion of the investigator and medical monitor. Patients who withdrew from the trial or who chose not to enter the open-label study had their dosages of trial drug tapered off.

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Exhibit 2.3.-1. Summary of safety parameters evaluated in oxcarbazepine clinical trials

Protocol	Vital Signs and Weight	Complete Labs ¹	ECG	Physical Exam	Neurological Exam
001	Yes	Yes	Yes	Yes	Yes
002	Yes	Yes ⁵	Yes	Yes	Yes
003	Yes	Yes	Yes ²	Yes	No
004	Yes	Yes ⁵	Yes	Yes	Yes
006	Yes	Yes	Yes	Yes	Yes
009	Yes	No ⁴	Yes	Yes	No
010	Yes	Yes ⁵	Yes	Yes	Yes
011	Yes	Yes	Yes	Yes	Yes
013	Yes	Yes	Yes	Yes ²	No
021	Yes	Yes	Yes ²	Yes ²	No
022	Yes	Yes	Yes	Yes ²	No
025	Yes	Yes ⁵	Yes	Yes	Yes
026	Yes	Yes ⁵	Yes	Yes	Yes
027	Yes	Yes	Yes	Yes ²	No
028	Yes	Yes	Yes	Yes	Yes
FTRI01	Yes	No ³	No	Yes ²	Yes ²
FTRI02	Yes	No ³	No	Yes ²	Yes ²
NGB90027	No	Yes	No	Yes ²	Yes ²
NIOC03	No	No ³	No	Yes	Yes
OT/E25	No	No ³	No	Yes ²	Yes ²
OT/E26	Yes	Yes	Yes	Yes	Yes
OT/E27	Yes	Yes	Yes	Yes	Yes
OT/E28	Yes	Yes	Yes	Yes	No
OT/F01	Yes	Yes ⁵	Yes	Yes	Yes
OT/F02	Yes	Yes	Yes	Yes	Yes
OT/F04	Yes	Yes ⁵	Yes	Yes	Yes
OT/F10	Yes	Yes	Yes	Yes	Yes
OT/F11	No	No ³	No	No	No
OT/PE1	Yes	Yes ⁵	Yes	Yes	Yes

¹ Complete labs includes test for hematology, blood chemistry, and urinalysis

² Tests performed at baseline/screening only

³ Urinalysis tests were not performed

⁴ Hematology tests were not performed

⁵ Thyroid tests were also performed

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Appendix VI.1

Listing 6.3.1-1B: Serious or potentially serious adverse events up to March 31, 1998 - by patient (all OXC-treated subjects with epilepsy)

Body System	Term	Treatment (prev. treatment)	Trial	Country/Center	Patient	Age/ Sex	Last Dose (mg/day)	Dur. to Onset (days)	Rel. to Tr. Drug	Action Taken	Outcome
Other gastrointestinal disorders	Vomiting, asthenia, anorexia	OXC	FTRI02	F/1	103/	2/M	750 MG	155	1	5,7,8	1
Convulsive disorders	Convulsions grand mal	OXC	FTRI02	F/10	1011/	3/F	750 MG	116	0	3,6,7	3
Other and non classifiable complaints	Procedure central and peripheral nervous system	OXC	FTRI02	F/11	1103/	9/F	600 MG	87	0	0,7	
No adverse reaction	Fracture	OXC	FTRI02	F/11	1104/	/F	2400 MG	81	0	7	1
Disorders of coagulation or haemostasis disorders	Hematoma	OXC	FTRI02	F/13	1301/	8/F	900 MG	190	0	4,5,7	1
Convulsive disorders	Convulsions local, convulsions local	OXC	FTRI02	F/14	1402/	8/F	750 MG	27	2	6,7	1
Other gastrointestinal disorders	Diarrhea	OXC	FTRI02	F/15	1503/	8/M	600 MG	98	0	0,7	1
No adverse reaction	Procedure musculo-skeletal	OXC	FTRI02	F/6	601/	12/M	600 MG	184	0	0,7	1
Other gastrointestinal disorders	Vomiting	OXC	FTRI02	F/7	702/	8/F	300 MG	0	1	6,7	1
Convulsive disorders	Convulsions	OXC	FTRI02	F/9	915/	9/M	900 MG	220	0	5,7	3
Dermatitis or eczema	Rash erythematous	OXC	FTRI02	F/9	925/	2/M	600 MG	87	2	7	4
Convulsive disorders	Convulsions, hemiplegia	OXC	FTRI02	F/9	932/	2/F	450 MG	153	1	7	3
Convulsive disorders	Convulsions	OXC	FTRI02E	F/10	1004/	9/F	600 MG	693	0	7	1
Convulsive disorders	Cranial injury nos	OXC	FTRI02E	F/11	1102/	10/F	1200 MG	653	0	0	1
Convulsive disorders	Convulsions local	OXC	FTRI02E	F/13	1301/	11/F	900 MG	1880	1	6,7	1
Hepatitis without jaundice, toxic hepatitis, hepatotoxicity	Hepatitis	OXC	FTRI02E	F/13	1303/	5/M	750 MG	680	2	3	1
Convulsive disorders	Convulsions	OXC	FTRI02E	F/15	1501/	12/F	900 MG	384	0	6,7	1
No adverse reaction	Sprains and strains	OXC	FTRI02E	F/6	601/	13/M	1200 MG	898	0	4,7	1
Convulsive disorders	Convulsions aggravated	OXC	FTRI02E	F/6	602/	14/M	1500 MG	810	0	5,7	1
Other gastrointestinal disorders	Diarrhea	OXC	FTRI02E	F/6	602/	16/M	1500 MG	1006	0	7	1
Other gastrointestinal disorders	Vomiting	OXC	FTRI02E	F/6	602/	17/M	900 MG	1367	0	7	1
No adverse reaction	Deformity skeletal	OXC	FTRI02E	F/6	602/	14/M	1500 MG	749	0	4,7	2
Intracranial and spinal cord disorders	Hypertension intracranial	OXC	FTRI02E	F/8	807/	9/F	300 MG	354	0	7	1
Intracranial and spinal cord disorders	Hypertension intracranial	OXC	FTRI02E	F/8	807/	9/F	300 MG	377	0	7	1
Intracranial and spinal cord disorders	Hypertension intracranial	OXC	FTRI02E	F/8	807/	9/F	300 MG	435	0	7	3
Intracranial and spinal cord disorders	Hypertension intracranial	OXC	FTRI02E	F/8	807/	9/F	300 MG	464	0	7	1

Body System	Term	Treatment (prev. treatment)	Trial	Country/ Center	Patient	Age/ Sex	Last Dose (mg/day)	Dur. to Onset (days)	Rel. to Tr. Drug	Action Taken	Outcome
No adverse reaction	Deformity skeletal	OXC	FTRI02E	F/9	904/	12/M	900 MG	811	0	4,7	2
Convulsive disorders	Convulsions grand mal	OXC	FTRI02E	F/9	917/	9/M	900 MG	1295	0	6,7	1
Convulsive disorders	Convulsions grand mal	OXC	FTRI02E	F/9	919/	12/M	600 MG	1190	0	0	6
Convulsive disorders	Convulsions local, convulsions aggravated	OXC	FTRI02E	F/9	938/	11/M	1050 MG	709	0	3,7	1
Convulsive disorders	Convulsions	OXC	OT/E25	F/12	46/	33/F	900 MG	51	0	3,6,7	3
Electrolyte disturbances	Hyponatremia, cramps muscle	OXC	OT/E25	F/13	464/	52/F	1350 MG	315	3	3,6,7	1
Convulsive disorders	Convulsions, convulsions local	OXC	OT/E25	F/2	5/	44/M	1800 MG	64	0	3,4,7	1
No adverse reaction	Fracture	OXC	OT/E25	F/2	5/	44/M	NA	28	0	7	1
Convulsive disorders	Convulsions grand mal	OXC	OT/E25	F/22	87/	52/M	900 MG	304	0	7	1
Other urinary system disorders†	Pain renal, pain abdominal	OXC	OT/E25	F/24	93/	24/F	1350 MG	153	0	6,7	1
Convulsive disorders	Convulsions grand mal	OXC	OT/E25	F/32	127/	25/M	1200 MG	72	0	1,7	1
Infection or sepsis related effects	Abscess	OXC	OT/E25	F/33	130/	33/M	2100 MG	187	0	4,7	1
Anaphylactoid reaction without shock	Angioedema	OXC	OT/E25	F/38	149/	58/M	300 MG	12	1	1,6	1
Affect disorders	Therapeutic response increased, suicide attempt	OXC	OT/E25	F/49	195/	50/M	900 MG	131	0	0	1
Other gastrointestinal disorders	Pain abdominal, vomiting	OXC	OT/E25	F/49	195/	49/M	NA	42	0	2,4,7	1
Convulsive disorders	Convulsions grand mal	OXC	OT/E25	F/49	544/	29/M	1200 MG	34	0	1,7	1
Convulsive disorders	Convulsions grand mal	OXC	OT/E25	F/49	544/	29/M	900 MG	17	0	0,7	1
Other and non classifiable complaints	Fracture	OXC	OT/E25	F/49	546/	37/M	900 MG	25	0	2,4,7	3
Convulsive disorders	Convulsions grand mal	OXC	OT/E25	F/5	286/	28/F	1200 MG	316	1		6
Convulsive disorders	Convulsions grand mal, convulsions	OXC	OT/E25	F/5	323/	21/M	1800 MG	121	0	4,7	1
Convulsive disorders	Convulsions, tremor, syncope	OXC	OT/E25	F/5	446/	23/F	1200 MG	47	2	3,6,7	1
Combined gastric and duodenal ulcer without complications	Gastric ulcer, duodenal ulcer	OXC	OT/E25	F/5	505/	30/M	900 MG	133	1	6,7	3
Convulsive disorders	Convulsions grand mal	OXC	OT/E25	F/5	506/	22/M	900 MG	42	0	1,7	1
Convulsive disorders	Convulsions grand mal	OXC	OT/E25	F/5	562/	19/F	900 MG	46	0	6,7	3
Balance, gait, or coordination disorders	Dizziness	OXC	OT/E25	F/52	205/	41/F	NA	3	3	5,7	1
Temperature changes (nos)	Fever	OXC	OT/E25	F/58	232/	58/F	900 MG	150	0	6	1
Blood pressure changes	Syncope	OXC	OT/E25	F/66	262/	74/F	600 MG	80	0	5,6,7	1
Electrolyte disturbances	Therapeutic response increased, overdose nos	OXC	OT/E25	F/66	330/	69/M	900 MG	347	0	2,5,6,7	1
Myocardial ischaemia	Procedure surgical	OXC	OT/E25	F/66	330/	69/M	900 MG	174	0	7	1

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Body System	Term	Treatment (prev. treatment)	Trial	Country/ Center	Patient	Age/ Sex	Last Dose (mg/day)	Dur. to Onset (days)	Rel. to Tr. Drug	Action Taken	Outcome
Excitation	Neurosis	OXC	OT/E25	F/69	348/	46/F	600 MG	11	0	7	1
Behaviour and personality disorders	Neurosis, ataxia	OXC	OT/E25E	F/26	102/	19/F	1200 MG	418	0	3,6,7	3
Convulsive disorders	Convulsions grand mal	OXC	OT/E25E	F/32	127/	26/M	1500 MG	450	0	7	1
Neoplasms unspecified	Procedure central and peripheral nervous system	OXC	OT/E25E	F/4	16/	57/F	1500 MG	619	0	1,7	1
Heart rate and rhythm disorders	Arrhythmia, sudden death	OXC	OT/E25E	F/50	537/	60/M	900 MG	936	0	0	6
Pharynx, larynx or trachea, nasal disorders (nos)	Laryngismus	OXC	OT/E25E	F/51	203/	36/F	600 MG	561	0	0	6
Infection or sepsis related effects	Infection viral, respiratory disorder	OXC	OT/E25E	F/54	213/	27/M	900 MG	1669	0	6,7	1
Infection or sepsis related effects	Circulatory failure	OXC	OT/E25E	F/66	330/	70/M	1200 MG	534	0	3,4,5,6,7	3
Myocardial ischaemia	Myocardial infarction	OXC	OT/E25E	F/68	270/	55/M	600 MG	753	0	3,4,7	2
Convulsive disorders	Convulsions grand mal	OXC	OT/E25E	F/74	302/	48/M	900 MG	741	0	7	1
Affect disorders	Suicide attempt	OXC	OT/E25E	F/74	302/	48/M	900 MG	716	0	7	1
Convulsive disorders	Convulsions local, trauma	OXC	OT/E25E	F/8	429/	31/F	1050 MG	570	0	5,7	1
Heart rate and rhythm disorders	Tachycardia, fever	OXC	OT/F01	D/2	109/	48/M	1200 MG	172	1	0,7	1
Convulsive disorders	Concussion, hemorrhage nos	OXC	OT/F01	D/2	94/	43/M	300 MG	313	1	1,7	1
Electrolyte disturbances	Hypocalcemia	OXC	OT/F01	D/2	94/	43/M	1800 MG	405	1	6	4
Myocardial ischaemia	Angina pectoris	OXC	OT/F01	D/2	94/	43/M	1800 MG	320	2	7	1
Allergic skin reactions (nos)	Rash erythematous, pruritus	OXC	OT/F01	D/3	31/	28/F	900 MG	11	4	3,6	1
Other allergic reactions	Rash, pruritus, lymphadenopathy, conjunctivitis	OXC	OT/F01	D/3	39/	29/F	900 MG	10	3	3,6	1
Behaviour and personality disorders	Psychic disorder	OXC	OT/F01	D/3	45/	20/M	1500 MG	304	1	3,6,7	1
Pancytopenia with or without bone marrow disorders	Colitis, marrow depression	OXC	OT/F01	D/3	98/	26/F	900 MG	159	1	5,6,7	3
Deterioration of concomitant or underlying illness	Arthritis, polyarthritis	OXC	OT/F01	D/3	98/	27/F	900 MG	148	0	7	4
Deterioration of concomitant or underlying illness	Arthritis, polyarthritis	OXC	OT/F01	D/3	98/	27/F	900 MG	188	0	7	4
Deterioration of concomitant or underlying illness	Polyarthritis	OXC	OT/F01	D/3	98/	27/F	900 MG	336	0	0	2
Deterioration of indication for treatment and lack of efficacy	Therapeutic response decreased	OXC	OT/F01	D/4	55/	30/F	3300 MG	120	2	7	4
Bronchi and lower airways disorders	Asthma	OXC	OT/F01	D/4	71/	65/M	900 MG	407	0	0	3
No adverse reaction	Death	OXC	OT/F01	E/5	7109/	48/M	900 MG	274	0	0	6

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Body System	Term	Treatment (prev. treatment)	Trial	Country/Center	Patient	Age/Sex	Last Dose (mg/day)	Dur. to Onset (days)	Rel. to Tr. Drug	Action Taken	Outcome
Sexual function disorders, male	Impotence	OXC	OT/F01	E/5	7112/	41/M	1800 MG	180	3	0	1
Convulsive disorders	Convulsions grand mal	OXC	OT/F01	F/12	7001/	57/M	1200 MG	67	2	3,7	1
Rashes, exanthematous or eruptive dermatosis	Rash maculopapular, nausea, hematuria, fever, weight decrease, malaise	OXC	OT/F01	GB/2	215/	41/F	900 MG	1	4	3,6	1
Convulsive disorders	Convulsions, injury	OXC	OT/F01	GB/2	221/	19/M	1500 MG	191	0	2,7	1
Affect disorders	Anxiety, emotional lability, stupor	OXC	OT/F01	ZA/1	966/	37/F	1200 MG	162	0	6,7	1
Peripheral and cranial nerve disorders	Neuritis	OXC	OT/F01	ZA/4	985/	27/F	300 MG	1	0	7	1
Electrolyte disturbances	Hyponatremia	OXC	OT/F01E	D/1	2/	56/F	900 MG	804	4	6	1
Electrolyte disturbances	Hyponatremia	OXC	OT/F01E	D/1	8/	53/F	1800 MG	441	3	0,1,7	1
Joint disorders	Periarticular disorder	OXC	OT/F01E	D/1	81/	32/F	NA	489	0	0	1
Rashes, exanthematous or eruptive dermatosis	Rash, condition aggravated	OXC	OT/F01E	D/2	17/	29/F	1800 MG	309	2	0,3,6,7	3
Convulsive disorders	Convulsions grand mal	OXC	OT/F01E	D/2	24/	44/M	2100 MG	406	0	1,7	1
Deterioration of concomitant or underlying illness	Asthma	OXC	OT/F01E	D/3	33/	27/F	900 MG	764	0		2
Deterioration of concomitant or underlying illness	Asthma	OXC	OT/F01E	D/3	33/	28/F	600 MG	1448	1	6,7	3
Pregnancy and maternal breastfeeding disorders	Abortion	OXC	OT/F01E	D/3	42/	34/F	2100 MG	1127	0	7	1
Paretic symptoms nos	Paresis	OXC	OT/F01E	D/3	48/	53/M	2100 MG	905	0	7	1
Deterioration of concomitant or underlying illness	Arthritis	OXC	OT/F01E	D/3	98/	28/F	900 MG	685	0	7	3
No adverse reaction	Trauma	OXC	OT/F01E	D/4	56/	39/M	600 MG	1093	0	0	1
Headache	Headache, procedure surgical	OXC	OT/F01E	D/4	76/	24/F	2100 MG	68	0	7	1
Failure of contraception	Pregnancy unintended, abortion, abortion	OXC	OT/F01E	D/4	76/	24/F	2100 MG	0	4	0	1
Rashes, exanthematous or eruptive dermatosis	Rash	OXC	OT/F02	MEX/1	26/	27/F	900 MG	10	3	3,6	1
Other and non classifiable complaints	Therapeutic response increased	OXC	OT/F02	MEX/3	23/	17/M	1200 MG	203	0	2	1
Intracranial and spinal cord disorders	Hemiplegia	OXC	OT/F02	MEX/4	67/	21/F	1800 MG	171	0	3,6,7	3
Balance, gait, or coordination disorders	Ataxia, vomiting, tremor, hypoesthesia, cerebellar syndrome, nausea, vertigo, coordination abnormal	OXC	OT/F02	ZA/1	426/	63/M	900 MG	18	3	0,3	1
Consciousness, mentation, and selective brain disorders	Confusion	OXC	OT/F02	ZA/1	426/	64/M	900 MG	386	1	2,7	2

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Body System	Term	Treatment (prev. treatment)	Trial	Country/Center	Patient	Age/Sex	Last Dose (mg/day)	Dur. to Onset (days)	Rel. to Tr. Drug	Action Taken	Outcome
Myocardial ischaemia	Sudden death	OXC	OT/F02E	BR/1	110/	63/M	1500 MG	1255	0	0	6
No adverse reaction	No reaction/indication	OXC	OT/F02E	BR/3	189/	20/M	DOSE NOT GIVEN	426	0	0	6
Other gastrointestinal disorders	Pain abdominal	OXC	OT/F02E	BR/4	142/	50/M	1800 MG	702	0	0	1
Intracranial and spinal cord disorders	Cerebrovascular disorder, prophylaxis	OXC	OT/F02E	ZA/1	426/	65/M	900 MG	725	0	7	1
Intracranial and spinal cord disorders	Hemorrhage intracranial, coma	OXC	OT/F02E	ZA/2	424/	22/M	1800 MG	634	1	3,7	1
Other gastrointestinal disorders	Pain abdominal	OXC	OT/F04	BR/3	276/	8/M	300 MG	88	1	0	1
Infection or sepsis related effects	Bronchitis, fever	OXC	OT/F04	BR/3	347/	5/F	600 MG	50	0	0	1
Sedation	Somnolence	OXC	OT/F04E	BR/3	235/	16/F	NA	566	0	7	1
Infection or sepsis related effects	Bronchopneumonia nos	OXC	OT/F04E	BR/3	347/	5/F	300 MG	145	0	0	1
Infection or sepsis related effects	Pneumonia	OXC	OT/F04E	BR/3	347/	7/F	450 MG	465	0	0	1
Affect disorders	Suicide attempt, somnolence, therapeutic response increased	OXC	OT/F04E	BR/5	267/	17/F	1200 MG	733	4	7	3
No adverse reaction	No reaction/indication	OXC	OT/F10	A/201	105/	25/F	1800 MG	172	0	0	2
Delirium or psychotic symptoms	Hallucination, agitation, coordination abnormal, hallucination, amnesia, delusion	OXC	OT/F10	A/201	122/	40/F	2100 MG	48	1	3,6	1
Joint disorders	Nerve root lesion	OXC	OT/F10	A/202	111/	35/F	2100 MG	321	0	6,7	1
Convulsive disorders	Convulsions	OXC	OT/F10	A/202	112/	38/F	900 MG	21	0		1
Convulsive disorders	Convulsions grand mal	OXC	OT/F10	A/202	112/	38/F	1800 MG	252	0	6	1
Behaviour and personality disorders	Aggressive reaction, hysteria, nervousness	OXC	OT/F10	A/202	114/	42/F	1200 MG	184	1	7	3
Delirium or psychotic symptoms	Psychosis, suicide attempt	OXC	OT/F10	A/203	117/	29/M	1800 MG	41	2	3,7	1
Malignant neoplasms	Lymphoma malignant	OXC	OT/F10	D/103	30/	41/M	1200 MG	371	0	4,7	3
Balance, gait, or coordination disorders	Ataxia, vomiting, diplopia, vertigo, convulsions grand mal	OXC	OT/F10	D/105	49/	28/M	900 MG	4	2	3,5,7	1
Convulsive disorders	Convulsions local	OXC	OT/F10	D/105	50/	42/M	2700 MG	132	1	6,7	3
Benign neoplasms	Glioma	OXC	OT/F10	D/105	56/	62/F	1800 MG	134	1	6,7	3
Convulsive disorders	Convulsions local, convulsions grand mal	OXC	OT/F10	D/105	60/	55/M	1500 MG	42	2	3,5,6,7	1
Convulsive disorders	Convulsions local, convulsions grand mal	OXC	OT/F10	D/105	60/	55/M	900 MG	22	0	1,5,6,7	1
Convulsive disorders	Convulsions grand mal	OXC	OT/F10	D/108	67/	45/M	1200 MG	39	2	7	4
Sudden unexpected death without other details	Death	OXC	OT/F10	D/112	79/	64/F	1500 MG	445	1	0	6

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Body System	Term	Treatment (prev. treatment)	Trial	Country/ Center	Patient	Age/ Sex	Last Dose (mg/day)	Dur. to Onset (days)	Rel. to Tr. Drug	Action Taken	Outcome
Anaphylactoid reaction without shock	Allergic reaction, edema lips, rash	OXC	OT/F10	I/301	162/	28/F	1200 MG	56	3	3	1
Convulsive disorders	Convulsions aggravated, nausea, somnolence	OXC	OT/F10	I/302	170/	34/F	2100 MG	226	3	0,3	1
Sedation	Somnolence, nausea, headache	OXC	OT/F10	I/302	172/	20/F	1500 MG	97	2	3	1
Convulsive disorders	Convulsions aggravated, hemorrhage nos, nausea, pain abdominal, intermenstrual bleeding	OXC	OT/F10	I/302	174/	35/F	450 MG	19	1	1,3	1
Excitation	Nervousness, coordination abnormal, muscle contractions involuntary, convulsions aggravated	OXC	OT/F10	I/302	176/	26/F	1500 MG	31	3	1,3	1
No adverse reaction	Falling down nos	OXC	OT/F10	I/302	179/	34/M	450 MG	430	0	0	6
Convulsive disorders	Convulsions local	OXC	OT/F10	I/303	223/	32/F	1500 MG	112	0	1,3,7	4
Joint disorders	Joint dislocation, procedure surgical	OXC	OT/F10	I/304	208/	34/M	2700 MG	242	0	7	1
No adverse reaction	Fracture	OXC	OT/F10E	D/103	8/	55/M	2700 MG	643	1	4,7	3
Intracranial and spinal cord disorders	Cerebrovascular disorder	OXC	OT/F10E	D/112	80/	57/M	900 MG	797	0	7	1
White blood cells decreased	Granulocytopenia	OXC	OT/PE1	CDN/1	2503/256	35/F	1200 MG	20	2	3	4
Other allergic reactions	Rash erythematous, myalgia, arthralgia	OXC	OT/PE1	CDN/3	2584/263	24/M	1200 MG	1	4	3,6,7	1
Convulsive disorders	Trauma	OXC	OT/PE1	CDN/3	2585/274	58/F	1200 MG	3	0	7	1
Consciousness, mentation, and selective brain disorders	Somnolence, vomiting, ataxia, nausea	OXC	OT/PE1	CDN/3	2588/275	55/F	600 MG	112	2	1,3	1
Electrolyte disturbances	Hyponatremia	OXC	OT/PE1	CDN/5	2518/247	39/F	2400 MG	26	3	3	1
Balance, gait, or coordination disorders	Ataxia	OXC	OT/PE1	CH/1	2003/102	45/M	1800 MG	10	4	3	1
Balance, gait, or coordination disorders	Ataxia, diplopia, vertigo	OXC	OT/PE1	CH/4	2063/150	34/M	1800 MG	10	4	3	1
Convulsive disorders	Convulsions grand mal	OXC	OT/PE1	CH/4	2064/151	25/F	600 MG	11	1	3,6,7	1
Convulsive disorders	Loss of consciousness nos	OXC	OT/PE1	CH/4	2066/155	51/M	2400 MG	112	0	0	1
Lower intestinal tract disorders	Anus disorder	OXC	OT/PE1	D/8	1046/48	42/M	600 MG	46	0	4,7	1
Balance, gait, or coordination disorders	Dizziness, gait abnormal	OXC	OT/PE1	F/5	7036/769	24/F	900 MG	3	3	3	1
Delirium or psychotic symptoms	Hallucination	OXC	OT/PE1	GB/13	8132/874	28/M	1800 MG	132	1	3,7	1
Involuntary movements / movement disorders	Choreoathetosis	OXC	OT/PE1	GB/15	8007/888	16/F	300 MG EVERY DAY 8 SINGLE DOSE	13	3	7	1

BEST POSSIBLE COPY

Body System	Term	Treatment (prev. treatment)	Trial	Country/ Center	Patient	Age/ Sex	Last Dose (mg/day)	Dur. to Onset (days)	Rel. to Tr. Drug	Action Taken	Outcome
Convulsive disorders	Sudden death	OXC	OT/PE1	GB/19	8114/933	34/M	600 MG	105	1	0	6
Blood pressure changes	Circulatory failure, cranial injury nos	OXC	OT/PE1	H/1	9270/4458	20/M	600 MG	98	0	0	6
Excitation	Hyperkinesia	OXC	OT/PE1	I/2	6019/619	50/F	2400 MG	66	0	4,7	1
Female genital disorders	Cyst ovarian	OXC	OT/PE1	I/4	6037/637	37/F	600 MG	51	0	4,7	1
Venous thrombosis and/or embolism	Embolism pulmonary	OXC	OT/PE1	I/4	6046/646	60/M	2400 MG	103	0	0	6
No adverse reaction	Fracture, fracture	OXC	OT/PE1	I/4	6046/646	60/M	MAX DOSE: 2400MG (8X300MG)	86	0	2,4,6,7	3
Peripheral vascular disorders	Thrombophlebitis superficial	OXC	OT/PE1	I/4	6047/647	46/M	600 MG	106	0	6,7	2
Peripheral vascular disorders	Thrombophlebitis superficial	OXC	OT/PE1	I/4	6047/647	46/M	600 MG	144	0	6,7	2
Balance, gait, or coordination disorders	Ataxia, vertigo	OXC	OT/PE1	I/4	6096/694	33/F	1500 MG	10	2	6,7	1
Non specific complaints	Asthenia	OXC	OT/PE1	I/4	6113/706	64/M	300 MG	1	2	1,3,7	1
Balance, gait, or coordination disorders	Vertigo	OXC	OT/PE1	I/5	6052/652	35/M	2400 MG	17	3	1,2,3,7	1
Hepatitis without jaundice, toxic hepatitis, hepatotoxicity	Hepatitis	OXC	OT/PE1	I/6	6100/686	49/M	2400 MG	32	3	3,5,6,7	3
Convulsive disorders	Convulsions aggravated, headache	OXC	OT/PE1	NZ/11	9109/4007	18/F	600 MG	107	0	6,7	1
Infection or sepsis related effects	Pneumonia	OXC	OT/PE1	NZ/11	9121/4018	16/M	2400 MG	62	0	6,7	1
Other liver and biliary system disorders	Cholelithiasis	OXC	OT/PE1	RA/11	3107/385	40/F	1200 MG	8	0	4,6,7	1
Balance, gait, or coordination disorders	Ataxia, vomiting, nausea, dysmetria, nystagmus, somnolence	OXC	OT/PE1	RA/15	3147/419	22/F	2400 MG	9	3	3,6,7	1
Balance, gait, or coordination disorders	Ataxia, vomiting, tremor, somnolence	OXC	OT/PE1	RA/16	3151/421	22/F	2400 MG	6	3	3,6,7	1
Balance, gait, or coordination disorders	Gait abnormal, vomiting	OXC	OT/PE1	RA/16	3153/423	64/F	1200 MG	11	3	3,6,7	1
Convulsive disorders	Convulsions grand mal	OXC	OT/PE1	RA/2	3013/311	17/M	NA	149		0	1
Headache	Headache, vomiting	OXC	OT/PE1	RA/20	3193/453	30/F	1200 MG	9	2	3	4
Rashes, exanthematous or eruptive dermatosis	Rash	OXC	OT/PE1	RA/21	3202/461	24/M	2400 MG	59	0	6,7	1
Other gastrointestinal disorders	Vomiting	OXC	OT/PE1	RA/22	3251/497	34/M	600 MG	118	0	2,5,6,7	1
Infection or sepsis related effects	Appendicitis	OXC	OT/PE1	RA/23	3261/409	16/M	2400 MG	18	0	3,4,7	1
Balance, gait, or coordination disorders	Ataxia, somnolence, diplopia, dizziness	OXC	OT/PE1	RA/26	3124/399	31/F	300 MG	1	3	1,6,7	1
Blood pressure changes	Hypertension aggravated	OXC	OT/PE1	RA/9	3083/367	52/M	1200 MG	96	0	6,7	1
Intracranial and spinal cord disorders	Cerebral hemorrhage	OXC	OT/PE1	ZA/6	5560/583	58/F	600 MG	130	1	4,6,7	6

BEST POSSIBLE COPY

Body System	Term	Treatment (prev. treatment)	Trial	Country/Center	Patient	Age/Sex	Last Dose (mg/day)	Dur. to Onset (days)	Rel. to Tr. Drug	Action Taken	Outcome
Balance, gait, or coordination disorders	Interaction	OXC	OT/PE1	ZA/6	5561/585	17/M	900 MG	14	3	3,7	1
Convulsive disorders	Convulsions	OXC	OT/PE1	ZA/6	5563/586	27/M	1200 MG	195	0	2,7	1
Collagen disorders	LE syndrome, pericardial effusion, pericarditis, pleurisy, pericardial effusion	OXC	OT/PE1E	CDN/2	2561/249	42/M	2400 MG	689	2	3	3
Other gastrointestinal disorders	Irritable bowel syndrome	OXC	OT/PE1E	CDN/4	2524/244	47/F	900 MG EVERY DAY 2 SINGLE DOSE	561	0	7	3
No adverse reaction	Fracture	OXC	OT/PE1E	CDN/9	2596/237	38/F	600 MG	330	0	7	1
Convulsive disorders	Convulsions aggravated	OXC	OT/PE1E	F/1	7057/803	22/M	1800 MG	347	0	5,6,7	1
Convulsive disorders	Convulsions grand mal	OXC	OT/PE1E	GB/13	8133/875	21/F	1800 MG	370	2	1,7	1
Convulsive disorders	Convulsions grand mal	OXC	OT/PE1E	GB/20	8104/952	32/F	1800 MG	229	1	0	6
Excitation	Agitation	OXC	OT/PE1E	I/2	6021/621	47/M	600 MG	493	0	5,7	1
Malignant neoplasms	Neoplasm endometrial malignant	OXC	OT/PE1E	I/4	6096/694	34/F	1800 MG	433	0	4,7	3
Infection or sepsis related effects	Bronchopneumonia nos, cardiac arrest	OXC	OT/PE1E	I/7	6091/689	47/M	1800 MG	384	0	3,4,6,7	6
Affect disorders	Emotional lability	OXC	OT/PE1E	NZ/11	9119/4015	38/M	450 MG	50	4	3	1
Convulsive disorders	Convulsions grand mal	OXC	OT/PE1E	NZ/11	9120/4017	36/F	300 MG	253	1	4,5,6,7	1
Other gastrointestinal disorders	Appendicitis	OXC	OT/PE1E	NZ/11	9133/4028	20/M	600 MG	681	0	4,5,7	1
Convulsive disorders	Convulsions grand mal	OXC	OT/PE1E	NZ/14	9143/4037	50/M	600 MG	787	1	6,7	1
Infection or sepsis related effects	Cellulitis	OXC	OT/PE1E	NZ/14	9143/4037	49/M	600 MG	304	0	6,7	3
Convulsive disorders	Convulsions local	OXC	OT/PE1E	NZ/14	9144/4035	27/M	900 MG	703	0	5,6,7	1
Convulsive disorders	Convulsions aggravated	OXC	OT/PE1E	RA/1	3002/301	23/F	900 MG	184	3	1	3
Convulsive disorders	Convulsions grand mal, cranial injury nos	OXC	OT/PE1E	RA/1	3002/301	23/F	1500 MG	358	0	3,4,6	3
Electrolyte disturbances	Hypokalemia	OXC	OT/PE1E	RA/11	3104/383	58/F	900 MG	180	1	3,6	1
Convulsive disorders	Convulsions aggravated	OXC	OT/PE1E	RA/11	3105/388	26/M	900 MG	528	0	0,6,7	1
Deterioration of concomitant or underlying illness	Pain biliary	OXC	OT/PE1E	RA/11	3107/385	42/F	1200 MG	435	0	4,6,7	1
Other gastrointestinal disorders	Gastroenteritis	OXC	OT/PE1E	RA/12	3118/395	42/F	900 MG	271	0	4,7	1
Laboratory, instrumental, or physical examination	Laboratory tests abnormal	OXC	OT/PE1E	RA/15	3142/414	44/M	600 MG	196	2	1	1
Affect disorders	Suicide attempt	OXC	OT/PE1E	RA/2	3011/309	40/M	1200 MG	293	1	7	3
Blood pressure changes	Hypertension	OXC	OT/PE1E	RA/21	3207/466	39/F	1200 MG	488	1	3,4,7	1

BEST POSSIBLE COPY

Body System	Term	Treatment (prev. treatment)	Trial	Country/ Center	Patient	Age/ Sex	Last Dose (mg/day)	Dur. to Onset (days)	Rel. to Tr. Drug	Action Taken	Outcome
Heart rate and rhythm disorders	Tachycardia ventricular	OXC	OT/PE1E	RA/22	3316/8015	57/M	1800 MG	476	1	1	4
Lung parenchyma disorders	Pneumonia	OXC	OT/PE1E	RA/23	3262/410	36/M	300 MG	295	0	6,7	1
Malignant neoplasms	Urinary tract disorder, neoplasm muscle benign, carcinoma cervix	OXC	OT/PE1E	RA/23	3264/412	37/F	600 MG	357	0	4,7	3
Convulsive disorders	Cranial injury nos, fracture	OXC	OT/PE1E	RA/23	3265/469	28/F	900 MG	407	0	7	1
Convulsive disorders	Convulsions grand mal	OXC	OT/PE1E	RA/24	3292/458	36/M	1200 MG	307	1	7	1
Other gastrointestinal disorders	Pain abdominal, vomiting, dehydration	OXC	OT/PE1E	RA/4	3034/328	28/F	2400 MG	431	2	1,5,6,7	1
Intracranial and spinal cord disorders	Cyst cerebral	OXC	OT/PE1E	RA/4	3289/8017	33/F	1500 MG	477	0	0	4
Other gastrointestinal disorders	Anus disorder, constipation, constipation	OXC	OT/PE1E	RA/6	3190/8037	20/F	900 MG	356	2	4,7	1
Disorders of coagulation or haemostasis disorders	Hematoma	OXC	OT/PE1E	ZA/1	5506/529	63/M	600 MG	296	0	5,7	1
Electrolyte disturbances	Hyponatremia	OXC	OT/TE1	GB/14	1047/85	69/M	600 MG	22	2	3	4
Consciousness, mentation, and selective brain disorders	Confusion, amnesia, loss of consciousness nos	OXC	OT/TE1	GB/17	1317/78	83/M	600 MG	20	1	3,7	1
Affect disorders	Personality disorder, apathy	OXC	OT/TE1	GB/19	1078/95	81/F	600 MG	52	0	7	1
Deterioration of concomitant or underlying illness	Death, cardiac failure, hepatic function abnormal, fracture, bronchopneumonia nos, malaise	OXC	OT/TE1	GB/5	1041/22	88/F	600 MG	86	0	3	7
Intracranial and spinal cord disorders	Cerebrovascular disorder	OXC	OT/TE1	GB/6	1051/91	84/M	300 MG	372	1	7	2
Consciousness, mentation, and selective brain disorders	Dizziness	OXC	OT/TE1	GB/6	1052/92	82/F	450 MG	15	2	3,7	1
Convulsive disorders	Convulsions	OXC	OT/TE1	GB/6	1103/88	89/F	NA	39	0	3,7	1
Convulsive disorders	Convulsions, paralysis	OXC	OT/TE1	GB/8	1054/70	79/F	300 MG	2	1	3,6,7	2
Deterioration of concomitant or underlying illness	Glaucoma	OXC	OT/TE1	RA/1	1111/190	65/M	600 MG	52	0	4,6,7	1
Convulsive disorders	Convulsions grand mal	OXC	01	USA/M7361A	2/	50/M	600 MG	2	3	3	1
Electrolyte disturbances	Hyponatremia, suicide attempt	OXC	011	RA/M0657D	104/1080	18/F	1800 MG	72	0	6,7	1
Balance, gait, or coordination disorders	Ataxia, diplopia, nystagmus, dizziness	OXC	011	RA/M0658H	132/1087	9/M	900 MG	39	3	6,7	3
Other gastrointestinal disorders	Vomiting	OXC	011	RA/M0814J	172/1110	15/F	1800 MG	56	3	2,6,7	1
Infection or sepsis related effects	Pneumonia	OXC	011	USA/M0063E	110/555	12/M	900 MG	8	1	7	1
Convulsive disorders	Death, convulsions	OXC	011	USA/M8783G	109/733	5/M	600 MG	9	1	3	6
Teeth and mucosal disorders unspecified	Tooth disorder	OXC	011	USA/M8783G	110/648	12/M	300 MG	36	0	0	3

BEST POSSIBLE COPY

Body System	Term	Treatment (prev. treatment)	Trial	Country/ Center	Patient	Age/ Sex	Last Dose (mg/day)	Dur. to Onset (days)	Rel. to Tr. Drug	Action Taken	Outcome
Convulsive disorders	Convulsions aggravated	OXC	011	USA/M8790V	101/625	16/F	1050 MG	10	1	5	1
Consciousness, mentation, and selective brain disorders	Somnolence, apathy, aversion food	OXC	011	USA/M8792F	109/558	17/F	1650 MG	74	1	7	1
Convulsive disorders	Convulsions aggravated	OXC	011E	AUS/M0670H	183/1023	10/M	1200 MG	156	1	1,6,7	1
Convulsive disorders	Convulsions aggravated	OXC	011E	AUS/M0670H	183/1023	10/M	1800 MG	355	0	6,7	1
Convulsive disorders	Convulsions aggravated	OXC	011E	AUS/M0670H	183/1023	10/M	1800 MG	410	0	6,7	1
Convulsive disorders	Convulsions aggravated	OXC	011E	AUS/M0670H	184/1031	10/F	750 MG	38	0	5,6,7	1
Convulsive disorders	Convulsions grand mal, vomiting, dizziness	OXC	011E	RA/M0690N	191/1125	17/M	1800 MG	73	0	3,6,7	1
Convulsive disorders	Convulsions local	OXC	011E	RA/M0763S	158/1134	7/M	900 MG	187	1	6,7	1
Convulsive disorders	Convulsions aggravated	OXC	011E	USA/M0183M	110/737	14/F	3000 MG	298	0	7	1
Convulsive disorders	Muscle contractions involuntary	OXC	011E	USA/M0183M	110/737	14/F	2400 MG	387	1	7	1
Behaviour and personality disorders	Personality disorder	OXC	011E	USA/M0183M	111/738	12/M	1800 MG	106	0	0	4
Other gastrointestinal disorders	Ear infection nos, gastrointestinal disorder nos	OXC	011E	USA/M0183M	116/514	7/F	1200 MG	175	0	7	1
Sedation	Somnolence, ataxia, headache, convulsions aggravated	OXC	011E	USA/M0220K	103/679	11/M	1200 MG	8	3	1	3
Other psychiatric disorders	Emotional lability	OXC	011E	USA/M0230N	101/665	15/M	1425 MG	80	1	7	3
Cardiac inflammatory and fibrotic changes	Myocarditis, circulatory failure, respiratory failure, fever, uremia, adult respiratory distress syn	OXC	011E	USA/M0230N	107/571	14/F	1200 MG	147	1	2,7	3
Other gastrointestinal disorders	Infection viral	OXC	011E	USA/M8781 W	101/516	12/F	1200 MG	185	0	0	
Consciousness, mentation, and selective brain disorders	Anxiety	OXC	011E	USA/M8782B	101/693	5/F	900 MG	249	0	7	1
Intracranial and spinal cord disorders	Hypertension intracranial	OXC	011E	USA/M8782B	101/693	5/F	300 MG	11	0	7	1
Intracranial and spinal cord disorders	Myelitis	OXC	011E	USA/M8782B	101/693	5/F	750 MG	52	0	0	2
Infection or sepsis related effects	Infection viral	OXC	011E	USA/M8783G	102/642	11/F	150 MG	16	0	4,7	1
Other gastrointestinal disorders	Gastroenteritis	OXC	011E	USA/M8783G	103/643	17/M	OTHER EVEN DAYS- 1950MG/OD D-2100MG	542	0	7	1
Other gastrointestinal disorders	Gastroesophageal reflux, somnolence, gait abnormal	OXC	011E	USA/M8783G	103/643	16/M	1650 MG	213	1	4,6,7	3
Infection or sepsis related effects	Infection viral, dehydration	OXC	011E	USA/M8783G	103/643	16/M	1800 MG	196	1	4,7	1
Other gastrointestinal disorders	Gastroenteritis	OXC	011E	USA/M8783G	114/741	14/M	1350 MG	174	1	7	2
Convulsive disorders	Convulsions grand mal	OXC	011E	USA/M8784L	106/654	15/M	1950 MG	310	0	2,6	1

BEST POSSIBLE COPY

Body System	Term	Treatment (prev. treatment)	Trial	Country/ Center	Patient	Age/ Sex	Last Dose (mg/day)	Dur. to Onset (days)	Rel. to Tr. Drug	Action Taken	Outcome
Convulsive disorders	Convulsions grand mal	OXC	011E	USA/M8784L	106/654	15/M	900 MG	383	0	6	1
Infection or sepsis related effects	Infection viral, gastroenteritis, myalgia	OXC	011E	USA/M8784L	108/525	17/F	3000 MG	586	0	4,5,7	1
Convulsive disorders:	Convulsions aggravated	OXC	011E	USA/M8786V	103/663	8/F	900 MG	550	0	7	1
Paretic symptoms nos	Hemiparesis	OXC	011E	USA/M8787A	105/605	6/F	1200 MG	242	0	2	2
Infection or sepsis related effects	Infection viral	OXC	011E	USA/M8787A	107/607	7/F	900 MG	533	0	5,6,7	1
Infection or sepsis related effects	Abscess renal	OXC	011E	USA/M8789K	101/531	17/M	1800 MG	59	0	7	3
Affect disorders	Personality disorder, appetite disturbances	OXC	011E	USA/M8792F	109/558	17/F	1500 MG	40	1	7	1
Infection or sepsis related effects	Upper resp tract infection	OXC	011E	USA/M8792F	109/558	17/F	1500 MG	124	0	7	1
Behaviour and personality disorders	Personality disorder	OXC	011E	USA/M8794P	106/595	10/M	750 MG	199	0	0,7	1
Convulsive disorders	Convulsions aggravated	OXC	011E	USA/M8794P	107/597	12/F	600 MG	584	0	5,6	1
Intracranial and spinal cord disorders	Hemorrhage intracranial	OXC	011E	USA/M8794P	107/597	12/F	150 MG	637	0	4,5,7	1
Behaviour and personality disorders	Personality disorder, drug abuse	OXC	025	USA/M8701Q	101/541	15/M	600 MG	48	1	7	4
Excitation	Anxiety	OXC	025E	USA/M0205Y	103/535	42/M	1200 MG	237	1	0	1
No adverse reaction	Fracture	OXC	025E	USA/M0205Y	104/536	22/M	1200 MG	240	0	0	3
Affect disorders	Suicide attempt, depression	OXC	025E	USA/M0214X	106/570	29/F	1800 MG	645	0	7	1
Oesophageal disorders	Pain chest, pain chest	OXC	025E	USA/M8697B	101/509	71/F	300 MG	595	0	5,6,7	3
Malignant neoplasms	Basal cell carcinoma	OXC	025E	USA/M8702V	109/613	62/M	1800 MG	452	0	4	1
Non specific complaints	Pain chest	OXC	025E	USA/M8702V	111/615	54/F	1200 MG	126	1	6	1
Rashes, exanthematous or eruptive dermatosis	Rash, fever	OXC	026	USA/M0206C	114/	44/F	1200 MG	12	2	3	4
Convulsive disorders	Convulsions aggravated	OXC	026	USA/M0314Z	115/612	50/F	2400 MG	99	0	3	3
Convulsive disorders	Convulsions aggravated	OXC	026	USA/M8705K	109/	25/M	1200 MG	26	1	0	1
Convulsive disorders	Convulsions aggravated	OXC	026	USA/M8705K	112/546	31/F	2400 MG	149	1	1	3
Convulsive disorders:	Convulsions aggravated	OXC	026	USA/M8706P	110/	44/M	600 MG	15	0	5,6,7	1
Electrolyte disturbances	Hyponatremia, convulsions grand mal	OXC	026	USA/M8707U	101/	22/F	1200 MG	72	4	1,6,7	3
Convulsive disorders	Convulsions aggravated	OXC	026	USA/M8707U	105/520	30/F	2400 MG	162	0	1	
Non specific complaints	Death	OXC	026	USA/M8707U	107/522	50/M	2400 MG	88	1		6
Convulsive disorders	Convulsions grand mal	OXC	026	USA/M8708Z	104/	20/F	OXCARBAZE PINE D/C 5 DAYS PRIOR	16	1	7	1
Convulsive disorders	Convulsions grand mal	OXC	026	USA/M8708Z	104/	20/F	600 MG	13	1	3	1

BEST POSSIBLE COPY

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Convulsive disorders	Convulsions grand mal	OXC	026	USA/M8712Z	106/569	35/F	2400 MG	106	0	0	1
Intracranial and spinal cord disorders	Vasospasm, cramps muscle, vision abnormal, hypoesthesia, dizziness	OXC	026	USA/M8712Z	106/569	35/F	1800 MG	37	0	0	1
Other gastrointestinal disorders	Pain abdominal	OXC	026	USA/M8712Z	106/569	35/F	2400 MG	120	1	0	1
Electrolyte disturbances	Hyponatremia	OXC	026	USA/M8712Z	108/	47/F	2100 MG	61	3	1	1
Balance, gait, or coordination disorders	Ataxia, somnolence, confusion	OXC	026	USA/M8714J	106/	45/F	1200 MG	50	4	3	1
Delirium or psychotic symptoms	Confusion	OXC	026E	USA/M0206C	104/574	48/M	900 MG	758	0	5	1
Myocardial ischaemia	Death	OXC	026E	USA/M0206C	109/	58/F	1800 MG	175	1		6
Delirium or psychotic symptoms	Psychosis, convulsions	OXC	026E	USA/M0206C	118/579	42/F	3000 MG	192	1	1,6	3
Rashes, exanthematous or eruptive dermatosis	Rash maculopapular, leukopenia, fever, coughing	OXC	026E	USA/M0206C	124/	36/F	2100 MG	192	2	2,7	3
Other and non classifiable complaints	Interaction, convulsions aggravated	OXC	026E	USA/M0313V	101/585	49/M	1800 MG	636	0	0	1
No adverse reaction	Spleen disorder	OXC	026E	USA/M0313V	103/	42/M	1800 MG	196	0	7	1
Convulsive disorders	Convulsions grand mal	OXC	026E	USA/M0313V	104/588	42/M	1200 MG	449	0	3	1
Convulsive disorders	Convulsions aggravated	OXC	026E	USA/M0314Z	101/	40/F	1200 MG	621	0	1,6	3
Vision disorders	Vision abnormal, dizziness	OXC	026E	USA/M0314Z	109/592	43/M	1800 MG	175	4	3,7	3
Vision disorders	Intoxication/poisoning	OXC	026E	USA/M0314Z	112/	34/M	2400 MG	121	3	3,7	1
Delirium or psychotic symptoms	Psychosis, convulsions aggravated	OXC	026E	USA/M8706P	109/556	43/F	3000 MG	256	1	0	1
Infection or sepsis related effects	Cellulitis	OXC	026E	USA/M8706P	114/604	53/M	2400 MG	241	0	7	1
Infection or sepsis related effects	Pneumonia	OXC	026E	USA/M8706P	116/606	30/F	2400 MG	261	0	6	1
Convulsive disorders	Death, convulsions aggravated, cardiorespiratory arrest	OXC	026E	USA/M8707U	103/518	31/M	2400 MG	369	1	0	6
Convulsive disorders	Convulsions aggravated	OXC	026E	USA/M8712Z	103/565	21/F	3000 MG	522	0	1,6,7	1
Behaviour and personality disorders	Aggressive reaction	OXC	026E	USA/M8712Z	103/565	22/F	3000 MG	734	1	6	1
Other gastrointestinal disorders	Gastritis, dehydration, bronchitis	OXC	026E	USA/M8712Z	106/569	35/F	2400 MG	244	0	0	1
Balance, gait, or coordination disorders	Apraxia	OXC	026E	USA/M8712Z	114/596	33/F	2400 MG	335	1	7	1
White blood cells decreased	Granulocytopenia, fever, pharyngitis	OXC	026E	USA/M8712Z	118/600	49/M	3000 MG	378	1	4,5,7	1
Affect disorders	Depression	OXC	026E	USA/M8712Z	123/619	34/M	2700 MG	298	1	6,7	3
Other musco-skeletal disorders	Costochondritis	OXC	026E	USA/M8714J	103/534	30/F	3300 MG	950	0	0	1
Electrolyte disturbances	Hyponatremia, hypomagnesemia, aphasia	OXC	028	USA/M0587K	525/	58/M	1800 MG	20	2	0	3

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Body System	Term	Treatment (prev. treatment)	Trial	Country/ Center	Patient	Age/ Sex	Last Dose (mg/day)	Dur. to Onset (days)	Rel. to Tr. Drug	Action Taken	Outcome
Blood pressure changes	Hypotension postural, pain chest, dizziness	OXC	028	USA/M0587K	525/	58/M	1800 MG	10	1	0	1
Convulsive disorders	Convulsions aggravated	OXC	028	USA/M0587K	531/	44/F	2400 MG	18	0	0	4
Delirium or psychotic symptoms	Paranoid reaction	OXC	028	USA/M0661I	574/	39/M	300 MG	27	3	3	1
Convulsive disorders	Convulsions aggravated	OXC	028	USA/M0662M	545/	18/F	300 MG	59	1	6	4
Convulsive disorders	Convulsions aggravated	OXC	028	USA/M0665Y	540/	38/F	300 MG	46	0	1,7	3
Electrolyte disturbances	Hyponatremia, hypernatremia, convulsions aggravated	OXC	028E	USA/M0587K	526/	48/M	2800 MG	308	2	4,7	3
Non specific complaints	Injury	OXC	028E	USA/M0587K	531/	45/F	3000 MG	313	0	0	1
Intracranial and spinal cord disorders	Meningitis, cerebrospinal fluid discharge, convulsions grand mal	OXC	028E	USA/M0587K	580/	30/M	3000 MG	271	0	0	1
Convulsive disorders	Convulsions grand mal	OXC	028E	USA/M0587K	601/	14/F	5400 MG	164	1	3,7	3
Convulsive disorders	Convulsions aggravated, encephalopathy	OXC	028E	USA/M0589S	521/	35/F	1800 MG	100	0	1	1
Convulsive disorders	Convulsions aggravated, encephalopathy	OXC	028E	USA/M0589S	521/	35/F	300 MG	16	0	1	1
Delirium or psychotic symptoms	Psychosis	OXC	028E	USA/M0591P	505/	40/F	1050 MG	174	2	7	4
Convulsive disorders	Convulsions aggravated	OXC	028E	USA/M0591P	509/	26/M	3300 MG	172	0	7	1
Convulsive disorders	Convulsions grand mal	OXC	028E	USA/M0591P	512/	23/M	1800 MG	413	1	7	1
Behaviour and personality disorders	Personality disorder	OXC	028E	USA/M0591P	512/	22/M	1800 MG	282	1	6,7	1
Failure of contraception	Pregnancy unintended	OXC	028E	USA/M0592T	554/	25/F	2400 MG	278	0	7	1
Infection or sepsis related effects	Pneumonia	OXC	028E	USA/M0592T	612/	11/M	3000 MG	182	0	1,6	1
Delirium or psychotic symptoms	Psychosis	OXC	028E	USA/M0665Y	540/	38/F	1800 MG	55	3	3,7	3
Electrolyte disturbances	Hyponatremia, anemia, uterine hemorrhage	OXC	028E	USA/M0945Y	561/	44/F	1200 MG	20	3	3	
Affect disorders	Depression	OXC	030	USA/M1538A	2/	36/F	300 MG	21	1	3,6,7	3
Delirium or psychotic symptoms	Depression psychotic	OXC	04	USA/M8456A	113/510	41/M	2400 MG	8	2	3	1
No adverse reaction	Vasospasm	OXC	04E	USA/M8454Q	103/503	18/M	1200 MG	180	0	6,7	1
Electrolyte disturbances	Hyponatremia	OXC	04E	USA/M8454Q	105/505	43/F	1800 MG	30	3	3	3
Convulsive disorders	Convulsions aggravated	OXC	04E	USA/M8456A	110/507	48/F	3000 MG	111	0	3,7	3
Convulsive disorders	Convulsions grand mal	OXC	04E	USA/M8456A	112/509	22/F	3000 MG	891	1	5,6,7	1
Infection or sepsis related effects	Abscess	OXC	04E	USA/M8456A	112/509	20/F	2400 MG	74	0	0,7	3
Convulsive disorders	Fibrillation ventricular, cardiac arrest, cardiac arrest,	OXC	04E	USA/M8456A	117/514	37/M	2400 MG	604	1	3	6

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Body System	Term	Treatment (prev. treatment)	Trial	Country/ Center	Patient	Age/ Sex	Last Dose (mg/day)	Dur. to Onset (days)	Rel. to Tr. Drug	Action Taken	Outcome
	convulsions										
Convulsive disorders	Convulsions local	OXC	04E	USA/M8456A	118/515	39/F	600 MG	696	1	3,5,6,7	1
Convulsive disorders	Complement factor abnormality, convulsions local	OXC	04E	USA/M8459P	103/502	54/F	1500 MG	35	0	1	4
Convulsive disorders	Convulsions aggravated	OXC	04E	USA/M8459P	106/506	27/M	2400 MG	5	1	6	4
Excitation	Agitation, vomiting, anxiety	OXC	04E	USA/M8459P	106/506	27/M	3000 MG	22	1	7	3
Electrolyte disturbances	Hyponatremia	OXC	04E	USA/M8462K	102/502	30/F	1200 MG	7	4	3,6,7	1
Delirium or psychotic symptoms	Psychosis	OXC	04E	USA/M8462K	104/504	43/M	2250 MG	98	0	3,6,7	1
Delirium or psychotic symptoms	Psychosis	OXC	04E	USA/M8462K	104/504	43/M	2400 MG	18	0	1	1
Balance, gait, or coordination disorders	Vertigo, vomiting, nausea	OXC	04E	USA/M8462K	105/505	42/F	3600 MG	751	0	7	1
Convulsive disorders	Convulsions aggravated, intoxication/poisoning	OXC	04E	USA/M8462K	118/518	35/M	600 MG	86	0	7	1
Convulsive disorders	Convulsions aggravated	OXC	04E	USA/M8462K	120/520	33/M	3000 MG	80	0	5	1
Delirium or psychotic symptoms	Psychosis, convulsions local	OXC	04E	USA/M8462K	120/520	35/M	3600 MG	690	0	1	1
Other gastrointestinal disorders	Vomiting, nausea	OXC	04E	USA/M8462K	122/522	35/M	3000 MG	12	4	3	4
Convulsive disorders	Convulsions grand mal	OXC	04E	USA/M8464U	104/504	41/F	900 MG	122	0	7	1
Delirium or psychotic symptoms	Psychosis, convulsions grand mal	OXC	04E	USA/M8464U	104/504	41/F	1800 MG	201	1	5,6,7	3
Balance, gait, or coordination disorders	Ataxia, diplopia	OXC	04E	USA/M8464U	108/508	35/F	2100 MG	671	0	7	1
Liver function disorders	Liver enzymes elevated	OXC	04E	USA/M8464U	108/508	33/F	1200 MG	3	2	0	1
Affect disorders	Depression	OXC	04E	USA/M8464U	109/509	45/F	2700 MG	929	1	1,4,5,6,7	1
Rashes, exanthematous or eruptive dermatosis	Rash maculopapular	OXC	04E	USA/M8464U	112/511	34/M	3000 MG	750	0	2	1
Other liver and biliary system disorders	Procedure gastrointestinal	OXC	04E	USA/M8464U	117/514	25/F	2700 MG	370	0	0	1

Relation to trial drug:	Action taken:		Outcome:
0 = None	0 = No action/No new action taken	4 = Non-drug therapy	1 = Recovered
1 = Unlikely	1 = Trial drug dosage changed	5 = Concomitant therapy changed or discontinued	2 = Sequelae
2 = Possible	2 = Trial drug temporarily changed	6 = New drug therapy added	3 = Improving
3 = Probable	3 = Trial drug permanently discontinued	7 = Hospitalization/prolonged hospitalization	4 = Unchanged
4 = Highly probable			5 = Deteriorated
			6 = Death
			7 = Death not related

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Pregnancy/ outcome tables

Exhibit 15.1.1.-1. Pregnancies reported in OXC-treated patients in primary database trials

Protocol	Patient	Age (years)	Total OXC Exposure	Daily Dose of OXC	Outcome
OT/PE1	H/2/4423	17	4 weeks	1200	Abortion (induced)
	RA/26/402	21	4 months	1200	Abortion (induced)
OT/PE1E	6/645 T97HQ0041	31	n/a	1200	Normal baby. AED phenytoin 350 mg/day
025	Hasegawa 101/581	22	2 weeks	n/a	Discontinued for trial, unknown outcome
OT/E25	131/52	21	218 days	1500	Normal baby Concomitant AED Tegretol SR 1000 mg
OT/E25E	F/03/289	24	335 days	1800	Termination at 9 weeks Concomitant AED. VPA. Alepsal.
OT/F01	GB 6/271 T995GB00015	18	168 days	1500	Normal baby
OT/F01	GB/1/255	na	10 mo.	1200	Abortion (induced)
OT/F02	MX 5/83	28	1.5 mo.	900	Normal baby
OT/F02	BR/7/ 179	22	212 days	900	Normal baby
OT/F02	BR/3/154	24	81 days	900	unknown
OT/F02	BR/6/169	na	56 days	900 mg	Abortion (induced)
OT/F02	SA/2/420	17	12 months	900 mg	Normal baby
OT/F01E	D/3/42	34	3 years	2100 mg	Abortion (induced)
OT/F01E	D/4/76	24	13 months	2100 mg	Abortion (induced)
OT/F02E	BR/11/215	21	24 months	450 mg	Normal baby
OT/F02E	MX/3/24	20	6 mo.	1200 mg	Miscarriage (1st. trimester)
OT/F02E	RA/1/337	17	16 mo.	900 mg	Unknown
OT/F04E	BR/1/206	16	1044 days	450 mg	Unknown
OT/F04E	BR/3/235	17	1125 days	600 mg	Normal baby
026E	Sachdeo/566	29	450	2700 mg	Normal female baby
026E	Sachdeo/570	36	390	1200 mg	Normal male baby
026E	MO592T/554	31	9 months	2400 mg	Due July 98. 60 mg phenobarbital iron+vitamins+folic acid

na = not available

Exhibit 15.1.1.-1. New pregnancies reported in the Primary Database

Protocol	Patient	Age (years)	Total OXC Exposure	Dose of OXC at onset	Outcome
Abortions					
OT/PE1	RA/8013	26	4 months	1200 mg	induced abortion on 17-Jul-96
Unknown outcome					
024E	USA/M8456A/509	24	3 years	not available	discontinued OXC 4 weeks post pregnancy: due in March, 1999

One patient had an induced abortion, and one patient is due to give birth in March 1999.

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Exhibit 15.1.3.-1. Pregnancies reported on Named Patient Program

Patient identification	Total Exposure	Daily Dose of OXC	Outcome
Center 7/ Patient 25 ¹ / 36 years	na	600 mg	Normal baby girl, OXC discontinued at onset of pregnancy.

na = not available

¹ Reported in SAERs database (T95GB0020)

Exhibit 15.1.3.-1. New pregnancies reported in the Named Patient Program

Patient identification (center/patient)	Age (years)	Total OXC Exposure	Daily dose of OXC	Outcome
F17/25 ¹	38	7 years	1200 mg	miscarriage at 12 weeks

na = not available
¹ Reported in SAERS database (T98HQ01126)

Exhibit 15.1.4.-1. Pregnancies reported in Post-marketing Experience

Patient identification	Total Exposure	Daily Dose of OXC	Outcome
Normal births			
S8455651	week 1-12 week 13-40	2400 mg 2700 mg	Normal baby
S8612311	week 1-12 and probably through pregnancy	900 mg	Normal baby
97DK10028	na	1200 mg	Normal baby Concomitant 0.4 mg folic acid
97DK10033	na	na	Normal newborn, small hemangioma, concomitant 0.4 mg folic acid
97DK10035	na	na	Normal newborn concomitant folic acid
Spontaneous abortions			
99BR10000	8 months	1200 mg	Spontaneous abortion, anembryonic pregnancy, D&C performed
97ERD1022	na	na	Spontaneous abortion
Miscarriage			
S8609841	na	1200 mg	Premature birth in week 22 and death of fetus. No evidence of malformations. 2 previous miscarriages, on AEDs VPA and clobazam.
Malformations			
S9309301	na	1000 mg	Unspecified heart malformation, Concomitant AED CBZ 800 mg
96DK100045	na	3600 mg	Cleft palate and ear malformation, AEDs vigabatrin 5g/day; and clonazepam 3mg/day
S9404031	na	1800 mg	Cleft palate, clonazepam 6 mg/day week 1-11
96SF10003	whole pregnancy	600 mg	Cleft palate of the soft palate
S9114771	270 days	900 mg	Face malformation, epicanthus.
Low birth weight			
99E10048	week 1-40	1800 mg	Low birth weight (1980 gr) APGAR 9/10/10 Conc. AED Clobazam 80 mg/day
97DK10003	week 1-38	600 mg	Low birth weight (2550 gr) and folic acid 0.4 mg/day
Unknown outcome			
97D10076	na	na	Unknown outcome AED vigabatrin

na = not available

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Exhibit 15.1.4-1. New pregnancies reported in Post-marketing Experience

Patient identification	Total exposure	Daily dose of OXC	Outcome
Normal births			
98DK10013	all pregnancy	1800 mg	normal newborn concomitant folic acid
98DK10014	not available	900 mg	normal newborn
98DK10024	not available	not available	normal newborn concomitant folic acid
98N10010	all pregnancy	900 mg	normal newborn

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Serious Balance, gait, coordination adverse events from the epilepsy trials

Subject	Age/Sex	Dose/Dur of therapy	Description
026E USA/M8712Z 596	33/F	2400mg/174d	Sudden inability to walk, hospitalized, CT-no changes, resolved in 1 day, required no treatment, continued in the study
OT/PE1 CH/1 102	45/M	1800mg/18d	3d after randomization-ataxia on walking, sx progressed and patient was withdrawn from the study, sx resolved with discontinuation
OT/F02 ZA/1 426	63/M	900mg/392d	18d after randomization developed ataxia, tremor, vertigo, diplopia, numbness in hand, N,V. He was taking double dose (1800mg) for several days prior. Sx resolved when reduced to 900mg dose
04E USA/M8464U 508	35/F	2100mg/710d	Developed double vision and ataxia, admitted for medication adjustment, no details, oxcarbazepine was continued
11 RA/2 1087	9/M	UKN/42d	11d after initiating oxc, blurred vision, gait unsteadiness, 28d later, severe ataxia, diplopia, dizziness 3 days later bradyphrenia, dysarthria and nystagmus. He was hospitalized, tx with diazepam, carbamazepine and dextrose and discontinued from the study. Symptoms persisted
26 USA/M8714J 106	45/F	2400mg/50d	47d after initiation of oxc, developed lethargy, confusion and ataxia and the next day had asterixis and nystagmus. Hospitalized, hydrated and concern arose about patient taking too many pills. OXC was tapered and sx resolved
OT/PE1 RA/26 399	31/F	300mg/26d	Patient hospitalized on day of randomization for epigastralgia, nausea vomiting and drowsiness. She was treated with metoclopramide and sx resolved. She continued in the study.
OT/PE1 I/4 694	33/F	1500mg/181d	9d after randomization developed ataxia and vertigo and was hospitalized 5d later for these events. Sx were improving (no dose adjustment) and she continued in the trial. Open label phase, at reduced dose (900mg) sx completely resolved
OT/PE1 CH/4 150	34/M	1800mg/10d	10d after randomization developed ataxia, vertigo, diplopia, and inability to walk. Patient was discontinued from the study and the patient completely recovered.
OT/F10 D/105 49	28/M	900mg/4d	1 day after increasing oxc dose (to 900mg/day) the patient was hospitalized for seizures and gait ataxia, vertigo, vomiting and diplopia. Oxc was discontinued and the patient completely recovered.
OT/PE1 RA/15 419	22/F	1500mg/11d	8d after randomization developed ataxia and 1 day later N/V. Oxc was discontinued and patient was hospitalized with severe ataxia, drowsiness, N/V, dysmetria, and nystagmus. Tx included thiethylperazine, ranitidine, domperidone, and dextrose soln. Sx completely resolved w/in 1 day.

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OT/PE1 RA/16 421	22/F	2400mg/9d	6d after randomization, developed vomiting, 2d later ataxia, and 2 d later dysmetria and tremor. She was hospitalized and Oxc was dc/d. The sx completely resolved within 2 d.
OT/PE1 F/52 205	41/F	UKN/5d	3d after randomization, pt was hospitalized with severe nausea and dizziness. She was discharged and experienced a simple partial seizure with generalization and was re-hospitalized. Oxc was dc/d and sx resolved.
OT/PE1 F/5 769	24/F	900mg/4d	2d after randomization, she experienced dizziness and 2d later gait difficulties, which led to hospitalization. Oxc was dc/d and the sx completely resolved within 3d.
OT/PE1 RA/16 423	64/F	1200mg/10d	10d after randomization she was hospitalized with N/V, lower limb myoclonia, ataxia, nystagmus, and falls w/o LOC. Oxc was dc/d and sx completely resolved.
OT/PE1 ZA/6 585	17/M	900mg/15d	4d after randomization, the patient experienced unsteadiness, drowsiness and nystagmus. Sx resolved after patient stopped medication for religious fast. 2d after re-starting, he developed unsteadiness, drowsiness, vomiting, myoclonus of upper limbs, ataxia, and inability to stand. Oxc was dc/d and pt was admitted to a hospital. All symptoms completely resolved by the next day.
OT/PE1 I/5 652 ¹	35/M	2400mg/16d	16d after randomization he was hospitalized with ataxia, nystagmus, and vomiting. Oxc dose was reduced with improvement. Sx worsened when dose was increased. Oxc was dc/d and sx completely resolved.
04E USA/M8462K 505	40/F	3600mg/893d	738 days after initiation of oxc, she developed N/V, and vertigo and was hospitalized and treated with IV hydration and antivert. Sx resolved within 5d and she continued in the study.

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Post Marketing Reports

Exhibit 17.3.1.-1. Distribution of spontaneous reports by Drug Safety Organ Class

Code	Drug Safety Organ Class (DSOC)	ISS	120-day Safety Update			
		Total No. of reports	Total No. of reports	No. of non-serious reports	No. of serious reports	No. of unclassified reports ¹
0100	Skin and appendages disorders ²	98	102	84	13	5
0300	Collagen disorders	1	1	0	1	0
0410	Central and peripheral nervous system disorders ²	34	36	21	12	3
0431	Vision disorders	3	3	3	0	0
0433	Special senses, other disorders	1	1	1	0	0
0500	Psychiatric disorders	12	12	11	0	1
0600	Gastrointestinal disorders	22	22	17	4	1
0700	Liver and biliary system disorders	8	8	2	5	1
0800	Metabolic and nutritional disorders ²	52	55	11	23	21
0900	Endocrine disorders	2	2	1	1	0
1020	Myo-endo- pericardial and valve disorders ²	1	2	0	2	0
1030	Heart rate and rhythm disorders	8	8	1	7	0
1040	Vascular (extracardiac) disorders	1	1	0	1	0
1100	Respiratory system disorders	2	2	1	1	0
1220	White blood cell disorders	3	3	1	1	1
1230	Platelet, bleeding and clotting disorders	3	3	2	1	0
1240	Hemic and lymphatic and reticula-endothelial disorders	6	6	4	2	0
1300	Urinary system disorders	3	3	2	1	0
1410	Reproductive disorders, male	2	2	2	0	0
1420	Reproductive disorders, female	7	7	2	3	2
1500	Fetal disorders	5	5	1	4	0
1600	Neonatal and infancy disorders ²	7	11	9	0	2
1700	Neoplasm, benign/malignant/un-specified	2	2	0	2	0
1810	Body, as a whole - general disorders	18	18	13	5	0
1930	Resistance mechanism disorders	22	22	4	11	7
	Total number of reports	323	337	193	100	44

¹ "Unclassified reports" means that these reports were not provided with an assessment of seriousness.
² Category containing new reports)

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