TABLE 7h

SK&F 101468 INTEGRATED SUMMARY OF SAFETY

EMERGENT ADVERSE EXPERIENCES BY BODY SYSTEM AND PREFERRED TERM IN THERAPEUTIC STUDIES - ALL PARKINSONIAN PATIENTS IN CLINICAL PHARMA

TREATMENT GROUP		ROPINIROLE	
TOTAL NUMBER OF PATIENTS	:	47	100.0%
PATIENTS WITH ADVERSE EXPERIENCES	:	32	68.1%
WHO BODY SYSTEM : PREFERRED TERM		**N**	**%**
AUTONOMIC NERVOUS SYSTEM		4	8.5
SWEATING INCREASED		4	8.5
BODY AS A WHOLE GENERAL		8	17.0
CHEST PAIN		1	2.1
FATIGUE		1	2.1
MALAISE		1	2.1
PALLOR		3	6.4
RIGORS		3	6.4
CARDIOVASCULAR GENERAL		7	14.9
HYPERTENSION		2	4.3
HYPOTENSION		3	6.4
HYPOTENSION POSTURAL		2	4.3
CENTRAL AND PERIPHERAL NERVOUS SYSTEM		21	44.7
CHOREOATHETOSIS		1	2.1
DIZZINESS		9	19.1
DYSKINESIA		1	2.1
HEADACHE		8	17.0
HYPERKINESIA		1	2.1
HYPOKINESIA		1	2.1
PARESIS		1	2.1
PARESTHESIA		3	6.4
TREMOR		5	10.6
VERTIGO		3	6.4
GASTROINTESTINAL SYSTEM		15	31.9
DIARRHEA		1	2.1
NAUSEA		13	27.7
VOMITING		2	4.3
HEARING AND VESTIBULAR		1	2.1
EAR DISORDER NOS		1	2.1
HEART RATE AND RHYTHM		3	6.4
BRADYCARDIA		2	4.3
FIBRILLATION ATRIAL		1	2.1
LIVER AND BILIARY SYSTEM		1	2.1

EVT001/ISS_AES_7H/09JUN95:09:22/FERGUSONR1/DEV8/UKPAT/SK101468_ISS/

Ropinirole

TABLE 7h

SK&F 101468 INTEGRATED SUMMARY OF SAFETY

EMERGENT ADVERSE EXPERIENCES BY BODY SYSTEM AND PREFERRED TERM IN THERAPEUTIC STUDIES - ALL PARKINSONIAN PAT

TREATMENT GROUP		ROPINIROLE	
TOTAL NUMBER OF PATIENTS	:	47	100.0%
PATIENTS WITH ADVERSE EXPERIENCES	:	32	68.1%
WHO BODY SYSTEM : PREFERRED TERM		**N**	**%**
SGPT INCREASED		1	2.1
METABOLIC AND NUTRITIONAL		1	2.1
BLOOD UREA NITROGEN INCREASED		1	2.1
PSYCHIATRIC		10	21.3
CONFUSION		3	6.4
NERVOUSNESS		1	2.1
SOMNOLENCE		9	19.1
RESISTANCE MECHANISM		2	4.3
UPPER RESP TRACT INFECTION		2	4.3
RESPIRATORY SYSTEM		2	4.3
DYSPNEA		2	4.3
VISION		1	2.1
VISION ABNORMAL		1	2.1

EVT001/ISS_AES_7H/09JUN95:09:22/FERGUSONR1/DEV8/UKPAT/SK101468_ISS/
Ropinirole

Table 8.0: All serious, non-fatal adverse experiences reported up to May 31, 1995

Ropinirole

PID	Sex	Age (Years)	Verbatim Term	WHO Preferred Term	On/Off Therapy At Time of Event (days post Rx)	Duration of Treatment*
003.001.00001	M	31	Severe vasovagal syncope	Syncope	1 hour	single oral dose
007.001.00002	F	66	Orthostatic hypotension	Hypotension postural	on	4 days
019.001.00004	M	51	Nausea	Nausea	on	3 days
019.001.00004	M	51	Cold sweat	Sweating increased	on	3 days
020.001.00006	M	56	Sinus bradycardia	Bradycardia	on	1 day
020.001.00006	M	56	Vasovagal episode	Syncope	on	1 day
021.001.00006	F	61	Hypertension	Hypertension	on	1 day
023.003.03002	M	66	Severely symptomatic postural hypotension	Hypotension postural	on	20 days
023.003.03024	M	46	Confusion	Confusion	on	30 days
023.003.03024	M	46	Visual hallucinations	Hallucination	on	30 days
023.006.06010	M	65	Visual hallucinations	Hallucination	on	68 days
023.009.00001	M	71	Acute inflammatory arthritis	Arthritis	on	59 days
023.010.00007	M	62	Overdose (unintentional)	Therapeutic response increased	on	59 days
023.003.03012 [026]	M	46	Possible deterioration of Parkinsonian symptoms (hospitalized)	Parkinsonism aggravated	on	292 days
027.001.00009	M	68	Hypertensive crisis	Hypertension	on	3 days

Table 8.0: All serious, non-fatal adverse experiences reported up to May 31, 1995
Ropinirole

PID	Sex	Age (Years)	Verbatim Term	WHO Preferred Term	On/Off Therapy At Time of Event (days post Rx)	Duration of Treatment*
030.002.00034	M	54	Hospitalization for inefficacy of treatment	Therapeutic response decreased	on	57 days
030.002.00043 [031]	F	67	Severe dyskinesia leading to several falls and hosp.	Dyskinesia	on	266 days
030.002.00044 [031]	M	47	Dystonia leading to hosp.	Dystonia	on	295 days
030.002.00044 [031]	M	47	Unpredictable fluctuations leading to hosp. (worsening of Parkinsons)	Parkinsonism aggravated	on	295 days
032.004.00040	F	49	Stroke {left-side}	Cerebrovascular disorder	on	43 days
032.006.00064	F	43	Faintness with or without loss of consciousness	Syncope	on	379 days
032.006.00064	F	43	Severe faintness	Dizziness	on	379 days
032.006.00064	F	43	Severe loss of consciousness	Syncope	on	379 days
032.006.00064	F	43	Severe drop in blood pressure	Hypotension	on	379 days
032.010.00115	M	48	Severe vasovagal attack (possible accidental overdose)	Syncope	on	321 days
032.010.00115	M	48	Dizziness	Dizziness	on	321 days
032.010.00115	M	48	Faintness	Dizziness	on	321 days
032.010.00115	M	48	Nausea	Nausea	on	321 days

Table 8.0: All serious, non-fatal adverse experiences reported up to May 31, 1995
Ropinirole

PID	Sex	Age (Years)	Verbatim Term	WHO Preferred Term	On/Off Therapy At Time of Event (days post Rx)	Duration of Treatment*
034.005.00050	M	54	Severe rigidity (worsening of Parkinson's)	Parkinsonism aggravated	on	216 days
034.008.00096	M	64	Pain in left leg	Pain	on	141 days
034.004.00042 [035]	F	69	Worsening dyskinesias	Parkinsonism aggravated	on	114 days
034.004.00042 [035]	F	69	Anxiety	Anxiety	on	114 days
034.005.00050 [035]	M	51	Hospitalised for bp stabilisation (increased)	Hypertension	on	216 days
034.005.00050 [035]	M	51	Anxiety	Anxiety	on	216 days
034.008.00085 [035]	M	52	Anxiety	Anxiety	on	345 days
034.008.00092 [035]	F	79	Fever	Fever	on	354 days
034.008.00092 [035]	F	79	Possible erysipelas	Infection bacterial	on	354 days
034.008.00094 [035]	F	72	Overdose {unintentional}	Therapeutic response increased	on	343 days

Table 8.0: All serious, non-fatal adverse experiences reported up to May 31, 1995
Ropinirole

PID	Sex	Age (Years)	Verbatim Term	WHO Preferred Term	On/Off Therapy At Time of Event (days post Rx)	Duration of Treatment*
034.009.00100 [035]	F	65	Dyskinesias	Dyskinesia	on	121 days
034.009.00100 [035]	F	65	Headache	Headache	1 day post	121 days
034.009.00100 [035]	F	65	Blood pressure increased	Hypertension	1 day post	121 days
034.009.00100 [035]	F	65	Sweating	Sweating increased	1 day post	121 days
034.009.00100 [035]	F	65	Mild tachycardia	Tachycardia	1 day postday 120	121 days
034.009.00108 [035]	F	70	Deterioration of Parkinson's symptoms (worsened symptoms)	Parkinsonism aggravated	off (between 1 and 51 days post)	304 days
036.002.00016	F	74	Persistant anemia	Anemia	on	73 days
036.002.00016	F	74	Lipothymia without loss of consciousness (overdosage)	Therapeutic response increased	on	73 days
036.002.00016	F	74	Accidental overdose	Therapeutic response increased	on	73 days
036.006.00062			Confusion	Confusion	on	10 days

Table 8.0: All serious, non-fatal adverse experiences reported up to May 31, 1995

Ropinirole

PID	Sex	Age (Years)	Verbatim Term	WHO Preferred Term	On/Off Therapy At Time of Event (days post Rx)	Duration of Treatment*
036.007.00075 [037]	M	71	Adenocarcinoma of lung	Pulmonary carcinoma	off (6 months post)	339 days
038.005.00049	F	51	Emotional breakdown (anxiety)	Anxiety	on	3 days
038.005.00049	F	51	Dyskinesia	Dyskinesia	on	3 days
038.005.00054	M	78	Hallucinations	Hallucination	on	89 days
038.005.00054	M	78	Hallucinations	Hallucination	on	89 days
038.005.00055			Vomiting	Vomiting	on	41 days
038.002.00014 [039]	M	71	Gastrointestinal bleeding	Gi hemorrhage	on	379 days
038.003.00027 [039]	F	67	Progressive deterioration; unable to swallow	Dysphagia	on	363 days
038.003.00027 [039]	F	67	Syncope (5 minutes) (recurred 2nd time when dose restored)	Syncope	on	363 days
040.002.00021	M	74	Acute depression	Depression	on	27 days
040.002.00021	M	74	Psychosis	Psychosis	on	27 days
040.002.00021	M	74	Urinary retention	Urinary retention	on	27 days
040.009.00100	M	59	Recurrent left inguinal hernia (hospitalized for herniorrhaphy)	Injury	on	707 days

Table 8.0: All serious, non-fatal adverse experiences reported up to May 31, 1995
Ropinirole

PID	Sex	Age (Years)	Verbatim Term	WHO Preferred Term	On/Off Therapy At Time of Event (days post Rx)	Duration of Treatment*
040.010.00124	M	62	Toxic delirium due to high dose sinemet (hospitalization)	Delirium toxic	off (29 days post)	17 days on placebo portion of study (never received ropinirole)
040.013.00068	M	62	Basal cell carcinoma	Basal cell carcinoma	on	49 days
040.014.00079	F	67	Darrack procedure right wristbone (possible ulna nerve compression)	Nerve damage	on	211 days
040.001.00055 [041]	M	60	Forgetfulness	Amnesia	on	127 days
040.001.00055 [041]	M	60	Chest pain	Chest pain	on	127 days
040.001.00055 [041]	M	60	Confusion	Confusion	on	127 days
040.001.00055 [041]	M	60	Depression	Depression	off (7 days post)	127 days
040.001.00055 [041]	M	60	Benign hallucinations	Hallucination	on	127 days
040.001.00055 [041]	M	60	Orthostatic hypotension	Hypotension postural	on	127 days

Table 8.0: All serious, non-fatal adverse experiences reported up to May 31, 1995

Ropinirole

PID	Sex	Age (Years)	Verbatim Term	WHO Preferred Term	On/Off Therapy At Time of Event (days post Rx)	Duration of Treatment*
040.001.00055 [041]	M	60	Accidental overdose (lightheaded clammy pale)	Therapeutic response increased	on	127 days
040.001.00055 [041]	M	60	Increased anxiety	Anxiety	off (7 days post)	127 days
040.001.00055 [041]	M	60	Threats of suicide	Suicidal tendency	off (7 days post)	127 days
040.001.00057 [041]	F	77	Right hip pain	Arthralgia	on	932 days
040.001.00057 [041]	F	77	Back pain	Back pain	on	932 days
040.001.00057 [041]	F	77	Buttocks pain	Pain	on	932 days
040.002.00019 [041]	F	74	Subcapital fracture left hip after fall	Injury	on	965 days
040.002.00023 [041]	M	36	Fell out of bed	Injury	off (2 days post)	123 days
040.002.00023 [041]	M	36	Renal disorders	Renal function abnormal	off (5 days post)	123 days

Table 8.0: All serious, non-fatal adverse experiences reported up to May 31, 1995
Ropinirole

PID	Sex	Age (Years)	Verbatim Term	WHO Preferred Term	On/Off Therapy At Time of Event (days post Rx)	Duration of Treatment*
040.003.00111 [041]	M	67	Hallucinations	Hallucination	on	181 days
040.003.00114 [041]	M	85	Subendocardial myocardial infarction	Myocardial infarction	off (1 day post)	71 days
040.003.00114 [041]	M	85	Gangrene of right foot	Peripheral gangrene	on	71 days
040.003.00114 [041]	M	85	Peripheral vascular disease (pre-existing)	Peripheral ischemia	off (1 day post)	71 days
040.003.00114 [041]	M	85	Aspiration pneumonia	Pneumonia	on	71 days
040.004.00101 [041]	M	64	Right prostate adenocarcinoma	Adenocarcinoma nos	on	619 days
040.004.00101 [041]	M	64	Left prostate necrosis	Necrosis ischemic	on	619 days
040.004.00101 [041]	M	64	Bladder tumors	Neoplasm nos	on	619 days
040.004.00101 [041]	M	64	Left prostate inflammation	Prostatic disorder	on	619 days

Table 8.0: All serious, non-fatal adverse experiences reported up to May 31, 1995

Ropinirole

PID	Sex	Age (Years)	Verbatim Term	WHO Preferred Term	On/Off Therapy At Time of Event (days post Rx)	Duration of Treatment*
040.004.00103 [041]	M	79	Upper gastrointestinal bleed probably secondary to gastritis	Gastritis hemorrhagic	on	707 days
040.004.00103 [041]	M	79	Transurethral resection of prostate (benign prostatic hypertrophy)	Prostatic disorder	off (10 days post)	707 days
040.004.00103 [041]	M	79	Prostate infection	Prostatic disorder	on	707 days
040.004.00104 [041]	M	64	Transurethral resection (turp) (benign prostatic hypertrophy)	Prostatic disorder	on	729 days
040.004.00107 [041]	M	70	Syncopal episode	Syncope	on	217 days
040.005.00038 [041]	M	72	Prostatic cancer	Carcinoma	on	996 days
040.005.00039 [041]	M	60	Right hip pain	Arthralgia	on	967 days
040.005.00039 [041]	M	60	Stenosis of lumbar spine	Arthropathy	off (2 days post)	967 days
040.005.00039 [041]	M	60	Basal cell carcinoma of forehead	Basal cell carcinoma	on	967 days

Table 8.0: All serious, non-fatal adverse experiences reported up to May 31, 1995
Ropinirole

PID	Sex	Age (Years)	Verbatim Term	WHO Preferred Term	On/Off Therapy At Time of Event (days post Rx)	Duration of Treatment*
040.005.00039 [041]	M	60	Prostate carcinoma	Carcinoma	on	967 days
040.005.00039 [041]	M	60	Fell left hip injury	Injury	on	967 days
040.005.00039 [041]	M	60	Bilateral knee replacements (pre-existing polio)	Poliomyelitis	on	967 days
040.005.00039 [041]	M	60	Urinary retention	Urinary retention	on	967 days
040.005.00039 [041]	M	60	Spinal stabilization surgery	Arthropathy	off (8 days post)	967 days
040.005.00040 [041]	M	50	Mild cardiac septal defect	Atrial septal defect	on	917 days
040.005.00040 [041]	M	50	Dizziness	Dizziness	on	917 days
040.005.00040 [041]	M	50	Shortness of breath	Dyspnea	on	917 days
040.005.00040 [041]	M	50	Two small subpleural lesions in right lung (ct-scan)	Neoplasm nos	on	917 days

Table 8.0: All serious, non-fatal adverse experiences reported up to May 31, 1995
Ropinirole

PID	Sex	Age (Years)	Verbatim Term	WHO Preferred Term	On/Off Therapy At Time of Event (days post Rx)	Duration of Treatment*
040.005.00040 [041]	M	50	Palpitations	Palpitation	on	917 days
040.006.00028 [041]	F	51	Worsening left shoulder pain	Arthralgia	off (2 days post)	129 days
040.006.00028 [041]	F	51	Worsening of depression	Depression aggravated	off (2 days post)	129 days
040.008.00089 [041]	M	66	Abdominal edema	Ascites	on	686 days
040.008.00089 [041]	M	66	Bilateral pitting ankle edema	Edema dependent	on	686 days
040.008.00089 [041]	M	66	Chest sounds on right (rales)	Respiratory disorder	on	686 days
040.008.00137 [041]	M	76	Right ankle and lower leg swelling	Edema legs	on	751 days
040.009.00097 [041]	M	63	Pyelonephritis right kidney	Pyelonephritis	on	680 days
040.009.00097 [041]	M	63	Urinary tract infection	Urinary tract infection	on	680 days

Table 8.0: All serious, non-fatal adverse experiences reported up to May 31, 1995
Ropinirole

PID	Sex	Age (Years)	Verbatim Term	WHO Preferred Term	On/Off Therapy At Time of Event (days post Rx)	Duration of Treatment*
040.009.00097 [041]	M	63	Urinary tract infection	Urinary tract infection	on	680 days
040.009.00100 [041]	M	60	Worsening of right inguinal hernia	Injury	on	707 days
040.011.00127 [041]	M	37	Punctured left lung and 5 broken ribs (due to motor vehicle accident)	Injury	on	766 days
040.011.00127 [041]	M	37	Bruised spleen and pulled muscle in back (due to motor vehicle accident)	Injury	on	766 days
040.012.00064 [041]	M	67	Dyskinesia	Dyskinesia	on	568 days
040.014.00075 [041]	F	67	Herniated disc (back)	Injury	on	339 days
040.014.00075 [041]	F	67	Herniated disc (back)	Injury	on	339 days
040.014.00078 [041]	F	54	Left ankle spur	Bone disorder	on	463 days
040.014.00078 [041]	F	54	Scraping of heel calcification	Bone disorder	off (33 days post)	463 days

Table 8.0: All serious, non-fatal adverse experiences reported up to May 31, 1995
Ropinirole

PID	Sex	Age (Years)	Verbatim Term	WHO Preferred Term	On/Off Therapy At Time of Event (days post Rx)	Duration of Treatment*
040.014.00078 [041]	F	54	Reattachment of left achilles tendon (severed achilles tendon)	Injury	on	463 days
040.014.00079 [041]	F	67	Epidural stimulator implantation (secondary to chronic right arm pain)	Pain	on	211 days
040.015.00049 [041]	M	60	Cervical fusion c4-5 and anterior cervical diskectomy (neck injury)	Injury	on	708 days
043.010.01085	M	66	Elevated creatine phosphokinase	Creatine phosphokinase increased	on	336 days
043.010.01085	M	66	Hypothyroidism	Hypothyroidism	on	336 days
043.010.01085	M	66	Elevated LDH level	LDH increased	on	336 days
043.012.01199	F	59	Depression	Depression	on	341 days
043.013.01174	M	66	Nocturnal awakening	Insomnia	on	169 days
043.015.01225	M	79	Cardiac insufficiency	Cardiac failure	on	66 days
043.015.01225	M	79	Dyspnoea	Dyspnea	on	66 days
043.015.01225	M	79	Lower limb oedema	Edema legs	on	66 days
043.015.01367	F	70	Right elbow fracture	Injury	on	66 days
043.020.01171	M	71	Fracture of left hip	Injury	on	214 days
043.023.01009	M	74	Breathlessness	Dyspnea	on	359 days
043.023.01009	M	74	Low chloride	Hypochloremia	on	359 days

Table 8.0: All serious, non-fatal adverse experiences reported up to May 31, 1995
Ropinirole

PID	Sex	Age (Years)	Verbatim Term	WHO Preferred Term	On/Off Therapy At Time of Event (days post Rx)	Duration of Treatment*
043.023.01009	M	74	Hyponatraemia	Hyponatremia	on	359 days
043.023.01009	M	74	Raised LDH	LDH increased	on	359 days
043.023.01009	M	74	Raised white blood cell count	Leukocytosis	on	359 days
043.023.01009	M	74	Pneumonia	Pneumonia	on	359 days
043.028.01420	M	74	Inguinal hernia operation	Injury	on	336 days
043.028.01484	F	69	Surgery to cataracts on both eyes	Cataract	on	239 days
043.030.01470	M	62	Duodenal ulcer	Duodenal ulcer	on	253 days
043.030.01470	M	62	Digestive bleeding	Gi hemorrhage	on	253 days
043.032.00628	M	59	Enlarged glands	Lymphadenopathy	on	169 days
043.032.00628	M	59	High grade lymphoma	Lymphoma malignant	on	169 days
043.032.00645	F	63	Fracture of left hip	Injury	on	337 days
043.035.00070	F	69	Worsening of symptoms-Parkinson's disease	Parkinsonism aggravated	on	103 days
043.040.00721	M	69	Investigational operation on left knee (osteoarthritis)	Arthritis	on	385 days
043.045.01947	M	64	Subarachnoid haemorrhage	Subarachnoid hemorrhage	on	133 days
043.051.00503	M	48	Visual hallucinations	Hallucination	on	191 days
043.051.00503	M	48	Visual hallucinations	Hallucination	on	191 days

Table 8.0: All serious, non-fatal adverse experiences reported up to May 31, 1995

Ropinirole

PID	Sex	Age (Years)	Verbatim Term	WHO Preferred Term	On/Off Therapy At Time of Event (days post Rx)	Duration of Treatment*
043.051.01051	F	64	Mammary carcinoma (female)	Breast neoplasm malignant female	on	222 days
043.059.00530	M	72	Hospitalisation for dose level stabilization (worsening of Parkinson)	Parkinsonism aggravated	on	329 days
043.060.00388	M	71	Dyskinesia	Dyskinesia	on	197 days
043.060.00388	M	71	Freezing	Rigors	on	197 days
043.060.00457	F	54	Breast galactophoric adenocarcinoma (female)	Breast neoplasm malignant female	on	315 days
043.062.00336	M	56	Inguinal hernia	Injury	on	325 days
043.064.00432	M	67	Delirious speech	Delirium	off (1 day post)	6 days
043.064.00432	M	67	Visual hallucinations	Hallucination	off (1 day post)	6 days
043.064.00432	M	67	Clinical aggravation of akinesia	Hypokinesia	off (1 day post)	6 days
043.064.00432	M	67	Clinical aggravation of rigidity (worsening of Parkinson's)	Parkinsonism aggravated	off (1 day post)	6 days
043.072.01606	M	79	Carcinoma on bridge of the nose	Carcinoma	on	337 days
043.074.01635	M	61	Broken heel bone	Injury	on	495 days
043.074.01635	M	61	Broken arm	Injury	on	495 days
043.076.01537	M	76	Sino-atrial block	Arrhythmia	on	85 days

Table 8.0: All serious, non-fatal adverse experiences reported up to May 31, 1995

Ropinirole

PID	Sex	Age (Years)	Verbatim Term	WHO Preferred Term	On/Off Therapy At Time of Event (days post Rx)	Duration of Treatment*
043.076.01537	M	76	Orthostasis - vertigo by rising to the erect position	Vertigo	on	85 days
043.076.01541	M	65	Cardiac arrhythmia	Arrhythmia	on	187 days
043.076.01541	M	65	Tachycardia	Tachycardia	on	187 days
043.076.01555	F	78	Polymyalgia rheumatica	Polymyalgia rheumatica	on	34 days
043.076.01558	M	73	Low back pain	Back pain	on	319 days
043.078.00887	M	51	Ataxia	Ataxia	on	191 days
043.081.00817	F	60	Confusion	Confusion	off (1 day post)	38 days
043.081.00817	F	60	Depression	Depression	off (1 day post)	38 days
043.081.00817	F	60	Dyskinesia	Dyskinesia	off (1 day post)	38 days
043.081.00817	F	60	Hallucinations	Hallucination	off (1 day post)	38 days
043.081.00817	F	60	Freezing	Rigors	off (1 day post)	38 days
043.084.01512	F	87	Fracture of vertebrae	Injury	on	94 days
044.001.00106	M	84	Urosepsis	Urinary tract infection	on	365 days
044.003.00088	M	66	Chest pain possible related to adverse reaction to study drug	Chest pain	on	12 days
044.003.00088	M	66	Chest tightness	Chest pain	on	12 days
044.003.00088	M	66	Burning substernal chest pain radiating to right shoulder	Chest pain substernal	on	12 days

Table 8.0: All serious, non-fatal adverse experiences reported up to May 31, 1995
Ropinirole

PID	Sex	Age (Years)	Verbatim Term	WHO Preferred Term	On/Off Therapy At Time of Event (days post Rx)	Duration of Treatment*
044.003.00088	M	66	Choreiform movements	Choreoathetosis	on	12 days
044.003.00088	M	66	Shortness of breath	Dyspnea	on	12 days
044.003.00088	M	66	Restless	Nervousness	on	12 days
044.003.00088	M	66	Diaphoretic	Sweating increased	on	12 days
044.005.00109	F	68	Study medication overdose (accidental/asymptomatic)	Therapeutic response increased	on	43 days
044.006.00094	F	77	Grogginess (accidental overdose)	Therapeutic response increased	on	159 days
044.006.00094	F	77	Questionable sedation (accidental overdose)	Therapeutic response increased	on	159 days
044.007.00137	M	54	Staphylococcus sepsis (lumbar disc space)	Sepsis	off (17 days post)	159 days
044.007.00138	M	57	Overdose of study medication (accidental/asymptomatic)	Therapeutic response increased	on	366 days
044.008.00014	F	62	Overdose of study medication (accidental/asymptomatic)	Therapeutic response increased	on	522 days
044.008.00083	F	65	Study medication overdose (accidental/asymptomatic)	Therapeutic response increased	on	503 days
044.012.00026	M	63	Unintentional overdose of study medication (asymptomatic)	Therapeutic response increased	on	391 days

Table 8.0: All serious, non-fatal adverse experiences reported up to May 31, 1995
Ropinirole

PID	Sex	Age (Years)	Verbatim Term	WHO Preferred Term	On/Off Therapy At Time of Event (days post Rx)	Duration of Treatment*
044.012.00029	M	55	Overdose {accidental/asymptomatic}	Therapeutic response increased	on	263 days
044.012.00029	M	55	Overdose {accidental/asymptomatic} {second recurrence}	Therapeutic response increased	on	263 days
044.012.00029	M	55	Overdose {accidental/asymptomatic} {recurrence}	Therapeutic response increased	on	263 days
044.012.00030	F	66	Unintentional overdose of study medication {asymptomatic}	Therapeutic response increased	on	379 days
044.012.00030	F	66	Unintentional overdose of study medication {asymptomatic} {2 occurrence}	Therapeutic response increased	on	379 days
044.014.00048	M	65	Overdose of study medication {unintentional/asymptomatic}	Therapeutic response increased	on	192 days
044.015.00063	M	59	Thoracic spine stabilization to repair fractured lumbar vertebrae	Injury	on	518 days
044.015.00063	M	59	Study medication overdose {accidental/asymptomatic}	Therapeutic response increased	on	518 days
044.015.00066	M	58	Study medication overdose {asymptomatic/accidental}	Therapeutic response increased	on	286 days

Table 8.0: All serious, non-fatal adverse experiences reported up to May 31, 1995
Ropinirole

PID	Sex	Age (Years)	Verbatim Term	WHO Preferred Term	On/Off Therapy At Time of Event (days post Rx)	Duration of Treatment*
043.005.01080 [050]	M	64	Epididymitis	Epididymitis	off (28 days post)	545 days
043.005.01080 [050]	M	64	Worsening parkinsonian gait	Parkinsonism aggravated	off (27 days post)	545 days
043.009.01299 [050]	F	78	Basocellular epithelioma finger skin excision and graft	Basal cell carcinoma	on	266 days
043.010.01101 [050]	M	62	Surgery for cataract	Cataract	on	302 days
043.010.01101 [050]	M	62	Diplopia	Diplopia	on	302 days
043.010.01101 [050]	M	62	Visual hallucinations	Hallucination	on	302 days
043.010.01101 [050]	M	62	Paranoid delusions	Paranoid reaction	on	302 days
043.012.01199 [050]	F	60	Hospitalisation for depression	Depression	on	341 days
043.014.01107 [050]	F	74	Oedema (ankle, bilateral)	Edema dependent	on	270 days

Table 8.0: All serious, non-fatal adverse experiences reported up to May 31, 1995
Ropinirole

PID	Sex	Age (Years)	Verbatim Term	WHO Preferred Term	On/Off Therapy At Time of Event (days post Rx)	Duration of Treatment*
043.015.01367 [050]	F	70	Abdominal pain	Abdominal pain	on	214 days
043.015.01367 [050]	F	70	Diarrhoea	Diarrhea	on	214 days
043.015.01367 [050]	F	70	Gastric ulcer	Gastric ulcer	on	214 days
043.015.01367 [050]	F	70	Vomiting	Vomiting	on	214 days
043.023.01009 [050]	M	75	Confusion	Confusion	on	359 days
043.023.01009 [050]	M	75	Dyspnea	Dyspnea	on	359 days
043.023.01009 [050]	M	75	Aspiration pneumonia	Pneumonia	on	359 days
043.023.01009 [050]	M	75	Aspiration pneumonia	Pneumonia	on	359 days
043.025.00815 [050]	F	71	Tumour of ovary	Neoplasm nos	on	359 days

Table 8.0: All serious, non-fatal adverse experiences reported up to May 31, 1995
Ropinirole

PID	Sex	Age (Years)	Verbatim Term	WHO Preferred Term	On/Off Therapy At Time of Event (days post Rx)	Duration of Treatment*
043.030.01437 [050]	F	61	Visual and auditory hallucinations	Hallucination	on	217 days
043.030.01437 [050]	F	61	Tactile hallucinations	Hallucination	on	217 days
043.030.01469 [050]	M	62	Fall {postural instability}	Ataxia	on	259 days
043.030.01469 [050]	M	62	Femoral bone fracture	Injury	on	259 days
043.030.01470 [050]	M	63	Hip operation {programmed, due to arthrosis}	Arthrosis	on	253 days
043.030.01486 [050]	F	62	Psychotic delirium	Delirium	on	310 days
043.030.01486 [050]	F	62	Auditory hallucinations	Hallucination	on	310 days
043.032.00629 [050]	M	76	Gangrene	Gangrene	on	281 days
043.049.01825 [050]	F	NS	Fractured fibula	Injury	on	323 days

Table 8.0: All serious, non-fatal adverse experiences reported up to May 31, 1995
Ropinirole

PID	Sex	Age (Years)	Verbatim Term	WHO Preferred Term	On/Off Therapy At Time of Event (days post Rx)	Duration of Treatment*
043.049.01829 [050]	F	90	Pulmonary embolism	Embolism pulmonary	on	313 days
043.053.00526 [050]	F	72	Dyskinesia	Dyskinesia	on	249 days
043.055.00386 [050]	M	66	Adenocarcinoma of prostate	Adenocarcinoma nos	off (110 days post)	191 days
043.055.00386 [050]	M	66	Fecaloma	Constipation	off (110 days post)	191 days
043.055.00410 [050]	M	55	Fall - postural instability	Ataxia	off (17 days post)	266 days
043.055.00410 [050]	M	55	Fall - postural instability	Ataxia	off (14 days post)	266 days
043.055.00410 [050]	M	55	Low blood pressure	Hypotension	off (14 days post)	266 days
043.055.00410 [050]	M	55	Crush syndrome	Renal failure acute	off (17 days post)	266 days
043.055.00410 [050]	M	55	Fainting	Syncope	off (21 days post)	266 days

Table 8.0: All serious, non-fatal adverse experiences reported up to May 31, 1995
Ropinirole

PID	Sex	Age (Years)	Verbatim Term	WHO Preferred Term	On/Off Therapy At Time of Event (days post Rx)	Duration of Treatment*
043.055.00410 [050]	M	55	Blocking during the day (worsening of Parkinson's)	Parkinsonism aggravated	on	266 days
043.055.01131 [050]	F	63	Sebaceous cysts	Skin hypertrophy	off (21 days post)	250 days
043.059.00365 [050]	F	71	Sprain right knee	Injury	on	281 days
043.059.00530 [050]	M	72	Parkinsonism	Extrapyramidal disorder	on	329 days
043.060.00457 [050]	F	54	Agitation	Agitation	on	315 days
043.060.00457 [050]	F	54	Dyskinesia	Dyskinesia	on	315 days
043.060.00457 [050]	F	54	Hallucination	Hallucination	on	315 days
043.061.00381 [050]	M	61	Subdural hematoma	Hemorrhage intracranial	day 343	343 days
043.069.00358 [050]	M	62	Lumbar intervertebral disk hernia	Injury	off (3 days post)	347 days

Table 8.0: All serious, non-fatal adverse experiences reported up to May 31, 1995
Ropinirole

PID	Sex	Age (Years)	Verbatim Term	WHO Preferred Term	On/Off Therapy At Time of Event (days post Rx)	Duration of Treatment*
043.070.00143 [050]	M	72	High fever	Fever	on	437 days
043.070.00143 [050]	M	72	Syncope	Syncope	on	437 days
043.072.01606 [050]	M	79	Excision of carcinoma of left vocal cord	Larynx neoplasm malignant	on	337 days
043.073.01611 [050]	M	60	Benign prostatic hypertrophy [prostatectomy]	Prostatic disorder	on	336 days
043.074.01635 [050]	M	61	Right ileofemoral vein thrombosis	Thrombosis	on	495 days
043.076.01558 [050]	M	73	Loss of consciousness	Syncope	on	319 days
043.076.01558 [050]	M	73	Dorsalgia	Back pain	on	319 days
043.076.01558 [050]	M	73	Peptic ulcer	Peptic ulcer	on	319 days
043.077.01400 [050]	M	58	Ruptured cartilage removed from right knee	Injury	on	260 days

Table 8.0: All serious, non-fatal adverse experiences reported up to May 31, 1995
Ropinirole

PID	Sex	Age (Years)	Verbatim Term	WHO Preferred Term	On/Off Therapy At Time of Event (days post Rx)	Duration of Treatment*
043.077.01415 [050]	M	69	Atrial fibrillation	Fibrillation atrial	on	356 days
043.080.00914 [050]	F	67	Delirium	Delirium	on	266 days
043.080.00914 [050]	F	67	Visual hallucinations	Hallucination	on	266 days
043.080.00914 [050]	F	67	Pneumonia (right lung)	Pneumonia	on	266 days
044.001.00106 [051]	M	84	Congestive heart failure	Cardiac failure	on	365 days
044.001.00106 [051]	M	84	Pneumonia	Pneumonia	on	365 days
044.003.00164 [051]	M	59	Cholecystitis	Cholecystitis	off (2 days post)	351 days
044.003.00164 [051]	M	59	Cholelithiasis	Cholelithiasis	off (2 days post)	351 days
044.009.00031 [051]	M	61	Congestive heart failure	Cardiac failure	on	275 days

Table 8.0: All serious, non-fatal adverse experiences reported up to May 31, 1995
Ropinirole

PID	Sex	Age (Years)	Verbatim Term	WHO Preferred Term	On/Off Therapy At Time of Event (days post Rx)	Duration of Treatment*
044.009.00031 [051]	M	61	Violent dyskinesias	Dyskinesia	on	275 days
044.009.00031 [051]	M	61	Hallucination episodes	Hallucination	on	275 days
044.009.00200 [051]	M	46	Post traumatic stress syndrome	Anxiety	off (12 days post)	204 days
044.009.00200 [051]	M	46	Depression	Depression	on	204 days
044.009.00200 [051]	M	46	Substance abuse	Drug abuse	off (12 days post)	204 days
044.009.00200 [051]	M	46	Attempted suicide {intentional overdose of sertraline and klonopin}	Suicide attempt	on	204 days
044.012.00026 [051]	M	64	Hallucinations	Hallucination	on	391 days
044.012.00026 [051]	M	64	Paranoia	Paranoid reaction	on	391 days
044.012.00029 [051]	M	55	Confusion	Confusion	on	263 days

Table 8.0: All serious, non-fatal adverse experiences reported up to May 31, 1995

Ropinirole

PID	Sex	Age (Years)	Verbatim Term	WHO Preferred Term	On/Off Therapy At Time of Event (days post Rx)	Duration of Treatment*
044.012.00029 [051]	M	56	Hallucinations	Hallucination	on	263 days
044.012.00029 [051]	M	56	Psychosis	Psychosis	on	263 days
044.015.00061 [051]	M	58	Overdose of study medication (accidental/asymptomatic)	Therapeutic response increased	on	269 days
053.005.00366	M	67	Cellulitis right leg	Cellulitis	on	582 days
053.005.00366	M	66	Hyperglycaemia	Hyperglycemia	on	582 days
053.005.00366	M	66	Septicaemia	Sepsis	on	582 days
053.005.00368	M	59	Weakness (left side)	Hemiparesis	on	386 days
053.005.00368	M	59	Drowsiness	Somnolence	on	386 days
053.011.00076	F	58	Thyroidectomy for thyroid nodules	Goitre	on	370 days
053.021.00215	M	70	Cerebrovascular accident	Cerebrovascular disorder	on	169 days
053.021.00262	F	79	Dyspnoea	Dyspnea	on	168 days
053.024.00841	F	62	Pneumonia	Pneumonia	on	518 days
053.024.00987	F	68	Angina pectoris	Angina pectoris	on	385 days
053.024.00987	F	68	Congestive heart failure (increasing symptoms)	Cardiac failure	on	385 days
053.024.00987	F	68	Dyspnoea	Dyspnea	on	385 days

Table 8.0: All serious, non-fatal adverse experiences reported up to May 31, 1995
Ropinirole

PID	Sex	Age (Years)	Verbatim Term	WHO Preferred Term	On/Off Therapy At Time of Event (days post Rx)	Duration of Treatment*
053.024.00987	F	68	Oedema (lower limbs)	Edema legs	on	385 days
053.026.00890	F	64	Hyperthyroidism	Hyperthyroidism	on	407 days
053.026.00891	M	71	Abdominal pain (right inguinal region)	Abdominal pain	on	370 days
053.026.00909	M	68	Bradycardia	Bradycardia	on	175 days
053.026.00909	M	68	Hypotension	Hypotension	on	175 days
053.026.00909	M	68	Myocardial infarction	Myocardial infarction	on	175 days
053.026.00910	F	77	General weakness	Asthenia	on	336 days
053.026.00910	F	77	General weakness	Asthenia	on	336 days
053.026.00910	F	77	Increased blood urea	Blood urea nitrogen increased	on	336 days
053.026.00910	F	77	Increased blood urea	Blood urea nitrogen increased	on	336 days
053.026.00910	F	77	Congestive heart failure	Cardiac failure	on	336 days
053.026.00910	F	77	Congestive heart failure	Cardiac failure	on	336 days
053.026.00910	F	77	Dyspnoea	Dyspnea	on	336 days
053.026.00910	F	77	Oedema	Edema	on	336 days
053.026.00910	F	77	Visual hallucinations	Hallucination	on	336 days
053.026.00910	F	77	Increased blood creatinine	Npn increased	on	336 days
053.026.00910	F	77	Collapse	Syncope	on	336 days

Table 8.0: All serious, non-fatal adverse experiences reported up to May 31, 1995
Ropinirole

PID	Sex	Age (Years)	Verbatim Term	WHO Preferred Term	On/Off Therapy At Time of Event (days post Rx)	Duration of Treatment*
053.027.00916	F	82	Anaemia	Anemia	on	407 days
053.027.00916	F	82	Exsiccosis	Dehydration	on	407 days
053.027.00916	F	82	Hypotonia	Hypotonia	on	407 days
053.027.00916	F	82	Collapse	Syncope	on	407 days
053.028.00937	M	69	Rectum carcinoma	Rectal carcinoma	on	508 days
053.030.00358	M	77	Insolation [heat stroke]	Asthenia	on	167 days
053.030.00358	M	77	Rapid progression akinetic crisis	Hypokinesia	on	167 days
053.034.00837	F	53	Erysipelas cruris	Infection bacterial	on	334 days
053.035.01030	F	68	Orthostatic hypotension	Hypotension postural	on	41 days
053.036.00676	M	69	Cerebral ischemia	Cerebrovascular disorder	on	490 days
053.036.00676	M	69	Hallucination	Hallucination	on	490 days
053.036.00676	M	69	Inguinal hernial repais	Injury	on	490 days
053.036.00694	M	62	Inguinal hernia	Injury	on	257 days
053.043.00193	M	67	Sinus bradycardia	Bradycardia	on	274 days
053.043.00193	M	67	Ventricular premature beats	Extrasystoles	on	274 days
053.043.00193	M	67	Ventricular tachycardia	Tachycardia ventricular	on	274 days
053.043.00212	M	73	Stroke	Cerebrovascular disorder	on	238 days
053.043.00212	M	73	Pulmonary embolism	Embolism pulmonary	off (4 days post)	238 days
053.043.00212	M	73	Renal failure [acute]	Renal failure acute	on	238 days

Table 8.0: All serious, non-fatal adverse experiences reported up to May 31, 1995
Ropinirole

PID	Sex	Age (Years)	Verbatim Term	WHO Preferred Term	On/Off Therapy At Time of Event (days post Rx)	Duration of Treatment*
053.043.00213	M	69	Confusional state	Confusion	on	85 days
053.043.00213	M	69	Prostatectomy (benign prostatic hypertrophy)	Prostatic disorder	on	85 days
054.001.00026	M	79	Embolic left toe	Embolism limb	on	341 days
054.002.00186	M	74	Sick sinus syndrome	Arrhythmia	on	163 days
054.002.00209	M	80	Right parieto-sagittal meningioma	Brain neoplasm benign	off (1 day post)	75 days
054.002.00209	M	80	Grand mal seizure	Convulsions grand mal	off (1 day post)	75 days
054.002.00209	M	80	Left hemiparesis	Hemiparesis	off (3 days post)	75 days
054.002.00212	F	63	Overdose of study medication (accidental/asymptomatic)	Therapeutic response increased	on	451 days
054.004.00146	M	60	Sinus bradycardia	Bradycardia	off (3 days post)	113 days
054.004.00146	M	60	Chest pain	Chest pain	off (3 days post)	113 days
054.004.00146	M	60	Bigeminy	Extrasystoles	off (3 days post)	113 days
054.008.00004	F	66	Unintentional overdose of study medication (asymptomatic)	Therapeutic response increased	on	113 days
054.009.00051	F	60	Paroxysmal supraventricular tachycardia exacerbated	Tachycardia supraventricular	on	106 days
054.011.00065	F	63	Oral-facial chorea	Choreoathetosis	on	342 days

Table 8.0: All serious, non-fatal adverse experiences reported up to May 31, 1995
Ropinirole

PID	Sex	Age (Years)	Verbatim Term	WHO Preferred Term	On/Off Therapy At Time of Event (days post Rx)	Duration of Treatment*
054.011.00065	F	63	Inadvertent overdose of study medication	Therapeutic response increased	on	342 days
054.011.00241	F	71	Chronic headache	Headache	off (1 day post)	120 days
054.011.00241	F	71	Vertigo	Vertigo	off (1 day post)	120 days
054.012.00010	M	62	Thrombophlebitis right leg	Thrombophlebitis leg	on	133 days
054.013.00069	F	52	Accidental overdose of study medication (asymptomatic)	Therapeutic response increased	on	384 days
054.015.00109	M	70	Excision of basal cell carcinoma (pre-existing)	Basal cell carcinoma	on	588 days
054.015.00160	M	58	Unintentional overdose of study medication (asymptomatic)	Therapeutic response increased	on	575 days
054.017.00216	M	75	Recurrent atrial fibrillation	Fibrillation atrial	on	6 days
054.019.00125	M	63	Sinus bradycardia	Bradycardia	on	113 days
054.020.00181	M	65	Intestinal gas pain	Flatulence	on	169 days
054.020.00181	M	65	Pre-syncopal episode	Syncope	on	169 days
054.021.00230	M	78	Deep vein thrombosis right leg	Thrombophlebitis deep	on	169 days
054.022.00022	F	58	Gallbladder pain	Biliary pain	on	175 days
054.023.00042	M	64	Peyronie's syndrome surgical repair	Peyronie's disease	on	378 days

Table 8.0: All serious, non-fatal adverse experiences reported up to May 31, 1995
Ropinirole

PID	Sex	Age (Years)	Verbatim Term	WHO Preferred Term	On/Off Therapy At Time of Event (days post Rx)	Duration of Treatment*
054.025.00014	M	50	Overdose (unintentional/asymptomatic)	Therapeutic response increased	on	426 days
054.025.00015	F	63	Overdose (unintentional)	Therapeutic response increased	on	352 days
054.026.00275	M	69	Transperineal prostate needle biopsy (adenocarcinoma of prostate)	Adenocarcinoma nos	on	248 days
054.004.00148 [055]	M	48	Pancreatic tumor probably malignant	Pancreas neoplasm malignant	off (92 days post)	351 days
054.015.00109 [055]	M	71	Removal of basal cell carcinoma left forearm	Basal cell carcinoma	on	588 days
054.015.00109 [055]	M	71	Basal cell carcinoma of scalp and forehead	Basal cell carcinoma	on	588 days
054.018.00074 [055]	F	57	Swelling in breast (female)	Breast enlargement female	on	331 days
054.018.00074 [055]	F	57	Mastitis	Mastitis	on	331 days
054.018.00074 [055]	F	57	Generalized body pain	Myalgia	on	331 days

Table 8.0: All serious, non-fatal adverse experiences reported up to May 31, 1995
Ropinirole

PID	Sex	Age (Years)	Verbatim Term	WHO Preferred Term	On/Off Therapy At Time of Event (days post Rx)	Duration of Treatment*
054.018.00074 [055]	F	57	Pain	Pain	on	331 days
054.018.00289 [055]	F	75	Bilateral lobar pneumonia	Pneumonia	off (2 days post)	299 days
054.025.00062 [055]	M	37	Metastasis of carcinoma to lymphatic system	Neoplasm malignant	off (272 days post)	331 days
054.025.00062 [055]	M	37	Embryonal testicular carcinoma	Testis neoplasm malignant	off (257 days post)	331 days
054.025.00245 [055]	F	74	Rectocele	Rectal disorder	on	202 days
056.001.00003	F	78	Suspicion of basocellular epithelioma	Basal cell carcinoma	on	705 days
056.001.00003	F	78	Hip fracture	Injury	on	705 days
056.001.00008	M	70	Falls	Injury	on	481 days
056.001.00008	M	70	Blood pressure fluctuant (high and low)	Hypertension	on	481 days
056.001.00008	M	70	Blood pressure fluctuant (high and low)	Hypotension	on	481 days
056.001.00008	M	70	Hospitalisation for balancing patient's treatment lack of efficacy	Therapeutic response decreased	on	481 days
056.001.00009	M	58	Somnolence	Somnolence	on	407 days

Table 8.0: All serious, non-fatal adverse experiences reported up to May 31, 1995
Ropinirole

PID	Sex	Age (Years)	Verbatim Term	WHO Preferred Term	On/Off Therapy At Time of Event (days post Rx)	Duration of Treatment*
056.001.00009	M	58	Efficacy, lack of	Therapeutic response decreased	on	407 days
056.001.00016	F	69	Traumatisms	Injury	on	481 days
056.001.00016	F	69	Syncope	Syncope	on	481 days
056.001.00018	F	73	Uterine prolapse	Uterine disorder nos	on	511 days
056.001.00021	F	53	Microcalcifications of the left breast (female patient) (fibrocystic)	Breast fibroadenosis	on	608 days
056.001.00022	M	74	Ischemic colitis	Colitis	on	622 days
056.004.00043	M	70	Suspicion of ejaculation at the end of micturition	Ejaculation disorder	on	228 days
056.004.00046	F	60	Left hemiparesia brachial predominance	Hemiparesis	on	540 days
056.004.00046	F	60	Hemiparesis	Hemiparesis	on	540 days
056.007.00145	M	69	Dyskinesias	Dyskinesia	on	19 days
056.007.00148	F	74	Rbc decreased	Anemia	on	507 days
056.007.00148	F	74	Hepatic enzymes increased	Hepatic enzymes increased	on	507 days
056.007.00148	F	74	Leucopenia	Leukopenia	on	507 days
056.007.00168	F	73	Hospitalised for social reasons {unable to cope}	Anxiety	on	796 days

Table 8.0: All serious, non-fatal adverse experiences reported up to May 31, 1995

Ropinirole

PID	Sex	Age (Years)	Verbatim Term	WHO Preferred Term	On/Off Therapy At Time of Event (days post Rx)	Duration of Treatment*
056.008.00142	M	71	Sympathectomy for arteriopathy [lower limbs]	Peripheral ischemia	on	270 days
056.008.00144	M	69	Fractured left foot	Injury	on	403 days
056.008.00191	M	71	Bladder polyp	Neoplasm nos	on	742 days
056.008.00191	M	71	Endoscopic prostatectomy for adenoma	Neoplasm nos	on	742 days
056.008.00191	M	71	Endoscopic polypectomy for bladder carcinoma	Bladder carcinoma	on	742 days
056.008.00191	M	71	Salivary calculus resection (salivary calculus)	Salivary duct obstruction	on	742 days
056.008.00198	F	72	Fracture of ribs	Injury	on	266 days
056.009.00215	F	76	Asthmatic bronchitis	Bronchitis	on	626 days
056.010.00220	M	85	Accidental overdose	Therapeutic response increased	on	596 days
056.010.00238	M	76	Fall [postural instability]	Ataxia	on	673 days
056.010.00238	M	76	Hyponatremia	Hyponatremia	on	673 days
056.010.00238	M	76	Fracture of the collum femoris	Injury	on	673 days
056.010.00238	M	76	Inappropriate adh secretion (syndrome)	Siadh	on	673 days
056.010.00241	M	76	Oesophagitis	Esophagitis	on	209 days
056.010.00241	M	76	Unstoppable hiccups	Hiccup	on	209 days

Table 8.0: All serious, non-fatal adverse experiences reported up to May 31, 1995
Ropinirole

PID	Sex	Age (Years)	Verbatim Term	WHO Preferred Term	On/Off Therapy At Time of Event (days post Rx)	Duration of Treatment*
056.010.00241	M	76	Overdose {unintentional, asymptomatic}	Therapeutic response increased	on	209 days
056.010.00241	M	76	Urinary tract infection	Urinary tract infection	on	209 days
056.010.00281	M	68	Non-intentional overdose	Therapeutic response increased	on	307 days
056.011.00257	M	59	Unintentional overdose	Therapeutic response increased	on	461 days
056.011.00258	M	64	Elevated creatine phosphokinase levels	Creatinine phosphokinase increased	on	581 days
056.011.00259	M	67	Surgery {knee replacement,osteoporosis}	Osteoporosis	on	364 days
056.011.00263	F	56	Spondylolistesis {l5-s1}	Arthritis	off (2 days post)	606 days
056.011.00263	F	56	Low back pain	Back pain	off (2 days post)	606 days
056.011.00263	F	56	Severe gait disturbance	Gait abnormal	off (2 days post)	606 days
056.011.00263	F	56	Parkinsonism aggravated	Parkinsonism aggravated	off (2 days post)	606 days
056.012.00266	M	68	Coronary insufficiency	Angina pectoris	on	176 days
056.012.00266	M	68	Angina pectoris	Angina pectoris	on	176 days
056.012.00266	M	68	Unstable angina	Angina pectoris aggravated	on	176 days

Table 8.0: All serious, non-fatal adverse experiences reported up to May 31, 1995

Ropinirole

PID	Sex	Age (Years)	Verbatim Term	WHO Preferred Term	On/Off Therapy At Time of Event (days post Rx)	Duration of Treatment*
056.012.00266	M	68	Unstable angina pectoris	Angina pectoris aggravated	on	176 days
056.012.00266	M	68	Chest pain	Chest pain	on	176 days
056.012.00266	M	68	Heart catheterization {ischemic heart disease}	Myocardial ischemia	on	176 days
056.012.00266	M	68	Nausea	Nausea	on	176 days
056.012.00284	M	73	Acute organic psychosis	Psychosis	on	329 days
056.014.00333	M	62	Visual hallucinations	Hallucination	on	214 days
056.016.00376	F	72	Angina	Angina pectoris	on	390 days
056.017.00385	M	70	Confusion	Confusion	on	636 days
056.017.00385	M	70	Subdural haematoma	Hemorrhage intracranial	on	636 days
056.017.00385	M	70	Elevated blood sugar levels	Hyperglycemia	on	636 days
056.017.00385	M	70	Debridement of septic foot	Infection	off (57 days post)	636 days
056.017.00385	M	70	Infection of leg ulcers	Infection	off (46 days post)	636 days
056.017.00385	M	70	Worsening of leg ulcers	Skin ulceration	on	636 days
056.017.00385	M	70	Worsening of leg ulcers	Skin ulceration	on	636 days
056.017.00385	M	70	Leg ulcers	Skin ulceration	on	636 days
056.017.00385	M	70	Removal of two toes (leg/feet ulceration)	Skin ulceration	on	636 days
056.017.00408	F	74	Repair of dupuytren's contracture	Dupuytren's contracture	on	567 days

Table 8.0: All serious, non-fatal adverse experiences reported up to May 31, 1995
Ropinirole

PID	Sex	Age (Years)	Verbatim Term	WHO Preferred Term	On/Off Therapy At Time of Event (days post Rx)	Duration of Treatment*
056.017.00408	F	74	Removal of rectal polyp	Neoplasm nos	on	567 days
056.018.00432	M	51	Worsening of parkinson's disease	Parkinsonism aggravated	off (36 days post)	279 days
056.024.00575	M	68	Blackouts	Syncope	on	219 days
056.025.00577	F	59	Hospitalised hip replacement (osteoarthritis)	Arthritis	on	587 days
056.025.00577	F	59	Worsening osteoarthritis in left hip	Arthritis aggravated	on	587 days
056.025.00581	M	68	Oesophageal carcinoma	Esophageal carcinoma	off (1 day post)	278 days
056.025.00585	M	65	Dislocated shoulder	Injury	on	Ongoing (non-core patient)
056.025.00598	M	60	Possible unstable angina	Angina pectoris aggravated	on	135 days (non-core patient)
056.025.00598	M	60	Chest pain	Chest pain	on	135 days (non-core patient)
056.028.00654	M	55	Dizziness	Dizziness	on	249 days
056.028.00654	M	55	Vertigo episodes	Vertigo	on	249 days
056.028.00668	M	62	Haematuria	Hematuria	on	38 days (non-core patient)
056.028.00668	M	62	Immune thrombocytopenia	Thrombocytopenia	on	38 days (non-core patient)
057.001.00009	F	57	Bradycardia	Bradycardia	on	1 day

Table 8.0: All serious, non-fatal adverse experiences reported up to May 31, 1995

Ropinirole

PID	Sex	Age (Years)	Verbatim Term	WHO Preferred Term	On/Off Therapy At Time of Event (days post Rx)	Duration of Treatment*
057.001.00009	F	57	Dizziness	Dizziness	on	1 day
057.001.00009	F	57	Hypotension	Hypotension	on	1 day
057.001.00009	F	57	Nausea	Nausea	on	1 day
057.001.00009	F	57	Vomiting	Vomiting	on	1 day
023.003.03010 [090]	F	75	Passing blood in faeces	Melena	off (7 days prior to entry into 090)	440 days
023.003.03010 [090]	F	75	Deterioration of Parkinson's disease	Parkinsonism aggravated	off (7 days prior to entry into 090)	440 days
023.003.03010 [090]	F	75	Weight loss	Weight decrease	off (7 days prior to entry into 090)	440 days
023.003.03017 [090]	F	70	Dislocated right head humerus	Injury	on	479 days
030.001.00003 [090]	F	72	Peripheral neuropathy	Neuropathy peripheral	on	573 days
040.001.00054 [090]	F	73	Frozen deterioration in Parkinson's disease	Parkinsonism aggravated	on	879 days
040.001.00054 [090]	F	73	Fell (possible postural instability)	Balance difficulty	on	879 days

Table 8.0: All serious, non-fatal adverse experiences reported up to May 31, 1995
Ropinirole

PID	Sex	Age (Years)	Verbatim Term	WHO Preferred Term	On/Off Therapy At Time of Event (days post Rx)	Duration of Treatment*
040.001.00054 [090]	F	73	Contusion left leg	Injury	on	879 days
040.001.00054 [090]	F	73	Strained left shoulder	Injury	on	879 days
040.012.00063 [090]	M	63	Cardiac ischemia	Myocardial ischemia	on	773 days
043.002.00650 [090]	F	81	Pulmonary metastasis of right breast cancer	Neoplasm malignant	unknown	126 days
043.002.00650 [090]	F	81	Axillary metastasis of right breast cancer	Neoplasm malignant	unknown	126 days
043.013.01176 [090]	M	50	Behavioural problems (paranoid reaction)	Paranoid reaction	on	20 days
043.014.01127 [090]	F	65	Off reaction (worsening of Parkinson's)	Parkinsonism aggravated	on	553 days
043.023.01031 [090]	M	55	Stomach perforation	Stomach perforation	on	448 days
043.040.00745 [090]	M	73	Cataract operation on right eye	Cataract	on	579 days

Table 8.0: All serious, non-fatal adverse experiences reported up to May 31, 1995
Ropinirole

PID	Sex	Age (Years)	Verbatim Term	WHO Preferred Term	On/Off Therapy At Time of Event (days post Rx)	Duration of Treatment*
043.040.00746 [090]	F	67	Epigastric pain	Abdominal pain	on	567 days
043.050.00264 [090]	M	71	Infectious bronchopneumopathy	Respiratory disorder	on	366 days
043.053.00269 [090]	M	64	Myocardial infarction	Myocardial infarction	on	582 days
043.059.00531 [090]	M	66	Off periods during night (worsening of Parkinson)	Parkinsonism aggravated	on	327 days
043.070.00125 [090]	M	72	Ischemic heart disease	Myocardial ischemia	on	354 days
043.070.00125 [090]	M	72	Iron deficiency	Serum iron decreased	on	354 days
043.085.01682 [090]	M	58	Fracture of upper arm	Injury	on	339 days
043.085.01682 [090]	M	58	Fall	Injury	on	339 days
044.004.00004 [090]	M	NS	Sinus arrhythmia	Arrhythmia	on	503 days

Table 8.0: All serious, non-fatal adverse experiences reported up to May 31, 1995
Ropinirole

PID	Sex	Age (Years)	Verbatim Term	WHO Preferred Term	On/Off Therapy At Time of Event (days post Rx)	Duration of Treatment*
044.004.00004 [090]	M	NS	Chest pain	Chest pain	on	503 days
044.004.00004 [090]	M	NS	Chest pressure	Chest pain	on	503 days
044.004.00004 [090]	M	NS	Elevated blood pressure	Hypertension	on	503 days
044.004.00004 [090]	M	NS	Tachycardia	Tachycardia	on	503 days
044.004.00004 [090]	M	NS	Atrial Fibrillation	Fibrillation atrial	on	503 days
054.015.00109 [090]	M	72	Basal cell carcinoma right ear	Basal cell carcinoma	on	588 days
054.015.00109 [090]	M	72	Squamous cell carcinoma right ear	Skin neoplasm malignant	on	588 days
063.003.00309 [090]	M	64	Dizziness	Dizziness	on	Ongoing
063.003.00309 [090]	M	64	Malaise	Malaise	on	Ongoing
092.016.00012	M	79	Prostatism	Prostatic disorder	on	Ongoing

Table 8.0: All serious, non-fatal adverse experiences reported up to May 31, 1995
Ropinirole

PID	Sex	Age (Years)	Verbatim Term	WHO Preferred Term	On/Off Therapy At Time of Event (days post Rx)	Duration of Treatment*
092.016.00033	M	71	Adenocarcinoma of prostate	Adenocarcinoma nos	on	375 days
092.016.00033	M	71	Groin hernia (laproscopic repair)	Injury	on	375 days
092.016.00034	M	75	Fluid retention	Edema generalised	off (14 days post)	291 days
092.016.00034	M	75	Vomiting blood	Hematemesis	off (14 days post)	291 days
092.016.00034	M	75	Bowel obstruction	Intestinal obstruction	off (14 days post)	291 days
092.016.00034	M	75	Renal failure	Renal failure acute	off (14 days post)	291 days
092.016.00034	M	75	Sepsis (staphylococcal)	Sepsis	off (14 days post)	291 days
092.016.00034	M	74	Cellulitis of right foot	Cellulitis	on	291 days
092.016.00034	M	74	Diabetic gangrene right fifth toe	Peripheral gangrene	on	291 days
092.016.00034	M	74	Femoral-popliteal bypass {?peripheral vascular disease}	Peripheral ischemia	on	291 days
092.016.00036	M	76	Fractured right hip	Injury	on	515 days
092.016.00038	F	63	Worsening anxiety	Anxiety	2 days post	515 days
092.016.00040	M	74	Urinary tract infection	Urinary tract infection	off (11 days post)	294 days
092.017.00043	F	66	Bruised calf	Purpura	on	229 days
092.017.00043	F	66	Syncope	Syncope	on	229 days
092.017.00043	F	66	Deep vein thrombophlebitis right lower extremity	Thrombophlebitis deep	on	229 days
092.017.00046	M	38	Chest pain {cardiac etiology ruled out}	Chest pain	on	75 days

Table 8.0: All serious, non-fatal adverse experiences reported up to May 31, 1995

Ropinirole

PID	Sex	Age (Years)	Verbatim Term	WHO Preferred Term	On/Off Therapy At Time of Event (days post Rx)	Duration of Treatment*
092.017.00046	M	38	Shortness of breath	Dyspnea	on	75 days
092.017.00046	M	38	Arms locking up	Hypertonia	on	75 days
092.017.00046	M	38	Arms became rigid	Hypertonia	on	75 days
092.017.00046	M	38	Mouth became dry	Mouth dry	on	75 days
092.017.00046	M	38	Vision blurring	Vision abnormal	on	75 days
099.003.00027	F	57	Broken arm	Injury	on	75 days
099.003.00027	F	57	Dislocated olecranon process	Injury	on	35 days
099.003.00027	F	57	Broken leg	Injury	on	35 days
099.003.00027	F	57	Extrapyramidal symptoms (Parkinsons disease worsening)	Parkinsonism aggravated	on	35 days
099.004.00039	M	69	Inguinal hernia	Injury	on	28 days
099.008.00067	F	73	Right hip fracture	Injury	on	139 days
099.008.00067	F	73	Parkinsonism aggravated	Parkinsonism aggravated	on	139 days
099.008.00073	F	71	Agitation	Agitation	on	123 days
099.008.00073	F	71	Anxiety	Anxiety	on	123 days
099.008.00073	F	71	Confusion	Confusion	on	123 days
099.010.00099	M	69	Hypotension orthostatic	Hypotension postural	on	43 days
099.010.00099	M	69	Hip fracture right	Injury	off (43 days post)	43 days
099.012.00096	M	74	Micturition disorder aggravated	Micturition disorder	on	18 days

Table 8.0: All serious, non-fatal adverse experiences reported up to May 31, 1995
Ropinirole

PID	Sex	Age (Years)	Verbatim Term	WHO Preferred Term	On/Off Therapy At Time of Event (days post Rx)	Duration of Treatment*
099.014.00091	F	64	Social reason (unable to cope)	Mental distress	on	13 days
099.014.00094	F	84	Fall	Injury	on	7 days
099.016.00101	F	74	Cholesteatoma right ear	Ear disorder nos	on	82 days
099.016.00109	M	59	Diplopia	Diplopia	on	33 days
099.016.00110	M	44	Hospitalisation for balancing patient's treatment	Parkinsonism aggravated	on	33 days
099.016.00134	F	64	Asthenia	Asthenia	on	Ongoing
099.016.00134	F	64	Fever	Fever	on	Ongoing
099.016.00134	F	64	Pneumopathy	Respiratory disorder	on	Ongoing
099.022.00051	F	64	Anxiety	Anxiety	on	56 days
099.022.00051	F	64	Depressive attack	Depression	on	56 days
099.022.00052	F	71	Parkinson's disease assessment (no ae)	Parkinsonism	on	147 days
099.022.00113	U	70	Confusional syndrome	Confusion	on	33 days
099.022.00113	M	69	Hyperalgesia sciatica	Hyperesthesia	on	33 days

* Clincal cut-off for duration of treatment was 31 October 1994, therefore, durations only include treatment up to this date.

Table 8.0: All serious, non-fatal adverse experiences reported up to May 31, 1995
Placebo

Table 8.1 The number and percent of patients with serious adverse experiences in the All Patients Exposed Population

	Ropinirole N=1423		Placebo N=298		Bromocriptine N=355		L-dopa N=89	
Serious Adverse Experience	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Angina/Myocardial Ischemia/Chest Pain	11	0.8	3	1.0	8	2.3	3	3.4
Arrhythmia*	15	1.1	3	1.0	1	0.3	2	2.2
Cardiac Failure	5	0.4	1	0.3	4	1.1	0	0.0
Cerebrovascular Disease	4	0.3	0	0.0	2	0.6	0	0.0
CNS Events**	23	1.6	3	1.0	3	0.8	0	0.0
Dyskinesia	10	0.7	0	0.0	1	0.3	0	0.0
Dyspnea	8	0.6	0	0.0	2	0.6	1	1.1
Edema	7	0.5	0	0.0	0	0.0	0	0.0
Hallucination	19	1.3	1	0.3	6	1.7	0	0.0
Injury	39	2.7	6	2.0	10	2.8	1	1.1
Myocardial Infarction	3	0.2	2	0.7	1	0.3	1	1.1
Neoplasm	25#	1.8	6##	2.0	6	1.7	3	3.4
Parkinson's Disease Aggravated	19	1.3	1	0.3	5	1.4	1	1.1
Peripheral Ischemia/Embolism Limb/Peripheral Gangrene	4	0.3	1	0.3	0	0.0	0	0.0
Pneumonia	6	0.4	2	0.7	2	0.6	0	0.0
Postural Hypotension	5	0.4	0	0.0	2	0.6	0	0.0
Prostatic Disorder	6	0.4	1	0.3	0	0.0	0	0.0
Pulmonary Embolism/Infiltration	2	0.1	0	0.0	1	0.3	0	0.0
Syncope	14	1.0	1	0.3	3	0.8	2	2.2
Therapeutic Response Increased /Drug Level Increased (Unintentional Overdose)	27	1.9	10	3.4	1	0.3	1	1.1

* includes arrhythmia, bradycardia, extrasystoles, fibrillation atrial, palpitation, tachycardia (ventricular, supraventricular)
**includes amnesia, confusion, delirium, depression, paranoid reaction, psychosis
#5 of these patients had basal cell carcinoma
2 of these patients had basal cell carcinoma

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Table 8.3 Serious adverse experiences resulting in discontinuation of at least 3 ropinirole patients and/or at least 2 patients in other groups

	Ropinirole N=255		Placebo N=44		Bromocriptine N=68		L-dopa N=17	
Serious Adverse Experience	n	%	n	%	n	%	n	%
Angina/Myocardial Ischemia/Chest Pain	3	1.2	2	4.5	1	1.4	0	0.0
Anxiety	3	1.2	0	0.0	0	0.0	0	0.0
Arrhythmia*	11	4.3	2	4.5	0	0.0	0	0.0
Cerebrovascular Disorder	3	1.2	0	0.0	1	1.5	0	0.0
CNS Events**	13	5.1	2	4.5	1	1.5	0	0.0
Dyskinesia	5	2.0	0	0.0	0	0.0	0	0.0
Hallucination	11	4.3	1	2.3	3	4.4	0	0.0
Hypotension postural	3	1.2	0	0.0	0	0.0	0	0.0
Injury	0	0.0	2	4.5	2	2.9	0	0.0
Myocardial Infarction	2	0.8	2	4.5	0	0.0	1	5.6
Neoplasm	3	1.2	1	2.3	1	1.5	0	0.0
Parkinsonism Aggravated	9	3.5	2	4.5	0	0.0	0	0.0
Syncope	4	1.6	0	0.0	0	0.0	2	11.8

N=total number of patients with a serious adverse experience

* includes arrhythmia, bradycardia, extrasystoles (supraventricular), fibrillation atrial, palpitation, tachycardia (ventricular, supraventricular)

**includes amnesia, confusion, delirium, depression, paranoid reaction, psychosis

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Table 8.4 Serious adverse experiences resulting in patient discontinuation from therapy

ROPINIROLE

PID	Sex	Age (Years)	Verbatim Term	WHO Preferred Term	Duration of Treatment*	Causality
007.001.00002	F	66	Orthostatic hypotension	Hypotension postural	4 days	Possibly Related
019.001.00004	M	51	Nausea	Nausea	3 days	Possibly Related
			Cold sweat	Sweating increased		Possibly Related
020.001.00006	M	56	Sinus bradycardia	Bradycardia	1 day	Possibly Related
			Vasovagal episode	Syncope		Possibly Related
021.001.00006	F	61	Hypertension	Hypertension	1 day	Possibly Related
023.003.00002	M	66	Severely symptomatic postural hypotension	Hypotension postural	20	Related
023.003.03024	M	46	Confusion	Confusion	30 days	Related
			Visual hallucinations	Hallucination		Related
023.003.03012 [026]	M	46	Possible deterioration of Parkinsonian symptoms (hospitalized)	Parkinsonism aggravated	292 days	Possibly Related
027.001.00009	M	68	Hypertensive crisis	Hypertension	3 days	Not Specified
030.002.00034	M	54	Hospitalization for inefficacy of treatment	Therapeutic response decreased	57 days	Unrelated
030.002.00043 [031]	F	67	Severe dyskinesia leading to several falls and hospitalization.	Dyskinesia	266 days	Possibly Related
030.002.00044 [031]	M	47	Dystonia leading to hospitalization	Dystonia	295 days	Possibly Related
			Unpredictable fluctuations leading to hospitalization. (worsening Parkinsons)	Parkinsonism aggravated		Possibly Related
032.004.00040	F	49	Stroke (left-side)	Cerebrovascular disorder	43 days	Possibly Related
034.004.00042 [035]	F	69	Worsening dyskinesias	Parkinsonism aggravated	114 days	Possibly Related
			Anxiety	Anxiety		Unrelated
034.005.00050 [035]	M	51	Hospitalized for bp stabilization (increased)	Hypertension	216 days	Possibly Related
			Anxiety	Anxiety		Possibly Related
034.009.00100 [035]	F	65	Dyskinesias	Dyskinesia	121 days	Possibly Related
036.002.00016	F	74	Persistant anemia	Anemia	73 days	Possibly Related
036.006.00062			Confusion	Confusion	10 days	Unrelated
038.005.00049	F	51	Emotional breakdown (anxiety)	Anxiety	3 days	Possibly Related
038.005.00054	M	78	Hallucinations	Hallucination	89 days	Related
038.005.00055			Vomiting	Vomiting	41 days	Related
040.002.00021	M	74	Acute depression	Depression	27 days	Possibly Related
			Psychosis	Psychosis	27 days	Possibly Related
040.003.00111	M	67	Hallucinations	Hallucination	181 days	Possibly Related

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[041]						
040.003.00114	M	85	Gangrene of right foot	Peripheral gangrene	71 days	Unrelated
[041]						
040.004.00101	M	64	Right prostate adenocarcinoma	Adenocarcinoma nos	619 days	Unrelated
[041]			Left prostate necrosis	Necrosis ischemic		Unrelated
			Left prostate inflammation	Prostatic disorder		Unrelated
040.004.00107	M	70	Syncopal episode	Syncope	217 days	Possibly Related
[041]						
040.006.00028	F	51	Worsening left shoulder pain	Arthralgia	129 days	Unrelated
[041]			Worsening of depression	Depression aggravated		Unrelated
043.035.00070	F	69	Worsening of symptoms-Parkinson's disease	Parkinsonism aggravated	103 days	Probably Unrelated
043.045.01947	M	64	Subarachnoid haemorrhage	Subarachnoid hemorrhage	133 days	Probably Unrelated
043.051.00503	M	48	Visual hallucinations	Hallucination	191 days	Related
043.064.00432	M	67	Delirious speech	Delirium	6 days	Possibly Related
			Visual hallucinations	Hallucination		Possibly Related
			Clinical aggravation of akinesia	Hypokinesia		Possily Related
			Clinical aggravation of rigidity (worsening of Parkinson's)	Parkinsonism aggravated		Possibly Related
043.076.01537	M	76	Sino-atrial block	Arrhythmia	85 days	Possibly Related
			Orthostasis - vertigo by rising to the erect position	Vertigo		Related
043.076.01541	M	65	Cardiac arrhythmia	Arrhythmia	187 days	Possibly Related
			Tachycardia	Tachycardia		Possibly Related
043.076.01555	F	78	Polymyalgia rheumatica	Polymyalgia rheumatica	34 days	Probably Unrelated
043.078.00887	M	51	Ataxia	Ataxia	191 days	Probably Unrelated
043.081.00817	F	60	Confusion	Confusion	38 days	Possibly Related
			Depression	Depression		Possibly Related
			Dyskinesia	Dyskinesia		Related
			Hallucinations	Hallucination		Possibly Related
			Freezing	Rigors		Related
044.003.00088	M	66	Chest pain possible related to adverse reaction to study drug	Chest pain	12 days	Related
			Chest tightness	Chest pain		Related
			Burning substernal chest pain radiating to right shoulder	Chest pain substernal		Related
			Choreiform movements	Choreoathetosis		Related
			Shortness of breath	Dyspnea		Related
			Restless	Nervousness		Related
			Diaphoretic	Sweating increased		Related
044.007.00137	M	54	Staphylococcus sepsis (lumbar disc space)	Sepsis	159 days	Unrelated
043.010.01101	M	62	Visual hallucinations	Hallucination	302 days	Related
[050]			Paranoid delusions	Paranoid reaction		Related

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043.030.01437 [050]	F	61	Visual and auditory hallucinations	Hallucination	217 days	Related
			Tactile hallucinations	Hallucination		Related
043.030.01486 [050]	F	62	Psychotic delirium	Delirium	310 days	Possibly Related
			Auditory hallucinations	Hallucination		Possibly Related
043.032.00629 [050]	M	76	Gangrene	Gangrene	281 days	Probably Unrelated
043.055.00410 [050]	M	55	Blocking during the day (worsening of Parkinson's)	Parkinsonism aggravated	266 days	Possibly Related
043.060.00457 [050]	F	54	Agitation	Agitation	315 days	Related
			Dyskinesia	Dyskinesia		Related
			Hallucination	Hallucination		Related
043.076.01558 [050]	M	73	Loss of consciousness	Syncope	319 days	Possibly Related
			Dorsalgia	Back pain		Unrelated
			Peptic ulcer	Peptic ulcer		Unrelated
044.009.00031 [051]	M	61	Congestive heart failure	Cardiac failure	275 days	Probably Unrelated
044.009.00200 [051]	M	46	Attempted suicide {intentional overdose of sertraline and klonopin}	Suicide attempt	204 days	Probably Unrelated
044.012.00029 [051]	M	56	Psychosis	Psychosis	263 days	Possibly Related
044.015.00061 [051]	M	58	Overdose of study medication {accidental/asymptomatic}	Therapeutic response increased	269 days	Related
053.021.00215	M	70	Cerebrovascular accident	Cerebrovascular disorder	169 days	Probably Unrelated
053.026.00909	M	68	Bradycardia	Bradycardia	175 days	Unrelated
			Hypotension	Hypotension		Unrelated
			Myocardial infarction	Myocardial infarction		Unrelated
053.030.00358	M	77	Rapid progression akinetic crisis	Hypokinesia	225 days	Unrelated
053.035.01030	F	68	Orthostatic hypotension	Hypotension postural	41 days	Related
053.043.00193	M	67	Sinus bradycardia	Bradycardia	274 days	Possibly Related
			Ventricular premature beats	Extrasystoles		Possibly Related
			Ventricular tachycardia	Tachycardia ventricular		Possibly Related
053.043.00212	M	73	Stroke	Cerebrovascular disorder	238 days	Probably Unrelated
053.043.00213	M	69	Confusional state	Confusion	85 days	Probably Unrelated
054.002.00186	M	74	Sick sinus syndrome	Arrhythmia	163 days	Unrelated
054.002.00209	M	80	Right parieto-sagittal meningioma	Brain neoplasm benign	75 days	Unrelated
			Grand mal seizure	Convulsions grand mal		Unrelated
054.004.00146	M	60	Sinus bradycardia	Bradycardia	113 days	Probably Unrelated
			Chest pain	Chest pain		Probably Unrelated
			Bigeminy	Extrasystoles		Probably Unrelated
054.009.00051	F	60	Paroxysmal supraventricular tachycardia exacerbated	Tachycardia supraventricular	106 days	Possibly Related
054.011.00241	F	71	Chronic headache	Headache	120 days	Possibly Related

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			Vertigo	Vertigo		Possibly Related
054.012.00010	M	62	Thrombophlebitis right leg	Thrombophlebitis leg	133 days	Unrelated
054.017.00216	M	75	Recurrent atrial fibrillation	Fibrillation atrial	6 days	Probably Unrelated
054.019.00125	M	63	Sinus bradycardia	Bradycardia	113 days	Unrelated
056.007.00145	M	69	Dyskinesias	Dyskinesia	19 days	Related
056.011.00263	F	56	Spondylolistesis {l5-s1}	Arthritis	606 days	Not Specified
			Low back pain	Back pain		Probably Unrelated
			Severe gait disturbance	Gait abnormal		Probably Unrelated
			Parkinsonism aggravated	Parkinsonism aggravated		Possibly Related
056.012.00266	M	68	Coronary insufficiency	Angina pectoris	176 days	Unrelated
			Angina pectoris	Angina pectoris		Unrelated
056.012.00284	M	73	Acute organic psychosis	Psychosis	329 days	Possibly Related
056.014.00333	M	62	Visual hallucinations	Hallucination	214 days	Possibly Related
056.018.00432	M	51	Worsening of parkinson's disease	Parkinsonism aggravated	279 days	Possibly Related
056.024.00575	M	68	Blackouts	Syncope	219 days	Possibly Related
056.025.00581	M	68	Esophageal carcinoma	Esophageal carcinoma	278 days	Unrelated
056.028.00668(1)	M	62		Hematuria	Hematuria	38 daysProbably Unrelated
			Immune thrombocytopenia	Thrombocytopenia		Probably Unrelated
057.001.00009	F	57	Bradycardia	Bradycardia	12 days	Related
			Dizziness	Dizziness		Related
			Hypotension	Hypotension		Related
			Nausea	Nausea		Related
			Vomiting	Vomiting		Related
043.013.01176 [090]	M	50	Behavioral problems {paranoid reaction}	Paranoid reaction	20 days	Possibly Related
043.053.00269 [090]	M	64	Myocardial infarction	Myocardial infarction	582 days	Possibly Related
099.010.00099	M	69	Hypotension orthostatic	Hypotension postural	43 days	Possibly Related
099.016.00110	M	44	Hospitalization for balancing patient's treatment	Parkinsonism aggravated	33 days	Related
099.022.00113	U	70	Confusional syndrome	Confusion	33 days	Possibly Related

* Duration of treatment includes treatment up to clinical cut-off

Numbers in brackets [ ] indicate that the serious adverse experience occurred during the designated extension or compassionate use study

Table 8.4 Serious adverse experiences resulting in patient discontinuation from therapy

PLACEBO

PID	Sex	Age (Years)	Verbatim Term	WHO Preferred Term	Duration of Treatment*	Causality

[redacted]

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030.001.00015	M	71	Confusional delirious state	Delirium	79 days	Possibly Related
			Hallucinations	Hallucination		Possibly Related
030.001.00022	M	51	Inferior myocardial infarction	Myocardial infarction	48 days	Unrelated
032.009.00101	F	72	Rapid increase in akinesia	Hypokinesia	67 days	Unrelated
			Falls [1]	Injury		Unrelated
034.004.00045 [035]	F	70	Crushed vertebrae	Injury	183 days	Unrelated
038.004.00040	F	NS	Prolonged "off" periods	Parkinsonism aggravated	40 days	Unrelated
038.005.00052	M	43	Mental incoherence (confusion)	Confusion	208 days	Related
[039]	M	43	Delusion	Delusion		Related
044.002.00150	M	65	Severe "off "periods {worsening Parkinson's disease}	Parkinsonism aggravated	30 days	Unrelated
044.005.00111	M	66	Cellulitis of left lower extremity	Cellulitis	12 days	Unrelated
			Blood in urine	Hematuria		Possibly Related
044.009.00032	M	68	Atrial flutter	Arrhythmia atrial	30 days	Possibly Related
			Increased atrial fibrillation	Fibrillation atrial		Possibly Related
054.001.00028	M	64	Abnormal electrocardiogram (ischemia)	Myocardial ischemia	99 days	Possibly Related
054.003.00097	F	77	Clostridium difficile colitis	Colitis	71 days	Prabably Unrelated
			Dehydration	Dehydration		Probably Unrelated
			Viral gastroenteritis	Gastroenteritis		Unrelated
054.011.00094	F	44	Migraine headaches	Migraine	49 days	Unrelated
054.011.00271	M	68	Angina pectoris	Angina pectoris	151 days	Possibly Related
054.013.00204	F	77	Coronary artery disease	Coronary artery disorder	8 days	Unrelated
			Non-specific ventricular tachycardia	Tachycardia ventricular		Possibly Related
054.018.00142	M	74	Myocardial infarction	Myocardial infarction	248 days	Unrelated
[055]			Congestive heart failure {exacerbation}	Cardiac failure		Unrelated
054.025.00016 [055]	M	72	Colon carcinoma	Colon carcinoma	240 days	Unrelated

* Duration of treatment includes treatment up to clinical cut-off

Numbers in brackets [ ] indicate that the serious adverse experience occurred during the designated extension or compassionate use study

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Table 8.4 Serious adverse experiences resulting in patient discontinuation from therapy

L-DOPA

PID	Sex	Age (Years)	Verbatim Term	WHO Preferred Term	Duration of Treatment*	Causality
056.012.0287	F	63	Nausea	Nausea	77 days	Related
			Sweating	Sweating increased		Related

[redacted]

[redacted]

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ON ORIGINAL

			Vomiting	Vomiting		Related
056.016.00381	F	66	Hospitalization due to abdominal pain of unknown cause	Abdominal pain	7 days	Possibly Related
056.016.00382	F	66	Vasovagal attack	Syncope	70 days	Related
			Blackout	Syncope		Related
056.017.00407	M	75	Myocardial infarction	Myocardial infarction	159 days	Possibly Related

* Duration of treatment includes treatment up to the clinical cut-off
Numbers in brackets [ ] indicate that the serious adverse experience occurred during the designated extension or compassionate use study

Table 8.4 Serious adverse experiences resulting in patient discontinuation from therapy

BROMOCRIPTINE

PID	Sex	Age (Years)	Verbatim Term	WHO Preferred Term	Duration of Treatment*	Causality
043.007.01370	F	76	Dehydration	Dehydration	68 days	Unrelated
			Raised temperature	Fever		Unrelated
			Ear infection	Otitis media		Unrelated
043.040.00747	F	67	Visual hallucinations	Hallucination	2 days	Related
			Hysteria	Hysteria		Related
			Vomiting	Vomiting		Related
043.049.01830	M	51	Carcinoma of prostate	Carcinoma	126 days	Unrelated
043.058.00454	M	76	Hip fracture	Injury	49 days	Probably Unrelated
043.072.01588	F	70	Visual and tactile hallucinations	Hallucination	45 days	Possibly Related
043.028.01421 [050]	M	73	Cerebrovascular accident	Cerebrovascular disorder	186 days	Unrelated
043.051.00502(2) Related [050]		M	68	Suicide attempt	Suicide attempt	181 daysPossibly
053.010.00050	F	75	Hepatomegalia	Hepatomegaly	592 days	Unrelated
053.016.00313	F	64	Mental confusion	Confusion	28 days	Related
			Suspicion of right hemiparesis	Hemiparesis		Related
			Loss of consciousness with cranial traumatism	Injury		Related
			Urine loss (incontinent)	Urinary incontinence		Related
053.034.00840	M	66	Hallucination	Hallucination	318 days	Related
053.037.00718	F	55	Chest pain	Chest pain	11 days	Probably Unrelated
	F	55	Shortness of breath	Dyspnea		Probably Unrelated
	F	55	Hypertension exercise induced	Hypertension		Probably Unrelated

[redacted]

APPEARS THIS WAY
ON ORIGINAL

* Duration of treatment includes treatment up to the clinical cut-off
Numbers in brackets [ ] indicate that the serious adverse experience occurred during the designated extension or compassionate use study

[redacted]

Endnotes

1 (Popup)
Non-core patient
No CRT

2 (Popup)
Patient withdrawn Visit 13 in CPMS-043

[redacted]

Table 11.1 Number of patients exhibiting abnormal involuntary movements at a study visit

	Ropinirole		Placebo		Bromocriptine	
	n/N	%	n/N	%	n/N	%
Baseline*	260/767	33.9	61/130	46.9	40/185	21.6
Week 4	268/732	36.6	48/120	40.0	50/181	27.6
Week 12	182/590	30.8	26/73	35.6	40/166	24.1
Week 24	169/527	32.1	17/54	31.5	37/155	23.9
Week 36	140/431	32.5	10/40	25.0	26/125	20.8
Week 48	115/323	35.6	5/22	22.7	15/91	16.5
Week ≥ 54	14/38	36.8	1/5	20.0	1/2	50.0

Data Source Table 11

*Baseline is the last assessment conducted prior to the initiation of coded or open-label study medication

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Table 13.14 Number and percent of patients with a single extreme value-Hematological parameters - All Patients Exposed Population

		Ropinirole		Placebo		Active Comparators	
		n/N	%	n/N	%	n/N	%
Hemoglobin	low	12/1268	0.9	1/271	0.4	9/420	2.1
Hematocrit	low	10/1261	0.8	1/282	0.4	7/420	1.7
RBC	low	16/1244	1.3	1/282	0.4	7/420	1.7
	high	2/1244	0.2	0/282	0.0	3/420	0.7
Platelets	low	12/1267	0.9	2/282	0.7	5/420	1.2
	high	4/1267	0.3	1/282	0.4	0/420	0.0
Lymphocytes	low	3/1262	0.2	0/283	0.0	3/416	0.7
	high	2/1262	0.2	2/283	0.7	3/416	0.7
Neutrophils	low	14/926	1.5	0/78	0.0	12/416	2.9
	high	2/926	0.2	1/78	1.2	1/416	0.2

n = number of patients with a single extreme value of potential clinical concern
N = number of patients tested
Data Source Table 13.40

Table 13.15 Number and percent of patients with a single extreme value - Blood chemistry parameters - All Patients Exposed Population

		Ropinirole		Placebo		Active Comparators	
		n/N	%	n/N	%	n/N	%
ALT	high	1/1236	0.1	0/272	0	0/420	0
AST	high	1/1263	0.1	0/284	0	0/420	0
Alkaline phosphatase	high	0/1266	0	0284	0	2/420	0.5
Total bilirubin	high	1/1265	0.1	0/282	0	0/420	0
Creatinine	high	8/1269	0.6	0/284	0	1/420	0.2
Urea/BUN	high	4/1268	0.3	0/284	0	0/420	0
Calcium	low	5/1189	0.4	0284	0	3/420	0.7
	high	1/1189	0.1	0/284	0	0/420	0
Sodium	low	0/1267	0.0	0/284	0	1/420	0.2
	high	2/1267	0.1	0/284	0	0/420	0
Albumin	low	5/1232	0.4	0/284	0	1/414	0.2
Random glucose	low	6/581	1.0	3/249	1.2	0/87	0
	high	29/581	5.0	9/249	3.6	8/87	9.1

n = number of patients with a single extreme value of potential clinical concern
N = number of patients tested
Data Source Table 13.4

[redacted]

Table 13.16 Emergent adverse experiences associated with abnormalities in hematological parameters - All Patients Exposed Population

Body system	Ropinirole N=1423		Placebo N=298		Active Comparators N=444	
Preferred term	n	%	n	%	n	%
Platelet bleeding and clotting						
Thrombocythemia	0	0.0	1	0.3	0	0.0
Thrombocytopenia	3	0.2	4	1.3	4	0.9
Red blood cells						
Anemia	18	1.3	1	0.3	9	2.0
Anemia B12 Deficiency	1	0.1	0	0.0	0	0.0
Anemia hypochromic	4	0.3	0	0.0	1	0.2
Polycythemia	1	0.1	1	0.3	0	0.0
White cell and reticuloendothelial system						
Eosinophilia	3	0.2	3	1.0	1	0.2
Granulocytopenia	0	0.0	1	0.3	0	0.0
Leucocytosis	11	0.8	1	0.3	3	0.7
Leukopenia	5	0.4	2	0.7	1	0.2
Lymphocytosis	2	0.1	0	0	1	0.2
Lymphopenia	3	0.2	1	0.3	1	0.2
Monocytosis	0	0.0	1	0.3	0	0.0

Data Source Table 7

Table 13.17 Emergent adverse experiences associated with abnormalities in blood chemistry laboratory parameters - All Patients Exposed Population

	Ropinirole N=1423		Placebo N=298		Active Comparators N=444	
	n	%	n	%	n	%
Liver and biliary system						
Bilirubinemia	5	0.4	0	0.0	4	0.9
Bilirubinemia aggravated	1	0.1	0	0.0	0	0.0
Gamma GT increased	7	0.5	1	0.3	2	0.5
Hepatic enzymes increased	17	1.2	1	0.3	9	2.0
Hepatic function abnormal	8	0.6	0	0.0	5	1.1
SGOT (AST) increased	1	0.1	0	0.0	2	0.5
SGPT (ALT) increased	9	0.6	2	0.7	2	0.5
Metabolic and nutritional						
Acidosis	3	0.2	1	0.3	0	0.0
BUN increased	17	1.2	0	0.0	6	1.4
CPK increased	1	0.1	0	0.0	0	0.0
Diabetes mellitus	4	0.3	1	0.3	1	0.2
Diabetes mellitus aggravated	2	0.1	0	0.0	1	0.2
Electrolyte abnormality	1	0.1	0	0.0	0	0.0
Enzyme abnormality	1	0.1	0	0.0	0	0.0
Gout	8	0.6	3	1.0	4	0.9
Hyperammonemia	0	0.0	0	0.0	1	0.2
Hypercholesterolemia	4	0.3	0	0.0	0	0.0
Hyperglycemia	20	1.4	5	1.7	11	2.5
Hyperphosphatemia	6	0.4	0	0.0	2	0 5
Hyperkalemia	2	0.1	0	0.0	3	0.7
Hyperuricemia	7	0.5	0	0.0	2	0.5
Hypochloremia	1	0.1	0	0.0	0	0.0
Hypoglycemia	4	0.3	0	0.0	2	0.5
Hypokalemia	3	0.2	0	0.0	0	0.0
Hyponatremia	3	0.2	0	0.0	0	0.0
Hypophosphatemia	0	0.0	1	0.3	0	0.0
Hypoproteinemia	0	0.0	1	0.3	0	0.0
LDH increased	8	0.6	1	0.3	7	1.6
NPN (creatinine) increased	9	0.6	1	0.3	3	0.7
Phosphatase acid increased	1	0.1	0	0.0	0	0.0
Phosphatase alkaline increased	5	0.4	2	0.7	1	0.2
Urinary system						
Renal failure acute	2	0.1	0	0.0	0	0.0
Renal function abnormal	0	0.0	0	0.0	2	0.5
Uremia	1	0.1	0	0.0	0	0.0

Data Source Table 7

Table 13.7 Values of potential clinical concern (F3 flag) and extreme single values (F4 flag) for key parameters

	F3 Flag threshold		F4 Flag threshold	
	Low	High	Low	High
Hematology				
Hemoglobin (g/dl)	80% LLN	120% ULN	80% LLN	120% ULN
Hematocrit (vol %)	80% LLN	120% ULN	80% LLN	120% ULN
RBC (10^{12}/L)	80% LLN	120% ULN	80% LLN	120% ULN
WBC (10^9/L)	3	20		
Neutrophils (10^9/L) *or* %	0.0	15	1.5	20
Lymphocytes (%)	0.0	7.5	0.2	10
Monocytes (%)	0.0	1.6		
Eosinophils (%)	0.0	0.8		
Basophils (%)	0.0	0.2		
Platelets (10^9/L)	100	500	100	600
Blood chemistry				
Total Bilirubin (µmoles/L)		150% ULN		60
Total Protein (g/dl)	80% LLN	110% ULN		
Albumin (g/dl)	80% LLN	110% ULN	< 3. 0g/dl	
AST (SGOT) (units)		2.5 x ULN		4 x ULN
ALT (SGPT) (units)		2.5 x ULN		4 x ULN
GGT (units)		2.5 X ULN		
Alkaline Phosphatase (units)		2.5 X ULN		4 x ULN
LDH (units)		2.5 X ULN		
Creatinine (µmoles/L)	50% LLN	125% ULN		>150% ULN
Urea (mmol/L)		11		20
Uric Acid (mmol/L)	50%	125%		
Sodium (mmol/L)	130	150	110	160
Potassium (mmol/L)	3	5.5	3	
Chloride (mmol/L)	80% LLN	120% ULN		
Bicarbonate (mmol/L)	80% LLN	120% ULN		
Glucose (fasting) (mmol/L)	2.8	6.7		
Glucose (random) (mmol/L)	2.8	9.7	< 2.5	> 11.1
Calcium (mmol/L)	1.9	2.8	1.9	> 4
Phosphate (mmol/L)	0.6	2.0		

ULN= upper limit of normal range, LLN= lower limit of normal range

[redacted]

Table 15.3 Emergent adverse experiences (incidence ¤ 20% overall) by dose - Early Therapy Study Population

	Total Daily Dose of Ropinirole (mg)											
	0.1-1.0 N=501		1.1-4.5 N=502		4.6-7.5 N=451		7.6-12.0 N=326		12.1-18.0 N=207		>18.0 N=112	
	n	%	n	%	n	%	n	%	n	%	n	%
Dizziness	11	2.2	55	11.0	30	6.7	27	8.3	9	4.3	9	8.0
Nausea	24	4.8	122	24.3	67	14.9	36	11.0	18	8.7	15	13.4
Somnolence	7	1.4	38	7.6	27	6.0	21	6.4	15	7.2	12	10.7
Hypotension Postural	3	0.6	10	2.0	15	3.3	4	1.2	4	1.9	1	0.9
Syncope	2	0.4	12	2.4	8	1.8	8	2.5	4	1.9	2	1.8
Amnesia	0	0.0	4	0.8	3	0.7	0	0.0	0	0.0	2	1.8
Hallucination	0	0.0	5	1.0	6	1.3	7	2.1	10	4.8	6	5.4

Data Source Table 15.1a and 15.2a

[redacted]

Table 15.4 Emergent adverse experiences (incidence ≥ 20% overall) by dose - Adjunct Therapy Study Population

	Total Daily Dose of Ropinirole (mg)											
	0.1-1.0 N=647		1.1-4.5 N=769		4.6-7.5 N=642		7.6-12.0 N=525		12.1-18.0 N=326		>18.0 N=133	
	n	%	n	%	n	%	n	%	n	%	n	%
Dyskinesia	22	3.4	80	10.4	50	7.8	51	9.7	39	12.0	18	13.5
Nausea	24	3.7	109	14.2	46	7.2	36	6.9	12	3.7	8	6.0
Hypotension Postural	5	0.8	37	4.8	22	3.4	17	3.2	12	3.7	3	2.3
Confusion	6	0.9	19	2.5	14	2.2	14	2.7	9	2.8	3	2.3
Hallucination	4	0.6	23	3.0	16	2.5	25	4.8	21	6.4	15	11.3

Data Source Table 15.1b and 15.2b

Appendix 2

SKB Tables from the 054 Study Report that were Referenced in the Safety Review

Table 24 The number and percent of patients with adverse experiences leading to withdrawal

Body System/Preferred Term	Ropinirole (n=116)		Placebo (n=125)	
	N	(%)	N	(%)
Gastrointestinal	**11**	**(9.5%)**	**5**	**(4.0%)**
Nausea	8	(6.9)	2	(0.8)
Dyspepsia	2	(1.7)	1	(0.8)
Vomiting	1	(0.9)	1	(0.8)
Abdominal Pain	1	(0.9)	0	(0.0)
Central and Peripheral Nervous System	**6**	**(5.2)**	**6**	**(4.8)**
Dizziness	5	(4.3)	2	(1.6)
Headache	1	(0.9)	3	(2.4)
Dyskinesia	1	(0.9)	0	(0.0)
Tremor	0	(0.0)	1	(0.8)
Vertigo	1	(0.9)	0	(0.0)
Heart Rate and Rhythm	**7**	**(6.0)**	**1**	**(0.8)**
Bradycardia	2	(1.7)	0	(0.0)
Palpitation	2	(1.7)	0	(0.0)
Arrhythmia	1	(0.9)	0	(0.0)
Extrasystoles Supraventricular	1	(0.9)	0	(0.0)
Fibrillation Atrial	1	(0.9)	0	(0.0)
Tachycardia Supraventricular	1	(0.9)	0	(0.0)
Tachycardia Ventricular	0	(0.0)	1	(0.8)
Psychiatric	**4**	**(3.4)**	**1**	**(0.8)**
Somnolence	2	(1.7)	0	(0.0)
Amnesia	1	(0.9)	0	(0.0)
Depression	1	(0.9)	0	(0.0)
Hallucinations	1	(0.9)	0	(0.0)
Insomnia	0	(0.0)	1	(0.8)
Cardiovascular	**2**	**(1.7)**	**2**	**(1.6)**
Hypertension	1	(0.9)	2	(1.6)
Syncope	1	(0.9)	0	(0.0)

Data Source: SAS Table 7.3.10 and SAS Appendix 7.3 in Appendix D

NUMBER (%) OF PATIENTS WITH EMERGENT ADVERSE EXPERIENCES IN RANKED DESCENDING ORDER
INTENTION TO TREAT POPULATION

TREATMENT GROUP	ROPINIROLE		PLACEBO		TOTAL
TOTAL NUMBER OF PATIENTS :	116	100.0%	125	100.0%	241
PATIENTS WITH ADVERSE EXPERIENCES :	111	95.7%	113	90.4%	224
PREFERRED TERM	**N**	**%**	**N**	**%**	**N**
NAUSEA	61	52.6	27	21.6	88
DIZZINESS	42	36.2	23	18.4	65
SOMNOLENCE	42	36.2	6	4.8	48
HEADACHE	20	17.2	19	15.2	39
UPPER RESP TRACT INFECTION	17	14.7	18	14.4	35
INSOMNIA	13	11.2	13	10.4	26
CONSTIPATION	12	10.3	8	6.4	20
SYNCOPE	12	10.3	2	1.6	14
FATIGUE	11	9.5	5	4.0	16
DYSPEPSIA	10	8.6	7	5.6	17
INFECTION VIRAL	10	8.6	4	3.2	14
BACK PAIN	9	7.8	9	7.2	18
VOMITING	9	7.8	7	5.6	16
PAIN	7	6.0	6	4.8	13
DRUG LEVEL INCREASED	7	6.0	4	3.2	11
ABDOMINAL PAIN	7	6.0	3	2.4	10
HYPOTENSION POSTURAL	7	6.0	3	2.4	10
CONFUSION	7	6.0	2	1.6	9
EDEMA LEGS	7	6.0	1	0.8	8
EDEMA DEPENDENT	6	5.2	4	3.2	10

EVT001/AEMRG54/10MAR95:06:55/KILMINSTERK1/PROD/USPAT/SK101468/

SK&F 101468

TABLE 7.3.1.2

SK&F 101468 STUDY 054
NUMBER (%) OF PATIENTS WITH EMERGENT ADVERSE EXPERIENCES IN RANKED DESCENDING ORDER
INTENTION TO TREAT POPULATION

TREATMENT GROUP	ROPINIROLE	PLACEBO	TOTAL

TOTAL NUMBER OF PATIENTS	:	116	100.0%	125	100.0%	241
PATIENTS WITH ADVERSE EXPERIENCES	:	111	95.7%	113	90.4%	224
PREFERRED TERM		N	%	N	%	N
ARTHRALGIA		5	4.3	12	9.6	17
MOUTH DRY		5	4.3	5	4.0	10
VISION ABNORMAL		5	4.3	4	3.2	9
PHARYNGITIS		5	4.3	3	2.4	8
URINARY TRACT INFECTION		5	4.3	3	2.4	8
PALPITATION		5	4.3	2	1.6	7
ASTHENIA		5	4.3	1	0.8	6
INJURY		4	3.4	8	6.4	12
DIARRHEA		4	3.4	7	5.6	11
ATAXIA		4	3.4	6	4.8	10
SWEATING INCREASED		4	3.4	5	4.0	9
HYPERTENSION		4	3.4	4	3.2	8
CHEST PAIN		4	3.4	3	2.4	7
ANOREXIA		4	3.4	2	1.6	6
CRAMPS LEGS		3	2.6	6	4.8	9
DYSKINESIA		3	2.6	5	4.0	8
PARKINSONISM AGGRAVATED		3	2.6	5	4.0	8
ARTHRITIS		3	2.6	3	2.4	6
PARESTHESIA		3	2.6	3	2.4	6
RHINITIS		3	2.6	3	2.4	6

EVT001/AEMRG54/10MAR95:06:55/KILMINSTERK1/PROD/USPAT/SK101468/

SK&F 101468

TABLE 7.3.1.2

SK&F 101468 STUDY 054
NUMBER (%) OF PATIENTS WITH EMERGENT ADVERSE EXPERIENCES IN RANKED DESCENDING ORDER
INTENTION TO TREAT POPULATION

TREATMENT GROUP		ROPINIROLE		PLACEBO		TOTAL
TOTAL NUMBER OF PATIENTS	:	116	100.0%	125	100.0%	241
PATIENTS WITH ADVERSE EXPERIENCES	:	111	95.7%	113	90.4%	224
PREFERRED TERM		N	%	N	%	N
BRADYCARDIA		3	2.6	2	1.6	5
SINUSITIS		3	2.6	2	1.6	5
AMNESIA		3	2.6	1	0.8	4
HYPESTHESIA		3	2.6	1	0.8	4

IMPOTENCE	3	2.6	1	0.8	4
CONCENTRATION IMPAIRED	3	2.6	0	0.0	3
DEPRESSION	2	1.7	10	8.0	12
ANXIETY	2	1.7	7	5.6	9
NERVOUSNESS	2	1.7	6	4.8	8
WEIGHT DECREASE	2	1.7	5	4.0	7
SALIVA INCREASED	2	1.7	3	2.4	5
BASAL CELL CARCINOMA	2	1.7	2	1.6	4
EXTRASYSTOLES	2	1.7	1	0.8	3
EYE ABNORMALITY	2	1.7	1	0.8	3
MALAISE	2	1.7	1	0.8	3
URINARY RETENTION	2	1.7	1	0.8	3
DYSPNEA	2	1.7	0	0.0	2
FLUSHING	2	1.7	0	0.0	2
GAMMA-GT INCREASED	2	1.7	0	0.0	2
HALLUCINATION	2	1.7	0	0.0	2

EVT001/AEMRG54/10MAR95:06:55/KILMINSTERK1/PROD/USPAT/SK101468/

SK&F 101468

TABLE 7.3.1.2

SK&F 101468 STUDY 054
NUMBER (%) OF PATIENTS WITH EMERGENT ADVERSE EXPERIENCES IN RANKED DESCENDING ORDER
INTENTION TO TREAT POPULATION

TREATMENT GROUP	ROPINIROLE		PLACEBO		TOTAL
TOTAL NUMBER OF PATIENTS :	116	100.0%	125	100.0%	241
PATIENTS WITH ADVERSE EXPERIENCES :	111	95.7%	113	90.4%	224
PREFERRED TERM	N	%	N	%	N
HEMATURIA	2	1.7	0	0.0	2
HYPOGLYCEMIA	2	1.7	0	0.0	2
PERIPHERAL ISCHEMIA	2	1.7	0	0.0	2
TACHYCARDIA	2	1.7	0	0.0	2
TACHYCARDIA SUPRAVENTRICULAR	2	1.7	0	0.0	2
TINNITUS	2	1.7	0	0.0	2
VERTIGO	2	1.7	0	0.0	2
XEROPHTHALMIA	2	1.7	0	0.0	2

Appendix 3

SKB Tables from the 044 Study Report that were Referenced in the Safety Review

Table 27 - The number (%) of patients incidence of frequent emergent adverse experiences (10% or greater)

Adverse Experience	Ropinirole (n=95) N	%	Placebo (n=54) N	%
Dyskinesia	32	33.7	7	13.0
Parkinsonism Aggravated	20	21.1	12	22.2
Ataxia	19	20.0	7	13.0
Dizziness	19	20.0	6	11.1
Nausea	19	20.0	6	11.1
Somnolence	18	18.9	6	11.1
Hypotension Postural	16	16.8	10	18.5
Insomnia	13	13.7	11	20.4
Drug Level Increased	12	12.6	4	7.4
Confusion	11	11.6	0	0.0
Upper Resp Tract Infection	10	10.5	7	13.0
Headache	10	10.5	4	7.4
Injury	10	10.5	4	7.4

Data Source:SAS table 7.3.1, Appendix D (SAS appendix 7.3)

Table 30: The number(%) of patients withdrawn for at least one AE regardless of treatment attribution

Withdrawal Reason by Body System/Preferred Term*	Ropinirole 19/95 (20.0%)		Placebo 12/54 (22.2%)	
Autonomic Nervous System	N	%	N	%
Sweating Increased	1	1.1	0	0
Body as a Whole				
Chest Pain	1	1.1	0	0
Chest Pain Substernal	1	1.1	0	0
Edema Legs	0	0	1	1.9
Fatigue	0	0	1	1.9
Influenza-Like Symptoms	1	1.1	0	0
Malaise	1	1.1	0	0
Pain	1	1.1	1	1.9
Cardiovascular General				
Hypotension Postural	0	0	2	3.7

Table 30 (Cont). The number (%) of patients withdrawn for at least one AE regardless of treatment attribution

Withdrawal Reason by Body System/Preferred Term	Ropinirole 19/95 (20.0%)		Placebo 12/54 (22.2%)	
Central and Peripheral Nervous System	N	%	N	%
Ataxia	1	1.1	1	1.9
Choreoathetosis	1	1.1	0	0
Dizziness	1	1.1	0	0
Dyskinesia	2	2.1	0	0
Hypokinesia	1	1.1	0	0
Paresthesia	1	1.1	0	0
Parkinsonism Aggravated	1	1.1	4	7.4
Tremor	0	0	1	1.9
Gastrointestinal System				
Abdominal Pain	1	1.1	0	0
Diarrhea	1	1.1	0	0
Fecal Incontinence	1	1.1	0	0
Nausea	1	1.1	0	0
Vomiting	2	2.1	0	0
Hearing and Vestibular				
Vestibular Disorder	1	1.1	0	0
Heart Rate and Rhythm				
Cardiac Arrest	0	0	1	1.9
Fibrillation Atrial	0	0	1	1.9
Metabolic and Nutritional				
Weight Decrease	1	1.1	0	0
Musculoskeletal System				
Arthralgia	1	1.1	0	0
Torticollis	0	0	1	1.9
Psychiatric				
Amnesia	1	1.1	1	1.9
Confusion	2	2.1	0	0
Depression	2	2.1	1	1.9
Hallucination	1	1.1	0	0
Insomnia	1	1.1	0	0
Nervousness	2	2.1	0	0
Paranoid Reaction	1	1.1	0	0
Somnolence	1	1.1	0	0

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Resistance Mechanism				
Sepsis	1	1.1	0	0
Respiratory System				
Dyspnea	1	1.1	0	0
Urinary System				
Hematuria	0	0	1	1.9
Urinary Tract Infection	1	1.1	0	0

*The number of patients within a body system are not additive since a patient can have more than one withdrawal reason within a Body System

Data Source: SAS table 7.3.10; Appendix D (SAS appendix 7.3)

REVIEW AND EVALUATION OF CLINICAL DATA

NDA:	**20-658**
SPONSOR:	**SmithKline Beecham**
DRUG:	**Ropinirole(SK & F 101468-A) Reqip Tablets**
PHARMACOLOGIC CATEGORY:	**Dopamine D_2 Agonist**
INDICATION:	**Symptomatic treatment of Parkinson's disease**
DOSAGE FORM:	**Tablet 0.25, 0.5, 1.0, 2.0, 5.0 mg**
DATE OF DOCUMENT:	**4-1-97**
DATE OF REVIEW:	**5-1-97**
SUBJECT:	**Response to Approvable Letter**
MATERIAL REVIEWED:	**Vol. 17.0001-17.0043; IND Safety Report**

1.0 Background:

Contained within this submission are, among other things, reports of two double-blind, placebo-controlled 6 month extension studies from Protocol 54 and 44 of the original NDA. There is also new information from Foreign Marketing which impacts on Final Approved Labeling. Finally, there is an initial IND safety report of pleural effusion from SB sponsored Compassionate Use Study 090 in Italy.

2.0 Extension Studies

A Double-Blind, Placebo-Controlled, 6 month extension study to evaluate the long term efficacy and safety of Ropinirole in early Parkinsonian patients not receiving dopaminergic therapy-CPMS-055.

This was a placebo-controlled, double-blind extension study of Study 054 for six months' treatment in adult patients with early Parkinson's disease nor currently treated with anti-Parkinson' therapy. However, although the study was placebo-controlled and double-blind, it was not randomized, as patients entered the extension study by choice with no interruption in

the administration of double-blind medication from study 054.

A Double-Blind, Placebo-Controlled Extension Study of Ropinirole as Adjunct to l-Dopa in the Treatment of Parkinson's Disease-CPMS-051

This was a multicenter, double-blind, placebo-controlled, parallel group, six month extension study of Protocol 44 which examined the potential role of Ropinirole as adjunct therapy in adult parkinsonian patients not optimally controlled on l-dopa. Patients were given the option of entering the extension study at the completion of Study 44, and remained on the same double-blind regimen for the duration of study 51. Patients were not re-randomized at the start of study 51.

Again, although the study was double-blind and placebo-controlled, it was not randomized, therefore the study cannot contribute to the efficacy assessment.

3.0 Foreign Marketing History

3.1 Preclinical Opthalmologic Lesion

Ropinirole was first approved in the United Kingdom for the treatment of Parkinson's disease in July 1996 and it was subsequently launched there in September 1996. Approval in twelve of thirteen other European Union markets was achieved through the Mutual Recognition (MR) procedure with France as the Reference Member State. Requip has also been approved in Switzerland. Finland also participated in the MR procedure. However, the marketing application was withdrawn by SB in Finland due to the agency's requirement for specific opthalmologic data from controlled clinical trials. The requirement for such data was based on the increased incidence of retinal degeneration in the high dose group observed in the two year carcinogenicity study in rats. This finding was attributed by the sponsor to an age-related, light-induced lesion that was not caused by a direct ropinirole-induced injury.

This reviewer brought this issue to the attention of superivisory pharmacologist Dr. Glenna Fitzgerald. She discovered that this finding of retinal degeneration in the carcinogenicity study in rats was reported in the pharmacology review but was omitted from the approvable labeling. We both agreed that this finding should be included in the final labeling for Ropinirole, under "Clinical Pharmacology, Mechanism of Action/Human Pharmacology", the fifth paragraph beginning "In rats, Requip binds to melanin-containing tissues (e.g. eye)...".

This reviewer also spoke with Eloise Scott, regulatory manager of SmithKline Beecham, to inquire what action the firm was taking in regard to this lesion. She said that a preclinical study was planned. In addition, as part of a PET study to be performed in the UK, France, USA, and Canada, one of the centers would look at the eye.

3.2 Changes to the Prescribing Information for the UK and the European Union

During review and approval of the Marketing Authorization Application in Europe, several

additions to the prescribing information [Summary of Product Characteristics (SmPC)] for Reqip were made at the request of Regulatory Agencies. These additions are summarized below:

For both the UKSmPC and the SmPC agreed, pregnancy and lactation have been included under "Contraindications".

Under "Special Warnings", the UK SPC contains the additional statement: "Coadministration of ropinirole with anti-hypertensive and anti-arrythmic agents has not been studied. As with other dopaminergic drugs, caution should be exercised when these compounds are given concomitantly with ropinirole because of unknown potential for the occurrence of hypotension. bradycardia, or other arrythmias.

An additional statement has also been added to the UK SPC under "Undesirable side effects" stating that "symptomatic hypotension and bradycardia, occasionally severe, may occur".

3.3 Fibrotic Complications

In the Approvable labeling, the following statement was made "Requip is a non-ergoline dopamine agonist and has not been associated with pleuropulmonary fibrotic complications in clinical trials."

However, under IND ·Serial No. 171 dated April 24, 1997, an initial written Safety Report of bilateral pleural effusion from SB sponsored Compassionate Use Study 090 AE 97007555-1 in Italy was submitted:

A 69 year old male with Parkinson's disease enrolled in study 101468 093 entered the compassionate use protocol 101468 090 in April 1996. In January 1997, the patient experienced edema of the lower limbs and was admitted to a local hospital suffering from bilateral pleural effusion. He was discharged from this hospital 20 days later and was subsequently admitted to a neurological hospital for approximately 10 more days. On admission, a right pleural effusion was noted. This was confirmed a few days later by a second CXR which revealed a pleural effusion less extensive than that seen in the examination performed in January 1997. Fibrotic branches were recognized. There was also the presence of abnormal lung ventilation, due to obstructive lung disease. Unspecified diagnostic procedures failed to reveal TB or other bronchopulmonary infections. The patient discontinued ropinirole on 4 March 1997 and was treated with Calciparina for edema. He fully recovered from the edema and pleural effusion. In the opinion of the reporting physician, the edema was definitley related to ropinirole while the pleural effusion was considered possible related to ropinirole.

The Investigator's Brochure is being amended to include the adverse experience, and the labeling should be amended to include this adverse event.

Janeth Rouzer-Kammeyer, M.D.

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Review of Clinical Safety Data

NDA:	**NDA 20-658** **Response to Approvable Letter**
Date of Submission:	**March 28, 1997**
Sponsor:	**SmithKline Beecham**
Drug:	**Ropinirole 0.25 mg, 0.5 mg, 1 mg, 2 mg, and 5 mg Tablets**
Route of Administration:	**Oral Titration**
Proposed Indication:	**Symptomatic Treatment of Parkinson's Disease**
Material Reviewed:	**March 28 Submission that Responded to the FDA approvable letter**
Date of Review:	**July 24, 1997**
Reviewer:	**Greg Burkhart, M.D., M.S.**

Summary

SKB submitted a response to the approvable letter on March 28, 1997 that addressed the issues raised by the FDA and updated the safety experience with ropinirole. The safety update significantly expanded the experience with ropinirole particularly at doses greater than 12 mg per day addressing a primary concern raised by the FDA in the letter. Findings from review of the safety experience in the update were largely unchanged from those observed in the NDA. We still remain uncertain about the effect of dose and time since first use on AE occurrence because confounding introduced by the titration design used in all studies. More complicated techniques that can model time dependent dosing may be necessary to evaluate the issue further.

The sponsor also conducted more formal analyzes to evaluate the effects of coexisting diseases (general cardiovascular disease, hypertension, diabetes, etc.) and concomitant use of selected medications (selegiline, diuretics, etc.) on AE occurrence associated with ropinirole use. While these analyzes were mostly under powered to have observed meaningful increases in risk between patients with and without the risk factor of interest, no significant findings were observed. Since the medical severity of the underlying CVD identified in US patients was probably mild at most, the CVD analyzes, which were restricted to US patients, do not address the question of whether patients with more severe CVD could be at more risk from ropinirole CV effects.

However, the analyzes show that syncope, in particular, occurs with ropinirole in patients without any demonstrable CVD.

The sponsor also considered the FDA concern that pooling of US and non-US data may not be advisable given significant differences between the study populations. By comparing AE risks and by evaluating the effect of concomitant medication use on ropinirole risk, the sponsor showed that there were no material differences in AE risks between US and non-US study populations.

Since submission of the NDA, the application to market ropinirole was withdrawn from Finland. Apparently this withdrawal followed the Finish agency's request for human ophthalmologic data to address the albino rat study that observed changes in retinal histopathology that were similar to those observed with pramipexole. As with pramipexole, we should add a description of these findings to labeling if the pharmacology reviewer concurs. We also should consider the value of a post-marketing study to evaluate the effect of long-term ropinirole use on the retina in humans. However, since any ophthalmologic findings may be non-specific and occur, to some extent at detectable background rates in PD patients, a suitable control group may be necessary for proper interpretation of any findings.

We should also consider adding a short description of patient who developed pulmonary fibrosis and bilateral pleural effusions after taking ropinirole for 10 months. The case was reported to the FDA in an IND safety report after the cutoff date for the safety update. At the time of this memorandum, the report was still incomplete, in that findings from evaluation of the exudate and from pleural biopsy are pending. If this turns out to be a compelling case consistent with the fibrosing disease that has been associated with ergot use, then it may be important to also add it to labeling.

Background

Ropinirole is a dopamine agonist intended for symptomatic treatment of Parkinson's Disease (PD) that was evaluated in a multinational drug development program. The NDA provided safety experience for two distinct categories of PD patients; "early therapy" (ET) patients who were treated with ropinirole before or with limited preceding exposure to l-dopa, and "advanced therapy" (AT) patients in whom ropinirole was used concomitantly with l-dopa.

Review of the NDA safety experience suggested that orthostatic hypotension, bradycardia, syncope, hallucination, confusion and nausea were strongly associated with ropinirole use particularly in "healthy volunteers" (phase one studies) and in ET patients in controlled studies. In the US ET study (study 054), ropinirole use was associated with significant increases in the risks for dropout and serious AEs (all-cause) when compared to placebo. Reassuringly, there were no deaths in the study 054, and across the development program, ropinirole mortality was reduced when compared to that with either bromocriptine or placebo.

On January 2, 1997, the FDA issued an approvable letter along with proposed labeling that added a bolded warning specifically describing the extent and nature of the CV AEs that had been observed with ropinirole. The increased risk for syncope was also noted in the warning language.

In addition to adding a warning statement, the FDA also asked for clarification and /or new analyzes of the NDA and the safety update for several issues that are summarized below.

(1) Extent of Exposure

In the NDA, the extent of use at higher doses in the proposed range for marketing was poorly described and probably limited. Thus, SKB was asked to clearly describe use by dose in the update particularly focusing on the extent of use at doses greater than 12 mg. The FDA provided a sample table showing person-days as a function of dose and week of use.

(2) CV AE Risk

The FDA asked for clarification regarding the description of CV AEs that were observed with ropinirole. First, the sponsor was asked to describe any syncope occurring in patient or healthy volunteers in phase one studies. While the NDA described healthy volunteers who developed postural hypotension or who were so orthostatic that BP could not be measured, and the one healthy volunteer who experienced cardiac asystole and syncope, it was unclear whether other healthy and/or patient volunteers also experienced syncope in the absence of the other events noted. The FDA also noted that in general, the occurrence and nature of any CV AEs occurring in patient volunteers was not well described in the NDA.

The sponsor was also asked to describe the effect of dose and time since first use of ropinirole on CV AE risks, and in particular, the risk for syncope. The FDA suggesting focusing the analysis on RCTs so that placebo or an active comparator group could serve as a basis of comparison. This request was prompted by findings from the review of study 054 (US ET study), where a slightly more than two fold increase in AE dropout was observed at week 10. Many of the AEs associated with dropout in study 054 were cardiovascular in nature.

(3) The Effect of Underlying CVD on AE Risk

Since the NDA seemed to include proportionally fewer PD patients who had underlying CV disease than could be expected in the general PD population, the FDA proposed that the sponsor develop a definition of concurrent CV disease

and then conduct a stratified analysis[1] to compare the risk attributable to ropinirole in patients with and without underlying CV disease. The analysis was to focus on studies with active comparator and/or placebo arms so that there would be a basis of comparison. Suggested events to be included in these analyzes included hallucination, syncope, CV AEs, somnolence, dizziness, confusion and other frequently occurring AEs. The FDA suggested focusing the on US studies 054 and 044, conducting separate analyzes for these studies.

(4) The Effect of Dose and Time Since First Use on AE Risk

Similar to the proposal for CV AEs, the sponsor was asked to conduct an analysis of the effects of dose and time since first use on AEs that were strongly associated with ropinirole use in the NDA database. These AEs included confusion, hallucinations, dizziness etc.

(5) Comparability of US and non-US study populations

Because the non-US study investigators were allowed to use domperidone to control dopaminergic side effects, which is not available for use in the US, and because of greater use of selegiline in the US, the sponsor was asked to evaluate the effect of pooling data from US and non-US data on AE risk estimates. An additional concern for describing AE occurrence in ET patients was prompted by the marked difference in AE dropout rates between the US ET study 054 and the non-US ET studies. If significant differences are observed then separate AE tables may be necessary in product labeling.

(6) In the safety update, the sponsor was asked to separate the US from non-US experience to facilitate review.

(7) General AE Issues

The sponsor was asked to provide more detail and analyzes for a list of AEs. For example, the FDA asked for a detailed description of the nature and follow-up of patients who were coded with "confusion" or "abdominal pain". Likewise, more clinical follow-up was requested for patients with laboratory

[1] A stratified analysis can be used to evaluate the effect of risk factors on drug risk. One calculates the excess or relative risk for individual stratum of a potential risk factor. For a risk factor that is either present or absent, there would be two strata to consider. A significant increase in risk in presence of the risk factor, in this case the presence of CVD, may be worth noting in labeling. How much variation is judged to be important is debatable but the most compelling case occurs with the excess in risk associated with the drug is completely accounted for in patients with the risk factor. Because the analysis focuses on variation in excess or relative risk, it is inherently comparative requiring placebo or an active control group and is usually applied to commonly occurring AEs in RCTs. Thus, if there are 2 stratum as in this case, one must examine two 2x2 tables.

values of clinical concern. See the letter or the appropriate section of this review for a listing of these issues.

(8) Misclassification of AEs

The sponsor also addressed the concern raised by the FDA in a teleconference preceding the submission that some of the AE terms coded by the sponsor seemed misclassified because of the "enhancement" of some AE terms. Enhancement was the term used by SKB to describe the process of changing selected AE terms in the SKB dictionary to more clinically meaningful terms in their opinion. The FDA's concern was that in so doing some terms potentially identifying objective orthostatic events may be combined with less specific events.

On March 28, 1997, the sponsor responded to the approvable letter addressing the safety issues raised by the FDA in the letter and labeling, and providing a safety update.

Description of Materials Submitted in Response to the Approvable Letter

The response to the approvable letter consisted of a safety update and specific narrative sections that answered questions raised by the FDA. Supporting documentation was provided in appendices that listed the summary tables for person-time by dose, the tables used in the analysis of AE risk by dose and time, and the 2x2 tables produced to search for risk factors that may be related to AE occurrence. The sponsor also provided patient listings, CRF tabulations, CRFs for deaths and narrative summaries of deaths, dropouts and serious AEs. The narrative summary of the safety update and the response to the FDA questions was available electronically. The supporting materials were available for review in volumes 1-43 of the Clinical Data Section.

Critique of the Sponsor's Approach to Conducting the Stratified Analyzes

The FDA specifically requested that SKB examine the effect of underlying CVD on the risk for several AEs that were strongly associated with ropinirole use. The sponsor extended this approach to search for other risk factors by comparing risks between patients with and without other underlying disease such as diabetes, and between users and nonusers of commonly used medications such as selegiline.

SKB also conducted somewhat of a stratified analysis in considering the comparability of AE rates between US and non-US data. US event rates for ropinirole and placebo were compared to those for US and non-US combined. Although this last approach can be misleading in some circumstances, it still is useful way of addressing the general comparability question raised by the FDA.

Focusing on the more formal stratified analyzes conducted by SKB to identify risk factors, there was one general limitation in the sponsor's approach. In particular, the sponsor focused on findings where confidence intervals (CIs) could be calculated and then compared across each 2x2 table produced for each risk factor analysis. (For consideration of CVD, where it was either present or absent, there would be two 2x2 tables to examine.)

While restricting consideration to analyzes where CIs are calculable may seem reasonable, the result could be to exclude a risk factor from consideration even when there was compelling evidence that it had a significant effect upon AE risk attributable to the durg. For example, shown below are the two 2x2 tables from the ropinirole submission that examine the effect of concurrent hypertension on the risk of confusion.

Patients with hypertension

		Ropinirole	Placebo
Confusion	Yes	6	0
	NO	116	14

Patients without hypertension

		Ropinirole	Placebo
Confusion	Yes	13	2
	NO	380	131

To summarize the data, there were 6 ropinirole patients who had coexisting hypertension who were reported to have confusion at least once. The relative risk (RR) of confusion during ropinirole use when compared to placebo was (13/393) / (2/133) or 2.2 in patients without hypertension. However, neither the RR nor the CI are calculable for patients with hypertension because no placebo patients had the event. (Or course the excess risk could be calculated, but its absolute value, while important for public health management decisions, does not speak to the magnitude of the difference across strata and the CI would be very broad anyway between of no cases with placebo.)

If we modify these findings to create a hypothetical example, then one can easily see the limitations from not considering data where CIs can not be calculated. If we now let all the 19 patients (6+13) who developed confusion while on ropinirole also be patients with hypertension, the relative risks and CI would still not be calculable yet the evidence is compelling that patients with hypertension were more at risk for confusion when taking ropinirole. This approach works well when there are few, if any events, in the comparison group and when most cases are observed with the drug in the presence of the risk factor, as in the hypothetical example.

Thus, the sponsor's approach would have been fine if it had been augmented by searching for situations where the event of interest occurring with ropinirole mostly occurred in patients with the risk factor of interest and where there were few cases in the comparison group.

Methods of Review

Because of the approach used by SKB in the interpretation of the findings from the series of stratified analyzes, it was necessary to examine the 2x2 tables provided in the appendices. I limited this review to confusion, hallucination, and syncope with the focus on identifying any underlying diseases or concurrently used medications that accounted for a significant number of ropinirole associated events.

In addition, all the narrative summaries were reviewed to identify any AE occurrence that was not observed in the review of the NDA, particularly focusing on events that could have been hepatic failure, rhabodomyoloysis, serious skin rashes, hematologic and other events that have been classic manifestations drug toxicity. In addition, the CRFs for the five new ropinirole deaths were reviewed looking for associated AEs of interest.

While the sponsor provided a person-time description of ropinirole use by dose and time elapsing since first use, a total person-time calculation was apparently not provided. To estimate total person-time, I used SKB's description of the number of patients by duration of ropinirole use assuming that patients discontinuing in a duration interval did so half way through that interval.

Foreign Regulatory Update

Ropinirole was first marketed in the UK (September 1996) and is or is to be marketed shortly in several other countries. The application to market ropinirole was withdrawn, however, from Finland after its regulatory agency requested ophthalmologic data in humans. This request was apparently based upon findings from the albino rat study where pathological changes in the retina were observed with long term use. These findings may be similar to those noted in pramipexole's labeling and is being addressed by the pharmacology reviewer.

Inclusion Dates for the Safety update

The clinical cut-off for the safety update database was May 31, 1996. Information on deaths and serious AEs was provided up through August 31, 1996. In the NDA safety database, the corresponding dates were October 31, 1994 and May 31, 1995.

Number of Patients Exposed

The total number of patients exposed to ropinirole in the safety update was 1599 which represents an increase of 235 new exposures to ropinirole from the 1364 patients in the NDA. For placebo, there were 332 patients in the update compared to 298 in the NDA, and bromocriptine or L-dopa there were 452 patients in the update compared to 444 in the NDA. The number of patients that are still being followed by SKB are 488 in the ropinirole group, 48 in the placebo group and 262 exposed to either bromocriptine or l-dopa.

Of the 235 new ropinirole patients in the update database, 219 were enrolled in ET studies with all followed at non-US sites. Of the 34 additional placebo and 8 additional comparator patients, all were ET patients.

In addition to the increase in new ET patient exposures, there has been a substantial gain in patient experience at higher ropinirole doses from continued follow-up from both US an non-US patients. This additional experience is discussed in the next two sections.

Extent of Use

Although the sponsor calculated exact person-time of use by dose, I could not locate a total. Using SKB's Figure 1[2], which is included in appendix 1 of this review, I estimated that there were about 1709 person-years of total use included in the update database. I also estimated it from the SKB table that showed the number of patients by duration of ropinirole use (not shown, but similar to SKB table 5.2). From this table, I estimated that there were about 1740 person-years of use in the update, and from a similar designed table in the NDA, I estimated in the NDA review that there were 1165 person-years of use in the NDA.

Thus, the update has included an additional experience of about 500-550 person-years compared to that in the NDA database. As of the update, there now have been 428 PD patients who were treated with ropinirole for at least one year.

SKB Table 5.2 shows the duration of follow up separately for ET patients in the NDA and the update. As expected, the number of ET patients who were exposed to ropinirole and who have been followed longer than 96 weeks has increased several fold. Estimating as before, there were at least 984 person-years of ropinirole experience in ET patients with 110 patients having more than 144 weeks of experience. In the review of the NDA, I estimated that there were 514 person-years of ropinirole experience in ET patients in that database.

Extent of Use by Dose

In the safety update, the sponsor described the exposure by dose using several methods.

[2] SKB Figure 1 and SKB Tables referred to are shown in appendix one of this review.

In SKB Table 5.5, the number and percentages of patients reaching selected daily doses are shown. Overall, 12.7% or 203 patients of the combined population reached 24 mg per day, and as can be seen in SKB Table 5.6, 13.9% or 102 ET patients reached 24 mg per day. Overall, 103 patients reached 24 mg per day who were followed at this dose for 6 months or longer (62 ET patients.) In the NDA database, 176 reached 24 mg per day with 124 taking that dose for longer than 12 weeks. (In the NDA, I could not tell how many took that dose longer than 6 months.)

While the sponsor provided person-time as a function of daily dose and time since starting ropinirole, cumulative totals for doses equal to or larger than a dose were not provided. Estimating from SKB Figure 5.1, which shows person-time for each daily dose for ET and AT patients combined, there appear to be about 129 person-years (47,000 person-days) at 24 mg per day with about 50% of that use in ET patients (based upon other data provided by the sponsor and not shown in the figure). Likewise, there were about 712 person-years of use at 12 mg or more with about 50% of that use in ET patients. Overall about 41% of the experience (712 person-years / 1740 person-years) has been at doses greater or equal to 12 mg per day, but as in the NDA database, the majority of experience with ropinirole has been at doses less than 12 mg per day.

Mortality

A total of 8 new deaths were reported to SKB between June 1, 1995 and August 31, 1996; 5 exposed to ropinirole, 1 each assigned to placebo, bromocriptine or l-dopa. A review of the narrative summaries and CRF tabulations for these deaths did not reveal any unexpected AEs with these additional deaths SKB Table 10.1 shows these AEs both for deaths in the update and the NDA.

Patient Dropout

The pattern of AE dropout and overall dropout was unchanged in the update database when compared with the NDA database. SKB Table 7.2 updates the number and reasons for patient dropout in ET patients. There are no significant differences from the pattern observed in the NDA database. As before, ET patient dropouts were clearly associated with nausea/vomiting, confusion and hallucinations, and as before, the overall dropout rate in ET patients is less than that observed in US study 054, the only US ET study. In study 054, AE dropout on ropinirole was 25.9% on ropinirole compared to 13.6% on placebo while in non-US ET studies the ropinirole dropout was 15.7% compared to 19.6% with placebo.

Study 054 had a significant increase in dropout associated with AE occurrence while taking ropinirole that was apparent at week 10. Many of events associated with dropout were CV in nature and associated with bradycardia and/or syncope. While the update has provided a separate summary of study 054, none of the new experience in that study represents new patients, but instead extends the experience of existing patients.

The sponsor also analyzed the risk of dropout by dose and time but the analysis used the number of discontinuations at each time point and dose combination rather than the number of patients at risk. In any case, dropout associated with hallucinations still seemed more likely with increasing dose, particularly above 12 mg per day. In addition, the 4 syncopes that were identified as the reason for dropout all occurred at 6 mg and above. This finding is consistent with the observation that the probability of patient dropout starting diverging from that with placebo at about 10 weeks suggesting that some the events may be dose related.

Serious AE Occurrence

In the update database, there were 112 ropinirole patients who had at least one serious AE during the update period. Of these 112 patients, 86 were new and not in the NDA.

In reviewing the serious AE narrative summaries, the descriptions of the AE were similar to those observed in the NDA review. There were fractures, falls, confusion, occasional syncope and/or bradycardia, hallucination, chest pain and IHD events. Certainly some of these AEs could be related to the pharmacologic action of the drug, but they also are expected events, to some extent, in this population.

There was one poorly described event of prolonged anemia that was associated with sepsis. Since there was limited follow-up information, the cause or type of anemia is unknown. There was one additional case of testicular cancer and there was also one patient diagnosed with retinal degeneration (053.010.00070). Two children were born of mothers with exposure to ropinirole, one having hydrocephalus (058.001.00047) and the other a spine malformation (056.007.00168).

No events were observed that were consistent with aplastic anemia, rhabdomyolysis, hepatic failure, serious skin rash, hemolytic anemia or unexplained renal failure. The sponsor, using the terms retroperitoneal fibrosis, pleural fibrosis, pleuropulmonary disease, pleural thickening (preferred term of X-ray abnormal), intestinal obstruction, ureteral obstruction, elevated ESR, erythromelalgia searched but found no AEs suggestive of of these AEs. One bromocriptine patient was also diagnosed with retroperitoneal fibrosis in the update database.

Importantly, perhaps for labeling, is a recent IND report describing a 69 year old male Italian patient who developed bilateral pleural effusions and was then diagnosed with pulmonary fibrosis after using ropinirole for 10 months. Before starting ropinirole, there was no evidence of pleurpulmonary disease by xray or exam. The report did not mention whether he had been on another dopamine agonist prior to starting ropinirole. During the 10 months of ropinirole use, concomitant medications included selegiline, amlodipine and ticlopidine, and according to the investigator, there was no underlying disease that could explain for the findings. Findings from examination of the exudate and the pleural biopsy have not included in the IND report although the specimens were collected for analysis apparently under an open thoracotomy. In addition to follow-up these issues, a

clinical update would of interest to see what happened to the patient since ropinirole was discontinued.

Non-serious AE Occurrence

As with deaths, dropouts and serious AE occurrence, the overall the pattern of non-serious AE occurrence was unchanged in the update compared to the NDA.

AE Occurrence by Dose and Time Since First Use

As suggested in the approvable letter and in the proposed labeling, the sponsor conducted analyzes of the effect of dose and time since first use on AE occurrence. However, these analyzes were limited because of small cell numbers and because of the correlation between increasing dose and increasing length of use. In addition, the interpretation of the findings was complicated by the sponsor's method of analysis where the denominator in each cell was the total number of events as opposed to the total number of patients at risk at that time and that dose.

As in the NDA analysis, only the risk for hallucination clearly increased with increasing dose. While the sponsor also considered the effect of cumulative dose on AE occurrence, the analysis was also confounded by time since first use.

More complicated analytic techniques that can address time dependent co-variates, such as cox regression, may be necessary to evaluate the issue further. Since we observed a clear increase in study dropout with ropinirole that was difference from placebo at 10 weeks in study 054, a cox analysis conducted this study may be most informative. Developing a case definition for a CV event (syncope, bradycardia etc.) also may be required rather than focusing on individual AE terms. Separate analyzes could be conducted for other outcomes such as hallucination.

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Cardiovascular Effects in Phase One Studies

SKB clarified the CV events observed in patient and healthy volunteers in phase one studies. In patient volunteers, supine and standing BP measurement was not performed. Two patients were reported to have had syncope following a 1 mg dose and one patient was reported to have had documented hypotension following 2 mg dose on two occasions. There were no effects on the ECG in patients, however, there were some reports of bradycardia without ECG confirmation.

The sponsor also reported that there was one other syncope in healthy volunteers. According to the sponsor, there was no information for the BP or pulse in this patient at the time of the event.

Stratified Analysis to Evaluate the AE Risk in Patients with CVD

As the FDA suggested in the approvable letter, the sponsor developed a working definition to identify patients with evidence of underlying CVD either at baseline or that developed in study. The CVD definition included, for example, IHD and hypertension, but would have excluded patients with only peripheral vascular disease. It also included patients using CV medication at baseline or who started such medication during study. In these analyzes, the sponsor focused on AEs occurring in 5% or more of the study population. The analyzes were conducted only in the two US studies including their extensions.

The findings did not identify any AEs that were materially increased in patients with CVD compared to those without. Table 13.2 shows the findings for ET patients in study 054. As noted earlier, the sponsor did not focus on AEs if CIs could not be calculated in each strata. Thus, syncope is not listed in table 13.2 since there were no placebo patients who had syncope. Further review of the 2x2 tables for syncope that were included in the appendix showed that the risk for syncope during ropinirole use (ignoring placebo) was about the same in patients with CVD and in those without.

Because of limited cell sizes, there was limited power to detect significant differences in ropinirole risk. In addition, since patients with moderate or severe CVD were not including in the studies, the analyzes could not address the question of whether such patients are at increased risk for CV AEs when taking ropinirole.

Stratified Analysis to Evaluate the AE Risk in Patients With Selected Concurrent Diseases other than CVD

The sponsor also conducted a series of stratified analyzes to evaluate the separate effects of hypertension, ischemic heart disease, diabetes, constipation, depression, anxiety, rheumatism, prostate disorder, insomnia, and conduction disorder on ropinirole risk. These analyzes focused on AEs that occurred in more than 10% of the ET and AT

populations and, as requested by the FDA, on confusion, hallucinations, syncope, and postural hypotension.

As was observed in series of stratified analyzes of patients with and without CVD, most were under powered to have observed material differences in AE risks between patients with and without the disease of interest. As before, review of the 2x2 tables provided by the sponsor did not identify any situation where the AE of interest was mostly observed in ropinirole patients in the presence of the risk factor of interest.

Stratified Analysis to Evaluate the AE Risk in Patients Using Selected Concurrent Medications

SKB also conducted stratified analyzes of concomitant medication use. For these analyses, AEs were selected that were observed in 10% or more of ropinirole ET or AT patients in the NDA database, and as suggested by the FDA in the approvable letter, confusion, hallucinations, syncope and postural hypotension were also included. Ten concomitant medications were evaluated selected on their extent of use in the NDA: acetylsalicylic acid, amantidine, beta-blockers, NSAIDs, selegiline, paracetamol, thiazide diuretics, tocopherol, tricyclic anti-depressants and trihexphenidyl.

In ET patients, there were no striking differences between users and non-users of any the studied concomitant medications with the magnitude of none of the differences large enough to place in labeling in my opinion. The largest most compelling difference across users and non-users was observed for ASA and vomiting. In users, the RR (risk with ropinirole / risk with placebo) was 5.0 (95% CI; 1.1, 23.0) while in non-users it was 1.5 (95% CI; 0.7,3.2) in non-users. A similar difference between users and non-users also occurred for vomiting and selegiline use. In non-users, the RR was 5.9 (95% CI; 1.4,25.1) while in users the RR was 0.9 (95% CI; 0.4,2.1) . However, in both analyzes there was significant overlap in the CIs. For both analyzes, it would have been helpful for the sponsor to provide the findings from statistically evaluating the homogeneity of the relative risk across the strata.

In AT patients, there were some differences across users of tocopherol compared to non-users. For dyskinesia, the RR was 10.91 (95% CI; 1.4,85.2) in users and 2.1 (1.2,3.5) in non-users. For injury, the RRs were 8.5 (95% CI; 1.1,66.6) and 1.0 (95% CI; 0.5,1.9). As in ET patients, the estimates are imprecise with the differences probably not large enough to place in labeling.

As in the other stratified analyzes, these were also limited by small cell numbers in many cases reducing the power to detect meaningful differences and there were no risk factor/AE analyzes identified where use of one of these medications concomitantly with ropinirole accounted for most events.

Comparability of AE rates between US and non-US studies

In the approval letter, the FDA expressed concern about the comparability of US and non-US data particularly pointing out the variation in concomitant medication use. US studies, for example, were stratified by selegiline use and non-US studies could use domperidone for control of symptoms thought to be related to increased peripheral dopamine activity. The letter suggested that the two sets of data may be so different as to justify separate AE tables.

The sponsor provided tables showing AE risks for ropinirole and placebo respectively for US conducted studies along with risks for US and non-US studies combined. There was no material difference observed for either ET or AT patients. The sponsor also made the point that the risks were no different in the stratified analyzes for selegiline.

The Effect of Coding Enhancement on Observed AE Risks

In the NDA review, there was concern about what the sponsor meant when referring to "enhancement" of selected AE terms. This concern was conveyed in a teleconference that preceded the response to the approvable letter. The sponsor has addressed this concern providing a discussion on the methods applied for coding AEs.

Of particular concern to the sponsor were investigator verbatims of events associated with PD and how to code them. For example, "freezing" would have be encoding with "rigors" according to the SKB clinical dictionary, but since the investigators were using this description to indicate a worsening of PD, this term was "enhanced" as "worsening of PD". SKB Table 8.1 shows the terms that were enhanced within the NDA coding while table 8.2 shows the number of times that the preferred term resulted from enhanced terms.

As an example, consider the 146 patients coded with postural hypotension. Of these 146, 62 had verbatims that were consistent with orthostatic dizziness, presumably without any objective change in BP. A more striking misclassification occurs for the "preferred term" ataxia which actually represents mostly falls. The sponsor concluded from its review that neither ataxia nor postural hypotension should be used in labeling proposing that "falls" and "orthostatic symptoms" be used instead.

Follow-up For Ocular Findings, Abdominal Pain, Laboratory Abnormalities and Other AEs

The sponsor confirmed that the risk for any ocular abnormality was increased with ropinirole use compared to placebo in study 054. In ropinirole patients, there were 13 patients with some ocular finding as shown in SKB Table 13.9. In study 032, there were three ropinirole patients with an ocular AE. All 16 of these patients completed either study 054 or 032. There was no additional clinical information in these patients.

SKB also addressed the increased risk for abdominal pain that was observed in study 054. As with the ocular abnormalities, these reports captured a broad clinical spectrum

of symptoms/events and no additional information was available. One patient was withdrawn from 054 because of the abdominal pain.

There were nine patients in study 054 who developed confusion while on ropinirole, seven were on ropinirole and two on placebo. In study 044 (the US AT study), there were 11 patients who were reported as having confusion all on ropinirole. None of the ET patients were withdrawn, but 2 of the patients in 044 were withdrawn because of confusion. In all patients, there was a wide range of doses noted at the time when confusion was first noted. There was also a wide range of investigator verbatims that were coded as confusion ranging from non-specific events to delirium. Confusion is one of the terms that underwent enhancement by SKB.

There were no differences in the percentages of patients diagnosed with gout, found to have increased uric acid or who used uricosuric drugs between ropinirole, placebo or active comparator.

The sponsor also summarized the follow-up for patients with a laboratory value of potential concern. For the 318 ropinirole patients with 2 consecutive values of concern (F3 flags), the value was abnormal at clinical cutoff or at endpoint in almost 85% whereas for the 170 ropinirole patients with a single value of clinical concern (F4 flag) about 50% were abnormal at clinical cutoff or endpoint. These percentages were similar to those with placebo or active comparator groups.

Discussion

The safety update provided by SKB has provided significantly more experience on ropinirole than included in the NDA. In particular, the extent of use at higher ropinirole doses has increased substantially particularly in ET patients. There are now at least several hundred person-years of use at 12 mg or more in ET patients and about 100 person-years at 24 mg per day.

Overall, the safety experience in the update was similar to that in the NDA. There were no new AEs that were observed that could change in the labeling. There was, however, an IND safety report of pulmonary fibrosis and pleural effusions in a patient receiving ropinirole for 10 months. Findings from analysis of the exudative effusion and pleural biopsy were not available at the time of this memorandum.

The analysis of the effects of dose and time since first use of ropinirole were not that helpful and were technically not conducted appropriately by the sponsor. However, because of the correlation between increasing dose and increasing duration of use, these analyses were unlikely to have been particularly helpful. Conducing a cox regression for selected events observed in study 054 may be more revealing regarding the relationship between dose, time of use and event occurrence.

The stratified analyzes conducted by the sponsor that examined the effects of CVD and

several other diseases, and selected concomitant medication use on ropinirole AE risk were largely unrevealing. Most of these analyzes were limited by small numbers and were hence generally under powered to detect meaningful differences in risk. In addition, the CVD analysis does address whether there is increased risk of CV events when ropinirole is used in patients with moderate or severe CVD since such patients were not included in the US studies.

While the sponsor provided follow-up information on patients with ocular AEs, abdominal pain and laboratory abnormalities of potential concern, the clinical detail and follow-up was limited. Since similar rat pathological findings in the retina were observed with ropinirole as with pramipexole, and since an increased risk of general ocular abnormalities were observed study 054, perhaps a phase 4 commitment to evaluate ropinirole long term users may be of value. However, the value of such studies would probably be limited unless there a suitable comparative population since ophthalmologic findings may be non-specific and expected, to some extent, in a PD population.

Conclusion

The sponsor has provided a safety update that significantly expands the experience with ropinirole particularly at doses greater than 12 mg per day. For the most part, the findings and conclusions reached on review of the NDA are unchanged. There was one IND safety report submitted to the FDA after the clinical cutoff for the safety update in patient who developed bilateral pleural effusion and pulmonary fibrosis after 10 months of ropinirole use. Further follow-up of this case is necessary and we may want to include such a short description of the case in labeling. Some consideration should be given to a phase 4 commitment to study potential ophthalmologic effects of long term ropinirole use.

7/24/97

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Appendix 1: SKB Tables Referred to in the Review

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Table 5.2 Overall Duration of Exposure - Early Therapy Study Population

	Requip		Placebo		L-dopa		Bromocriptine	
	NDA	Update	NDA	Update	NDA	Update	NDA	Update
Weeks	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
≤1	8 (1.6)	10 (1.4)	2 (1.4)	2 (1.1)	2 (2.2)	2 (2.1)	2 (1.2)	2 (1.2)
2-4	15 (2.9)	21 (2.9)	3 (2.0)	4 (2.2)	1 (1.1)	1 (1.0)	6 (3.6)	6 (3.6)
5-8	18 (3.5)	31 (4.2)	3 (2.0)	3 (1.7)	1 (1.1)	1 (1.0)	4 (2.4)	4 (2.4)
9-12	20 (3.9)	85 (11.6)	13 (8.8)	13 (7.2)	4 (4.5)	4 (4.1)	4 (2.4)	4 (2.4)
13-24	45 (8.7)	92 (12.5)	14 (9.5)	15 (8.3)	3 (3.4)	3 (3.1)	12 (7.2)	7 (4.2)
25-48	160 (31.1)	67 (9.1)	55 (37.4)	43 (23.8)	21 (23.6)	4 (4.1)	55 (32.9)	13 (7.8)
49-72	162 (31.5)	99 (13.5)	57 (38.8)	70 (38.7)	23 (25.8)	3 (3.1)	51 (30.5)	6 (3.6)
73-96	64 (12.4)	32 (4.4)	0 (0.0)	8 (4.4)	23 (25.8)	6 (6.2)	31 (18.6)	3 (1.8)
97-144	23 (4.5)	187 (25.5)	0 (0.0)	18 (9.9)	11 (12.4)	36 (37.1)	2 (1.2)	84 (50.3)
≥145	0 (0.0)	110 (15.0)	0 (0.0)	5 (2.8)	0 (0.0)	37 (38.1)	0 (0.0)	38 (22.8)
Total	515	734	147	181	89	97	167	167

Data Source Tables 1.2 a and 1.2b

Table 5.5 Number of Patients Ever Receiving Each Dose of Requip and Number of Patients Receiving Each Dose at Endpoint -Therapeutic Study Population

Requip total daily dose in mg	Number of patients ever receiving each dose		Number of patients with each dose at endpoint	
	n	%	n	%
<0.75	26	1.6	9	0.6
0.75	1429	89.4	66	4.1
1.5	1412	88.3	69	4.3
2.25	1120	70.0	27	1.7
3	1425	89.1	116	7.3
4.5	1294	80.9	82	5.1
6	1305	81.6	173	10.8
7.5	1156	72.3	186	11.6
9	984	61.5	197	12.3
12	786	49.2	161	10.1
15	619	38.7	168	10.5
18	418	26.1	113	7.1
21	293	18.3	75	4.7
24	203	12.7	157	9.8
Total no. patients	1599		1599	100

Data Source Tables A1.1, A2.1

Table 5.6 Number of Patients Ever Receiving Each Dose of Requip and Number of Patients Receiving Each Dose At Endpoint - Early Therapy Study Population

Requip total daily dose in mg	Number of patients ever receiving each dose		Number of patients with each dose at endpoint	
	n	%	n	%
<0.75	7	1.0	3	0.4
0.75	728	99.2	24	3.3
1.5	708	96.5	22	3.0
2.25	656	89.4	9	1.2
3	690	94.0	34	4.6
4.5	671	91.4	35	4.8
6	661	90.1	83	11.3
7.5	583	79.4	112	15.3
9	471	64.2	90	12.3
12	372	50.7	88	12.0
15	289	39.4	73	10.0
18	204	27.8	54	7.4
21	157	21.4	31	4.2
24	102	13.9	76	10.4
Total no. patients	734		734	100

Data Source Tables A1.2, A2.2

Figure 5.1 Person Time on Each Dose Level

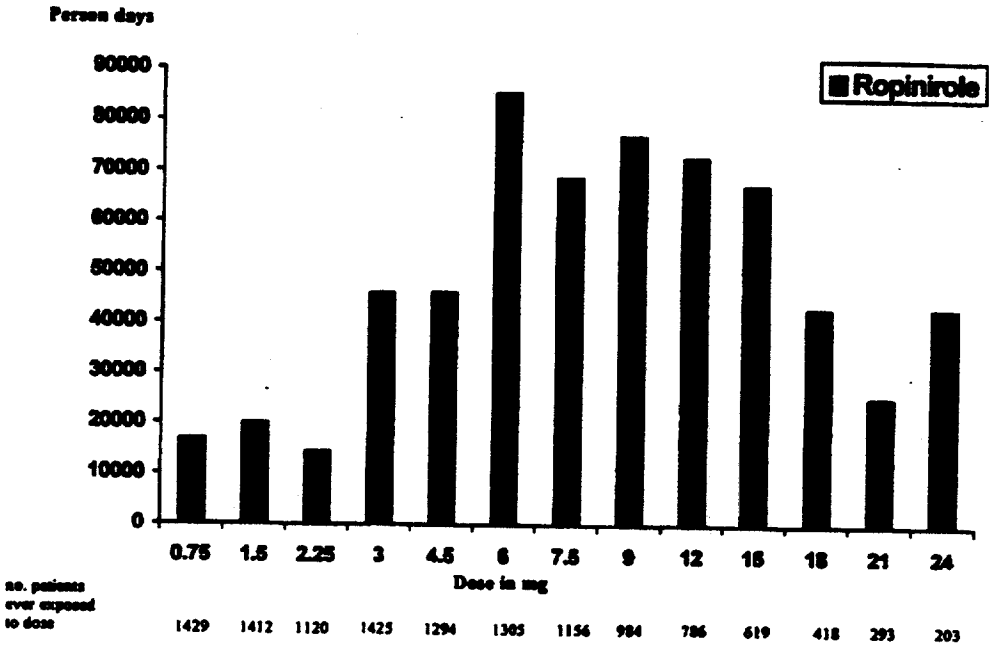

Table 10.1 Serious Adverse Experiences Resulting in Death

	Requip		Placebo		Bromocriptine		L-dopa	
	NDA N=1423	Update N=1765	NDA N=298	Update N=332	NDA N=355	Update N=355	NDA N=89	Update N=97
	n	n	n	n	n	n	n	n
Total	21	26	4	5	11	12	0	1
Anemia	0	0	0	0	1	2	0	0
Atherosclerosis	0	0	0	0	0	1	0	0
Bronchitis	0	2	0	0	0	0	0	0
Cachexia	0	0	0	0	0	1	0	0
Cardiac Failure/ Cardiac Arrest	3	5	2	0	1	2	0	0
Cerebral Infarction	2	2	1	2	1	1	0	0
Coma Diabetic	0	1	0	0	0	0	0	0
Diarrhea	0	0	0	0	0	1	0	0
Extrapyramidal Disorder	0	0	0	0	0	1	0	0
Fibrillation Atrial	0	0	0	1	0	0	0	0
Neoplasm nos	3	3	0	0	4	5	0	1
Osteoporosis	0	0	0	0	0	1	0	0
Pneumonia	3	4	0	0	1	1	0	0
Pyelonephritis	0	0	0	0	0	1	0	0
Sepsis	1	3	0	0	1	1	0	0
Syncope	0	1	0	0	0	0	0	0

n=number of patients with a serious adverse experience

Table 7.2 Discontinuations by Reason - Early Therapy Study Population

	Requip		Placebo		L-dopa		Bromocriptine	
	NDA	Update	NDA	Update	NDA	Update	NDA	Update
	N=515	N=734	N=147	N=181	N=89	N=97	N=167	N=167
Reason	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Completed	94 (18.3)	234 (31.9)	95 (64.6)	112 (61.9)	0 (0.0)	0 (0.0)	0 (0.0)	28 (16.8)
Ongoing	281 (54.6)	271 (36.9)	18 (12.2)	26 (14.4)	74 (83.2)	68 (70.1)	130 (77.8)	87 (52.1)
Withdrawn								
AE	88 (17.1)	127 (17.3)	19 (12.9)	28 (15.5)	14 (15.7)	19 (19.6)	25 (15.0)	32 (19.2)
LOE	13 (2.5)	27 (3.7)	7 (4.8)	7 (3.9)	1 (1.1)	2 (2.1)	3 (1.8)	4 (2.4)
Deviation	17 (3.3)	29 (4.0)	2 (1.4)	2 (1.1)	0 (0.0)	1 (1.0)	2 (1.2)	3 (1.8)
Lost to F/U	9 (1.8)	16 (2.2)	1 (0.7)	1 (0.6)	0 (0.0)	1 (1.0)	4 (2.4)	6 (3.6)
Other	13 (2.5)	30 (4.1)	5 (3.4)	5 (2.8)	0 (0.0)	6 (6.2)	3 (1.8)	7 (4.2)

AE = adverse experience, LOE = lack of efficacy, Deviation = deviation form protocol, F/U = follow-up

Data Source Tables 3.2a and 3.2b

Table 8.6 Emergent Adverse Experiences* Occurring in ≥1%# of Requip Treated Patients and More Frequently Than On Placebo in All Placebo-Controlled Studies and US-Placebo Controlled Studies - Early Therapy

	All Placebo-Controlled Studies		US Placebo Controlled-Studies	
	Requip N=157 n (%)	Placebo N=147 n (%)	Requip N=116 n (%)	Placebo N=125 n (%)
Autonomic Nervous System				
Flushing	5 (3.2)	1 (0.7)	2 (1.7)	0 (0.0)
Mouth Dry	8 (5.1)	5 (3.4)	7 (6.0)	5 (4.0)
Sweating Increased	10 (6.4)	6 (4.1)	6 (5.2)	6 (4.8)
Body As A Whole				
Asthenia	10 (6.4)	2 (1.4)	7 (6.0)	1 (0.8)
Cellulitis	2 (1.3)	0 (0.0)	2 (1.7)	0 (0.0)
Chest Pain	6 (3.8)	3 (2.0)	6 (5.2)	3 (2.4)
Drug Level Increased	7 (4.5)	4 (2.7)	7 (6.0)	4 (3.2)
Edema Dependent	10 (6.4)	5 (3.4)	9 (7.8)	5 (4.0)
Edema Legs	11 (7.0)	1 (0.7)	10 (8.6)	1 (0.8)
Fatigue	17 (10.8)	6 (4.1)	15 (12.9)	5 (4.0)
Malaise	5 (3.2)	1 (0.7)	2 (1.7)	1 (0.8)
Pain	12 (7.6)	6 (4.1)	11 (9.5)	6 (4.8)
Therapeutic Response Decreased	3 (1.9)	1 (0.7)	[redacted]	
Cardiovascular General				
Hypertension	7 (4.5)	5 (3.4)	6 (5.2)	4 (3.2)
Hypotension	3 (1.9)	0 (0.0)	[redacted]	
Hypotension Postural	10 (6.4)	7 (4.8)	9 (7.8)	6 (4.8)
Syncope	18 (11.5)	2 (1.4)	14 (12.1)	2 (1.6)
Central/Peripheral Nervous System				
Carpal Tunnel Syndrome	2 (1.3)	1 (0.7)	2 (1.7)	1 (0.8)
Dizziness	63 (40.1)	32 (21.8)	48 (41.4)	28 (22.4)
Headache	27 (17.2)	25 (17.0)	25 (21.6)	22 (17.6)
Hyperkinesia	4 (2.5)	2 (1.4)	4 (3.4)	2 (1.6)
Hypesthesia	6 (3.8)	3 (2.0)	5 (4.3)	3 (2.4)
Vertigo	3 (1.9)	0 (0.0)	2 (1.7)	0 (0.0)
Gastrointestinal System				
Abdominal Pain	10 (6.4)	4 (2.7)	7 (6.0)	3 (2.4)

Table 8.6 Emergent Adverse Experiences* Occurring in ≥1%# of Requip Treated Patients and More Frequently Than On Placebo in All Placebo-Controlled Studies and US-Placebo Controlled Studies - Early Therapy

	All Placebo-Controlled Studies		US Placebo Controlled-Studies	
	Requip N=157 n (%)	Placebo N=147 n (%)	Requip N=116 n (%)	Placebo N=125 n (%)
Anorexia	6 (3.8)	2 (1.4)	4 (3.4)	2 (1.6)
Colitis	2 (1.3)	0 (0.0)	2 (1.7)	0 (0.0)
Constipation	13 (8.3)	11 (7.5)	13 (11.2)	11 (8.8)
Dyspepsia	15 (9.6)	7 (4.8)	11 (9.5)	7 (5.6)
Dysphagia	2 (1.3)	0 (0.0)	2 (1.7)	0 (0.0)
Flatulence	4 (2.5)	2 (1.4)	3 (2.6)	2 (1.6)
Gingivitis	[redacted]		2 (1.7)	2 (1.6)
Nausea	94 (59.9)	32 (21.8)	66 (56.9)	29 (23.2)
Periodontitis	2 (1.3)	0 (0.0)	2 (1.7)	0 (0.0)
Tooth Disorder	3 (1.9)	1 (0.7)	3 (2.6)	1 (0.8)
Vomiting	19 (12.1)	10 (6.8)	13 (11.2)	8 (6.4)
Hearing/Vestibular				
Tinnitus	2 (1.3)	0 (0.0)	2 (1.7)	0 (0.0)
Heart Rate/Rhythm				
Bradycardia	[redacted]		3 (2.6)	2 (1.6)
Extrasystoles	3 (1.9)	1 (0.7)	2 (1.7)	1 (0.8)
Fibrillation Atrial	3 (1.9)	0 (0.0)	3 (2.6)	0 (0.0)
Palpitation	5 (3.2)	3 (2.0)	5 (4.3)	2 (1.6)
Tachycardia	3 (1.9)	0 (0.0)	2 (1.7)	0 (0.0)
Tachycardia Supraventricular	2 (1.3)	0 (0.0)	2 (1.7)	0 (0.0)
Liver/Biliary System				
Gamma-GT Increased	2 (1.3)	1 (0.7)	2 (1.7)	0 (0.0)
Hepatic Enzymes Increased	2 (1.3)	0 (0.0)	[redacted]	
Metabolic/Nutritional				
Hypoglycemia	2 (1.3)	0 (0.0)	2 (1.7)	0 (0.0)
Phosphatase Alkaline Increased	4 (2.5)	2 (1.4)	4 (3.4)	2 (1.6)
Musculoskeletal System				
Arthritis Aggravated	2 (1.3)	0 (0.0)	2 (1.7)	0 (0.0)
Myocardial/Endocardial/				

Table 8.6 Emergent Adverse Experiences* Occurring in ≥1%# of Requip Treated Patients and More Frequently Than On Placebo in All Placebo-Controlled Studies and US-Placebo Controlled Studies - Early Therapy

	All Placebo-Controlled Studies		US Placebo Controlled-Studies	
	Requip N=157 n (%)	Placebo N=147 n (%)	Requip N=116 n (%)	Placebo N=125 n (%)
Pericardial Valve				
Myocardial Ischemia	2 (1.3)	1 (0.7)	2 (1.7)	1 (0.8)
Neoplasm				
Basal Cell Carcinoma	[redacted]		2 (1.7)	2 (1.6)
Platelet Bleeding/Clotting				
Purpura	2 (1.3)	0 (0.0)	2 (1.7)	0 (0.0)
Psychiatric				
Agitation	2 (1.3)	1 (0.7)	2 (1.7)	1 (0.8)
Amnesia	4 (2.5)	2 (1.4)	4 (3.4)	2 (1.6)
Concentration Impaired	3 (1.9)	0 (0.0)	3 (2.6)	0 (0.0)
Confusion	8 (5.1)	2 (1.4)	8 (6.9)	2 (1.6)
Hallucination	8 (5.1)	2 (1.4)	7 (6.0)	2 (1.6)
Illusion	2 (1.3)	0 (0.0)	2 (1.7)	0 (0.0)
Insomnia	[redacted]		16 (13.8)	17 (13.6)
Somnolence	63 (40.1)	9 (6.1)	50 (43.1)	9 (7.2)
Yawning	5 (3.2)	0 (0.0)	[redacted]	
Reproductive Male				
Impotence	4 (2.5)	2 (1.4)	3 (2.6)	2 (1.6)
Prostatic Disorder	[redacted]		2 (1.7)	2 (1.6)
Resistance Mechanism				
Infection Viral	17 (10.8)	5 (3.4)	12 (10.3)	4 (3.2)
Respiratory System				
Bronchitis	4 (2.5)	2 (1.4)	4 (3.4)	2 (1.6)
Dyspnea	5 (3.2)	0 (0.0)	3 (2.6)	0 (0.0)
Pharyngitis	10 (6.4)	6 (4.1)	8 (6.9)	5 (4.0)
Pneumonia	2 (1.3)	1 (0.7)	2 (1.7)	1 (0.8)
Respiratory Disorder	3 (1.9)	2 (1.4)	[redacted]	
Rhinitis	6 (3.8)	4 (2.7)	4 (3.4)	4 (3.2)
Sinusitis	6 (3.8)	4 (2.7)	6 (5.2)	4 (3.2)
Urinary System				
Cystitis	2 (1.3)	1 (0.7)	[redacted]	
Hematuria	[redacted]		2 (1.7)	2 (1.6)

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Table 8.6 Emergent Adverse Experiences* Occurring in ≥1%# of Requip Treated Patients and More Frequently Than On Placebo in All Placebo-Controlled Studies and US-Placebo Controlled Studies - Early Therapy

	All Placebo-Controlled Studies		US Placebo Controlled-Studies	
	Requip N=157 n (%)	Placebo N=147 n (%)	Requip N=116 n (%)	Placebo N=125 n (%)
Urinary Retention	2 (1.3)	1 (0.7)	2 (1.7)	1 (0.8)
Urinary Tract Infection	8 (5.1)	6 (4.1)	7 (6.0)	5 (4.0)
Vascular Extracardiac				
Peripheral Ischemia	4 (2.5)	0 (0.0)	4 (3.4)	0 (0.0)
Vision				
Eye Abnormality	5 (3.2)	2 (1.4)	5 (4.3)	2 (1.6)
Vision Abnormal	9 (5.7)	5 (3.4)	6 (5.2)	5 (4.0)
Xerophthalmia	3 (1.9)	0 (0.0)	3 (2.6)	0 (0.0)

* Patients may have reported multiple adverse experiences during the study or at discontinuation; thus, patients may be included in more than one category

Shaded events failed to meet an incidence of ≥1% in Requip-treated patients

Data Source Tables A8.3, A8.4

Table 8.7 Emergent Adverse Experiences* Occurring in ≥1%# of Requip Treated Patients and More Frequently Than On Placebo in All Placebo-Controlled Studies and US Placebo-Controlled Adjunct Therapy Studies

	All Placebo-Controlled Studies		US Placebo-Controlled Studies	
	Requip N=208 n (%)	Placebo N=120 n (%)	Requip N=95 n (%)	Placebo N=54 n (%)
Autonomic Nervous System				
Flushing	3 (1.4)	1 (0.8)	[redacted]	
Mouth Dry	11 (5.3)	1 (0.8)	6 (6.3)	1 (1.9)
Sweating Increased	15 (7.2)	2 (1.7)	7 (7.4)	1 (1.9)
Body As A Whole				
Chest Pain	[redacted]		4 (4.2)	2 (3.7)
Chest Pain Substernal			1 (1.1)	0 (0.0)
Drug Level Increased	14 (6.7)	4 (3.3)	13 (13.7)	4 (7.4)
Edema Dependent	6 (2.9)	3 (2.5)	[redacted]	
Edema Peripheral	2 (1.0)	0 (0.0)	1 (1.1)	0 (0.0)
Fever	3 (1.4)	0 (0.0)	1 (1.1)	0 (0.0)
Influenza-Like Symptoms	2 (1.0)	0 (0.0)	2 (2.1)	0 (0.0)
Injury	22 (10.6)	11 (9.2)	14 (14.7)	6 (11.1)
Malaise	3 (1.4)	1 (0.8)	1 (1.1)	0 (0.0)
Pain	11 (5.3)	4 (3.3)	9 (9.5)	3 (5.6)
Pallor	2 (1.0)	1 (0.8)	[redacted]	
Rigors	2 (1.0)	1 (0.8)		
Cardiovascular General				
Cardiac Failure	2 (1.0)	0 (0.0)	2 (2.1)	0 (0.0)
ECG Abnormal Specific	[redacted]		1 (1.1)	0 (0.0)
Hypertension	7 (3.4)	4 (3.3)	[redacted]	
Hypotension	5 (2.4)	1 (0.8)	3 (3.2)	0 (0.0)
Syncope	6 (2.9)	2 (1.7)	3 (3.2)	0 (0.0)
Central/Peripheral Nervous System				
Aphasia	[redacted]		1 (1.1)	0 (0.0)
Ataxia	20 (9.6)	8 (6.7)	20 (21.1)	7 (13.0)
Choreoathetosis	[redacted]		1 (1.1)	0 (0.0)
Dizziness	54 (26.0)	19 (15.8)	22 (23.2)	7 (13.0)
Dyskinesia	70 (33.7)	15 (12.5)	38 (40.0)	9 (16.7)
Dysphonia	[redacted]		1 (1.1)	0 (0.0)

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Table 8.7 Emergent Adverse Experiences* Occurring in ≥1%# of Requip Treated Patients and More Frequently Than On Placebo in All Placebo-Controlled Studies and US Placebo-Controlled Adjunct Therapy Studies

	All Placebo-Controlled Studies		US Placebo-Controlled Studies	
	Requip N=208 n (%)	Placebo N=120 n (%)	Requip N=95 n (%)	Placebo N=54 n (%)
Dystonia	9 (4.3)	5 (4.2)	6 (6.3)	3 (5.6)
Headache	35 (16.8)	14 (11.7)	11 (11.6)	6 (11.1)
Hypesthesia	[redacted]		1 (1.1)	0 (0.0)
Hypokinesia	11 (5.3)	5 (4.2)	6 (6.3)	3 (5.6)
Muscle Contractions Involuntary	2 (1.0)	0 (0.0)	1 (1.1)	0 (0.0)
Paresis	6 (2.9)	0 (0.0)	4 (4.2)	0 (0.0)
Paresthesia	11 (5.3)	3 (2.5)	8 (8.4)	2 (3.7)
Parkinsonism Aggravated	44 (21.2)	25 (20.8)	30 (31.6)	17 (31.5)
Speech Disorder	2 (1.0)	0 (0.0)	2 (2.1)	0 (0.0)
Tremor	13 (6.3)	3 (2.5)	9 (9.5)	2 (3.7)
Gastrointestinal System				
Abdominal Pain	18 (8.7)	9 (7.5)	[redacted]	
Constipation	12 (5.8)	4 (3.3)	8 (8.4)	1 (1.9)
Diarrhea	10 (4.8)	3 (2.5)	5 (5.3)	1 (1.9)
Diverticulitis	[redacted]		1 (1.1)	0 (0.0)
Dysphagia	5 (2.4)	1 (0.8)	4 (4.2)	1 (1.9)
Eructation	3 (1.4)	0 (0.0)	2 (2.1)	0 (0.0)
Esophageal Stricture	[redacted]		1 (1.1)	0 (0.0)
Esophagitis	[redacted]		1 (1.1)	0 (0.0)
Fecal Incontinence	2 (1.0)	0 (0.0)	2 (2.1)	0 (0.0)
Flatulence	4 (1.9)	1 (0.8)	2 (2.1)	0 (0.0)
Gastroenteritis	2 (1.0)	1 (0.8)	2 (2.1)	1 (1.9)
Gastroesophageal Reflux	2 (1.0)	0 (0.0)	2 (2.1)	0 (0.0)
Gastrointestinal Disorder Nos	2 (1.0)	0 (0.0)	1 (1.1)	0 (0.0)
Hemorrhoids	2 (1.0)	0 (0.0)	1 (1.1)	0 (0.0)
Nausea	62 (29.8)	22 (18.3)	22 (23.2)	8 (14.8)
Pancreatitis	[redacted]		1 (1.1)	0 (0.0)
Periodontitis	3 (1.4)	1 (0.8)	[redacted]	
Saliva Altered	[redacted]		1 (1.1)	0 (0.0)
Saliva Increased	5 (2.4)	1 (0.8)	[redacted]	

Table 8.7 Emergent Adverse Experiences* Occurring in ≥1%# of Requip Treated Patients and More Frequently Than On Placebo in All Placebo-Controlled Studies and US Placebo-Controlled Adjunct Therapy Studies

	All Placebo-Controlled Studies		US Placebo-Controlled Studies	
	Requip N=208 n (%)	Placebo N=120 n (%)	Requip N=95 n (%)	Placebo N=54 n (%)
Tenesmus			1 (1.1)	0 (0.0)
Tongue Disorder			1 (1.1)	0 (0.0)
Tongue Edema			1 (1.1)	0 (0.0)
Tooth Ache	2 (1.0)	0 (0.0)	1 (1.1)	0 (0.0)
Tooth Disorder	2 (1.0)	1 (0.8)	2 (2.1)	1 (1.9)
Vomiting	15 (7.2)	5 (4.2)	4 (4.2)	1 (1.9)
Hearing/Vestibular				
Hyperacusis			1 (1.1)	0 (0.0)
Vestibular Disorder			1 (1.1)	0 (0.0)
Heart Rate/Rhythm				
Bradycardia	2 (1.0)	0 (0.0)	1 (1.1)	0 (0.0)
Extrasystoles			1 (1.1)	0 (0.0)
Extrasystoles Supraventricular	2 (1.0)	1 (0.8)		
Palpitation	6 (2.9)	3 (2.5)	2 (2.1)	1 (1.9)
Tachycardia	2 (1.0)	0 (0.0)	1 (1.1)	0 (0.0)
Liver/Biliary System				
Cholecystitis			1 (1.1)	0 (0.0)
Gamma-GT Increased	2 (1.0)	0 (0.0)	1 (1.1)	0 (0.0)
Metabolic/Nutritional				
Hypokalemia			1 (1.1)	0 (0.0)
Phosphatase Alkaline Increased	2 (1.0)	0 (0.0)	2 (2.1)	0 (0.0)
Weight Decrease	5 (2.4)	1 (0.8)	4 (4.2)	1 (1.9)
Musculoskeletal System				
Arthralgia	14 (6.7)	6 (5.0)	12 (12.6)	5 (9.3)
Arthritis	6 (2.9)	1 (0.8)	1 (1.1)	0 (0.0)
Arthritis Aggravated	3 (1.4)	0 (0.0)	2 (2.1)	0 (0.0)
Back Pain			6 (6.3)	3 (5.6)
Myositis			1 (1.1)	0 (0.0)
Osteoporosis			1 (1.1)	0 (0.0)
Tendinitis			1 (1.1)	0 (0.0)

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Table 8.7 Emergent Adverse Experiences* Occurring in ≥1%# of Requip Treated Patients and More Frequently Than On Placebo in All Placebo-Controlled Studies and US Placebo-Controlled Adjunct Therapy Studies

	All Placebo-Controlled Studies		US Placebo-Controlled Studies	
	Requip N=208 n (%)	Placebo N=120 n (%)	Requip N=95 n (%)	Placebo N=54 n (%)
Myocardial/Endocardial/ Pericardial Valve				
Myocardial Infarction	2 (1.0)	1 (0.8)	1 (1.1)	0 (0.0)
Myocardial Ischemia	[redacted]		1 (1.1)	0 (0.0)
Neoplasm				
Neoplasm Nos	2 (1.0)	0 (0.0)	2 (2.1)	0 (0.0)
Psychiatric				
Agitation	2 (1.0)	0 (0.0)	[redacted]	
Amnesia	10 (4.8)	1 (0.8)	8 (8.4)	1 (1.9)
Anxiety	13 (6.3)	4 (3.3)	6 (6.3)	1 (1.9)
Apathy	2 (1.0)	0 (0.0)	[redacted]	
Concentration Impaired	2 (1.0)	0 (0.0)	1 (1.1)	0 (0.0)
Confusion	18 (8.7)	2 (1.7)	11 (11.6)	0 (0.0)
Depersonalization	3 (1.4)	0 (0.0)	2 (2.1)	0 (0.0)
Depression Aggravated	[redacted]		1 (1.1)	0 (0.0)
Dreaming Abnormal	6 (2.9)	2 (1.7)	6 (6.3)	2 (3.7)
Hallucination	21 (10.1)	5 (4.2)	15 (15.8)	4 (7.4)
Illusion	[redacted]		1 (1.1)	0 (0.0)
Insomnia	30 (14.4)	17 (14.2)	[redacted]	
Libido Increased	2 (1.0)	0 (0.0)		
Nervousness	10 (4.8)	3 (2.5)	8 (8.4)	3 (5.6)
Paranoid Reaction	3 (1.4)	0 (0.0)	3 (3.2)	0 (0.0)
Paroniria	4 (1.9)	2 (1.7)	[redacted]	
Personality Disorder	2 (1.0)	0 (0.0)		
Psychosis	[redacted]		1 (1.1)	0 (0.0)
Sleep Disorder			1 (1.1)	0 (0.0)
Somnolence	42 (20.2)	10 (8.3)	20 (21.1)	6 (11.1)
Suicide Attempt	[redacted]		1 (1.1)	0 (0.0)
Thinking Abnormal	3 (1.4)	1 (0.8)	[redacted]	
Yawning	[redacted]		1 (1.1)	0 (0.0)
Red Blood Cell				

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Table 8.7 Emergent Adverse Experiences* Occurring in ≥1%# of Requip Treated Patients and More Frequently Than On Placebo in All Placebo-Controlled Studies and US Placebo-Controlled Adjunct Therapy Studies

	All Placebo-Controlled Studies		US Placebo-Controlled Studies	
	Requip N=208 n (%)	Placebo N=120 n (%)	Requip N=95 n (%)	Placebo N=54 n (%)
Anemia	5 (2.4)	0 (0.0)	4 (4.2)	0 (0.0)
Reproductive Male				
Impotence	[redacted]		1 (1.1)	0 (0.0)
Penis Disorder	2 (1.0)	0 (0.0)	1 (1.1)	0 (0.0)
Prostatic Disorder	2 (1.0)	0 (0.0)	2 (2.1)	0 (0.0)
Resistance Mechanism				
Infection Viral	15 (7.2)	8 (6.7)	[redacted]	
Moniliasis	2 (1.0)	1 (0.8)		
Sepsis	[redacted]		1 (1.1)	0 (0.0)
Upper Respiratory Tract Infection	18 (8.7)	10 (8.3)	15 (15.8)	8 (14.8)
Respiratory System				
Bronchitis	[redacted]		1 (1.1)	0 (0.0)
Coughing	3 (1.4)	1 (0.8)	[redacted]	
Dyspnea	6 (2.9)	2 (1.7)	5 (5.3)	2 (3.7)
Pleurisy	[redacted]		1 (1.1)	0 (0.0)
Pneumonia	2 (1.0)	1 (0.8)	2 (2.1)	1 (1.9)
Respiratory Disorder	4 (1.9)	0 (0.0)	1 (1.1)	0 (0.0)
Skin/Appendages				
Dermatitis Fungal	[redacted]		1 (1.1)	0 (0.0)
Pruritus	2 (1.0)	0 (0.0)	1 (1.1)	0 (0.0)
Rash	4 (1.9)	2 (1.7)	4 (4.2)	1 (1.9)
Rash Erythematous	2 (1.0)	1 (0.8)	2 (2.1)	0 (0.0)
Seborrhea	[redacted]		1 (1.1)	0 (0.0)
Special Senses Other				
Taste Perversion	[redacted]		1 (1.1)	0 (0.0)
Urinary System				
Dysuria	2 (1.0)	0 (0.0)	2 (2.1)	0 (0.0)
Micturition Frequency	3 (1.4)	0 (0.0)	2 (2.1)	0 (0.0)
Nocturia	[redacted]		1 (1.1)	0 (0.0)
Pyuria	4 (1.9)	1 (0.8)	4 (4.2)	1 (1.9)

Table 8.7 Emergent Adverse Experiences* Occurring in ≥1%# of Requip Treated Patients and More Frequently Than On Placebo in All Placebo-Controlled Studies and US Placebo-Controlled Adjunct Therapy Studies

	All Placebo-Controlled Studies		US Placebo-Controlled Studies	
	Requip N=208 n (%)	Placebo N=120 n (%)	Requip N=95 n (%)	Placebo N=54 n (%)
Urinary Incontinence	4 (1.9)	1 (0.8)	3 (3.2)	1 (1.9)
Urinary Tract Infection	13 (6.3)	3 (2.5)	9 (9.5)	1 (1.9)
Urine Abnormal	[redacted]		1 (1.1)	0 (0.0)
Vision				
Cataract	3 (1.4)	1 (0.8)	3 (3.2)	1 (1.9)
Diplopia	4 (1.9)	1 (0.8)	3 (3.2)	1 (1.9)
Eye pain	[redacted]		1 (1.1)	0 (0.0)
Lacrimation Abnormal	3 (1.4)	0 (0.0)	3 (3.2)	0 (0.0)
Xerophthalmia	3 (1.4)	1 (0.8)	2 (2.1)	1 (1.9)
White Cell /Reticuloendothelial System				
Eosinophilia	3 (1.4)	0 (0.0)	3 (3.2)	0 (0.0)
Lymphadenopathy	[redacted]		1 (1.1)	0 (0.0)

*Patients may have reported multiple adverse experiences during the study or at discontinuation; thus, patients may be included in more than one category

Shaded events failed to meet an incidence of ≥1% in Requip treated patients

Data Source Tables A8.7, A8.8

Table 13.2 Relative Risk for Patients with and without CVD in Study 054/05

Adverse Experience[1]	With CVD (N=70) RR	With CVD (N=70) 95% CI for RR	Without CVD (N=171) RR	Without CVD (N=171) 95% CI for RR
Arthralgia	1.37	0.21, 8.74	0.78	0.31, 1.94
Ataxia	0.57	0.09, 3.65	0.76	0.21, 2.81
Back pain	6.19	0.70, 54.46	0.50	0.18, 1.38
Chest pain	2.82	0.28, 28.56	1.78	0.29, 10.91
Constipation	0.88	0.17, 4.71	1.52	0.57, 4.07
Cramps legs	0.32	0.06, 1.78	1.17	0.16, 8.50
Dizziness	7.62	1.97, 29.49	1.82	0.96, 3.47
Dyskinesia	1.83	0.16, 21.15	0.36	0.10, 1.39
Dyspepsia	2.82	0.28, 28.56	1.62	0.54, 4.87
Edema dependent	5.00	0.55, 45.23	1.17	0.28, 4.85
Fatigue	5.00	0.55, 45.23	3.19	0.96, 10.60
Headache	0.86	0.29, 2.51	1.54	0.69, 3.45
Hypotension postural	3.88	0.41, 36.60	1.18	0.33, 4.22
Infection viral	2.42	0.44, 13.43	4.38	0.88, 21.71
Injury	0.20	0.02, 1.90	1.18	0.36, 3.81
Insomnia	1.08	0.30, 3.95	0.97	0.39, 2.37
Mouth dry	0.89	0.12, 6.67	2.00	0.46, 8.67
Myalgia	1.83	0.16, 21.15	0.56	0.16, 1.94
Nausea	4.75	1.59, 14.19	4.41	2.30, 8.45
Nervousness	0.89	0.05, 14.80	0.76	0.21, 2.81
Pain	0.88	0.17, 4.71	3.34	0.86, 13.06
Sinusitis	0.89	0.05, 14.80	2.00	0.46, 8.67

Table 13.2 Relative Risk for Patients with and without CVD in Study 054/055

	With CVD (N=70)		Without CVD (N=171)	
Adverse Experience[1]	**RR**	**95% CI for RR**	**RR**	**95% CI for RR**
Somnolence	10.57	2.19, 50.97	9.66	3.97, 23.51
Sweating increased	0.89	0.12, 6.67	1.17	0.28, 4.85
Tremor	1.83	0.16, 21.15	0.19	0.05, 0.67
URTI	4.28	0.84, 21.83	0.72	0.35, 1.48
Urinary tract infection	0.89	0.05, 14.81	1.81	0.49, 6.65
Vomiting	6.19	0.70, 54.46	1.18	0.40, 3.52
Body systems				
Heart rate and rhythm	0.64	0.13, 3.10	8.06	1.75, 37.22
Myocardial Endocardial Pericardial Valve	0.41	0.07, 2.43	0.38	0.04, 3.73

SAS Data Source Table A16.5

[1]For the adverse experiences, drug level increased, syncope, abdominal pain, diarrhea, anxiety, confusion, depression, hallucinations, pharyngitis, micturition frequency, vision abnormal, leg edema, and hypertension, relative risk could not be calculated because no patients in one of the groups reported these experiences.

Table 8.1 Adverse Event Term Enhancements in the Requip Clinical Program

Term	Normal WHOART preferred term	Enhancement	Requip WHOART preferred term
Freezing	Rigors	Worsening of PD	Parkinsonism aggravated
Rigidity	Hypokinesia	Worsening of PD	Parkinsonism aggravated
Stiffness (excl. joints)	Arthrosis	Worsening of PD	Parkinsonism aggravated
Stiffness	Hypokinesia	Worsening of PD	Parkinsonism aggravated
Shuffling gait	Gait abnormal	Worsening of PD	Parkinsonism aggravated
Jerking or twitching movements	Muscle contractions involuntary	Dyskinesias	Dyskinesias
Falls	Injury	Postural instability	Ataxia
Falling	Syncope	Postural instability	Ataxia
Postural or orthostatic dizziness or lightheadedness	Dizziness	Postural hypotension	Postural hypotension
Orthostasis	Dizziness	Postural hypotension	Postural hypotension
Dizziness on standing	Dizziness	Postural hypotension	Postural hypotension
Postural or orthostatic vertigo	Vertigo	Postural hypotension	Postural hypotension
Pre syncope or near syncope	Syncope	Dizziness	Dizziness

Table 8.2 Selected Preferred Terms and the Frequency of Enhancement from Categories of Verbatim Terms

Preferred Term	No. Patients With Event	No. Enhanced Terms	Categories of Verbatim Terms Enhanced
Postural Hypotension	146	76	62 - orthostatic dizziness
			14 - postural HT
Ataxia	128	132	122 - Falls
			10 - Balance problems
Syncope	91	20	12 - LOC[a]/fainting
			8 - Nonspecific[b]
Confusion	105	13	11 - delirium, disorientation
			2 - Nonspecific[c]
Hallucination	162	9	9 - Nonspecific[d]

Data Source Table A6.1

a. LOC = loss of consciousness

b. altered consciousness, lipothymic malaise, probable hypotension

c. muddled feeling (1), increase in CNS effects (1)

d. seeing bugs (1), familial presence (4), seeing shadows (4)

Table 13.9 Ocular Abnormalities Reported in Studies 054 and 032

Patient No.	Verbatim Term	History of ophthamologic problems
054/Requip		
054.016.00156	Decreased depth perception	none
	Difficulty focusing with eye	
054.025.00062	Right eye twitch	hazy vision
054.001.00026	Cataract left eye-lens implant	none
054.015.00160	Nausea "woozy" eyes tearing profusely	seasonal allergies
054.021.00019	Blurred vision	none
	Car lights bother at night	
054.001.00025	Brief flashes of light in right eye	none
054.005.00123	Visual floaters	none
	Visual distortions	
054.010.00164	Visual disturbances	none
054.011.00007	Visual distortion	none
054.022.00023	Floaters right eye	
	Flashing lights right eye	none
054.003.00082	Dry eyes	none
054.003.00099	Dry eyes	none
054.011.00096	Dry eyes	none
054/Placebo		
054.002.00277	Cataract surgery (outpatient/surgery)	cataracts
054.009.00089	Decreased night vision (cataract)	none
054.018.00142	Cataract right eye	cataract right eye
054.023.00044	Left eye infection	none
054.025.00016	Eyelids heavy	none
	Vision eyes feel unfocused	
054.003.00081	Glaucoma	diabetes

Table 13.9 Ocular Abnormalities Reported in Studies 054 and 032

Patient No.	Verbatim Term	History of ophthamologic problems
054/Placebo		
054.026.00293	Glaucoma	none
054.021.00017	Photophobia	none
032/Requip		
032.009.00100	Blurred vision	none
032.009.00105	Blurred vision left eye	none
032.010.00115	Felt tired, weak with very transient visual disturbance	none

Data Source : Appendix D