Cutoff 12/31/96	48	2	50
All Deaths thru 3/31/97	55	2	57
Deaths >30 days from last dose	24	1	25

Information on 49 of these deaths (the 48 deaths occurring by 12/31/96, plus an additional one) was available in the original NDA submission, and I reviewed the case report forms (CRF's) these deaths individually (section 8.2.3, Individual Deaths, 32). In addition, I reviewed the patient narratives for the additional deaths included in the 120 day safety update which were not reported in the NDA. The causes of death were varied, and typical of those seen in an elderly population.

The sponsor reports that the overall Exelon drug exposure in the NDA, including data from the120 day safety update, is 2354 patient-years, and for placebo is 481 patient-years (using the sponsor's numbers). Based on these numbers, the mortality rate is 20.4 per 1000 years for Exelon (48/2554 x 1000) and for placebo is 4.22 (2/481 x 1000). This continues to show an increased mortality rate in patients on Exelon compared to placebo, as also demonstrated in the NDA.

8.18.4 Serious Adverse Events

In all therapeutic studies (N=4218), 19% of patients reported at least one SAE (Exelon 19%, vs. placebo 13%). A relationship between incidence of SAE and Exelon dose was detected only with the highest dose group (>9-12 mg/d). The incidence of SAE's in this dose group was 24% compared with 13% in the placebo group. In phase 3 controlled studies (N=2791), 15% of patients experienced an SAE (15% for both Exelon and placebo). These findings are similar to those reported in the ISS (14% Exelon vs. 16% placebo). The incidence of SAE's in uncontrolled trials was 15% (same as reported in the ISS), but the SAE incidence in patients treated up to 78 weeks (n=609) was 25%. It indicates that the increased in SAE's seen in the entire study population is due to SAE's experienced during long term, open label treatment. This can be explained by the notion that the extended duration of treatment extends the time during which patients were at risk for the development of an SAE, since the incidence of SAE in controlled trials were the same between the treatment and placebo groups. The long term SAE data come from patients in uncontrolled trials, therefore no comparison can be made with a background rate in this population.

The sponsor does not break down the SAE's according to those which were reported in the ISS vs. those which were new since the NDA submission. Instead, only the new total is given. The actual types serious adverse events reported in the 120 day safety update were similar to those reported in the ISS. There were no new, unexpected reports. There were some differences noted, however, and I outline them briefly below.

The incidence of syncope was higher in the 120 day safety report (Exelon 0.7% vs. placebo 0.2%). The overall incidence of syncope (serious and non-serious AE's) was 3% for Exelon and 1% for placebo. In controlled trials, the incidence of syncope as an SAE was 1.1% vs. 0.5% for placebo. A similar incidence was reported in the ISS (1.2% vs. 0.5%).

A total of 17 patients on Exelon (0.5%) reported gastrointestinal hemorrhages in all therapeutic trials (N=4218), compared with 6 patients reported in the ISS. Ten of the 17 patients were in the high dose group (>9-12mg/d). Ten (10) of the 17 were upper gastrointestinal hemorrhages. Nine (9) of the 10 had no prior history of upper gastrointestinal bleeding. Five had been taking non-steroidal anti-inflammatory medications or corticosteroids before the bleeding occurred.

In summary, an increase in incidence of SAE's in the Exelon group compared with the placebo groups was detected in all therapeutic studies. This difference is attributable to the additional SAE's reported during the long-term extension studies (78 week data, 25% incidence), which have no placebo control group. In addition, no newly occurring or unusual SAE's were experienced by Exelon patients.

8.18.5 Adverse Dropouts (ADO)

As is the case throughout the safety update, the sponsor does not break down the ADO's according to those which were reported in the ISS vs. those which were new since the NDA submission. Instead, only the new total is given. In all therapeutic studies (N=4218) in the 120 day safety update, 19% of Exelon patients withdrew because of an adverse events, compared with 8% of placebo. In the original NDA, 16% of Exelon patients discontinued vs. 7% of placebo. The updated numbers are comparable to those reported in the NDA and continue to indicate that patients on Exelon discontinued treatment at slightly more than twice the rate of placebo patients. The majority of events were due to gastrointestinal AE's experienced during the forced titration phase of the studies. As reported in the NDA, very few patients discontinued because of an abnormal laboratory test result (<1%). As in the NDA, an increase in Exelon dose was associated with an increased rate of ADO's. This was especially apparent on the 78 week data.

The overall rate of ADO's was higher in the 78 week dataset compared to the 52 week dataset (16% vs. 12%) and is most probably due to the fact that with time and increasing age, patients are more likely to develop illnesses leading to discontinuation which are then mistakenly classified as ADO's.

8.18.6 Common Adverse Events

The pattern of adverse events reported for the 120 day safety update was similar to that found for the ISS. Notwithstanding amount of additional patient data included in the 120 day safety update, most of which was from uncontrolled phase 3 studies, the incidence of AE's in the Exelon patients were increased only slightly beyond those reported for the ISS. The slight increase stems from uncontrolled Exelon exposures over a long period. Table 97 is an updated version of Table 30: Common Adverse Events in All Therapeutic Studies, which is located on page 53. It shows all common adverse events, defined as occurring with an incidence of ≥10% in Exelon patients.

Table 97: Common Adverse Events (≥10%), 120 Day Safety Update, All Therapeutic Studies

	ISS DATA						120 Day Safety Update Totals					
	Exelon N =3006		Placebo N = 983		Total N =3886		Exelon N =3715		Placebo N = 1088		Total N =4218	
Body System/ Preferred Term	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
At Least One Adverse Event	2464	(82)	708	(72)	3172	(82)	3240	(87)	791	(73)	3599	(85)
CNS and PNS Disorders	1093	(36)	234	(24)	1327	(34)	1522	(41)	256	(24)	1678	(40)
DIZZINESS	571	(19)	102	(10)	673	(17)	826	(22)	107	(10)	894	(21)
HEADACHE	456	(15)	115	(12)	571	(15)	631	(17)	124	(11)	716	(17)
GASTROINTESTINAL DIS.	1719	(57)	303	(31)	2022	(52)	2458	(66)	345	(32)	2640	(63)
NAUSEA	1147	(38)	103	(10)	1250	(32)	1687	(45)	118	(11)	1765	(42)
VOMITING	682	(23)	49	(5)	731	(19)	1049	(28)	56	(5)	1094	(26)
DIARRHEA	452	(15)	93	(9)	545	(14)	668	(18)	107	(10)	474	(18)
ABDOMINAL PAIN	317	(11)	62	(6)	379	(10)	468	(13)	65	(6)	523	(12)
ANOREXIA	344	(11)	25	(3)	369	(9)	582	(16)	30	(3)	603	(14)
PSYCHIATRIC DISORDERS	902	(30)	239	(24)	1141	(29)	1377	(37)	267	(25)	1540	(37)
AGITATION	242	(8)	66	(7)	308	(8)	437	(12)	267	(25)	491	(12)
INSOMNIA	232	(8)	55	(6)	287	(7)	360	(10)	60	(6)	401	(10)
ACCIDENTAL TRAUMA	*	*	*	*	*	*	370	(10)	83	(8)	443	(11)

* not reported

The analogous table of common adverse events in controlled studies differs from the one reported in the ISS in that it includes an additional 332 patients from B304. The updated table is shown in Table 98 below. The percentages differ little from those seen in the ISS. As in the ISS, AE's were more common in females than in males, and most newly emergent AE's occurred during the titration phase.

Table 98: Common Adverse Events (≥10%), 120 Day Safety Update, Controlled Clinical Trials

Adverse Event	All Exelon N= 1923 n (%)	Exelon >9-12 mg/ d N= 611 n (%)	Placebo N= 868 n (%)	Total N= 2791 n (%)
At Least One Adverse Event	*1677 (87)*	*547 (90)*	*687 (79)*	*2364 (85)*
Central/ Peripheral Nervous System	*699 (36)*	*230 (38)*	*224 (26)*	*923 (33)*
Dizziness	364 (19)	108 (18)	95 (11)	459 (16)
Headache	297 (15)	99 (16)	107 (12)	404 (14)
Gastrointestinal System Disorders	*1152 (60)*	*403 (66)*	*300 (35)*	*1452 (52)*
Nausea	718 (37)	267 (44)	105 (12)	823 (29)
Vomiting	445 (23)	176 (29)	49 (6)	494 (18)
Diarrhea	307 (16)	117 (19)	99 (11)	406 (15)
Anorexia	257 (13)	111 (18)	27 (3)	284 (10)
Abdominal Pain	209 (11)	73 (12)	51 (6)	260 (9)

8.18.7 Nausea

As in the ISS, nausea was the most common AE reported and it occurred four times more often in Exelon patients (45%) compared with placebo (11%). Despite the frequency of this AE, only 3% of the nausea episodes were rated as severe. In most cases (~60%), the nausea resolved with dose reduction, dose skipping, or dose holding and in only 6% of cases was it a reason for discontinuation. In 80% of cases, nausea consisted of 1 or 2 episodes, with the median duration being 2-3 days and it was more frequent during the titration phase than during maintenance.

8.18.8 Laboratory Findings

Review of lab data from patients treated up to 18 months (including liver and kidney function) did not detect any treatment associated effects or organ toxicity≥ Both analysis of mean values, as well as analysis of clinically notable abnormalities were performed. Results were similar to those seen in the ISS.

8.18.9 ECG

The ECG findings in the 120 day safety update were similar to those reported in the ISS. A large percentage of patients (15-20%) experienced new abnormalities or worsening of their pre existing ECG findings. However, with up to 26 weeks of treatment, no clinically relevant differences were detected between Exelon and placebo in the proportion of patients with new c worsening ECG abnormalities (Exelon 16%, placebo 14%). There was a marginal increase to 20% in the incidence of abnormalities with exposure up to 18 months, probably reflecting a no specific consequence of the aging of the population, although this is not exactly known, as no placebo group was studied.

Only minimal changes associated with Exelon were seen, such as heart rate reduction of 1.1 bpm, or decrease in QTc interval of 2 msec. Specialized categorical analyses of the maximu increase from baseline in the PR QRS and QTc intervals for age, stratified by decade, gend

race and maximum prescribed dose indicated no difference in the proportion of patients experiencing maximal change in these intervals.

8.18.10 Vital Signs

There were no clinically meaningful effects of Exelon on pulse, blood pressure, respiratory rate, or body temperature with up to 18 months of treatment. Rapid titration was not associated with any additional vital sign risk when compared to slow titration rates. This indicates that routine monitoring of these parameters should not be required in patients treated with Exelon.

8.18.11 Long Term Safety and Tolerability

Only patients who received double-blind Exelon during short term treatment in the phase 3 controlled studies who then entered a long term extension were analyzed for long term safety. There were a total of 1099 patients treated 27-52 weeks, and 304 of these had data out to 53-78 weeks. Adverse events were more likely during titration (weeks 1-12) and re-titration (weeks 27-36). The incidence of AE's dropped after week 52 when maintenance conditions were present. The most frequent AE's were the same as those seen in the larger safety population: nausea, vomiting, abdominal pain, dizziness, and anorexia. Clinically notable weight decrease in long term study was more closely associated with anorexia than with nausea and/or vomiting.

Anorexia and weight decrease tended to increase with age, while nausea, vomiting, and abdominal pain tended to decrease with age. The incidence of newly emergent cases of anorexia during long term treatment (weeks 27-52) was comparable with that observed during short term treatment (weeks 1-26), while newly emergent cases of nausea, vomiting, and abdominal pain declined during long term treatment (weeks 27-52).

In general, no new or unexpected findings were observed with long term treatment with Exelon. In particular, there continued to be no evidence of systematic liver dysfunction over the long term.

8.18.12 Overdose

As in the ISS, overdose was defined liberally as any dose taken in excess of the prescribed dose, whether or not it led to an adverse event. Using this definition, 162 of 3,067 Exelon patients (5%) experienced 198 overdoses (some overdosed more than once). Of the 198 overdoses, 62 patients experienced 70 symptomatic overdoses (35%).

Not unexpectedly, the most notable AE associated with an overdose was nausea (45; 64%), and vomiting (43; 61%), followed by diarrhea (14%), dizziness (7%), sweating (7%), and confusion (7%). In general, these were not treated and patients were simply instructed to skip the next scheduled dose until all symptoms had subsided.

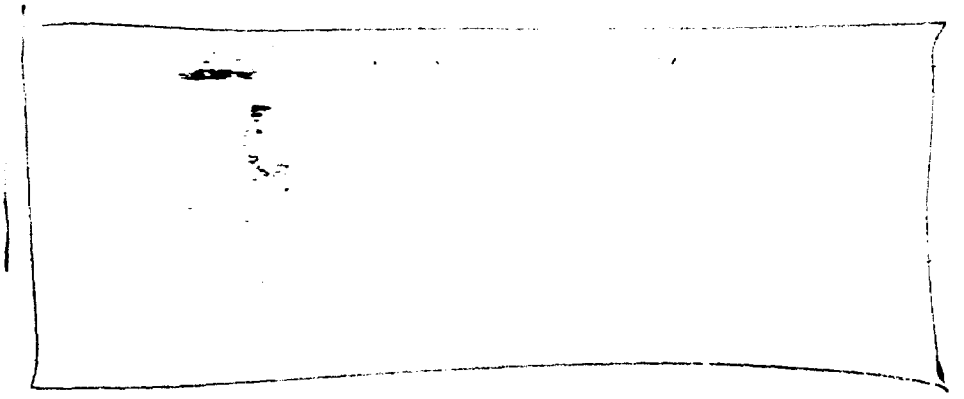
There were 6 (%) overdose events that required specific treatment of the associated symptoms. Treatment consisted of an anti-emetic (3), anti-emetic plus i.v. fluids (1), i.v. fluids and naloxone (1) and i.v. fluids alone (1).

9. Labeling Review

A comprehensive review of the proposed labeling beginning with "Indications and Usage" is provided below. Sponsor proposed labeling, submitted at the time of the 120 day safety update (8/27/97) is presented in standard text. Strike-through text indicates text which, in this reviewer's opinion, should be deleted. My recommended additions to labeling are underlined. I

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

7 Pages
draft labeling



10. Conclusions

1. The safety of patients treated with Exelon was assessed in a large patient population (>3700 patients, over 250 treated for 18 months and ~1000 treated for one year) characterized by high co-morbidity (85% of patients had current medical conditions) and polypharmacy (72% took concomitant medications). Long-term exposures exceed ICH guidelines.
2. The AE's seen predominantly involve the gastrointestinal system (nausea, vomiting, diarrhea, anorexia, weight loss, abdominal pain). They are dose dependent and are most likely related to the pharmacological action of the drug. Women appear to be more susceptible to these effects.
3. The low incidence of cardiac, respiratory, hepatic, renal, musculoskeletal , and psychiatric symptoms (all similar to placebo) indicates that the drug is otherwise generally well tolerated, assuming gastrointestinal symptoms can be ameliorated or avoided.
4. Exelon use is associated with higher mortality risk. According to sponsor's calculations, the mortality rate on Exelon is 20.4 per 1000 years compared with 4.22 per thousand patient years on placebo treatment. Furthermore, a nested case control study of phase 3 deaths suggest that patients receiving high dose Exelon (>9-12 mg last dose prescribed) had a 10 fold risk of death compared with low dose treatment (<4mg last dose prescribed). The reason for this remains unclear but may be due to adverse vagotonic cardiovascular effects of the drug. The increased weight loss seen in Exelon patients may also play a role.
5. Serious adverse events were similar in incidence between Exelon and placebo patients. The SAE's seen were largely related to its cholinergic effects.
6. Adverse dropouts were roughly twice more common with Exelon use. Females are less tolerant to Exelon than males, particularly to the higher doses. The increases in adverse dropouts are largely due to gastrointestinal related effects.
7. The most common AE seen was nausea, present in 35%. This was more common during the titration phase.
8. Symptomatic orthostatic hypotension (defined as orthostatic BP changes and dizziness) was more common with Exelon use. This is likely due to it's cardiovascular vagotonic effects and may also explain the increased incidence of syncope seen with Exelon treatment (though still infrequent).
9. Exelon patients experienced more clinically notable weight loss, with women being more affected. The weight loss tended to correlate with increased gastrointestinal symptoms (nausea, vomiting, anorexia). Women in the high dose group (≥9-12mg/d) had the highest incidence (26%). Patients on Exelon should undergo regular weight monitoring.

10. Gastrointestinal bleeding was more common with Exelon, although the numbers were small and no definite causation can be established. Nonetheless, given the drug's theoretical ability to increase gastric acid secretion, the potential risk for increased gastrointestinal bleeding exists.
11. Based on [redacted] review of the ECG and vitals signs data, there is evidence of drug-induced PR interval prolongation. After informal discussion with cardiorenal, 1st degree AV block is generally not considered a serious effect but should be mentioned in labeling. Due to the degree of PR prolongation seen in some patients, a formal cardiology consult to review the ECG findings is pending.
12. The effects on blood pressure and pulse are generally small, although there were a few cases of clinically significant bradycardia.
13. Exelon use was not associated with an increase in laboratory parameters (clinical chemistry, hematology, urinalysis). In particular, Exelon does not appear to elevate hepatic transaminases.
14. Long Term Therapy (up to one year) appears to be safe, without any newly emergent adverse effects. However, nausea, anorexia, agitation, BUN elevation and weight loss were more common during long term therapy. Women appeared to be more intolerant of the gastrointestinal effects with long term use.
15. The incidence of serious adverse events increased during long-term treatment (>26 wks). Since there was no placebo group for comparison, it remains unknown whether this increased incidence is due to Exelon, or whether it's a result of aging of the population.
16. No significant drug-drug interactions were identified with Exelon use. Despite changes in metabolism or excretion of Exelon in patients with liver or renal disease, no alteration in dose is recommended since dose titration in clinical practice will be based on drug tolerability.
17. The titration schedule proposed in the sponsor's draft labeling has not been used in controlled trials. Specifically, the 1.5mg bid starting dose is higher than starting doses used in the large phase 3 controlled trials. The sponsor recommends a titration to 6 mg bid as tolerated, reaching the maximum dose at week 7. This again, has not been used in clinical trials. I recommend a lower starting dose, *i.e.*, 1 mg bid, and slower titration, as tolerated, over 9-12 weeks to the maximum recommended dose. This more closely approximates the titration schedules actually used in the phase 3 clinical trials.

11. Recommendations

Based on the available data and the safety team review, Exelon appears to be associated with increased mortality which appears to be dose dependent, *i.e.*, patients exposed to higher doses appear to be at higher risk of death. The reason for this remains unclear. At the present time, I recommend a non-approvable action until the sponsor submits a more complete dose-response mortality analysis. Should this submission adequately address the mortality issue, then I can identify no other safety issues that would preclude approval with appropriate labeling changes as proposed in section 9, "Labeling Review", page 116.

/S/

Armando Oliva, M.D.
Medical Reviewer

R. Levin, M.D. /S/ 8
(see memo)

ao 3/10/98
cc:

HFD-120
NDA 20-823
electronic copy-Levin

APPEARS THIS WAY
ON ORIGINAL

Appendix A - Clinical Pharmacology Studies

Table 99: Clinical Pharmacology Studies

	Study	Design	Dose	Description	N	Age	Duration
1	A101	DBD, PBO	0.16, 0.3, 0.6, 1, 1.5, 2.3, 3, 4.6 mg	Healthy Volunteers	80	19-40	Single Dose
2	A102	DBD, PBO	1 mg bid or tid	Multidose in Healthy	22	21-32	5 Days
3	B151	Open Lbl	1 mg, 2.5 mg	Healthy Volunteers	12	21-36	Single Dose
4	W102	DBD	4 mg ER, 4 mg	Extended Release	22	20-28	3 Sgl Doses
5	W103	DBD	4 mg ER, 4 mg	Extended Release	18	20-39	3 Sgl Doses
6	W104	DBD, PBO	.05, .1, .2, .4, .8, 1.2, 1.8, 2.7 mg i.v.	Intravenous PK study	72	18-40	Single Dose
7	CVD/P1	SBD, PBO	0.5, 1, 2, 3, 4 mg	Food Interaction	10	25-46	6 Sgl Doses
8	P-1M	SBD, PBO	2 mg bid	Multidose in Healthy Vol.	8	21-40	7 Days
9	P-1A	SBD, PBO	2, 3 mg	Elderly Volunteers	7	66-79	Single Dose
10	A103	DBD, PBO	1 mg, 2 mg	Elderly Volunteers	20	60-75	Single Dose
11	W101	SBD	1, 1.75, 2.5 mg	Food Interaction	49	19-71	3-4 Sgl Doses
12	B102	DBD, PBO	1, 1.6, 2.5, 3 mg bid	Multidose in AD Patients	25	48-89	7-12 Days
13	B104	DBD, PBO	1-6 mg bid	Multidose in AD Patients	114	49-84	18 Weeks
14	A104	DBD, PBO	0.5, 1 mg	Healthy Volunteers	20	18-31	5 Days
15	A105E1	Open Lbl	1.5 mg	Scopolamine Challenge	11	19-24	Single Dose
16	A107	SBD, PBO	3 mg	Single Dose in NPH Pts	8	62-83	2 Sgl Doses
17	P106	SBD, PBO	3 mg	Healthy Volunteers	8	19-45	2 Sgl Doses
18	P106A1	SBD, PBO	3 mg	Sgl Dose in AD Patients	4	59-70	2 Sgl Doses
19	W251	Open Lbl	2, 3 mg	Liver Disease	21	43-68	3 Sgl Doses
20	W252	Open Lbl	1,2,3,4,5,6 mg bid	Multidose in AD Patients	18	48-82	4-67 Days
21	W253	Open Lbl	3 mg	Renal Disease	32	22-75	3 Sgl Doses
22	A106	DBD, PBO	0.46 -4.6 mg patch	Transdermal in Healthy	12	20-37	3 Days
23	A108	Mixed	5.8 - 33 mg patch	Transdermal in Healthy	74	21-45	1 Day
24	W151	DBD, PBO	1.5 mg patch	Transdermal in Elderly	32	51-77	21 Days
35	W152	DBD, PBO	1.5 mg patch	Transdermal in Healthy	150	N/A	39-50 Days
26	W153	Open Lbl	18 mg patch	Transdermal in Elderly	24	N/A	6 Sgl Doses
27	W361	DBD, PBO	1, 3 mg	Digoxin Study	13	21-33	10 Days
28	W362	DBD, PBO	3 mg	Warfarin Study	12	21-32	3 Days
29	W363	Open Lbl	3 mg	Diazepam Study	12	23-67	3 Days
30	W365	Open Lbl	3 mg	Fluoxetine Study	13	20-68	3 days
	PK Supplements to Phase 2/3 Trials						
	B103PK	DBD, PBO	2, 3 mg bid	Multidose in AD Patients	399	50-88	13 Weeks
	B103E2	DBD, PBO	1.25 mg	Effects on Sleep, in AD, Depression, and Healthy	149	46-83	3 Sgl Doses over 6 Days
	B351PK	DBD, PBO	1.5, 3, 4.5 mg bid	Multidose in AD Patients	330	51-92	26 Weeks
	B351/2	DBD, PBO	0.5 - 6 mg bid	Multidose in AD Patients	625	5-92	26 Weeks
	B353PK	Open Lbl	3, 6 mg bid	Bioavailability in AD Pts	18	N/A	2 Days

Table 100: Clinical Pharmacology Studies: Sex Demographics

Study Grouping	Exposure (weeks)			
	Any Exposure	≥1 n (%)	≥ 2 n (%)	≥4 n (%)
Phase I Total	585 (100)	45 (8)	18 (3)	11 (2)
Male	444 (100)	26 (6)	10 (2)	5 (1)
Female	139 (100)	19 (14)	8 (6)	6 (4)
Missing	2 (100)	0	0	0
Phase I (non- Japanese) Total	565 (100)	32 (6)	14 (2)	11 (2)
Male	424 (100)	13 (3)	6 (1)	5 (1)

Female	139 (100)	19 (14)	8 (6)	6 (4)
Missing	2 (100)	0	0	0
Phase I (Japanese) Total	20 (100)	13 (65)	4 (20)	0
Male	20 (100)	13 (65)	4 (20)	0
Female	0	0	0	0
Missing	0	0	0	0

Table 101: Clinical Pharmacology Studies: Race Demographics

Study Grouping	Exposure (weeks)			
	Any Exposure	1 n (%)	2 n (%)	4 n (%)
Phase I Total	585 (100)	45 (8)	18 (3)	11 (2)
Caucasian	445 (100)	13 (3)	11 (2)	9 (2)
Black	11 (100)	1 (9)	1 (9)	1 (9)
Asian/ Oriental	20 (100)	13 (65)	4 (20)	0
Other	18 (100)	2 (11)	2 (11)	1 (5)
Missing	91 (100)	16 (18)	0	0
Phase I (non- Japanese) Total	565 (100)	32 (6)	14 (2)	11 (2)
Caucasian	445 (100)	13 (3)	11 (2)	9 (2)
Black	11 (100)	1 (9)	1 (9)	1 (9)
Asian/ Oriental	0	0	0	0
Other	18 (100)	2 (11)	2 (11)	1 (5)
Missing	91 (100)	16 (18)	0	0
Phase I (Japanese) Total	20 (100)	13 (65)	4 (20)	0
Caucasian	0	0	0	0
Black	0	0	0	0
Asian/ Oriental	20 (100)	13 (65)	4 (20)	0
Other	0	0	0	0
Missing	0	0	0	0

Studies in Young, Non-Patient Volunteers

Study A101

This was a double blind, placebo controlled trial in young healthy male volunteers. It examined the PK, tolerability, and PD of single oral doses of rivastigmine. Doses ranged from 0.16 mg to 4.6 mg. A more than dose-proportional increase in C_{max} and AUC was seen, with T_{max} 0.86-1.33 h after administration. Elimination $T_{1/2}$ for the parent was 0.88 h, 0.83 h, and 1.04 h for 2.3 mg, 3 mg, and 4.6 mg, respectively.

Study A102

This was a double blind, placebo controlled multiple dose trial in young healthy male volunteers. Subjects received 1 mg bid or tid for 5 days. Parent drug and metabolite plasma levels could not be detected consistently at the doses employed. Safety and tolerability were good. One subject was discontinued due to elevated liver function tests that occurred prior to having received study drug.

Study B151

This was a study of the disposition of radio-labeled rivastigmine 1 mg and 2.5 mg. An absorption $T_{1/2}$ of 0.17-0.19 h was estimated. Greater than 96% of the drug was absorbed, based on radioactivity in the urine. T_{max} for parent drug was 0.67-0.75 h. Urinary excretion was the primary elimination route. An elimination $T_{1/2}$ for the parent was estimated at 0.6 h. No parent drug was recovered in the urine, indicating that rivastigmine was completely metabolized

prior to excretion. Relative bioavailability was 3% for the 1 mg dose and 11% for the 2.5 mg dose, suggesting a saturable first pass metabolism.

Study W101

This study measured the effect of food intake on the PK of rivastigmine. Healthy male volunteers took single doses of 1 mg and 2.5 mg in a fasting or fed state. Absorption was significantly slowed by food (*e.g.* T_{max} 0.78 and 2.16 h for the 1 mg dose) and AUC was significantly increased after a meal (23% for 2.5 mg and 39% for 1 mg). PD measurements (cholinesterase inhibition) were also increased under fed conditions, paralleling plasma levels.

Studies ENA/AD-VD-CVD/P-1, AD-VD/P-1M

These were two Japanese studies which assessed the PK, tolerability, and PD of single oral doses ranging from 0.5 mg to 4 mg (P-1) and of multiple oral doses of 2 mg bid for 7 days (P-1M) in healthy male volunteers. In the single dose study, rapid absorption and excretion were seen, with no detection of parent or its metabolite at 24 hours. In contrast to W101, no effect of food on the single dose PK of the drug was apparent. Single doses up to 2 mg were well tolerated, but at 3 mg and higher, cholinergic side effects of the drug began to appear (but no hypersalivation or pupillary effects). All other safety parameters revealed no clinically relevant changes. The maximum tolerated single oral dose was concluded to be 3 mg. No evidence of drug accumulation was detected in the multiple dose study.

Studies W361 and W251

In these studies, absolute bioavailability and intrasubject variability were assessed in healthy subjects. W251 showed that 3 mg dose administered as a capsule or drink solution were bioequivalent. Intrasubject variability in PK parameters for the capsule was small for the metabolite ZNS 114-666 and was somewhat larger for the parent (22.7% for AUC and 18.2% for C_{max}). W361 determined that the mean absolute bioavailability of the 3 mg service capsule was 35.5%.

Studies in Elderly, Non-Patient Volunteers

Study A103

Twenty (8M, 12F) elderly volunteers took single oral doses of 1 mg and 2 mg. PK profiles were largely similar to those found in other studies of young subjects. Plasma concentrations of the parent drug and primary metabolite were not detected for the lower dose. There was a more than dose proportional increase in C_{max} for the parent drug, with an essentially dose proportional increase in the metabolite. Absorption in the elderly subjects in this study was somewhat slower (T_{max} of 1.8-2 h) compared to the values seen in young subjects (A101), however the young subjects received the dose in a fasting state and the elderly volunteers had been fed. Cross-study comparisons should be made with caution. Rivastigmine was felt to be safe and well tolerated at these doses.

Study ENA/AD-VD/P-1A

This Japanese study administered single oral doses of 2 mg and 3 mg to elderly male volunteers under fasted conditions. T_{max} was about 1 hour. Elimination $T_{1/2}$ was 1.1-1.7 h, similar to A103 in elderly subjects under fed conditions. Typical cholinergic effects (nausea, vomiting) and headache were observed. The maximum single tolerated dose in elderly men was concluded to be 2 mg in this study.

Study W101

This study compared the PK profiles of young vs. elderly healthy male subjects given a single 1 mg and 2.5 mg dose under fasted conditions. It revealed higher C_{max} (by 35% for 1 mg and 30% for 2.5 mg) and somewhat longer $T_{1/2}$ in the elderly (0.88-1.25 h in elderly vs. 0.78-0.88 in the young). AUC were increased in the elderly by as much as 58-70%. The tendency towards greater than proportional increases in C_{max} and AUC's with increasing dose was even more pronounced in the elderly. While increased drug exposure appears to occur in elderly subjects

as compared to young, dosing recommendations are not affected, since the dosage will be titrated according to tolerability.

Studies in Elderly Patients

Study B102

This European study assessed the tolerability and PK of 25 (12M, 13F) hospitalized patients with mild AD. Multiple doses of 1 mg bid for 3 days, 2.5 mg bid for 3 days, and 2 mg bid for 3 days were administered to two groups. Less than half of the scheduled plasma samples were available for analysis, and those available demonstrated high intersubject variability. No evidence for accumulation of the drug was found. A tendency for more than dose proportional increases in plasma parent C_{max} with increasing dose was observed. Rivastigmine was generally well tolerated with some signs of peripheral cholinergic effects (orthostatic hypotension, sweating, dizziness) in the high dose group.

Study W252

This was a multiple dose, open label study evaluating the effects of rivastigmine on CSF AChE activity and cognitive performance in 18 patients with mild to moderate AD. Patients each received 1-6 mg bid for a minimum of 4 days and a maximum of 67 days. AE's were either cholinergic effects of medication or related to the lumbar puncture. Significant dose dependent inhibition of CSF AChE was observed 1.2 h after dosing and was maintained over 11.6 h. Inhibition of CSF AChE appeared to correlate with improved scores on several sub-scales of the computerized neuropsychological test battery (CNTB).

PK/PD Relationships

Study A107 and P106

A107 examined the effects of a single 3 mg dose in 8 patients (6M, 6F) with suspected normal pressure hydrocephalus. P106 assessed the effects of a single 3 mg dose in 8 normal male volunteers. Both studies demonstrated that maximum inhibition of AChE in the CSF and BChE in plasma and CSF paralleled the respective peak drug concentrations in the respective compartments. In A107, inhibition of CSF AChE correlated better with inhibition of plasma BChE than with inhibition of erythrocyte AChE, suggesting that plasma BChE may be a better surrogate index for central AChE inhibition by rivastigmine. Two patients had mild vomiting. The 3 mg dose was concluded to be safe and well tolerated in these patients.

Study P106A1

An amendment to P106 was made to assess the relationship between central and peripheral PK and PD effects of rivastigmine in patients with mild AD. Two (2) elderly non-patient volunteers and 6 patients with mild AD are to be studied. The study is ongoing at the time of the NDA submission. Thus far, 2 volunteers have completed the study and one AD patient. A second AD patient discontinued due to bradycardia.

Study A104

This European study examined the effect of single oral doses of rivastigmine from 0.5 mg to 2.0 mg on sleep parameters. It demonstrated that REM density was significantly increased at the three higher doses, and sleep time was significantly reduced at the 1 mg dose. No other significant effects were found on other sleep parameters, including slow wave and REM sleep percentages. Sleep quality was not affected by the drug.

Studies A015 and B103-E2

These two studies were performed to assess electrophysiological and cognitive effects in healthy volunteers and REM sleep in AD patients, depressed patients, and in healthy elderly volunteers. A105 was not completed. The study entailed scopolamine induction of cognitive and electrophysiological abnormalities but the scopolamine was so poorly tolerated that the study had to be terminated. In B103-E2, one of the centers prematurely terminated and no analyses

of data were performed. At single oral doses of 1.25 mg, the drug was concluded to be safe and well tolerated in the patients and volunteers studied, with no AE's or other significant abnormalities noted.

Special Population Studies

Study W251

In this study, 11 subjects will liver cirrhosis and 10 healthy controls took open label oral doses of 1, 2, and 3 mg (as tolerated). Statistically significant increases in plasma AUC (2.3 fold) for the parent drug and decreases for the primary metabolite (0.8 fold) were seen in the cirrhosis group. The conclusion is that liver disease reduces metabolic conversion of rivastigmine to its metabolite ZNS 114-666. No serious or unexpected AE's were observed, nor were there clinically relevant abnormalities in vital signs, ECG's or physical examinations. Although there appears to be reduced metabolism of rivastigmine in the presence of liver cirrhosis, no adjustment in dose is recommended since the drug was well tolerated and patients will be titrated in clinical practice up to the maximum tolerated dose.

Study W253

This study assessed the PK of rivastigmine in 20 patients with renal disease, compared to 10 matched healthy controls. Plasma concentrations of parent drug showed a marked intersubject variability in the renally impaired subjects. No alterations in PK parameters of the parent drug were found in the severely renally impaired patients. However, C_{max} and AUC were elevated in the moderately renally impaired patients. This finding may be related to study design since the controls were matched to the severely impaired, not to the moderately impaired. The mean elimination $T_{1/2}$ of the metabolite, ZNS 114-666 was significantly longer in the renal impairment groups (4.48-6.69 h vs. 3.37 h in controls). Vital sign abnormalities occurred in the renally impaired group (hypertension) as expected. Serum chemistry abnormalities related to renal disease were also seen as expected. Several renally impaired subjects had new or worsening cardiac conduction abnormalities. The sponsor recommend no dosage adjustment since patients will be titrated to tolerability.

Drug Interaction Studies

Study W361

This study evaluated the PK parameters of single doses (3 mg) of rivastigmine and digoxin (steady state 0.25 mg/d) given alone and in combination. Heart rate, PR interval, BP, and pulse in 13 male volunteers were monitored. There was no evidence for any PK interaction of the two drugs. A single oral dose of rivastigmine 3 mg administered with digoxin was safe and well tolerated.

Study W362

This study examined the possible interactions between a single dose (30 mg) of racemic warfarin and a single 3 mg dose of rivastigmine. There was no effect of rivastigmine on the PK of racemic warfarin or one of its enantiomers. There were only minor increases in AUC for ZNS 114-666 (10%). As the metabolite is only one-tenth as active as the parent, this is felt to be clinically insignificant. No changes in prothrombin time and no AE's involving the hematologic system was seen. Several subjects experienced orthostatic hypotension but this was not related to any specific treatment.

Study W363

This study examined the possible interactions between diazepam 2 mg and rivastigmine 3 mg. No PK interactions were seen and single doses in combination were safe and well tolerated.

Study W365

This study examined the possible interactions between fluoxetine 40 mg and rivastigmine 3 mg. No interactions were found and single doses in combination were safe and well tolerated.

Alternative Formulations
Study W104

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Appendix B - List of Patients in More Than One Study

Table 102: Patients Listed More Than Once

	Study	Subject #	Study	Subject#
	Phase 2			
1	B103	5406	B303	2211
2	B104	1109	B303	03006
3	B104	301	B303	06003
4	B104	302	B303	06006
5	B303	1105	B303	20003
6	B104	503	B304	1501
7	B103	3012	B304	1502
8	B103	3006	B304	1509
9	B103	3009	B304	1519
10	B104	409	B304	06006
11	B104	406	B304	06011
12	B104	601	B304	10001
13	B103	5406	B303	22011
14	W252	01004	B152	015
15	W252	01005	B354	0113
16	W252	01017	B351	0362
	Phase 3			
17	B351	09- 08	B354	01- 15
18	B351	06001 and 06037 were the same patient who was randomized twice to the same study		

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Appendix C - Cumulative Duration of Exposures - All Studies

Table 103: Cumulative Duration of Exposures: ENA 713 - All Studies

Study Grouping	Exposure in Weeks											
	Any Exposure n (%)	≥1 n (%)	≥2 n (%)	≥4 n (%)	≥12 n (%)	≥26 n (%)	≥38 n (%)	≥52 n (%)	≥65 n(%)	≥78 n(%)	≥91 n(%)	≥104 n(%)
Phase I Total	585 (100)	45 (8)	18 (3)	11 (2)	0	0	0	0	0	0	0	0
Phase I	565 (100)	32 (6)	14 (2)	11 (2)	0	0	0	0	0	0	0	0
Phase I Japanese	20 (100)	13 (65)	4 (20)	0	0	0	0	0	0	0	0	0
Phase 2 Total	648 (100)	641 (99)	629 (97)	609 (94)	503 (78)	157 (24)	107 (17)	95 (15)	82 (13)	74 (11)	72 (11)	43 (7)
Phase 2	399 (100)	396 (99)	388 (97)	374 (94)	298 (75)	157 (39)	107 (27)	95 (24)	82 (21)	74 (19)	72 (18)	43 (11)
Phase 2 Japanese	249 (100)	245 (98)	241 (97)	235 (94)	205 (82)	0	0	0	0	0	0	0
Phase 3 Total	2358 (100)	2343 (99)	2305 (98)	2223 (94)	1921 (81)	1092 (46)	179 (8)	125 (5)	0	0	0	0
Phase 3 Controlled	1696 (100)	1690 (100)	1671 (99)	1626 (96)	1388 (82)	989 (58)	0	0	0	0	0	0
Phase 3 Uncontrolled	869 (100)	860 (99)	840 (97)	799 (92)	711 (82)	197 (23)	0	0	0	0	0	0
Phase 2 and 3 Total	3006 (100)	2984 (99)	2934 (98)	2832 (94)	2424 (81)	1249 (42)	286 (10)	220 (7)	82 (3)	74 (2)	72 (2)	43 (1)
All Studies	3591 (100)	3029 (84)	2952 (82)	2863 (80)	2424 (67)	1249 (35)	286 (8)	220 (6)	82 (2)	74 (2)	72 (2)	43 (1)

Treatment Studies:

A) Phase 2 Studies - B103, B103-01, B103-04, B103-06, B901/B902, B104, B104-01, B104-02, and B105
B) Phase 2 Japanese Studies - ENA/AD/EP-II, ENA/VD/EP-II, and ENA/OR1/ALZ/PH2L/01
C) Phase 3 Controlled Studies - B303, B304, B351, and B352
D) Phase 3 Uncontrolled Studies - B305, B353, B354, and B355

APPEARS THIS WAY
ON ORIGINAL

Appendix D - Serious Adverse Events Line Listing

Table 104: Line Listing of Serious Adverse Events (Studies 103, 104, 105, 303, 304, 305, 351, 352, 353, 354, 355)

ID No.	STUDY	Prescr Dose	Dose Taken	Investigator Term	WHO Term	DUR
ENAB103 001 0004	103	.	.	AGITATION	AGITATION	.
ENAB103 001 0004	103	.	.	BEHAVIOUR TROUBLE	BEHAVIOURAL DISTURBANCE	.
ENAB103 013 0004	103	6	6	SCIATALGIA	BACK PAIN	16
ENAB103 013 0004	103	6	6	BEHAVIOUR TROUBLES	BEHAVIOURAL DISTURBANCE	64
ENAB103 015 0009	103	6	6	DELIRIUM	DELIRIUM	7
ENAB103 015 0009	103	6	6	HALLUCINOSIS	HALLUCINATION	5
ENAB103 033 0004	103	.	.	DEATH	DEATH	.
ENAB103 053 0006	103	6	6	NAUSEA	NAUSEA	1
ENAB103 054 0003	103	.	.	CEREBROVASCULAR ATTACK	CEREBROVASCULAR DISORDER	.
ENAB103 054 0003	103	6	6	UROGENITAL HEMORRHAGIA	HAEMATURIA	2
ENAB103 002 0005	103	4	4	ABDOMINAL PAIN	ABDOMINAL PAIN	4
ENAB103 004 0001	103	4	4	ARRHYTHMIA	ARRHYTHMIA	.
ENAB103 005 0002	103	.	.	DEATH	DEATH	1
ENAB103 005 0002	103	.	.	CAR ACCIDENT	ACCIDENTAL TRAUMA	1
ENAB103 012 0001	103	4	4	INGUINAL HERNIA	HERNIA	1
ENAB103 015 0004	103	4	4	TIA	CEREBROVASCULAR DISORDER	1
ENAB103 015 0004	103	.	.	HEAD TRAUMA	ACCIDENTAL TRAUMA	.
ENAB103 016 0001	103	4	4	CHOLEDOCHOLITHIASIS	CHOLELITHIASIS	6
ENAB103 016 0001	103	.	.	CAROTIC ENDARTERIECTOMY	ARTERY MALFORMATION	.
ENAB103 016 0001	103	.	.	AORTIC ANEURYSM	ANEURYSM	.
ENAB103 017 0001	103	.	.	DEMENTIA DETERIORATION	DEMENTIA	21
ENAB103 017 0008	103	.	.	FRACTURE OF FEMUR	FRACTURE PATHOLOGICAL	1
ENAB103 030 2908	103	4	4	HERNIA	HERNIA	1
ENAB103 030 2908	103	4	4	STRANGULATED HERNIA	HERNIA	3
ENAB103 035 0007	103	.	.	DEATH	DEATH	1
ENAB103 008 0003	103	0	0	FRACTURE RIGHT SHOULDER	BONE FRACTURE	.
ENAB103 008 0003	103	0	0	FALL	ACCIDENTAL TRAUMA	.
ENAB103 017 0004	103	0	0	VESICULAR LITHIASIS	CHOLELITHIASIS	27
ENAB104 002 0008	104	12	12	DIARRHOEA	DIARRHOEA	18
ENAB104 002 0008	104	12	12	ABDOMINAL PAIN	ABDOMINAL PAIN	18
ENAB104 002 0008	104	12	12	FEVER	FEVER	18
ENAB104 002 0009	104	12	12	HEMATOMA	HAEMATOMA	24
ENAB104 002 0009	104	12	12	FALL	ACCIDENTAL TRAUMA	1
ENAB104 003 0001	104	12	12	FRACTURE RIGHT HUMERUS	FRACTURE PATHOLOGICAL	.
ENAB104 004 0001	104	12	12	EXHAUSTION	ASTHENIA	3
ENAB104 004 0008	104	12	12	PARANOID HALLUCINATING PSYCHOSIS	HALLUCINATION	.
ENAB104 007 0013	104	12	12	CONFUSIONAL STATE	CONFUSION	28

				(HOSPITALIZATION)		
ENAB104 007 0015	104	.	.	HYPONATREMIA	HYPONATRAEMIA	.
ENAB104 007 0016	104	4.5	4.5	BRADYPSYCHIA	THINKING ABNORMAL	46
ENAB104 007 0016	104		.	DIFFICULTY TO WALK	GAIT ABNORMAL	.
ENAB104 010 0004	104	12	12	ABDOMINAL PAIN	ABDOMINAL PAIN	2
ENAB104 010 0010	104	10	10	NAUSEA	NAUSEA	1
ENAB104 011 0003	104	.	.	AGGRESSIVITY	AGGRESSIVE REACTION	.
ENAB104 011 0003	104	12	12	AGITATION	AGITATION	84
ENAB104 011 0003	104	.	.	HALLUCINATION	HALLUCINATION	.
ENAB104 011 0012	104	12	12	LEFT HEMIPLEGIA	HEMIPLEGIA	34
ENAB104 011 0012	104	12	12	LEFT FEMORAL BREACH	BONE FRACTURE	2
ENAB104 012 0002	104	12	12	HOSPITALIZED, KNEE SURGERY		1
ENAB104 001 0009	104	12	12	URINARY INFECTION	URINARY TRACT INFECTION	6
ENAB104 001 0009	104	12	12	FEVER	FEVER	2
ENAB104 002 0002	104	12	12	FEMORAL NECK BREAK	BONE FRACTURE	3
ENAB104 003 0002	104	12	12	LOSS OF CONSCIOUSNESS	COMA	2
ENAB104 003 0002	104	12	12	VOMITTING	VOMITING	2
ENAB104 005 0005	104	12	12	TEMPORAL LOBE EPILEPSY	CONVULSIONS	.
ENAB104 006 0001	104	.	.	RODENT ULCER L EAR	BASAL CELL CARCINOMA	.
ENAB104 007 0006	104	12	12	AGGRESSIVITY	AGGRESSIVE REACTION	13
ENAB104 008 0002	104	7	7	PARESIS OF THE MUSCLES RELATED TO SWALLOWING	PARESIS	51
ENAB104 008 0002	104	7	7	HYPERSALIVATION	SALIVA INCREASED	17
ENAB104 008 0002	104	7	7	WEIGHT LOSS	WEIGHT DECREASE	17
ENAB104 010 0003	104	9	9	CANCER	CARCINOMA	.
ENAB104 008 0010	104	0	0	MYOCARDIAL INFARCTION	MYOCARDIAL INFARCTION	2
ENAB104 010 0001	104	.	.	PULMONARY EMBOLISM	EMBOLISM PULMONARY	3
ENAB104 010 0001	104	0	0	PERIPHERAL VASCULAR DISEASE - POPLITEAL ANEURYSM SURGICALLY CORRECTED	ANEURYSM	108
ENAB105 001 0032	105	.	.	LETHARGIC	SOMNOLENCE	1
ENAB105 001 0032	105	.	.	FAINTING SPELL	SYNCOPE	1
ENAB105 001 0032	105	.	.	COLD	RHINITIS	1
ENAB105 001 0032	105	.	.	WEAKNESS	ASTHENIA	1
ENAB105 001 0016	105	.	.	ABNORMAL LIVER FUNCTION	HEPATIC FUNCTION ABNORMAL	22
ENAB105 001 0036	105	.	.	OVERDOSE	OVERDOSE	3
ENAB303 002 0017	303	4	2	SURGERY NASAL POLYPS	SURGERY	1
ENAB303 003 0001	303	10.5	10.5	VOMITING	VOMITING	2
ENAB303 003 0001	303	10.5	10.5	NAUSEA	NAUSEA	2
ENAB303 003 0001	303	10.5	10.5	MALAISE	MALAISE	2
ENAB303 003 0001	303	10.5	10.5	OVERDOSE	OVERDOSE	2
ENAB303 004 0006	303	7	7	OVERDOSE	OVERDOSE	1
ENAB303 005 0001	303	12	12	AGITATION	AGITATION	.
ENAB303 006 0001	303	4	4	DROWSINESS	SOMNOLENCE	2
ENAB303 006 0001	303	4	4	VOMITING	VOMITING	2
ENAB303 006 0001	303	4	4	OVERDOSE	OVERDOSE	2
ENAB303 007 0009	303	10.5	10.5	OVERDOSE	OVERDOSE	1

ENAB303 008 0016	303	6	6	DIARRHEA	DIARRHOEA	3
ENAB303 008 0016	303	6	6	VOMITING	VOMITING	3
ENAB303 009 0004	303	3	3	CARDIAC INSUFFICIENCY	CARDIAC FAILURE	18
ENAB303 009 0004	303			SUDDEN DEATH	SUDDEN DEATH	1
ENAB303 010 0003	303	8	8	DIZZINESS	DIZZINESS	2
ENAB303 010 0003	303	8	8	VOMITING	VOMITING	2
ENAB303 010 0003	303	8	8	NAUSEA	NAUSEA	2
ENAB303 011 0025	303	10.5	10.5	HOSPITALIZATION FOR COEXISTENT MEDICAL CONDITION	PROCEDURE NOS	4
ENAB303 011 0025	303	8	8	OVERDOSE	OVERDOSE	1
ENAB303 012 0011	303	12	12	SUPRAVENTRICULAR TACHYCARDIA	TACHYCARDIA SUPRAVENTRICULAR	10
ENAB303 012 0011	303	12	12	POST PRANDIAL MALAISE	MALAISE	1
ENAB303 012 0013	303	12	12	STROKE	CEREBROVASCULAR DISORDER	5
ENAB303 012 0025	303	12	12	HYPOTENSIVE SYNCOPE	SYNCOPE	1
ENAB303 013 0003	303	12	12	DIARRHOEA	DIARRHOEA	5
ENAB303 013 0003	303	12	12	VOMITING	VOMITING	5
ENAB303 013 0003	303	12	12	ABDOMINAL PAIN	ABDOMINAL PAIN	5
ENAB303 013 0003	303	12	12	HYPERLEUCOCYTOSIS	LEUKOCYTOSIS	5
ENAB303 013 0008	303	5	5	ANXIETY	ANXIETY	.
ENAB303 013 0008	303	5	5	ATYPICAL MALAISE	MALAISE	12
ENAB303 013 0008	303	5	5	HOSPITALISATION FOR CMC	PROCEDURE NOS	9
ENAB303 013 0011	303	10.5	10.5	CERVICAL ARTHROSIS	ARTHROSIS	11
ENAB303 013 0011	303	10.5	10.5	PARESIS LOWER LIMBS	PARESIS	15
ENAB303 013 0020	303	12	12	MALAISE	MALAISE	2
ENAB303 013 0020	303	12	12	TENOSYNOVITIS OF JUMP BACK LEFT FINGER	INFECTION	1
ENAB303 021 0001	303	6	6	GLOBAL TREMOR	TREMOR	2
ENAB303 021 0001	303	6	6	AGGRESSIVITY	AGGRESSIVE REACTION	4
ENAB303 021 0001	303	6	6	ANOREXIA	ANOREXIA	2
ENAB303 021 0001	303	7	7	HYPOTENSION	HYPOTENSION	.
ENAB303 021 0001	303	6	6	VOMITING	VOMITING	2
ENAB303 021 0001	303	6	6	NAUSEA	NAUSEA	2
ENAB303 021 0001	303	7	7	WEIGHT LOSS	WEIGHT DECREASE	.
ENAB303 021 0001	303	3	2.25	OVERDOSE	OVERDOSE	1
ENAB303 021 0007	303	12	12	DISORIENTATION	CONFUSION	.
ENAB303 021 0007	303	12	12	AGGRESSIVITY	AGGRESSIVE REACTION	.
ENAB303 022 0003	303	12	12	OVERDOSE	OVERDOSE	6
ENAB303 023 0002	303	7	7	OVERDOSE	OVERDOSE	1
ENAB303 024 0008	303	12	12	MYOCARDIAL INFARCTION	MYOCARDIAL INFARCTION	29
ENAB303 024 0009	303	4	4	VOMITING	VOMITING	2
ENAB303 024 0009	303	4	4	NAUSEA	NAUSEA	2
ENAB303 024 0009	303	4	4	OVERDOSE	OVERDOSE	1
ENAB303 027 0011	303	12	6	AGGRESSIVENESS	AGGRESSIVE REACTION	.
ENAB303 027 0011	303	12	6	WISH OF DEATH	SUICIDAL IDEATION	9
ENAB303 029 0001	303	6	6	NUMMULAR ECZEMA	ECZEMA	.
ENAB303 029 0009	303	12	12	SYNCOPY (FAINTING)	SYNCOPE	1
ENAB303 030 0004	303	12	12	DEHYDRATION	DEHYDRATION	11

ENAB303 020 0004	303	12	12	RESPIRATORY FAILURE	RESPIRATORY INSUFFICIENCY	4
ENAB303 030 0004	303	12	12	VIRAL INFECTION	INFECTION VIRAL	11
ENAB303 030 0004	303	12	12	HOSPITALISATION BECAUSE HIPJOINT IMPLANTATION	SURGERY	.
ENAB303 030 0007	303	2	2	OVERDOSE	OVERDOSE	1
ENAB303 030 0007	303	3	3	OVERDOSE	OVERDOSE	1
ENAB303 031 0002	303	9	9	ABRUPT ON SET OF CONFUSION	CONFUSION	.
ENAB303 031 0002	303	9	9	HYPOKINESIA	HYPOKINESIA	.
ENAB303 034 0018	303	.	.	MYOCARDIAL INFARCTION	MYOCARDIAL INFARCTION	1
ENAB303 035 0004	303	7	3.5	DIZZINESS	DIZZINESS	1
ENAB303 035 0004	303	7	3.5	IMPAIRED LOCOMOTION	HYPOKINESIA	1
ENAB303 035 0004	303	8	8	OVERDOSE 3 CAPSULES	OVERDOSE	1
ENAB303 035 0004	303	9	9	OVERDOSE 3 CAPSULES	OVERDOSE	1
ENAB303 035 0004	303	12	12	OVERDOSE 5 CAPSULES	OVERDOSE	6
ENAB303 035 0008	303	7	7	2 CAPSULES OVERDOSE	OVERDOSE	1
ENAB303 036 0008	303	12	12	HYPERTENSION	HYPERTENSION	1
ENAB303 036 0008	303	12	12	LOSS OF CONCIOUSNESS	SYNCOPE	1
ENAB303 036 0008	303	12	12	SUPRAVENTRICULAR ARRHYTHMIA	ARRHYTHMIA	1
ENAB303 036 0018	303	6	6	AGGRESSIVENESS	AGGRESSIVE REACTION	.
ENAB303 036 0018	303	6	6	RESTLESSNESS	AGITATION	.
ENAB303 038 0006	303	3	3	CONFUSION	CONFUSION	.
ENAB303 038 0006	303	7	7	DRUG-INDUCED HEPATITIS	HEPATITIS	.
ENAB303 038 0006	303	.	.	BILATERAL PHLEBITIS	PHLEBITIS	.
ENAB303 038 0006	303	.	.	OVERDOSE	OVERDOSE	1
ENAB303 042 0005	303	6	6	OPERATION OF VAGINAL STENOSIS	SURGERY	8
ENAB303 042 0013	303	7	7	DIARRHOE	DIARRHOEA	1
ENAB303 042 0014	303	12	12	PNEMONIA	PNEUMONIA	15
ENAB303 042 0020	303	7	7	OVERDOSE	OVERDOSE	1
ENAB303 043 0016	303	12	12	HIP FRACTURE	BONE FRACTURE	2
ENAB303 043 0051	303	6	6	UNSTABLE ANGINA	ANGINA PECTORIS	11
ENAB303 044 0011	303	7	7	BENIGN 5 CM VILLOUS MASS IN RECTUM	TUMOR BENIGN	28
ENAB303 045 0011	303	9	9	ATRIAL FIBRILLATION	FIBRILLATION ATRIAL	2
ENAB303 046 0017	303	.	.	DEPRESSION	DEPRESSION	.
ENAB303 002 0003	303	2.5	2.5	RESPITE CARE	PROCEDURE NOS	8
ENAB303 005 0019	303	1.5	1.5	ACUTE URINARY RETENTION	URINARY RETENTION	2
ENAB303 005 0019	303	1.5	1.5	FECALOMA	CONSTIPATION	2
ENAB303 005 0019	303	1	1	VERTEBRAL FRACTURE	BONE FRACTURE	29
ENAB303 006 0008	303	.	.	OVERDOSE	OVERDOSE	1
ENAB303 006 0012	303	4	4	HOSPITALISATION FOR CMC(ANAEMIA)	PROCEDURE NOS	5
ENAB303 007 0002	303	4	4	OVERDOSE	OVERDOSE	1
ENAB303 007 0015	303	4	4	OVERDOSE	OVERDOSE	1
ENAB303 008 0007	303	4	4	PROSTRATE ADENOMA	PROSTATIC DISORDER	1
ENAB303 011 0018	303	4	0	SURGERY ON HALLUX VALGUS	SURGERY	1
ENAB303 011 0029	303	4	4	RESPITE CARE	PROCEDURE NOS	10
ENAB303 011 0029	303	4	4	FALL DOWN	ACCIDENTAL TRAUMA	1

ENAB303 012 0019	303	1	1	BOWEL SUB OCCLUSION	INTESTINAL OBSTRUCTION	20
ENAB303 012 0018	303	4	4	SUBINFECTED BRONCHITIS	BRONCHITIS	13
ENAB303 012 0018	303	1	1	BLADDER DISTENSION	BLADDER DISORDERS NOS	20
ENAB303 012 0019	303	4	4	CATARACT OPERATED	SURGERY	1
ENAB303 020 0003	303	2	2	INSITUTIONALIZATION IN A HOME FOR THE ELDERLY.	PROCEDURE NOS	50
ENAB303 022 0020	303	4	4	OVERDOSE	OVERDOSE	1
ENAB303 023 0003	303	2	2	BRONCHITIS	BRONCHITIS	4
ENAB303 023 0003	303	2	2	BROKEN NOSE	BONE FRACTURE	8
ENAB303 023 0003	303	2	2	FALL	ACCIDENTAL TRAUMA	1
ENAB303 024 0013	303	3	3	OVERDOSE	OVERDOSE	1
ENAB303 024 0013	303	4	4	OVERDOSE	OVERDOSE	1
ENAB303 026 0002	303	1	1	OVERDOSE	OVERDOSE	1
ENAB303 028 0008	303	4	4	EPILEPTIC SEIZURE	CONVULSIONS	1
ENAB303 028 0008	303	1	1	RESPITE CARE	PROCEDURE NOS	8
ENAB303 029 0005	303	4	4	HYPERTENSIVE CRISIS	HYPERTENSION	1
ENAB303 029 0011	303	4	4	CHEST PAIN DUE TO ANXIETY	CHEST PAIN	1
ENAB303 031 0007	303	1.5	1.5	HOSPITALISATION BECAUSE OF ILLNESS OF THE CAREGIVER	PROCEDURE NOS	15
ENAB303 032 0006	303	4	4	COLON CARCINOMA	COLON CARCINOMA	.
ENAB303 033 0001	303	1	1	ABSCESS (LEFT LOWER LIMB)	ABSCESS	.
ENAB303 033 0001	303	1	1	INFLAMMATION (LEFT LOWER LIMB)	GENERALIZED INFLAMMATION LEG(S)	7
ENAB303 033 0002	303	.	.	OVERDOSE	OVERDOSE	8
ENAB303 034 0002	303	1	1	GLAUCOMA	SURGERY	6
ENAB303 034 0002	303	1	1	OVER-DOSE	OVERDOSE	8
ENAB303 034 0016	303	4	4	AGGRESIVE REACTION	AGGRESSIVE REACTION	80
ENAB303 034 0016	303	4	4	RESTLESNESS	AGITATION	80
ENAB303 035 0003	303	4	4	OVERDOSE 2 CAPS	OVERDOSE	1
ENAB303 035 0005	303	1	1	OVERDOSE 2 CAPSULES	OVERDOSE	1
ENAB303 035 0007	303	4	4	OVERDOSE 4 CAPSULES	OVERDOSE	9
ENAB303 035 0007	303	4	4	OVERDOSE 2 CAPS	OVERDOSE	1
ENAB303 036 0012	303	2	2	SUSPECTED OVERDOSE	OVERDOSE	1
ENAB303 036 0021	303	3	3	PATIENT COLLAPSED (TACHYARRYTHMIA)	SYNCOPE	1
ENAB303 042 0011	303	4	4	VULVA - CANCER	CARCINOMA	.
ENAB303 042 0023	303	4	4	RIGHT THIGH FRACTURE	BONE FRACTURE	30
ENAB303 043 0020	303	1.5	1.5	SYNCOPE	SYNCOPE	4
ENAB303 043 0020	303	1.5	1.5	STOMACH PAIN	ABDOMINAL PAIN	.
ENAB303 043 0031	303	4	2	ABDOMINAL CRAMPS	ABDOMINAL PAIN	2
ENAB303 043 0044	303	4	0	ANTRAL ULCERATION	GASTRIC ULCER	.
ENAB303 043 0044	303	4	2	ANEMIA DUE TO GI BLEED	GI HAEMORRHAGE	43
ENAB303 043 0044	303	4	0	BARRETT'S ESOPHAGITIS	OESOPHAGITIS	.
ENAB303 043 0048	303	.	.	RESPIRATORY DISTRESS	DYSPNOEA	5
ENAB303 043 0048	303	1	0.5	ANGIOPLASTY DUE TO CORONARY ARTERY DISEASE	SURGERY	1
ENAB303 044 0030	303	2.5	2.5	FRACTURED LEFT ARM DUE TO A	BONE FRACTURE	17

				FALL		
ENAB303 045 0005	303	2.5	2.5	UNSTABLE ANGINA	ANGINA PECTORIS	8
ENAB303 045 0012	303	1	1	NOSE BASAL CELL CARCINOMA	BASAL CELL CARCINOMA	22
ENAB303 045 0014	303	1.5	1.5	UNSTABLE ANGINA	ANGINA PECTORIS	7
ENAB303 046 0016	303	4	4	OVERDOSE	OVERDOSE	1
ENAB303 047 0014	303	1	1	DEHYDRATION DUE TO GASTROENTERITIS	DEHYDRATION	3
ENAB303 002 0001	303	0	0	RESPITE CARE	PROCEDURE NOS	30
ENAB303 002 0011	303	0	0	OVERDOSE	OVERDOSE	2
ENAB303 002 0011	303	0	0	OVERDOSE	OVERDOSE	1
ENAB303 002 0018	303	0	0	OVERDOSE	OVERDOSE	1
ENAB303 002 0018	303	0	0	OVERDOSE	OVERDOSE	1
ENAB303 002 0018	303	0	0	OVERDOSE	OVERDOSE	7
ENAB303 002 0018	303	0	0	OVERDOSE	OVERDOSE	1
ENAB303 003 0013	303	0	0	BREAST NEOPLASIA	BREAST NEOPLASM MALIGNANT FEMALE	.
ENAB303 003 0013	303	0	0	OVERDOSE	OVERDOSE	7
ENAB303 004 0004	303	0	0	RESPITE CARE	PROCEDURE NOS	.
ENAB303 007 0005	303	0	0	OVERDOSE	OVERDOSE	1
ENAB303 007 0007	303	0	0	OVERDOSE	OVERDOSE	1
ENAB303 007 0012	303	0	0	BLADDER CANCER	BLADDER CARCINOMA	4
ENAB303 007 0014	303	0	0	OCCIPITAL BONE FRACTURE	BONE FRACTURE	34
ENAB303 007 0014	303	0	0	COMMOTIO CEREBRII	ACCIDENTAL TRAUMA	1
ENAB303 007 0014	303	0	0	OVERDOSE	OVERDOSE	1
ENAB303 009 0010	303	0	0	CATARACTA SURGERY	SURGERY	1
ENAB303 012 0022	303	0	0	VOMIT	VOMITING	2
ENAB303 012 0022	303	0	0	GASTRITIS	GASTRITIS	.
ENAB303 012 0022	303	0	0	ESOPHAGITIS	OESOPHAGITIS	.
ENAB303 013 0023	303	0	0	HIP ARTHRITIS WORSENING	ARTHRITIS	54
ENAB303 017 0002	303	0	0	LUXATION OF THE RIGHT SHOULDER	JOINT DISLOCATION	10
ENAB303 019 0001	303	0	0	CONFUSIONAL STATE	CONFUSION	1
ENAB303 020 0007	303	0	0	THORACIC PAIN	CHEST PAIN	1
ENAB303 021 0004	303	0	0	ATRIAL FIBRILLATION	FIBRILLATION ATRIAL	10
ENAB303 021 0004	303	0	0	ATRIAL FIBRILLATION	FIBRILLATION ATRIAL	6
ENAB303 022 0005	303	0	0	OVERDOSE	OVERDOSE	9
ENAB303 022 0005	303	0	0	OVERDOSE	OVERDOSE	8
ENAB303 023 0001	303	0	0	BRONCHOPNEUMONIA	PNEUMONIA	5
ENAB303 023 0010	303	0	0	FRACTUR (FEMOR BROKEN)	BONE FRACTURE	106
ENAB303 023 0011	303	0	0	GONARTHROSIS	ARTHROSIS	.
ENAB303 023 0011	303	0	0	TEMPORAL ARTERITIS	ARTERITIS	.
ENAB303 024 0005	303	0	0	OVERDOSE	OVERDOSE	1
ENAB303 024 0014	303	0	0	OVERDOSE	OVERDOSE	1
ENAB303 024 0017	303	0	0	OVERDOSE	OVERDOSE	6
ENAB303 025 0004	303	0	0	CANCER - MALIGNANT BREAST MASS	BREAST NEOPLASM MALIGNANT FEMALE	.
ENAB303 025 0004	303	0	0	BREAST CANCER SURGERY	SURGERY	1
ENAB303 027 0001	303	.	.	HOSPITALIZATION FOR ANKLE	PROCEDURE NOS	.

				INJURY		
ENAB303 027 0008	303	0	0	RESPITE CARE	PROCEDURE NOS	22
ENAB303 028 0009	303	0	0	TRANSITORIC ISCHAEMIC ATTACK	CEREBROVASCULAR DISORDER	2
ENAB303 030 0001	303	0	0	HOSPITALISATION (EYE OPERATION - LENS IMPLANTATION)	SURGERY	5
ENAB303 030 0003	303	0	0	OVERDOSE	OVERDOSE	1
ENAB303 030 0008	303	0	0	BURSITUS HALLUX VALGUS LEFT JOINT	BURSITIS	15
ENAB303 030 0008	303	.	.	OVERDOSE	OVERDOSE	7
ENAB303 030 0008	303	0	0	OVERDOSE	OVERDOSE	1
ENAB303 031 0004	303	0	0	BACKPAIN	BACK PAIN	7
ENAB303 031 0009	303	0	0	FRACTURE OF CHEEK BONE	BONE FRACTURE	13
ENAB303 031 0009	303	0	0	COMOTIO CEREBRI	ACCIDENTAL TRAUMA	11
ENAB303 033 0006	303	0	0	HERNIA REPAIR	SURGERY	12
ENAB303 033 0007	303	0	0	SUBDURAL HEMATOMA	HAEMORRHAGE INTRACRANIAL	4
ENAB303 034 0010	303	0	0	PNEUMONIA	PNEUMONIA	53
ENAB303 035 0001	303	0	0	OVERDOSE 2 CAPS	OVERDOSE	1
ENAB303 035 0001	303	0	0	OVERDOSE 2 CAPS	OVERDOSE	1
ENAB303 035 0006	303	0	0	2 CAPSULES OVERDOSE	OVERDOSE	5
ENAB303 035 0012	303	.	.	OVERDOSE 2 CAPS	OVERDOSE	1
ENAB303 035 0012	303	0	0	OVERDOSE 2 CAPS	OVERDOSE	1
ENAB303 035 0012	303	0	0	OVERDOSE 3 CAPS	OVERDOSE	1
ENAB303 035 0013	303	0	0	LUMBARGO HOSPITALIS	BACK PAIN	43
ENAB303 035 0013	303	0	0	OPERATION DISCELETOMIA L5/S1	SURGERY	1
ENAB303 035 0013	303	0	0	OVERDOSE 2 KPS	OVERDOSE	1
ENAB303 035 0013	303	0	0	OVERDOSE 10 KAPS	OVERDOSE	1
ENAB303 036 0020	303	0	0	FRACTURE OF RIGHT THUMB	BONE FRACTURE	.
ENAB303 038 0001	303	0	0	OVERDOSE	OVERDOSE	1
ENAB303 042 0021	303	0	0	CONFUSIONAL STATE	CONFUSION	2
ENAB303 042 0021	303	0	0	OVERDOSE	OVERDOSE	2
ENAB303 043 0017	303	0	0	SUBDURAL HEMATOME	HAEMORRHAGE INTRACRANIAL	4
ENAB303 043 0022	303	0	0	LEFT INGUINAL HERNIA	HERNIA	1
ENAB303 043 0041	303	0	0	CARCINOMA OF VULVA W/MESTASES TO LOCAL LYMPH NODES	CARCINOMA	.
ENAB303 043 0041	303	0	0	SURGERY OR CA. VULVAE	SURGERY	6
ENAB303 043 0045	303	0	0	NEAR SYNCOPE	SYNCOPE	2
ENAB303 043 0050	303	0	0	DEPRESSION	DEPRESSION	.
ENAB303 045 0019	303	0	0	BROKEN HIP SECONDARY TO A FALL	BONE FRACTURE	1
ENAB304 001 0003	304	7	7	OVERDOSE	OVERDOSE	10
ENAB304 001 0009	304	4	4	OVERDOSE	OVERDOSE	1
ENAB304 001 0011	304	4	4	COLONOSCOPY	SURGERY	2
ENAB304 002 0010	304	4	4	CONFUSION	CONFUSION	.
ENAB304 002 0010	304	4	4	AGITATION	AGITATION	.
ENAB304 002 0010	304	8	8	PARANOIA	PARANOID REACTION	89
ENAB304 002 0020	304	12	12	TIA	CEREBROVASCULAR DISORDER	1
ENAB304 002 0022	304	.	.	ANAEMIA	ANAEMIA	1

ENAB304 002 0022	304			CONFUSION WORSE	CONFUSION	61
ENAB304 002 0022	304	.	.	CHEST INFECTION	INFECTION	27
ENAB304 002 0027	304	.	.	SUICIDAL IDEATION	SUICIDAL IDEATION	.
ENAB304 002 0027	304	.	.	ATTEMPT ON HER LIFE	SUICIDE ATTEMPT	1
ENAB304 002 0027	304	.	.	DEPRESSION	DEPRESSION	.
ENAB304 002 0031	304	.	.	FAINTING ATTACK	SYNCOPE	1
ENAB304 002 0031	304	.	.	FAINTING ATTACK	SYNCOPE	1
ENAB304 002 0041	304	.	.	TRANSIENT ISCHAEMIC ATTACK	CEREBROVASCULAR DISORDER	1
ENAB304 002 0042	304	.	.	TRANSIENT ISCHAEMIC ATTACK	CEREBROVASCULAR DISORDER	1
ENAB304 002 0057	304	.	.	CHEST INFECTION	INFECTION	24
ENAB304 003 0004	304	12	12	OVERDOSE	OVERDOSE	1
ENAB304 003 0004	304	6	6	OVERDOSE	OVERDOSE	1
ENAB304 003 0004	304	6	4	OVERDOSE	OVERDOSE	1
ENAB304 003 0009	304	.	.	SYNCOPAL ATTACK	SYNCOPE	1
ENAB304 004 0001	304	.	.	OVERDOSE OF 2 CAPS	OVERDOSE	1
ENAB304 004 0002	304	0	0	OVERDOSE OF 2 CAPS	OVERDOSE	1
ENAB304 004 0003	304	6	6	COLLAPSED AT HOME DUE TO TRANCIENT ISCHAEMIC ATTACK	CEREBROVASCULAR DISORDER	1
ENAB304 004 0012	304	.	.	HOSPITALIZATION FOR RESPITE	PROCEDURE NOS	15
ENAB304 006 0021	304	.	.	OVERDOSE	OVERDOSE	1
ENAB304 006 0021	304	.	.	OVERDOSE	OVERDOSE	1
ENAB304 007 0005	304	9	0	DIZZY SPELLS	DIZZINESS	3
ENAB304 007 0005	304	9	0	DIZZINESS	DIZZINESS	3
ENAB304 007 0005	304	9	0	LETHARGY	SOMNOLENCE	3
ENAB304 007 0005	304	9	0	TIREDNESS ++	FATIGUE	3
ENAB304 007 0010	304	.	.	PT HAS TAKEN 18 DL3 TABS THIS MORNING	OVERDOSE	1
ENAB304 007 0010	304	.	.	LEFT SIDED CEREBROVASCULAR ACCIDENT	CEREBROVASCULAR DISORDER	.
ENAB304 008 0005	304	.	.	OVERDOSE OF STUDY DRUG	OVERDOSE	1
ENAB304 008 0006	304	.	.	RESTLESSNESS (REQUIRING HOSPITALISATION)	AGITATION	.
ENAB304 008 0007	304	.	.	EXTRA DOSE OF STUDY MEDICATION TAKEN	OVERDOSE	2
ENAB304 008 0009	304	.	.	URGENT HOSPITAL ADMISSION FOR ASSESSMENT & CARER RESPITE	PROCEDURE NOS	.
ENAB304 008 0009	304	.	.	INCREASED RESTLESSNESS	AGITATION	.
ENAB304 008 0011	304	.	.	MYOCARDIAL INFARCTION	MYOCARDIAL INFARCTION	1
ENAB304 009 0003	304	.	.	G.I.T. BLEEDING	GI HAEMORRHAGE	.
ENAB304 009 0003	304	.	.	BREAST CANCER	BREAST NEOPLASM MALIGNANT FEMALE	.
ENAB304 010 0001	304	12	12	BROKEN HIP	BONE FRACTURE	1
ENAB304 010 0005	304	.	.	CEREBROVASCULAR ISCHEMIA	CEREBROVASCULAR DISORDER	1
ENAB304 010 0005	304	.	.	CEREBROVASCULAR ISCHEMIA	CEREBROVASCULAR DISORDER	.
ENAB304 011 0001	304	.	.	PNEUMONIA	PNEUMONIA	24
ENAB304 011 0001	304	.	.	PULMONARY EMBOLISM	EMBOLISM PULMONARY	17
ENAB304 011 0001	304	0	0	BROKEN LEG	BONE FRACTURE	1

ENAB304 011 0005	304	7	7	LACK OF APPETITE	ANOREXIA	20
ENAB304 011 0005	304	8	8	WEIGHT LOSS	WEIGHT DECREASE	29
ENAB304 011 0011	304			RESPITE CARE	PROCEDURE NOS	16
ENAB304 011 0012	304	.	.	RESPITE CARE	PROCEDURE NOS	20
ENAB304 012 0002	304	9	9	PLANNED HOSPITAL ADMISSION FOR RESPITE CARE	PROCEDURE NOS	8
ENAB304 012 0002	304	7	7	PLANNED HOSPITAL ADMISSION FOR RESPITE CARE	PROCEDURE NOS	15
ENAB304 013 0002	304	0	0	RESPITE CARE	PROCEDURE NOS	36
ENAB304 013 0004	304	12	12	FALL	ACCIDENTAL TRAUMA	3
ENAB304 013 0008	304	12	12	OVERDOSE	OVERDOSE	1
ENAB304 013 0008	304	12	12	RESPITE CARE	PROCEDURE NOS	8
ENAB304 013 0008	304	12	12	CHEST INFECTION	INFECTION	10
ENAB304 013 0008	304	12	12	CONGESTIVE HEART FAILURE	CARDIAC FAILURE	.
ENAB304 013 0011	304	10.5	10.5	INSOMNIA	INSOMNIA	14
ENAB304 013 0011	304	10.5	10.5	AGITATION	AGITATION	14
ENAB304 013 0011	304	10.5	10.5	FAILURE OF RECOGNITION	CONFUSION	14
ENAB304 013 0012	304	12	12	APRAXIA	APRAXIA	.
ENAB304 013 0012	304	12	12	PROGRESSION OF ALZHEIMERS	DEMENTIA	.
ENAB304 013 0012	304	12	12	ATAXIA	ATAXIA	.
ENAB304 013 0014	304	.	.	ACCIDENTAL OVERDOSE	OVERDOSE	1
ENAB304 013 0017	304	.	.	RESPITE CARE	PROCEDURE NOS	15
ENAB304 013 0017	304	.	.	RESPITE CARE	PROCEDURE NOS	17
ENAB304 013 0017	304	.	.	INCREASED CONFUSION	CONFUSION	.
ENAB304 013 0020	304	.	.	AGITATION	AGITATION	.
ENAB304 013 0020	304	.	.	WANDERING	AGITATION	.
ENAB304 013 0021	304	.	.	ABDOMINAL PAIN	ABDOMINAL PAIN	5
ENAB304 013 0021	304	.	.	NAUSEA	NAUSEA	5
ENAB304 013 0021	304	.	.	AD ASSESSMENT	PROCEDURE NOS	15
ENAB304 015 0019	304	0	0	SQUAMOUS CELL CARCINOMA	SKIN NEOPLASM MALIGNANT	1
ENAB304 015 0019	304	0	0	SURGERY FOR DUPUYTREN'S CONTRACTURE	SURGERY	1
ENAB304 015 0019	304	0	0	EXCISION OF SQUAMOUS CELL CA	SURGERY	12
ENAB304 016 0005	304	10.5	10.5	AGGRESSION	AGGRESSIVE REACTION	.
ENAB304 016 0007	304	0	0	SEIZURE	CONVULSIONS	1
ENAB304 016 0015	304	.	.	OVERDOSE	OVERDOSE	8
ENAB304 016 0015	304	.	.	ANGINA EPISODES	ANGINA PECTORIS	1
ENAB304 017 0012	304	.	.	SYNCOPE	SYNCOPE	1
ENAB304 017 0013	304	.	.	OVERDOSE	OVERDOSE	1
ENAB304 018 0003	304	5	5	TECHNICAL OVERDOSE	OVERDOSE	1
ENAB304 018 0006	304	0	0	OVERDOSE	OVERDOSE	1
ENAB304 018 0007	304	0	0	HIP REPLACEMENT SURGERY	SURGERY	6
ENAB304 018 0009	304	.	.	PSYCHIATRIC ASSESSMENT HOSPITALIZATION	PSYCHIATRIC DISORDERS NOS	57
ENAB304 018 0017	304	.	.	SEIZURE	CONVULSIONS	1
ENAB304 018 0018	304	.	.	ACCIDENTAL OVERDOSE	OVERDOSE	1
ENAB304 019 0008	304	.	.	ANTERIOR MYOCARDIAL INFARCT	MYOCARDIAL INFARCTION	.

ENAB304 019 0014	304		.	SYNCOPAL EPISODE	SYNCOPE	1
ENAB304 020 0018	304			SYNCOPE	SYNCOPE	1
ENAB304 022 0009	304	12	12	CYTOPLEGIA (HOSPITALISED - BLADDER PARALYSIS)	URINARY RETENTION	18
ENAB304 025 0007	304	0	0	SUPERFICIAL LEG VEIN PHLEBITIS	PHLEBITIS	5
ENAB304 026 0011	304	.	.	SOCIAL HOSPITALISATION	PROCEDURE NOS	13
ENAB304 027 0006	304	3	3	HOSPITALIZATION TO FIND OUT CAUSE OF ANAEMIA	ANAEMIA	3
ENAB304 027 0009	304	9	9	ASYMPTOMATIC OVERDOSE	OVERDOSE	1
ENAB304 028 0002	304	10.5	10.5	HUMERUS FRACTURE	BONE FRACTURE	29
ENAB304 028 0012	304	.	.	ABLATION COLONIC POLYPS/HEMERRHOIDS	SURGERY	1
ENAB304 028 0021	304	.	.	PROSTATIC ADENOCARCINOMA	NEOPLASM MALIGNANT	.
ENAB304 028 0024	304	.	.	SYNCOPE	SYNCOPE	1
ENAB304 028 0026	304	.	.	BREAK VERTABRAL L1 BODY	ACCIDENTAL TRAUMA	.
ENAB304 028 0027	304	.	.	NOT H. LYMPHOMA	LYMPHOMA MALIGNANT	.
ENAB304 029 0001	304	8	8	NEPHROLITHIASIS	RENAL CALCULUS	6
ENAB304 029 0006	304	4	4	AGGRESSIVITY	AGGRESSIVE REACTION	.
ENAB304 029 0006	304	4	4	AGITATION	AGITATION	10
ENAB304 029 0006	304	4	4	IRRITABILITY	NERVOUSNESS	.
ENAB304 029 0012	304	.	.	FRACTURE OF THE 9TH COSTA	BONE FRACTURE	24
ENAB304 030 0004	304	5	5	CRANIALIS TRAUMA (HOSPITALISED)	ACCIDENTAL TRAUMA	5
ENAB304 030 0006	304	12	12	TRANSIENT ISCHAEMIC ATTACK (HOSPITALISED)	CEREBROVASCULAR DISORDER	8
ENAB304 030 0007	304	.	.	GALLSTONES	CHOLELITHIASIS	9
ENAB304 030 0007	304	.	.	PANCREATITIS	PANCREATITIS	9
ENAB304 030 0011	304	.	.	SEIZURE (HOSPITALISED)	CONVULSIONS	1
ENAB304 031 0003	304	6	3	BLOODY DIARRHOEA	GI HAEMORRHAGE	1
ENAB304 031 0004	304	9	9	FRACTURED FEMUR (RIGHT)	BONE FRACTURE	12
ENAB304 031 0006	304	10.5	10.5	BRONCHOPNEUMONIA	PNEUMONIA	24
ENAB304 031 0010	304	0	0	OVERDOSE	OVERDOSE	1
ENAB304 031 0015	304	0	0	HOSPITALISATION-RESPITE CARE	PROCEDURE NOS	16
ENAB304 032 0001	304	9	9	GASTROENTERITIS	GASTROENTERITIS	3
ENAB304 032 0003	304	12	12	OVERDOSE	OVERDOSE	1
ENAB304 032 0004	304	5	5	OVERDOSE	OVERDOSE	1
ENAB304 032 0005	304	0	0	LIVER FAILURE	HEPATIC FAILURE	.
ENAB304 033 0002	304	0	0	OVERDOSE	OVERDOSE	1
ENAB304 033 0005	304	.	.	OVERDOSE	OVERDOSE	1
ENAB304 033 0013	304	.	.	OVERDOSE	OVERDOSE	1
ENAB304 033 0015	304	.	.	BURSITIS	BURSITIS	12
ENAB304 033 0020	304	.	.	ATRIAL FIBRILLATION	FIBRILLATION ATRIAL	1
ENAB304 033 0021	304	.	.	CA PROSTRATE	NEOPLASM MALIGNANT	.
ENAB304 034 0008	304	5	5	PULMONARY EMBOLUS	EMBOLISM PULMONARY	.
ENAB304 034 0011	304	0	0	OVERDOSE	OVERDOSE	1
ENAB304 034 0013	304	.	.	OVERDOSE	OVERDOSE	1
ENAB304 034 0015	304	.	.	BASAL CELL CARCINOMA IN SITU	BASAL CELL CARCINOMA	1
ENAB304 034 0018	304	.	.	BRADYARRHYTHMIA	ARRHYTHMIA	1

ENAB304 034 0019	304			IATROGENIC DIARRHOEA	DIARRHOEA	4
ENAB304 034 0019	304			WATERY DIARRHOEA	DIARRHOEA	2
ENAB304 034 0019	304			FAECAL INCONTINENCE	FAECAL INCONTINENCE	.
ENAB304 036 0001	304	0	0	FRACTURED L PATELLA	BONE FRACTURE	.
ENAB304 036 0004	304	10.5	10.5	OVERDOSE	OVERDOSE	1
ENAB304 036 0005	304	0	0	BASAL CELL CARCINOMAS	BASAL CELL CARCINOMA	71
ENAB304 036 0005	304	0	0	OVERDOSE	OVERDOSE	1
ENAB304 036 0007	304	0	0	ACUTE SYNOVITIS STERNOCLAVICULAR JOINT	SYNOVITIS	23
ENAB304 036 0008	304	12	12	UNSTABLE ANGINA	ANGINA PECTORIS	1
ENAB304 036 0011	304	10.5	10.5	FOOD POISONING	GASTRO-INTESTINAL DISORDER NOS	1
ENAB304 036 0012	304	7	4.5	OVERDOSE	OVERDOSE	1
ENAB304 037 0008	304	0	0	OVERDOSE	OVERDOSE	1
ENAB304 037 0008	304	0	0	OVERDOSE	OVERDOSE	1
ENAB304 037 0011	304	.	.	OVERDOSE	OVERDOSE	1
ENAB304 037 0015	304	.	.	OVERDOSE	OVERDOSE	1
ENAB304 037 0018	304	.	.	OVERDOSE	OVERDOSE	1
ENAB304 038 0002	304	10.5	10.5	HOSPITALISATION AFTER TRANSIENT ISCHAEMIC ATTACK WITH APHASIA	CEREBROVASCULAR DISORDER	1
ENAB304 038 0004	304	0	0	DIZZINESS	DIZZINESS	30
ENAB304 038 0004	304	0	0	CERVICAL ARTHRITIS	ARTHRITIS	30
ENAB304 038 0005	304	0	0	PALPITATION OF THE HEART	PALPITATION	1
ENAB304 038 0014	304	.	.	CARDIAC FAILURE	CARDIAC FAILURE	.
ENAB304 038 0021	304	.	.	DEEP VEINS THROMBOSIS	THROMBOSIS	15
ENAB304 038 0021	304	.	.	ABDOMINAL HAEMATOMA	HAEMATOMA	9
ENAB304 038 0021	304	.	.	HEART INFARCTION	MYOCARDIAL INFARCTION	.
ENAB304 038 0022	304	.	.	RIGHT LEG - THROMBOPHLEBITIS	THROMBOPHLEBITIS	18
ENAB305 302 0003	305	4	4	DEHYDRATION	DEHYDRATION	20
ENAB305 302 0004	305	8	8	HIP FRACTURE	SURGERY	1
ENAB305 302 0004	305	8	8	INSTITUTIONALISATION	PROCEDURE NOS	.
ENAB305 302 0004	305	8	8	SEPTICEMIA	SEPSIS	.
ENAB305 303 0003	305	8	8	THE PATIENT GO INTO MEDICAL INSTITUTION FOR 3 MONTHS	PROCEDURE NOS	.
ENAB305 304 0001	305	12	12	PULMONARY OEDEMA	PULMONARY OEDEMA	2
ENAB305 304 0004	305	12	12	HYPOTENSION	HYPOTENSION	7
ENAB305 304 0004	305	12	12	NAUSEA	NAUSEA	7
ENAB305 304 0004	305	0	0	RESPITE CARE	PROCEDURE NOS	.
ENAB305 305 0004	305	2	2	AGITATION	AGITATION	.
ENAB305 305 0005	305	2	2	OVERDOSE (2 CAPS TAKEN)	OVERDOSE	1
ENAB305 307 0004	305	4	4	PULMONARY EMBOLISM	EMBOLISM PULMONARY	8
ENAB305 307 0005	305	6	0	INSTITUTIONALISATION	PROCEDURE NOS	.
ENAB305 313 0002	305	.	.	MALAISE (HOSPITALISATION)	MALAISE	3
ENAB305 313 0005	305	6	6	MALAISE	MALAISE	105
ENAB305 313 0005	305	6	6	NAUSEA	NAUSEA	111
ENAB305 313 0006	305	4	4	HYPOTENSIVE SYNCOPE	SYNCOPE	1

ENAB305 313 0007	305	8	8	GASTRIC PAIN	ABDOMINAL PAIN	71
ENAB305 313 0007	305	8	8	LEFT ILIAC ANEURISM	ANEURYSM	14
ENAB305 313 0007	305	8	8	SURGERY FOR LEFT ILIAC ANEURISM	SURGERY	1
ENAB305 318 0001	305	10	2.5	CYSTITIS	CYSTITIS	4
ENAB305 321 0001	305	2	2	OVERDOSE	OVERDOSE	1
ENAB305 326 0003	305	8	8	URINARY RETENTION	URINARY RETENTION	15
ENAB305 402 0004	305	2	2	SUICIDE ATTEMPT	SUICIDE ATTEMPT	1
ENAB305 402 0006	305	4	4	INCREASED CONFUSION	CONFUSION	.
ENAB305 402 0007	305	8	8	TRANSIENT ISCHEMIC ATTACK	CEREBROVASCULAR DISORDER	1
ENAB305 402 0008	305	.	.	CONSTIPATION	CONSTIPATION	2
ENAB351 001 0003	351	3	3	RECTAL PROLAPSE REPAIR	SURGERY	1
ENAB351 001 0011	351	2	2	OVERDOSE	OVERDOSE	1
ENAB351 002 0005	351	3	1.5	SYNCOPE	SYNCOPE	1
ENAB351 002 0011	351	3.5	3.5	BRONCHOPNEMONIA	PNEUMONIA	5
ENAB351 002 0011	351	.	.	ATYPICAL CHEST PAIN	CHEST PAIN	2
ENAB351 002 0025	351	9	0	RT. HIP FRACTURE	BONE FRACTURE	2
ENAB351 002 0053	351	9	9	DVT, RT. LOWER EXTREMITY	THROMBOPHLEBITIS DEEP	6
ENAB351 002 0080	351	3	3	PROLONGED P-R INTERVAL	AV BLOCK	.
ENAB351 004 0022	351	.	.	SYNCOPE	SYNCOPE	1
ENAB351 005 0012	351	9	9	HYPERTENSIVE EPISODE	HYPERTENSION	1
ENAB351 005 0012	351	9	9	MYOCARDIAL INFARCTION	MYOCARDIAL INFARCTION	1
ENAB351 006 0006	351	9	9	OVERDOSE	OVERDOSE	1
ENAB351 008 0008	351	.	.	SPINAL STENOSIS	SPINE MALFORMATION	.
ENAB351 008 0008	351	.	.	VENTRICULO-PERITONEAL SHUNT PLACEMENT	SURGERY	1
ENAB351 008 0021	351	9	9	(L) KNEE REPLACEMENT	SURGERY	1
ENAB351 009 0019	351	9	9	ANGINA	ANGINA PECTORIS	1
ENAB351 010 0022	351	3	3	SYNCOPE	SYNCOPE	2
ENAB351 010 0030	351	5	5	OVERDOSE	OVERDOSE	1
ENAB351 010 0041	351	9	9	HYPOTENSIVE EPISODE	HYPOTENSION	3
ENAB351 010 0054	351	3.5	3.5	INC PARANOIA	PARANOID REACTION	.
ENAB351 011 0011	351	5	5	ABDOMINAL ADEMOCARCINOMA	CARCINOMA	.
ENAB351 012 0006	351	.	.	OVERDOSE	OVERDOSE	1
ENAB351 012 0006	351	9	9	OVERDOSE	OVERDOSE	1
ENAB351 012 0037	351	9	4.5	URETHERAL/STRUCTURE/TURP	SURGERY	2
ENAB351 012 0037	351	9	4.5	BLADDER NECK CONTRACTURE	BLADDER DISORDERS NOS	2
ENAB351 013 0001	351	.	.	PNEUMONIA	PNEUMONIA	10
ENAB351 013 0001	351	.	.	PRECANCEROUS POLYP	POLYP COLORECTAL	11
ENAB351 013 0028	351	5	5	BASAL CELL CARCINOMA	BASAL CELL CARCINOMA	1
ENAB351 001 0012	351	.	.	FRACTURED HIP	BONE FRACTURE	3
ENAB351 001 0025	351	.	.	HEARTATTACK	MYOCARDIAL INFARCTION	1
ENAB351 001 0025	351	3.5	3.5	OVERDOSE	OVERDOSE	1
ENAB351 001 0040	351	.	.	GASTRIC ULCER	GASTRIC ULCER	.
ENAB351 002 0040	351	.	.	LEFT KNEE TOTAL REPLACEMENT	SURGERY	1
ENAB351 003 0007	351	2	1	OVERDOSE	OVERDOSE	7
ENAB351 003 0008	351	1.5	1	OVERDOSE	OVERDOSE	1

ENAB351 003 0015	351	6	6	ATYPICAL CHEST PAIN	CHEST PAIN	1
ENAB351 003 0017	351	6	6	VASOVAGAL SYNCOPE DUE TO BRADYCARDIA	SYNCOPE	1
ENAB351 003 0030	351	.	.	LITHOTRIPSY	PROCEDURE NOS	1
ENAB351 003 0030	351	.	.	LITHOTRIPSY	PROCEDURE NOS	1
ENAB351 005 0003	351	4	4	STROKE	CEREBROVASCULAR DISORDER	9
ENAB351 006 0021	351	.	.	BOWEL OBSTRUCTION	INTESTINAL OBSTRUCTION	8
ENAB351 007 0010	351	6	6	OVERDOSE	OVERDOSE	1
ENAB351 007 0026	351	6	6	BLACKOUT	SYNCOPE	4
ENAB351 008 0015	351	.	.	DRUG OVERDOSE	OVERDOSE	7
ENAB351 009 0011	351	2.5	2.5	FRACTURE ® FEMUR	BONE FRACTURE	4
ENAB351 009 0032	351	3.5	3.5	OVERDOSE (4 EXTRA TABLETS)	OVERDOSE	1
ENAB351 010 0051	351	.	.	DEHYDRATION	DEHYDRATION	3
ENAB351 010 0051	351	.	.	SEPSIS	SEPSIS	19
ENAB351 010 0051	351	.	.	ATELECTASIS	ATELECTASIS	.
ENAB351 011 0009	351	3.5	3.5	SYNCOPAL EPISODE	SYNCOPE	1
ENAB351 011 0038	351	6	6	OVERDOSE-STUDY MEDICATION	OVERDOSE	1
ENAB351 012 0031	351	6	6	ATRIAL FIBRILLATION WITH RAPID VENTRICULAR RESPONSE	FIBRILLATION ATRIAL	3
ENAB351 012 0041	351	2	2	PNEUMONIA/LEFT LOBE INFILTRATE	PNEUMONIA	16
ENAB351 013 0008	351	5	5	SQUAMOUS CELL CARCINOMA	SKIN NEOPLASM MALIGNANT	15
ENAB351 014 0009	351	6	6	FAINTED	SYNCOPE	1
ENAB351 014 0015	351	4	4	POSSIBLE TIA	CEREBROVASCULAR DISORDER	1
ENAB351 014 0021	351	6	6	ATRIAL FIBRILLATION	FIBRILLATION ATRIAL	.
ENAB351 001 0004	351	1	1	PNEUMONIA	PNEUMONIA	8
ENAB351 002 0057	351	3	3	ABDOMINAL BLOATING	FLATULENCE	14
ENAB351 003 0011	351	.	.	METASTATIC PROSTATE CA	CARCINOMA	1
ENAB351 004 0011	351	2.5	2.5	ACCIDENTAL OVERDOSE	OVERDOSE	1
ENAB351 004 0021	351	3	3	RESPITE CARE HOSPITALIZATION	PROCEDURE NOS	8
ENAB351 004 0037	351	3	3	ACCIDENTAL OVERDOSE	OVERDOSE	1
ENAB351 004 0039	351	.	.	SEIZURE	CONVULSIONS	1
ENAB351 008 0013	351	3	3	OVERDOSE	OVERDOSE	1
ENAB351 008 0017	351	1	1	STUDY DRUG OVERDOSE	OVERDOSE	1
ENAB351 008 0045	351	1	1	OVERDOSE	OVERDOSE	1
ENAB351 009 0003	351	1	1	STROKE	CEREBROVASCULAR DISORDER	4
ENAB351 010 0014	351	1	1	NEAR SYNCOPE HYPOTENSION	SYNCOPE	1
ENAB351 010 0014	351	1	1	SUSPECTED GI BLEEDING	GI HAEMORRHAGE	3
ENAB351 010 0016	351	.	.	INTRACRANIAL BLEED SECONDARY TO DEPOSIT OF AMYLOID	HAEMORRHAGE INTRACRANIAL	.
ENAB351 010 0024	351	.	.	SEVERE COGNITIVE AND FUNCTIONAL DETERIORATION	DEMENTIA	.
ENAB351 010 0033	351	3	3	MECHANICAL G.I. BLEED	GI HAEMORRHAGE	2
ENAB351 010 0037	351	3	3	CHOLECYSTITIS	CHOLECYSTITIS	3
ENAB351 011 0013	351	.	.	AUTO ACCIDENT	ACCIDENTAL TRAUMA	.
ENAB351 011 0028	351	1	1	LOWER GI BLEEDING	GI HAEMORRHAGE	3
ENAB351 011 0028	351	1	0.5	LOWER GI BLEEDING	GI HAEMORRHAGE	9
ENAB351 011 0028	351	1	1	TRANSIENT ISCHEMIC ATTACK	CEREBROVASCULAR DISORDER	1

ENAB351 002 0061	351	0	0	GALLSTONES WITH ASSOCIATED BILIARY PANCREATITIS	PANCREATITIS	1
ENAB351 003 0045	351	.	.	STROKE (ACUTE CVA)	CEREBROVASCULAR DISORDER	1
ENAB351 004 0009	351	0	0	PARANOID REACTION	PARANOID REACTION	.
ENAB351 004 0036	351	0	0	CANCER (SQUAMOUS CELL, FOCAL TYPE)	SKIN NEOPLASM MALIGNANT	1
ENAB351 004 0036	351	0	0	CANCER RIGHT HAND (SQUAMOUS CELL,INVASIVE)	SKIN NEOPLASM MALIGNANT	1
ENAB351 006 0004	351	0	0	OVERDOSE	OVERDOSE	1
ENAB351 006 0048	351	0	0	OVERDOSE	OVERDOSE	1
ENAB351 007 0007	351	0	0	OVERDOSE	OVERDOSE	1
ENAB351 008 0002	351	0	0	SICK SINUS SYNDROME	SICK SINUS SYNDROME	29
ENAB351 008 0012	351	0	0	REOCURRANCE OF PROSTATIC CANCER	CARCINOMA	.
ENAB351 008 0029	351	0	0	ADENOCARCINOMA OF THE PROSTATE	CARCINOMA	.
ENAB351 008 0046	351	0	0	OVERDOSE (STUDY DRUG)	OVERDOSE	1
ENAB351 009 0020	351	0	0	HYPERTENSIVE EPISODE	HYPERTENSION	2
ENAB351 009 0020	351	0	0	® CAROTID STENOSIS	VASCULAR DISORDER	3
ENAB351 009 0030	351	0	0	SQUAMOUS CELL L EAR	SKIN NEOPLASM MALIGNANT	36
ENAB351 009 0030	351	0	0	SKIN LESION LEFT CHEST QUAMOUS CELL	SKIN NEOPLASM MALIGNANT	74
ENAB351 009 0030	351	0	0	BASAL CELL LEFT EAR	BASAL CELL CARCINOMA	36
ENAB351 010 0063	351	0	0	OVERDOSE	OVERDOSE	1
ENAB351 011 0019	351	0	0	LUMBAR ACQUIRED SPINAL STENOSIS	SPINE MALFORMATION	.
ENAB351 012 0044	351	0	0	DELUSIONS	DELUSION	.
ENAB352 002 0002	352	8	8	TWO DOSE OVERDOSE	OVERDOSE	1
ENAB352 002 0020	352	10.5	10.5	ACUTE MENTAL CONFUSION	CONFUSION	5
ENAB352 002 0023	352	12	12	TIA	CEREBROVASCULAR DISORDER	2
ENAB352 002 0023	352	.	.	CVA	CEREBROVASCULAR DISORDER	1
ENAB352 002 0023	352	12	6	PNEUMOTHORAX - RIGHT	PNEUMOTHORAX	12
ENAB352 004 0023	352	9	9	OVERDOSE	OVERDOSE	1
ENAB352 005 0008	352	9	9	UNSTABLE ANGINA	ANGINA PECTORIS	1
ENAB352 006 0028	352	6	6	HEART FAILURE	CARDIAC FAILURE	4
ENAB352 006 0046	352	7	7	OVERDOSE	OVERDOSE	1
ENAB352 007 0028	352	12	12	SQUAMOUS CELL CARCINOMA ® ARM	SKIN NEOPLASM MALIGNANT	1
ENAB352 007 0028	352	12	12	SQUAMOUS CELL CARCINOMA ® CHEEK	SKIN NEOPLASM MALIGNANT	1
ENAB352 007 0035	352	12	12	OVERDOSE	OVERDOSE	1
ENAB352 008 0019	352	7	7	FIBROMYALGIA	MYALGIA	3
ENAB352 008 0019	352	7	7	FUNCTIONAL PAIN DISORDER	PAIN	3
ENAB352 009 0013	352	6	6	OVERDOSE	OVERDOSE	1
ENAB352 009 0027	352	3	3	NEPHROLITHIASES	RENAL CALCULUS	3
ENAB352 010 0037	352	6	6	CANCER	CARCINOMA	.
ENAB352 011 0007	352	7	10.5	OVERDOSE	OVERDOSE	1

ENAB352 011 0010	352	3	3	OVERDOSE	OVERDOSE	1
ENAB352 015 0002	352	8	8	DRUG OVERDOSE	OVERDOSE	1
ENAB352 015 0033	352	12	12	FIRST DEGREE BURNS FACE & HANDS (ACCIDENTAL)	ACCIDENTAL TRAUMA	15
ENAB352 015 0039	352	6	6	POSSIBLE MYOCARDIAL INFARCTION	MYOCARDIAL INFARCTION	1
ENAB352 018 0007	352	9	9	OVERDOSE	OVERDOSE	1
ENAB352 019 0023	352	6	6	SYNCOPE	SYNCOPE	1
ENAB352 020 0003	352	7	7	STROKE	CEREBROVASCULAR DISORDER	2
ENAB352 020 0003	352	8	4	RIGHT BRACHIAL ARTERY EMBOLUS	EMBOLISM ARTERIAL	2
ENAB352 020 0003	352	10.5	5	EMBOLUS TO LEFT LEG	EMBOLISM LIMB	2
ENAB352 020 0008	352	7	7	ATRIAL FIBRILLATION	FIBRILLATION ATRIAL	.
ENAB352 020 0022	352	10.5	10.5	UNABLE TO STAND-SYNCOPE	SYNCOPE	1
ENAB352 020 0022	352	4	4	HIP FRACTURE	BONE FRACTURE	1
ENAB352 020 0030	352	12	12	ACCIDENTAL COLD EXPOSURE	ACCIDENTAL TRAUMA	1
ENAB352 021 0023	352	10.5	10.5	URI/VIRAL PNEUMONIA	INFECTION VIRAL	8
ENAB352 021 0029	352	9	4.5	PRE-SYNCOPE	SYNCOPE	1
ENAB352 022 0005	352	8	8	OVERDOSE	OVERDOSE	1
ENAB352 001 0012	352	.	.	CEREBELLAR INFARCTION	CEREBROVASCULAR DISORDER	.
ENAB352 002 0016	352	4	4	BREAST PAPILLARY NEOPLASM	BREAST NEOPLASM MALIGNANT FEMALE	68
ENAB352 002 0019	352	3	3	OVERDOSE	OVERDOSE	1
ENAB352 002 0022	352	4	4	ANGINA	ANGINA PECTORIS	4
ENAB352 002 0027	352	4	0	GI OBSTRUCTION (HERNIA)	HERNIA	3
ENAB352 002 0038	352	1	1	PAROXYSMAL ATRIAL FIBRILLATION WITH RAPID VENTRICULAR RESPONSE	FIBRILLATION ATRIAL	3
ENAB352 004 0008	352	1	1	® CVA	CEREBROVASCULAR DISORDER	.
ENAB352 004 0011	352	4	4	RENAL CORTICAL CYSTS	RENAL CYST	.
ENAB352 004 0043	352	4	4	ATRIAL FIBRILLATION	FIBRILLATION ATRIAL	3
ENAB352 004 0043	352	4	4	ATRIAL FIBRILLATION	FIBRILLATION ATRIAL	7
ENAB352 004 0043	352	4	4	CONGESTIVE HEART FAILURE	CARDIAC FAILURE	4
ENAB352 006 0037	352	3	3	OVERDOSE	OVERDOSE	1
ENAB352 008 0004	352	4	4	SILENT MI	MYOCARDIAL INFARCTION	1
ENAB352 008 0010	352	.	.	INCREASED LIVER ENZMES	HEPATIC ENZYMES INCREASED	.
ENAB352 008 0017	352	1	1	SQUAMOUS CELL CA	SKIN NEOPLASM MALIGNANT	12
ENAB352 009 0029	352	1	1	SQUANOUS CELL CARCINOMIA	SKIN NEOPLASM MALIGNANT	6
ENAB352 010 0039	352	4	4	LEFT FAILED HIP REPLACEMENT - SECONDARY TO ACETABULAR LOOSENING.	SURGERY	10
ENAB352 011 0008	352	.	.	BRADYCARDIA	BRADYCARDIA	1
ENAB352 011 0008	352	3	3	SYNCOPE	SYNCOPE	4
ENAB352 011 0012	352	4	4	MYOCARDIAL INFARCTION	MYOCARDIAL INFARCTION	.
ENAB352 013 0001	352	.	.	VERTIGO	VERTIGO	1
ENAB352 013 0001	352	4	4	OVERDOSE	OVERDOSE	1
ENAB352 015 0017	352	4	4	CA LESION ON RIGHT SHIN-BASAL CELL CARCINOMA	BASAL CELL CARCINOMA	32
ENAB352 015 0037	352	4	4	BASAL CELL CARCINOMA	BASAL CELL CARCINOMA	1

ENAB352 016 0032	352	4	0	(R) HIP FX	BONE FRACTURE	2
ENAB352 017 0004	352	4	4	ATYPICAL CHEST PAIN (GI)	GASTRO-INTESTINAL DISORDER NOS	1
ENAB352 018 0010	352	2.5	1.5	OVERDOSE	OVERDOSE	1
ENAB352 020 0033	352	1.5	1.5	TRANSIENT ISCHEMIC ATTACK	CEREBROVASCULAR DISORDER	1
ENAB352 022 0006	352	1	1	OVERDOSE	OVERDOSE	1
ENAB352 022 0006	352	1	1	OVERDOSE	OVERDOSE	1
ENAB352 022 0024	352	.	.	COMBATIVENESS	AGGRESSIVE REACTION	.
ENAB352 022 0024	352	.	.	VIOLENCE	AGGRESSIVE REACTION	.
ENAB352 022 0024	352	.	.	AGITATION	AGITATION	.
ENAB352 001 0010	352	0	0	CONGESTIVE HEART FAILURE	CARDIAC FAILURE	.
ENAB352 001 0013	352	0	0	PROBABLE OVERDOSE	OVERDOSE	1
ENAB352 002 0003	352	0	0	SEIZURE	CONVULSIONS	1
ENAB352 002 0011	352	0	0	ONE DOSE OVER DOSE	OVERDOSE	1
ENAB352 002 0026	352	0	0	SQUAMOUS CELL CARCINOMA	SKIN NEOPLASM MALIGNANT	1
ENAB352 004 0022	352	0	0	FALL	ACCIDENTAL TRAUMA	1
ENAB352 004 0045	352	0	0	TUBULAR ADENOMA WITH FOCAL DYSPLASTIC CHANGES	ADENOCARCINOMA NOS	1
ENAB352 005 0017	352	0	0	SILENT MYOCARDIAL INFARCT	MYOCARDIAL INFARCTION	1
ENAB352 006 0006	352	0	0	OVERDOSE	OVERDOSE	1
ENAB352 006 0008	352	0	0	GASTRITIS R/O PUD	GASTRITIS	1
ENAB352 006 0008	352	0	0	PAPILLARY TRANSTIONAL CELL CARCINOMA	BLADDER CARCINOMA	.
ENAB352 006 0043	352	0	0	OVERDOSE	OVERDOSE	1
ENAB352 007 0016	352	0	0	OVERDOSE	OVERDOSE	1
ENAB352 007 0021	352	0	0	OVERDOSE	OVERDOSE	2
ENAB352 007 0030	352	0	0	OVERDOSE	OVERDOSE	1
ENAB352 007 0030	352	0	0	OVERDOSE	OVERDOSE	1
ENAB352 008 0020	352	.	.	OVERDOSE	OVERDOSE	6
ENAB352 010 0007	352	0	0	SICK SINUS SYNDROME	SICK SINUS SYNDROME	54
ENAB352 010 0020	352	0	0	BASAL CELL CARCINOMA	BASAL CELL CARCINOMA	1
ENAB352 010 0034	352	0	0	LYMPHOMA	LYMPHOMA MALIGNANT	.
ENAB352 010 0038	352	0	0	SMALL BOWEL OBSTRUCTION DUE TO ADHESIONS	INTESTINAL OBSTRUCTION	3
ENAB352 011 0018	352	0	0	BENIGN PROSTATIC HYPERTROPHY	PROSTATIC DISORDER	7
ENAB352 011 0019	352	0	0	HERNIA, (L) INGUINAL	HERNIA	3
ENAB352 012 0011	352	0	0	FECAL IMPACTION	CONSTIPATION	1
ENAB352 012 0023	352	0	0	INGUINAL HERNIORRHAPHY	SURGERY	1
ENAB352 012 0023	352	0	0	PROSTATE SURGERY	SURGERY	1
ENAB352 014 0008	352	0	0	PLEURISY	PLEURISY	20
ENAB352 015 0019	352	0	0	OVERDOSE	OVERDOSE	1
ENAB352 016 0016	352	0	0	BEGIGN PROXYSMAL POSTIONAL VERTIGO	VERTIGO	1
ENAB352 016 0019	352	0	0	LOSS OF CONSCIOUSNESS	SYNCOPE	1
ENAB352 018 0005	352	0	0	OVERDOSE	OVERDOSE	1
ENAB352 019 0006	352	0	0	SUPRA VENTRICULAR TACHYCARDIA	TACHYCARDIA SUPRAVENTRICULAR	.
ENAB352 019 0008	352	0	0	STROKE	CEREBROVASCULAR DISORDER	.

ENAB352 019 0008	352	.		ASPIRATION PNEUMONIA	PNEUMONIA	14
ENAB352 019 0008	352	.		ABDOMINAL WALL CELLULITIS	CELLULITIS	11
ENAB352 019 0020	352	0	0	OVERDOSE	OVERDOSE	1
ENAB352 019 0020	352	0	0	OVERDOSE	OVERDOSE	1
ENAB352 021 0013	352	0	0	SKIN CANCER, LEFT-STERNUM	SKIN NEOPLASM MALIGNANT	14
ENAB352 021 0013	352	0	0	SKIN LESION, RIGHT-STERNUM, BOWEN'S DZ	SKIN NEOPLASM MALIGNANT	14
ENAB352 021 0013	352	0	0	SKIN CANCER, MD - UPPER CHEST	SKIN NEOPLASM MALIGNANT	1
ENAB352 021 0013	352	0	0	SKIN CANCER, LEFT BACK/SHOULDER	SKIN NEOPLASM MALIGNANT	1
ENAB352 021 0018	352	0	0	DIVERTICULOSIS	DIVERTICULITIS	7
ENAB352 022 0004	352	0	0	OVERDOSE	OVERDOSE	3
ENAB352 022 0007	352	0	0	OVERDOSE	OVERDOSE	1
ENAB352 022 0007	352	0	0	OVERDOSE	OVERDOSE	1
ENAB353 102 0003	353	.	.	AGITATION	AGITATION	.
ENAB353 102 0003	353	.	.	DELUSIONS	DELUSION	.
ENAB353 102 0006	353	12	12	DIAPHORESIS	SWEATING INCREASED	1
ENAB353 103 0026	353	.	.	ATYPICAL CHEST PAIN,CVS	CHEST PAIN	2
ENAB353 103 0027	353	.	.	SQUAMOUS CELL CARCINOMA	SKIN NEOPLASM MALIGNANT	1
ENAB353 103 0034	353	8	8	VASODEPRESSOR SYNCOPE	SYNCOPE	1
ENAB353 104 0021	353	10	10	RESPITE CARE HOSPITALIZATION	PROCEDURE NOS	8
ENAB353 105 0006	353	6	6	MALIGNANT MELANOMA (L) ARM	MELANOMA MALIGNANT	49
ENAB353 105 0010	353	4	2	ATYPICAL CHEST PAIN, CARDIAC	ANGINA PECTORIS	1
ENAB353 105 0010	353	.	.	LOWER GI BLEED DUE TO DIVERTICULITIS	DIVERTICULITIS	3
ENAB353 106 0007	353	10	5	PNEUMONIA	PNEUMONIA	2
ENAB353 107 0009	353	.	.	KIDNEY FAILURE	RENAL FAILURE ACUTE	.
ENAB353 107 0009	353	12	6	PNEUMONIA	PNEUMONIA	11
ENAB353 107 0015	353	.	.	AGITATION	AGITATION	.
ENAB353 110 0007	353	.	.	"COMPASSIONATE" ADMISSION	REACTION UNSPECIFIED	4
ENAB353 110 0026	353	6	6	TRANSIENT UNRESPONSIVENESS OF THE ELDERLY	CONCENTRATION IMPAIRED	4
ENAB353 110 0026	353	6	3	TRANSIENT UNRESPONSIVENESS OF THE ELDERLY	CONCENTRATION IMPAIRED	5
ENAB353 112 0008	353	6	6	BASAL CELL CA	BASAL CELL CARCINOMA	1
ENAB353 202 0012	353	6	6	OVERDOSE	OVERDOSE	1
ENAB353 203 0001	353	10	10	TIA	CEREBROVASCULAR DISORDER	1
ENAB353 205 0002	353	4	0	ELEVATED LIVER FUNCTIONS	HEPATIC ENZYMES INCREASED	127
ENAB353 205 0002	353	4	4	HOSPITALIZATION - LOW NA	HYPONATRAEMIA	3
ENAB353 205 0003	353	10	10	SYNCOPAL EPISODE	SYNCOPE	1
ENAB353 205 0003	353	.	.	SYSNCOPAL EPISODE/HOSPITALIZATION	SYNCOPE	1
ENAB353 207 0002	353	8	8	CHEST PAIN	CHEST PAIN	1
ENAB353 207 0002	353	.	.	OVERDOSE	OVERDOSE	1
ENAB353 207 0002	353	8	8	OVERDOSE	OVERDOSE	1
ENAB353 207 0003	353	12	12	MYOCARDIAL INFARCTION	MYOCARDIAL INFARCTION	1
ENAB353 210 0013	353	8	8	BRADYCARDIA	BRADYCARDIA	2

The evidence adduced in both Studies B303 and B 352 documents that patients with mild to moderate senile dementia of the Alzheimer's type have a better outcome after 26 weeks of treatment (nominal duration only as a substantial proportion of patients in the high dose group failed to complete their scheduled assignments[2]) when randomized to doses of rivastigmine in the 6-12 mg than those randomized to placebo as assessed by the two outcome measures the Division has relied upon for the past 8 years in its assessment of antidementia drug products (i.e., the ADAScog and the so-called CIBIC, a clinician's Interview based clinical global assessment of improvement). The outcomes of patients randomized to the lower dose range of rivastigmine (1 to 4 mg) were not statistically different from those randomized to placebo (despite the relatively large sample sizes employed), although the small differences observed were numerically favorable.

It is noteworthy, that the CIBIC, as used in the Exelon drug development program is probably different (is structured) than that used in previous trials of other antidementia drug products (i.e, with tacrine, mentane, and E2020). I have long been concerned that the use of a structured/semi structured global to some degree defeats the intent of the dual outcome assessment strategy that the Division developed in that it further[3]

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have (in theory) found the 9 mg arm statistically different from placebo (realized ITT CIBIC plus scores were 4.06 vs. 4.21, respectively, consistent with a modest superiority for rivastigmine). This again illustrates how inadequate a 'p' value actually is as a measure of the strength of evidence.

[2] In study 303, 157 of 242 hi dose vs 202 of 242 low dose and 205 of 238 placebo completed 26 weeks (completion rates of 65%, 83% and 86%). In Study 352, 157 of 231 hi dose, 194 of 233 lo dose and 192 of 234 placebo patients completed (completion rates of 68%, 83% and 82%)

reduces the relative contribution that the clinician's assessment of interview behavior makes to the score.

At this point in time, however, I believe the agency is essentially obliged, at least insofar as proof of principle of efficacy is concerned, to accept these variations in the use the global, for no other reason than the fact that it is literally impossible to control, at least in any practical sense, how a global assessment is actually made, whatever the protocol rules for a study may require.

The only point worth making about the evidence of effectiveness adduced in this application is that, to the extent it is possible to tell from the between group differences in ADAScog scores, the magnitude of Exelon's treatment effect seems roughly equivalent[4] to that found for both tacrine and E2020. Accordingly, although Exelon may be reasonably claimed to provide an advantage to tacrine in respect to convenience of use (there is no need for biweekly LFTs), it offers no advantage to E2020 (Aricept), a fact that is of importance in consideration of the risks and benefits of rivastigmine.

[4] This point deserves emphasis. In at least one public meetings that I attended, a Novartis spokesperson made a presentation emphasizing that patients randomized to rivastigmine actually improved over the 26 weeks of treatment in contrast to a study of a competitor's drug product (e.g., E2020 in particular), in which the within group status of patients deteriorated despite active treatment. The proper comparison, of course, is not within group changes from baseline, but the between group difference in the change from baseline. The difference in within group outcome among studies may reflect chance, or a systematic difference in the nature of the sample of patients recruited for study.

Safety in ~~Use~~

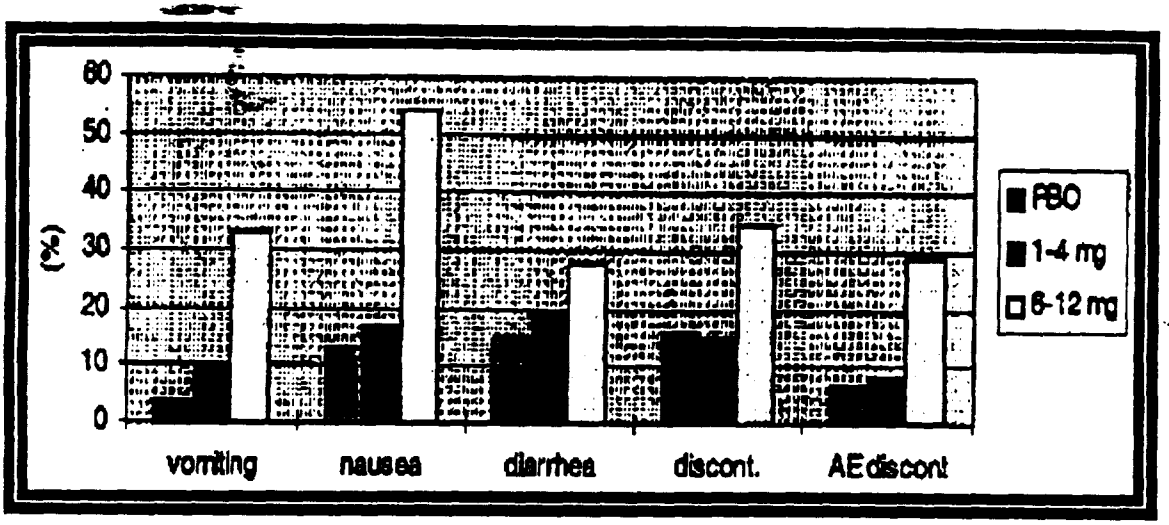
Extent of exposure

Mean Daily Dose mg/ day	Exposure (Weeks)							
	Any Exp. n (%)	≥1 n (%)	≥2 n (%)	≥4 n (%)	≥12 n (%)	≥26 n (%)	≥38 n (%)	≥52 n (%)
≤3	535 (100)	514 (96)	485 (91)	451 (84)	378 (71)	128 (24)	6 (1)	4 (1)
>3 - 6	1266 (100)	1265 (100)	1244 (98)	1178 (93)	971 (77)	513 (41)	91 (7)	74 (6)
>6 - 9	586 (100)	586 (100)	586 (100)	584 (100)	456 (78)	248 (42)	47 (8)	33 (6)
>9 - 12	619 (100)	619 (100)	619 (100)	619 (100)	619 (100)	360 (58)	142 (23)	109 (18)
Total	3006 (100)	2984 (99)	2934 (98)	2832 (94)	2424 (81)	1249 (42)	286 (10)	220 (7)

The table above, taken from Table 4, page 14 of the Oliva et al Safety review of 3/10/98, displays the cumulative distribution (by time) of exposure to rivastigmine by dose in all treatment studies. Even if interest is restricted to doses in the proposed therapeutic dose range (i.e., ≥ 6 mg a day), the there are more than sufficient to meet current ICH guidances for chronic exposure.

Clinical Adverse Events and discontinuations

Clinical trial experience with rivastigmine documents that the use of rivastigmine is associated with the a set of dose related cholinergic dysphoric untoward events typical of the drug class. The discontinuation rate follows an identical pattern as is illustrated by the table below for Study 352 (from page 25 of the Oliva et al 3/10/98 review).



Further analyses of the adverse reaction data reveal that female sex (see table from page 56 of the Oliva et al 3/10/98 review) and older age are associated with a higher incidence of these common cholinergic events.

Table 34: AE's by Sex, Phase 3 Controlled Trials

	Males			Females		
Body System Adverse Event	Exelon N= 711 n (%)	>6- 12 mg N= 218 n (%)	PBO N= 815 n (%)	Exelon N= 985 n (%)	> 9- 12 mg N= 258 n (%)	PBO N= 448 n (%)
At Least One AE	596 (84)	193 (89)	252 (80)	873 (89)	236 (91)	352 (79)
Gastrointestinal	347 (49)	123 (56)	100 (32)	636 (65)	185 (72)	158 (35)
Nausea	184 (26)	83 (38)	25 (8)	414 (42)	125 (48)	65 (15)
Vomiting	107 (15)	51 (23)	9 (3)	255 (26)	87 (34)	33 (7)
Diarrhea	115 (16)	44 (20)	40 (13)	166 (16)	53 (21)	45 (10)
Anorexia	65 (9)	33 (15)	7 (2)	144 (15)	47 (18)	15 (3)
Abdominal Pain	47 (7)	14 (6)	14 (4)	127 (13)	37 (14)	34 (8)

Other findings gained in the phase 3 controlled trials that occur a greater frequency among Exelon than placebo randomized patients are: anorexia and weight loss, abdominal pain, syncope, and dizziness. Dr. Oliva also believes there is a suggestion in the data that GI bleeding and melena may be more common among Exelon exposed patients.

A review of systems summary of the untoward clinical findings (pages 94 to 107 of the Oliva et al 3/10/98) review reveals that other potentially

clinically important events/findings occur at a more or less similar frequency among placebo and rivastigmine randomized patients. While superficially reassuring, the failure to find differences between rivastigmine and placebo for these low frequency events actually has little inferential value.

Lab Data, Vital signs and Special Tests

Less than 1% of premature discontinuations were attributed to adverse laboratory findings or a change in vital signs .

A review of laboratory tests results failed to identify any risk that could be specifically attributed to the use of rivastigmine.

EKG were obtained on several hundred patients and were deemed largely unremarkable although there were findings of first degree heart block (pr interval lengthening) and bradycardia as would be expected of a cholinomimetic drug that enhances vagal tone.

Mortality Risk and Exelon dose

Nothing so far described in this memorandum about untoward clinical events or laboratory findings reported in association with Exelon would preclude a determination that the product is, within the meaning of the Act, safe for use.

There is a finding that raises serious concerns about the Exelon's safety, however. The pattern of deaths reported in the sponsor's development program is, in the judgment of the Division's review team, "consistent" with the possibility that the use of rivastigmine at doses in the upper part of the range (9 to 12 mg/day) at which the drug has been shown effective in controlled trials, doses that, therefore, would be within the range of those recommended for use were Exelon to be approved, are associated with an increased risk of death..

The initial finding in the RCT data

Dr. Oliva became concerned about a possible linkage between rivastigmine

exposure and an excess risk of mortality when he discovered that the mortality rate (based on incidence density) among Exelon treated patients in "phase 2/3" controlled clinical trials was roughly six fold the rate observed among placebo patients. (30/1000 PY vs 5/1000 PYs) [PY=patient- years]. The patient time used by Dr. Oliva was only approximate, however, and Dr. Racoosin, a physician epidemiologist in the Division's Safety Unit was asked by Dr. Burkhart, accordingly, to re-evaluate the data using a more precise estimate, and, if the signal persisted, to use a nested case control analytic strategy to evaluate the signal in a manner that could account for the systematic differences in time at risk among placebo, low dose, and high dose patients.

In her 1/22/98 memorandum to the file, Dr. Racoonsin reported that an incidence density comparison based on a more accurate quantification of the time at risk from data available for patients in Studies 303, 351 and 352, the phase 3 controlled trials upon which the sponsor relies to support its claims of effectiveness, confirmed Dr. Oliva's original finding, revealing a mortality rate of 10.1 deaths per 1000 PYs [i.e. 6/592.3 PY] among rivastigmine randomized patients as compared to zero deaths among 286.1 patient years accumulated by placebo randomized patients.

Dr. Racoosin's nested case control analysis and risk sets

Dr. Racoosin then carried out the nested case control study using data extracted from a file the sponsor had submitted earlier (9/17/98) that contained information not only from the randomized segments of the controlled trials, but from open extensions to them as well.
Her results, repeated with two different matched[5] sets of controls, reveal

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[5] The fact that the controls were matched deserves emphasis because in its efforts to discount the positive findings of the case control analysis the firm asserts, incorrectly, that the controls used were taken from some common pool of all studies and, therefore, are a potentially biased reference group. Although such a bias might be operative in some case control studies, it is not a factor in Dr. Racoonsin's. In her study, controls were matched not only for time at risk, but for their study of origin and their domestic status. I note, too, that the firm's assertions about the control group are difficult to explain in that they were provided in January with a copy of Dr. Racoonsin's review in which the methodology she used, that which I just described, is outlined in depth.

an unambiguous dose related pattern of increasing dose related risk whether dose is expressed in terms of last prescribed dose or last prescribed dose adjusted for body weight.

Last prescribed dose **Last prescribed dose/kg**

Dose	Con-trol # 1	Con-trol # 2	Com-bined		Con-trol # 1	Con-trol # 2	Com-bined
	OR	OR	OR		OR	OR	OR
< 4 mg	1	1	1		1	1	1
4-6 mg	6.6	4.1	5.5		2	1.4	1.4
6.1- 9 mg	5.4	5.5	5.3		3.9	2.9	3.5
> 9 mg	11.5	8.1	9.8		6	4.8	4.7

The preceding table, derived from data presented in Table 1 of Dr. Racoosin's 1/22/98 review, presents ODDs ratios for 4 arbitrary dose range categories. Dr. Racoosin also evaluated the influence of dose on risk of mortality for the same data set and a continuous measure of dose and obtained, interestingly, for both the last prescribed dose, and last prescribed dose per kilogram nearly significant (p=0.063) and highly significant (p= 005) results, respectively. It deserves note that the correction for weight is somewhat problematic in that it reflects weight at baseline, not weight contemporaneous[6] with the time the risk set represents.

Case control risk set construction: a brief digression

A brief digression about the methodology used to construct risk sets is in order at this point. From the perspective of anyone who is not an

epidemiologist analyses that rely upon it, like nested case control, will have considerable appeal because an examination of risk sets provides a simple and readily understandable means to see the impact of a factor on the outcome without the need to resort to, and to understand, a complex mathematical model.

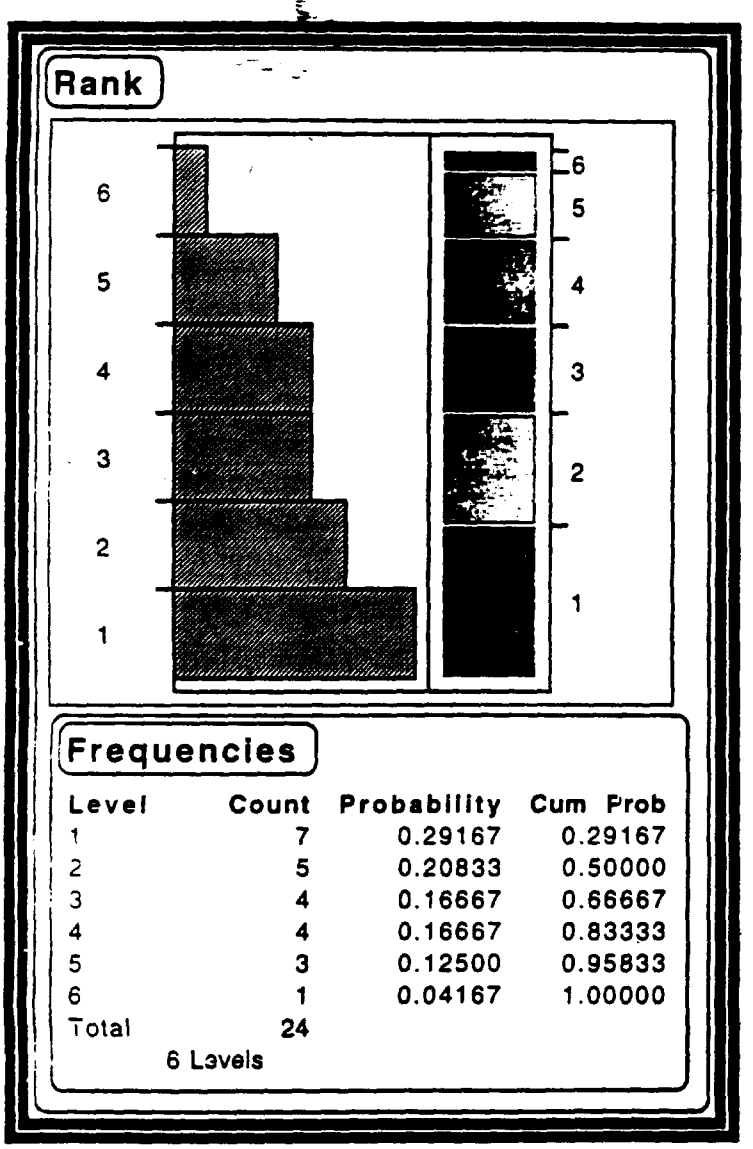
The logic of case matching and the construction of risk sets is, moreover, not only self evident logically, but widely accepted as a standard method among epidemiologists. Basically, each reported case (death) is associated with a set of controls (in this instance 5 controls for each death) drawn randomly from a "matched" subset of the population of patients alive and at risk for at least the same amount of time as the case. The group of individuals consisting of the case and its matched controls constitutes a "risk set." In a case control analysis, a risk set is generated for each death to be considered in the analysis.

The matching process removes all opportunity for the confounding of time and dose within a risk set. The matching procedure can also be used to ensure that the controls for a given case come from the same source population as the case (e.g., in Dr. Racoosin's study, the controls were patients from the same study and geographical area (US vs non-US)).

To illustrate how an examination of risk sets can be informative without resort to sophisticated mathematical manipulation, let us consider the risk sets used in Dr. Racoosin's analysis. Under the null, that is, if dose has no effect on risk of death (i.e.,of being a case), in only one of every 6 risk sets would the case rank first among the members of the set in the magnitude of the dose of rivastigmine being administered.

Specifically, among the 24 risk sets created for the 24 deaths in Dr. Racoosin's analysis, in only 4 (i.e., 1/6) would the case be expected under the null of no dose effect to rank first among the members of a set in respect to the dose of rivastigmine last administered. The summary table/illustration (following page) was generated from a JMP™ data set provided to me by Dr. Burkhart. It reveals that not only are their more risk sets (7/24)in which the case has the highest ranking dose (i.e., level one) that there is a general tendency of the cases to be among the higher ranks across all 24 risk sets.

The simplicity of this approach, in particular the lack of a need to decide on boundaries for dose categories as is necessary to construct ODDs ratios for dose range categories or specify a categorical covariate as is required in a poisson regression model deserves emphasis.



Steps taken to engage the sponsor in a joint effort to explore the signal of risk identified in the nested case control analysis

The findings of the nested case control were clearly consistent with a rivastigmine dose associated increase in the risk of mortality. Accordingly, I asked the review team to provide a copy of her report to the firm, and to call them so that we could explain to its representatives why the Division viewed the finding, which was carefully described as but a signal of risk, disconcerting.

Among many suggestions made and discussed, the Division encouraged the sponsor to obtain exposure data from additional patients who had been treated with rivastigmine in open titration studies as well as to report upon additional time that had accumulated since the submission of the safety update (data from patients in both the controlled trials and extensions to them). The goal was to include as many deaths as possible