Review of Clinical Data

NDA:	21-487
Drug Name:	Memantine
Sponsors:	Forest
Material Reviewed:	Response to Reviewer Safety Questions, 8/29/03
Reviewer:	Gerard Boehm, MD, MPH
Date Completed:	9/25/03

The purpose of this memo is to review Forest's responses to requests for additional safety information.

Background

As part of the NDA safety review, I asked Forest to provide additional information about several adverse events. Specifically, I requested follow up information for two post marketing reports of toxic epidermal necrolysis (TEN), one of aplastic anemia, and one for a 15 day report of an encephalopathy case. I also requested information for a subject in the NDA with an elevated sodium and a subject identified with a lymphoma-like reaction.

Response to Reviewer Questions

TEN Cases

Forest reported two cases of TEN in a submitted line listing of post marketing reports. I requested additional information about these cases.

Merz001#3#1992-10340000. A 65 year old female was treated with memantine, 10mg/day, from 1/8/91 to 1/17/91. On 1/15/91, she was diagnosed with TEN (no details about the event or the diagnosis). She was transferred to a specialty hospital on January 23, 1991 where she died of circulatory failure. The listed concomitant drugs included allopurinol, sulfamethoxazole, furosemide, triamterene, tetrazepam, norfloxazim, ethacrinic acid, clemastine, and dopamine. Forest noted that the dates of sulfamethoxazole treatment were 1/7/91 through 1/15/91.

BfArM 92008036. A 91 year old female was began treatment with memantine on 1/14/91. On 2/14/91, she was diagnosed with TEN (no details about the event or the diagnosis). She died and her death was attributed to TEN and circulatory failure. Forest noted that this patient had a history of allergic reaction to aspirin (exanthema) and a history of TEN following the use trimethoprim/sulfamethoxazole. Her concomitant medications at the time of the event were trimethoprim/sulfmethoxazole, allopurinol, furosemide, tramadol, captopril, clemastine, isosorbide dinitrate, digitoxin, prazosin, and nadroparin calcium.

Aplastic Anemia

Forest identified a case of aplastic anemia in a submitted line listing of post marketing reports. I requested additional information about this case.

Merz 001#1996-10525000. A 70 year old female began treatment with memantine on 7/3/95 and stopped on 9/25/95 (reason for stopping not provided). On 12/24/95, she was diagnosed with pancytopenia and aplastic anemia (no information about event or diagnosis). There were no concomitant drugs reported.

Encephalopathy

In the NDA safety review, I summarized details from a 15 day report that described an event of encephalopathy and tremor that occurred in a subject with Alzheimer's disease treated with memantine in an open label extension. I asked Forest to provide an update for this case. Forest provided blood chemistry results for this subject. Aside from an elevated C-reactive protein result of 1.73 (normal 0.2-0.6) and elevated glucose (highest reported around the time of the event 210mg/dL) Forest did not report any markedly abnormal blood chemistry results for this subject. Forest reported that a CSF analysis was not performed as part of the subject's evaluation. Forest asked the investigational site (Japan) if blood gases or cultures were performed and stated that this information would be forwarded to HFD-120 as it becomes available. Forest reported that memantine was discontinued on 4/2/03, and that the last occurrence of tremor was 4/9/03.

Elevated Sodium

9403-00035. A 73 year old male who received memantine in a placebo controlled trial, had an end-study sodium of 189 and potassium of 6.25 (two days after last memantine dose). These abnormalities were not associated with reported AEs. One month earlier his sodium was 142.5 and potassium was 4.4. Forest offered that these results may have been lab errors and reported that they had no follow up labs.

Lymphoma-like reaction

192944-004-138. A 74 year old man treated in a placebo controlled trial (treatment blind not yet broken), was hospitalized on 10/5/00 for fever. Study drug was stopped on 10/10/00, after approximately twelve months of treatment. The subject was discharged on 10/20/00 and the fever was reported to be unresolved. The subject was readmitted to a hospital on 11/9/00 and diagnosed with lymphoma. He began radiation treatment on 11/17/00 and he died 11/29/00. The subject was taking lisinopril, coumadin, and cerivastatin at the time of the event.

Discussion

Forest provided responses to reviewer safety questions and the responses included some useful information. None of the submitted information results in marked changes in our understanding of memantine's safety profile or requires inclusion in proposed memantine labeling. Both TEN cases are confounded by the use of other medications that can cause TEN, and therefore do not constitute a strong safety signal. The aplastic anemia case was reportedly diagnosed three months after stopping memantine and there is no information about the time course of this event. It would have been helpful to know the patient's CBC results at the time of discontinuation of memantine. While the aplastic anemia case does not constitute a strong safety signal, the division should be aware of this case in the event additional cases of aplastic anemia are reported following approval. The updates for the elevated sodium and lymphoma events provided little additional useful information.

Forest should report the lymphoma patient's treatment when the blind is broken. Forest should also report the requested blood gas and culture information for the subject with encephalopathy.

Recommendations

When the treatment blind is broken, Forest should report the treatment assignment for subject 192944-004-138.

Forest should report follow up information for the encephalopathy case (they already agreed to provide this information).

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/s/

Jerry Boehm
9/25/03 08:41:08 AM
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9/26/03 09:53:10 AM
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NDA Safety Review

NDA:	21-487
Drug Name:	Generic Name: Memantine Proposed Trade Name: Pending
Sponsor:	Forest Laboratories, Inc.
Reviewer:	Gerard Boehm, MD, MPH

The Executive Summary-Safety Review

Memantine is an NMDA receptor antagonist that is administered orally. Memantine has been marketed in Germany as Akatinol Memantine since 1982 for the treatment of Parkinsonism, cerebral and peripheral spasticity, and organic brain syndrome. In 2002, the European Union approved memantine for the treatment of Alzheimer's disease. Forest is seeking FDA approval to market memantine for the treatment of moderate to severe dementia of the Alzheimer's type. The currently approved Alzheimer's disease treatments are acetylcholinesterase inhibitors and are approved for the treatment of mild to moderate dementia of the Alzheimer's type.

The memantine NDA development program included primary safety data from eight phase II/III double blind, placebo controlled trials in dementia (vascular and Alzheimer's type), four open label extensions of these trials, and two phase II/III double blind, placebo controlled trials in neuropathic pain. Forest also submitted safety data from thirty clinical pharmacology trials, and limited safety data from completed trials exploring other treatment indications, from ongoing trials, and from post marketing reports.

The NDA includes 487 subjects exposed to memantine in clinical pharmacology trials and 1,748 subjects exposed to memantine in dementia and neuropathic pain trials. Forest reports that over 4,000 patients have been exposed in completed trials exploring other treatment indications and in ongoing trials. Forest estimates over 400,000 person years of memantine exposure in post marketing use.

The number of patients exposed in the primary safety data trials exceeds ICH guidelines, and Forest submitted adequate safety data for the intended recommended dose. However, only a subset of those exposed in the primary data had Alzheimer's disease. In the Group 1 dementia placebo controlled trials, approximately 42% of memantine exposed subjects had diagnoses of Alzheimer's dementia with the remaining subjects having vascular dementia. There did not appear to be meaningful differences in memantine's safety profile when comparing the Alzheimer's and vascular dementia populations.

The safety testing, capture of adverse events, coding of investigator terms and analyses of safety data were generally adequate. The safety data were consistent across the submitted case report forms, electronic data sets, and summary tables.

In the dementia placebo controlled trials, the percentage of subjects who died was similar in the memantine and placebo treatment groups. The reported causes of death were those expected in an elderly population.

Memantine and placebo subjects had similar SAE risks, and there did not appear to be clusters of unexpected SAEs in memantine exposed individuals. In the primary data trials there were no SAEs of liver failure, acute renal failure, rhabdomyolysis, aplastic anemia, serious skin reactions, or pancreatitis. Three SAEs of pancreatitis were reported in ongoing studies, one associated with elevated triglycerides and two with cholelithiasis. Four cases of renal failure were reported from ongoing trials. In three of these cases, the treatment assignment remains blinded. Forest identified memantine post marketing reports of epidermal necrolysis (2), aplastic anemia (1) and liver failure (1).

Common AEs that occurred more frequently among memantine subjects and in some cases that exhibited evidence of a dose response relationship included dizziness, headache, constipation, pain, and dyspnea.

In dementia placebo controlled trials but not neuropathic pain controlled trials, memantine was associated with a mean increase in alkaline phosphatase compared to placebo. Memantine was not associated with increases in transaminases or bilirubin.

Memantine was not associated with changes in blood pressure or pulse. Memantine did not appear to be associated with orthostatic blood pressure changes, although Forest was unable to provide sufficient information about the methodology used to measure orthostatic blood pressure to allow a complete assessment of these results.

Forest's analyses of ECGs did not suggest memantine related QT prolongation compared to placebo, but the ECG data were limited and the available ECGs were not adequately examined. For one of the three studies included in the pooled analysis, ECGs were measured at a central laboratory using standardized measuring methodology. For the remaining ECGs, the intervals analyzed were either the machine read intervals or were investigator over-read intervals.

Recommendations
Forest should reanalyze the available ECG interval data after all ECGs have been read by a central laboratory using standardized measuring methodology.

I recommend removing wording about memantine's lack of effect on orthostatic blood pressure from labeling. Forest was unable to provide sufficient information about BP measurement methodology to allow adequate assessment of this claim.

Forest should be asked to submit additional eye examination result information from ongoing studies (particularly the glaucoma studies) as it becomes available.

Forest should provide additional information for the post marketing reports of epidermal necrolysis and aplastic anemia and follow up for the 15 day IND encephalopathy report.

1. Materials Used in This Review

This safety review is based on the information included in the following submissions:

- December 19, 2002; NDA Integrated Summary of Safety (ISS)-paper copy with electronic post text tables, Study reports for individual studies-paper copies, electronic data sets, electronic Case Report Forms (CRFs),
- January 10, 2003; Final Study Report for MEM-MD-02-paper copy with electronic post text tables
- April 11, 2003 submission, Safety Update-paper copy with electronic post text tables, electronic data sets, electronic Case Report Forms (CRFs)
- January 24, 2003, May 15, 2003, July 3, 2003, July 9, 2003 submissions; responses to reviewer questions-electronic/paper submissions

2. Background

2.1 Name, Drug Class, Proposed Indication

Memantine (1-amino-3, 5-dimethyladamantane hydrochloride) is an NMDA receptor antagonist that is administered orally. Pre-clinical studies suggest that memantine can decrease neuronal toxicity associated with excessive glutamate release (NDA vol. 265, p.77). The sponsor, Forest Laboratories, seeks FDA approval to market memantine for the treatment of patients with moderate to severe dementia of the Alzheimer's type.

Memantine has been marketed in Germany as Akatinol Memantine since 1982 for the treatment of Parkinsonism, cerebral and peripheral spasticity, and organic brain syndrome. In 2022, the European Union approved memantine (trade name Axura) for the treatment of Alzheimer's disease.

2.2 State of Armamentarium- Safety

Currently, there are no NMDA receptor antagonists approved in the United States for the treatment of Alzheimer's disease. The PDR includes four cholinesterase inhibitors (tacrine, donepezil, rivastigmine and galantamine) approved in the United States for the treatment of Alzheimer's disease. The cholinesterase inhibitors are associated with cardiovascular effects (bradycardia), and GI effects (nausea and vomiting). In addition to the mentioned cardiovascular and GI effects, tacrine is associated with increased risk of transaminase elevations.

2.3 Proposed Memantine Label with Respect to Safety

Forest would contraindicate memantine use in patients with known hypersensitivity to memantine. Forest has no warnings in their proposed memantine label.

Forest would include a statement in the PRECAUTIONS section of the memantine label suggesting that caregivers be instructed about administration and dose escalation for memantine. Forest would also include a precaution statement noting that memantine use has not been evaluated in patients with seizure disorder and that patients with a history of seizure disorder be carefully monitored.

Forest comments that increases in urine pH may decrease elimination of memantine, resulting in increased plasma levels. Forest does not recommend dose adjustment with

hepatic impairment or with mild or moderate renal impairment. Forest does not recommend the use of memantine in patients with severe renal impairment. Forest notes that concomitant use of memantine and donepezil does not affect the pharmacokinetics of either compound. Co-administration of memantine with other drugs that are eliminated by the same renal cationic system (ex, HCTZ) could result in altered plasma levels of both drugs. Memantine is not highly protein bound (45%) and therefore interaction with highly protein bound drugs is unlikely. Effects of L-dopa, dopaminergic agents, or anticholinergics may be enhanced with concomitant memantine use requiring dose adjustment of these other agents.

Forest notes that in dementia trials where patients received memantine 20mg/day, no AE led to discontinuation of more than 1% of memantine subjects and at a rate greater than placebo.

Forest would include the following table of AEs in their memantine label. The table includes events reported by at least 2% of memantine subjects and at a rate greater than placebo.

Table 1: Adverse Events Reported in Controlled Clinical Trials in at Least 2% of Patients Receiving *TRADENAME*® and at a Higher Frequency than Placebo-treated Patients.

Body System Adverse Event	Placebo (N = 922) %	*TRADENAME*® (N = 940) %
Body as a Whole		
Fatigue	1	2
Pain	1	3
Cardiovascular System		
Hypertension	2	4
Central and Peripheral Nervous System		
Dizziness	5	7
Headache	3	6
Gastrointestinal System		
Constipation	3	5
Vomiting	2	3
Musculoskeletal System		
Back pain	2	3
Psychiatric Disorders		
Confusion	5	6
Somnolence	2	3
Hallucinations	2	3
Respiratory System		
Coughing	3	4
Dyspnea	1	2

Other adverse events occurring with an incidence of at least 2% in *TRADENAME*®-treated patients but at a greater or equal rate on placebo were agitation, fall, inflicted injury, urinary incontinence, diarrhea, bronchitis, insomnia, urinary tract infection, influenza-like symptoms, gait abnormal, depression, upper respiratory tract infection, anxiety, peripheral edema, nausea, anorexia, and arthralgia

Proposed labeling states that memantine was not associated with clinically important changes in vital signs or orthostatic changes, clinically important laboratory test changes, or clinically important ECG changes.

The proposed memantine label includes a list of all events observed during clinical trials and a list of events not seen in clinical trials but reported by more than one patient during post marketing use in other countries.

The proposed memantine label lists restlessness, psychosis, visual hallucinations, proconvulsiveness, somnolence, stupor, and loss of consciousness in a patient who took an overdose of memantine (400mg). Forest would note that elimination of memantine can be enhanced by acidification of the urine.

2.4 Animal Pharmacology and Toxicology
In section 16 of the memantine NDA ISS, Forest summarized data from their nonclinical studies. Forest reported that memantine doses of 100mg/kg produced decreased awareness, motor activity, and reflexes. Memantine doses ≥30mg/kg caused decreased cardiac output, stroke volume, and systolic left ventricular pressure. Forest reported that memantine inhibited intestinal motility in rats with an ED_{50} of 20mg/kg and produced diuresis and saluresis in rats at doses of 40mg/kg (SU vol. 1.11, p.316).

Forest reported that memantine was not carcinogenic in the 113-week mouse and 128-week rat studies, and that memantine tested negative in a battery of mutagenicity studies (SU vol. 1.11, p.317).

Forest reported that the lowest lethal dose in both mouse and rat was ≥300mg/kg. Ataxia, prone position, bradypnea, and tremor reportedly preceded death. In subchronic and chronic studies, ataxia, tremor, unsteadiness, and aggressiveness or hyperexcitability in rodents and apathy or quietness in dogs and baboons were among the most prominent clinical signs observed. Forest reported that at overtly toxic doses they observed foamy macrophages in the lungs, renal papillary mineralization, tubulointerstitial nephritis, vacuolization of defined cortical neurons, and corneal opacities. (SU vol. 1.11, p.317).

Forest further described the findings of corneal opacities and obscured retinal blood vessels in mouse, rat and dog studies. Specifically, Forest reported findings of corneal thickening, with thickening of corneal epithelium and endothelial vacuolization. The findings in dogs disappeared despite increases in dose and the findings in rodents were only present at doses associated with profound systemic toxicity and/or death. Effects seen in the 13-week rat study were reportedly not seen in the 12-month chronic feeding study. Forest feels that the eye findings reflect abnormal local drug storage due to saturated excretion mechanisms and are not clinically relevant (SU, vol. 1.11, p. 318).

Forest further described the findings of cortical neuron vacuolization. Forest stated that rodents are prone to cerebrocortical neuron injury, specifically Olney-type lesions, from NMDA receptor antagonists including (+) MK-801, PCP, and ketamine. Forest found that single oral memantine doses of 100mg/kg/day or greater produced a dose- related

increase in the frequency and severity of Olney-type lesions. Repeated daily oral doses of 40mg/kg/day administered in a dose escalation manner did not demonstrate evidence of neurotoxicity. Furthermore, Forest reports that numerous repeated dose studies were performed without any significant observations regarding neuropathology. Forest reported that histopathological examination revealed no evidence of vacuolization or necrosis in baboons (primates are considered resistant to NMDA antagonist induced Olney-type lesions). Forest concludes that the neuropathological lesions observed in high-dose rat studies are not expected to occur during therapeutic exposure in humans. They note that the lesions did not occur with slow escalation of dose and that primate brains are felt to be resistant to induction of these lesions (SU, vol. 1.11, p. 319).

2.5 Human Pharmacokinetics

Forest reports that memantine exhibited linear pharmacokinetics following single and multiple dose administration and that the terminal elimination half-life was 60 to 80 hours. Forest notes that T_{max} occurs at approximately 4 to 6 hours post dose. Memantine absorption from oral tablet formulations was complete and was not affected by food. Forest reports that memantine is primarily excreted unchanged in the urine (75-90%) and that acidic urine pH enhances memantine excretion. The major metabolites of memantine excreted in the urine were the memantine N-gludantan conjugate and 6-hydroxy memantine. Forest reports that the potential for interaction with drugs metabolized by cytochrome P450 is low. Memantine exhibits a low level of protein binding (45%).

In *in vitro* studies, memantine did not attenuate the inhibition of acetylcholinesterase caused by donepezil, galantamine and tetrahydroaminoacridine. In a study of 24 subjects, Forest found no differences in the pharmacokinetics of memantine or donepezil or in the inhibition of acetylcholinesterase by donepezil when the two drugs were administered alone and in combination. In an interaction study with hydrochlorothiazide/triamterene, memantine did not affect the bioavailablity of triamterene or its metabolite but did cause a 20% reduction in the bioavailability of hydrochlorothiazide (SU vol. 1.11, pp. 293-6).

3. Approach to Safety Review/Methods

Using the paper and electronic NDA ISS submissions, the two-month Safety Update, and responses to specific reviewer questions, I reviewed treatment emergent adverse events identified from the memantine development program. To verify the accuracy of the primary data for all deaths and serious adverse events summarized by the sponsor, I cross checked data from the sponsor's listings, case report forms (CRFs), narrative summaries, and electronic data sets. To evaluate the adverse event (AE) coding procedures, I compared investigator verbatim terms with the corresponding preferred terms assigned by the sponsor. For selected events (e.g., liver related abnormalities, rashes), I reviewed the coding in more detail by examining the CRF, electronic data sets, narrative summaries, and study report listings to determine if the coded terms accurately reflected the described events. I reviewed the death narratives for all study subjects who died and summarized the clinical details for selected deaths. In addition, I reviewed the CRFs, narrative summaries, data sets and study reports for serious adverse events (SAEs), selected AEs leading to discontinuation from a study, and any AE preferred terms suggestive of events of interest.

I reviewed the results of the sponsor's treatment emergent AE risk calculations. I reviewed the sponsor's lab and vital sign data analyses. I conducted additional analyses of extreme lab outliers, blood pressure outliers, and QTc data.

4. Review Findings

4.1 Description of Data Sources

Forest submitted safety data from fifty-three completed trials, and additional safety data from twenty-one ongoing studies through 4/30/02 in their NDA. In a supplement submitted 1/10/03, Forest submitted safety data from a recently completed placebo controlled trial MEM-MD-02. The safety update, submitted 4/11/03, integrated the data from MEM-MD-02 with the NDA analyses and updated deaths and SAEs through 9/30/02 for the twenty-one ongoing studies. The safety update also included data from three newly completed clinical pharmacology trials.

The fifty-seven completed trials submitted in the NDA and safety update include studies exploring a number of treatment indications including dementia, neuropathic pain, Parkinson's disease, organic brain syndrome, and spasticity. A list of the completed studies is provided as an appendix to this review.

Forest presented the memantine safety data using 4 major groupings. Group 1 data includes eight Phase II/III double blind, placebo-controlled studies in dementia, four open-label extensions of these trials and two phase II/III double-blind, placebo-controlled trials in neuropathic pain. Group 1 data constitute the primary safety data for the memantine NDA. Group 2 data includes thirteen studies in patients with dementia, organic brain syndrome, Parkinsonism, multiple sclerosis, and spasticity. In these studies, only AEs considered drug-related were reported and therefore these data are not complete with regard to safety data captured. Group 3A data includes eight completed clinical pharmacology studies in healthy subjects. Group 3B data includes twenty-two clinical pharmacology studies for which limited safety data are available. The safety data from group 3B studies could not be incorporated into the electronic ISS safety database and Forest summarized these data separately. Forest summarized separately limited safety data from 51 other completed memantine trials (3,750 subjects).

In their presentation of safety data, Forest provided analyses for various sub-groups of the Group 1 safety data. The subgroups are listed below.

FDA TABLE 1 Group 1 Safety data sub-groups

Subgroup	Trials
All Placebo Controlled Trials	9605, 9403, 9202, 9408, 9104, 9105, 9206, NTI 9702, NTI 9801, MEM-MD-02
Placebo Controlled Dementia Trials	9605, 9403, 9202, 9408, 9104, 9105, 9206, MEM-MD-02
Open Label Extension Dementia Trials	9605 OLEX, 9202 OLEX, 9408 OLEX, 9206 OLEX
Long-term dementia patients (≥12 months exposure to memantine)	9605+9605 OLEX, 9202+9202 OLEX, 9408+ 9408 OLEX, 9206+9206 OLEX
All memantine dementia patients	9605, 9403, 9202, 9408, 9104, 9105, 9206, MEM-MD-02, 9605 OLEX, 9202 OLEX, 9408

	OLEX, 9206 OLEX
Placebo controlled studies, dementia diagnosis (vascular vs. Alzheimer's)	9605, 9403, 9202, 9408, 9104, 9105, 9206, MEM-MD-02
Moderate to severe dementia	9605, 9403, 9202, 9408, 9104, 9105, 9206, MEM-MD-02

(From SU vol. 1.11, pp. 131-132)

4.1.1 Primary Safety Data

Group 1 studies

Group 1 double blind placebo-controlled dementia studies

Forest submitted data from eight double blind placebo-controlled dementia studies in the memantine NDA and safety update. The following table summarizes features of these studies.

FDA TABLE 2: Summary of Group 1 double blind placebo controlled dementia studies

Trial Number	Location	Dementia type	N	Duration	Dose
9605	USA	Alzheimer's	Memantine 126 Placebo 126	28 weeks	20mg
9403	Latvia	Alzheimer's or Vascular	Memantine 82 Placebo 84	12 weeks	10mg
9202	UK	Vascular	Memantine 295 Placebo 286	28 weeks	20mg
9408	France	Vascular	Memantine 165 Placebo 156	28 weeks	20mg
9104	France	Alzheimer's	Memantine 27 Placebo 29	13 weeks	20mg
9105	Portugal	Vascular	Memantine 15 Placebo 12	12 weeks	20mg
9206	Sweden	Vascular	Memantine 28 Placebo 28	14 weeks	20mg
MEM-MD-02	USA	Alzheimer's	Memantine 202 Placebo 201	24 weeks	20mg

Information from Forest Panel 1, SU vol. 1.11, pp. 95-100

Subjects randomized to memantine in the Group 1 placebo-controlled dementia trials were started at 5mg/day and were titrated to the study target dose by weekly increases of 5mg/day. Generally, these studies did not allow down-titration of dose. All subjects in MEM-MD-02 were also taking donepezil (patients had to have been taking donepezil for 3 months at a stable dose prior to randomization).

Group 1 open label dementia studies

Forest provided safety data from four open label extension trials. Studies 9605OLEX, 9202OLEX, 9408OLEX, and 9206OLEX enrolled subjects who completed the preceding placebo controlled trials. Studies 9605OLEX, 9202OLEX, 9408OLEX were 24 weeks long, while study 9206OLEX was up to 104 weeks long (NDA vol. 265, pp. 37-38).

Group 1 Placebo Controlled Neuropathic Pain Studies
Forest provided safety data from two neuropathic pain trials. Trial NTI9702 was an 8-week double blind placebo-controlled trial that randomized subjects with diabetic neuropathy or post herpetic neuralgia to memantine 40mg/day (n=58) or placebo (n=64). Trial NTI9801 was an 8-week double blind placebo-controlled trial that randomized subjects with diabetic neuropathy to placebo (n=85) or memantine (n=333) 20mg/day or 40mg/day (NDA vol. 265, p.113).

4.2 Exposure
4.2.1 Number of subjects
Forest reports memantine exposure that exceeds ICH guidelines with respect to total number of subjects exposed to the proposed effective dose and for 6 months and 1 year. Forest reported that they have safety information for 2,504 patients exposed to memantine and 1,288 exposed to placebo in group 1, 2 and 3A studies (SU vol. 1.11, p.93). Group 1 studies, which constitute the Primary safety data, include 1,748 memantine subjects and 1,071 placebo subjects.

Group 1 studies
The following table summarizes the number of subjects exposed by treatment in the Group 1 studies (Adapted from Forest Fig 2, SU vol. 1.11, p.124 and Panel 2, SU vol. 1.11, p.125).

FDA TABLE 3 Group 1 studies- Number of Subjects Exposed

Trial Number	Indication	Memantine	Placebo
9605	Alzheimer's dementia	126	126
9403	Vascular /Alzheimer's dementia mix	82	84
9202	Vascular dementia	295	286
9408	Vascular dementia	165	156
9104	Alzheimer's dementia	27	29
9105	Vascular /Alzheimer's dementia mix	15	12
9206	Vascular dementia	28	28
MEM-MD-02	Alzheimer's dementia	202	201
Dementia Placebo Controlled Trial Subtotal		*940*	*922*
NTI 9702	Peripheral Neuropathy	58	64
NTI 9801	Peripheral Neuropathy	333	85
Peripheral Neuropathy Placebo Controlled Trial Subtotal		*391*	*149*
Group 1 Placebo Controlled Trial Subtotal		*1,331*	*1,071*
9605 OLEX	Alzheimer's dementia	80/175*	
9202 OLEX	Vascular dementia	226/464*	
9408 OLEX	Vascular dementia	88/171*	
9206 OLEX	Vascular dementia	23/46*	
Dementia Open Label Trial Subtotal		*417/856**	
Dementia Subtotal (PC+OL first exposures)		*1,357*	
Group I Studies Total		**1,748**	**1,071**

*Number with first exposure to memantine/total number exposed to memantine during trial

Within the Group 1 studies, 476 of the 1,748 subjects (27%) exposed to memantine had Alzheimer's disease (Controlled trials N=194, NDA vol. 265, p. 116; MEM-MD-02 N=202, SU vol. 1.11, p.126, First exposure in open label extensions N=80, see above). For Group 1 dementia placebo controlled trials, 42% (396/940) had Alzheimer's dementia and 58% (544/940) had vascular dementia.

Exposure Group 2 studies
Forest reported that 549 subjects were exposed to memantine and 173 to placebo in Group 2 studies (NDA vol. 265, p.189).

Exposure Group 3 studies
Forest reported that 207 subjects were exposed to memantine in Group 3A studies, which include primarily pharmacokinetic study results (NDA vol. 265, p.190). Forest reported that 280 subjects were exposed in Group 3B studies, for which little safety data is available (SU vol. 1.11, p.122).

Additional exposure
Forest reported that 3,750 patients were exposed to memantine in clinical trials not included in the NDA safety and safety update databases (SU vol. 1.11, p.149). In addition, they state that there have been more than 400,000 person years of memantine use in Germany since approval in 1982.

4.2.2 Exposure by duration
Group 1 studies
Forest summarized exposure by duration for the Group 1 dementia studies (SU vol. 1.11, p.208, NDA vol. 265, p.184). I provide exposure by selected periods of duration in the following table.

FDA TABLE 4 Exposure by duration, Group 1 dementia studies

	Double Blind		***Open Label***	***Total***
	Placebo N=922	*Memantine N=939**	*Memantine N=856*	*Memantine N=1,357*
Treatment Duration (Days)				
Mean	150.7	151.2	173.8	214.4
SD	58.6	59.2	105.5	135.7
Median	171	172	168	169
Range	1 to 241	1 to 232	1 to 796	1 to 884
Treatment Duration n (%)				
≥4 weeks	884 (95.9%)	896 (95.4%)	835 (97.5%)	1,306 (96.3%)
≥24 weeks	553 (60%)	584 (62.2%)	506 (59.1%)	862 (63.6%)
≥52 weeks	0	0	32 (3.7%)	277 (20.4%)
≥78 weeks	0	0	23 (2.7%)	25 (1.8%)

*Missing exposure data for subject 9408-0162

Forest stratified exposure data for the Group 1 dementia trial subjects by dementia diagnosis type (Alzheimer's v. vascular). For all Group 1 dementia trials (placebo

controlled and open label) of the 862-dementia subjects exposed for ≥24 weeks, 276 (32%) had Alzheimer's dementia and 586 (68%) had vascular dementia (SU vol. 1.11, p.205). Of the 277-dementia subjects exposed for ≥52 weeks, 46 (17%) had Alzheimer's dementia and 231 (83%) had vascular dementia (Forest 1/24/03 submission, response to reviewer questions).

In table 3.1.4, Forest reported 796 person-years exposure to memantine for Group 1 dementia subjects. In the Group 1 dementia placebo-controlled trials, Forest reported 389 person-years exposure to memantine and 381 person-years exposure to placebo (SU Table 3.1.1). Forest reported 407 person-years exposure to memantine in Group 1 open-label dementia studies.

Group 1 Neuropathic pain studies
The neuropathic pain subjects had short-term exposures to memantine and Forest reported that only 1 memantine subject was exposed for 12 or more weeks in these studies (SU Table 3.1.5).

Group 2 Studies
Forest reported that 221 subjects received memantine for at least 24 weeks and 104 subjects received memantine for at least 48 weeks in Group 2 studies (SU Table 3.1.6). Forest reported 217 person years exposure to memantine and 19 person years exposure to placebo in Group 2 studies (SU Table 3.1.6).

Group 3 Studies
Forest reported that 207 subjects were exposed to memantine in Group 3A studies, with a mean exposure of 21 days (SU vol. 1.11, p.305). Forest reported that 280 subjects were exposed to memantine in Group 3B studies.

4.2.3 Exposure by Dose and Duration
Group 1 Exposure by Dose and Duration
In their summary of exposure dose by duration, Forest reported that most of the memantine exposures occurred at the proposed effective dose specified in labeling, 10-20mg/day. In their summary of duration by dose, Forest classified subjects by maximal daily dose and HFD-120 requested an additional table classifying exposure by modal dose. The results for 24 and 52 weeks were the same regardless of whether patients were classified by maximal or modal dose. For Group 1 subjects with at least 24 weeks exposure, 862 had a maximal/modal daily dose of 20mg. For Group 1 subjects with at least 52 weeks exposure, 277 had a maximal/modal daily dose of 20mg (SU Tables 3.1.9, 3.1.9A).

4.2.4 Exposure by Age
Group 1 Dementia Placebo Controlled Trials
The mean age of memantine subjects enrolled in Group 1 dementia placebo controlled trials was 75.7 years (median 76 years, range 50 to 97 years) compared to 76 years (median 76 years, range 50 to 96 years) in the placebo group (SU vol. 1.11, p.194).

Forest provided summary statistics for age stratified by dementia diagnosis for the Group 1 dementia placebo controlled trials. The mean age for memantine subjects with an Alzheimer's disease diagnosis was 75.3 years (median 76 years, range 50 to 92 years) compared to 75.7 years (median 76 years, range 50 to 93 years) for placebo subjects with and Alzheimer's disease diagnosis. For subjects with a vascular dementia diagnosis, the mean age of memantine subjects was 76.1 years (median 76 years, range 54 to 97 years) compared to 76.2 years (median 76 years, range 54 to 96 years) for placebo subjects with a vascular dementia diagnosis (SU table 12.1.1A).

4.2.5 Exposure by Sex

Group 1 Dementia Placebo Controlled Trials

Fifty-seven percent of memantine subjects in the Group 1 dementia trials were female compared to 55% of placebo subjects (SU vol. 1.11, p.194).

When stratified by dementia diagnosis, there was a predominance of females among subjects with an Alzheimer's disease diagnosis while the percentage of males and females was similar for subjects with a vascular dementia diagnosis. In these trials, 67.2% of memantine subjects with an Alzheimer's disease diagnosis were female compared to 65% of placebo subjects. Fifty percent of memantine subjects with a vascular dementia diagnosis were female compared to 47% of placebo subjects with a vascular dementia diagnosis (SU table 12.1.1A).

4.3 Review of AE Surveillance, Coding of AEs, and Approach to Evaluating Safety

Adverse events were captured by investigators using open ended questions. Forest summarized the SAEs, AEs leading to discontinuation and treatment emergent AEs from the memantine development program. SAEs were defined as "any untoward medical occurrence that resulted in death; was life-threatening; required inpatient hospitalization or prolonged an existing hospitalization; resulted in persistent or significant disability/incapacity; or was a congenital anomaly/birth defect" (SU vol. 1.11., p.181). Forest also considered other "medically important events that required intervention in order to prevent one of the above outcomes" as serious. Forest defined treatment emergent adverse events (AEs) as adverse events which started after the start date of dosing with study medication and occurred within 30 days following the last dose of study medication (SU vol. 1.11., p.181). Forest defined adverse events leading to discontinuation as those adverse events where the action taken with regard to study drug was associated with discontinuation and the AE onset date was on or before the last dose date of study medication (SU vol. 1.11, p.182).

AE investigator verbatim terms for AEs were mapped to World Health Organization Adverse Reaction Terminology (WHOART) Dictionary, version 1997/Q3 (SU vol. 1.11, p.179). Forest calculated AE risks by dividing the number of subjects in the treatment group with an AE by the total number of subjects in that treatment group for the particular safety database analysis group.

In addition to AE data, investigators collected vital sign data, laboratory data and ECGs during memantine studies. Orthostatic blood pressure measurements were not performed in phase II/III trials. In group 1 placebo controlled studies subjects had screening and end

study labs in two studies (MEM-MD-02, and 9206) and in the remaining studies, at least three and as many as five laboratory test evaluations (SU vol. 1.11, p.135). For group 1 placebo controlled studies, subjects had only screening ECGs in four studies (9202, 9104, 9105, and 9206). In studies 9605, MEM-MD-02, 9403, 9408, NTI-9702, and NTI-9801, ECGs were collected at screening or week 0 and at end of study (SU vol. 1.11, p.135).

4.4 Audit Findings and Evaluation of the AE Coding

I reviewed the investigator actual/verbatim terms listed in the CRFs of selected memantine subjects with serious AEs or who discontinued for AEs and the terms were accurately summarized in the narrative summaries, and the electronic data sets. I repeated these comparisons for lab and vital sign data across the available data sources. I found agreement between sources.

Using the electronic adverse event data sets, I reviewed the results of the coding process that the sponsor used to group the investigator terms for adverse event analyses. I compared investigator verbatim terms for adverse events to the coded terms (WHOART).

The coding of investigator verbatim adverse event terms to preferred terms was generally acceptable. Although I found infrequent inconsistencies that resulted from the coding process, none would markedly impact the safety assessment of the memantine NDA. There were occasional occurrences of splitting similar investigator terms to different preferred terms. One example of apparent splitting was for the preferred terms oedema, oedema dependent, and oedema peripheral. I found investigator terms of "swollen ankle", "swelling of feet", and "leg swelling" coded to oedema. The investigator terms "ankle oedema" and "bilateral ankle edema" were coded to the preferred term oedema dependent. The preferred term oedema peripheral included investigator verbatim terms of "bilateral ankle edema, edema (legs)", "leg oedema", and "swollen right ankle". In addition, I found the investigator term of apractic gait coded to the preferred term of ataxia while the investigator term of ataxic gait was coded to the preferred term gait abnormal. I also discovered an instance where the investigator term "moderate renal failure" was coded to the preferred term uremia, under the Metabolic and nutritional body system, even though there were preferred terms of renal function abnormal and renal failure acute under the Urinary system disorders body system. I did not find evidence of lumping of dissimilar investigator terms under single preferred terms. I rarely identified instances of incorrect coding (ex. investigator term T4 increased coded to TSH increased).

4.5 Clinical Pharmacology Studies, Safety

Forest presented safety data from their Clinical Pharmacology Studies as the Group 3 studies in the NDA and safety update. Forest identified thirty memantine Group 3 studies. Forest further divided the Group 3 studies into Group 3A and Group 3B studies on the basis of the adequacy of the data. Group 3A studies included safety data from eight studies that had adequate documentation to allow inclusion into the electronic ISS database. The group 3B studies include the safety data from the remaining twenty-two clinical pharmacology studies, where limited safety data were collected and the data could not be included in the electronic safety database (SU vol. 1.11, p.142).

4.5.1 Clinical Pharmacology, Exposure
Forest reported that 207 subjects were exposed to memantine in Group 3A studies, with a mean exposure of twenty-one days a median exposure of twenty-six days and a range of one to fifty days (SU vol. 1.11, p.305). Forest reported that 280 subjects were exposed to memantine in Group 3B studies.

The group 3A studies exposed healthy volunteers and used an immediate release memantine tablet dosage form that was used in the phase II-IV studies, as well as memantine drops, and a slow release tablet form of memantine. The group 3B studies exposed various subpopulations of users to various dosage forms of memantine and used various routes of administration.

4.5.2 Clinical Pharmacology Mortality
Forest reported no deaths from Group 3A studies (0/207) and one death from a Group 3B study (0.4%, 1/280). This Group 3B death occurred in an elderly subject with renal failure who experienced a myocardial infarction (NDA vol. 265, p.275).

4.5.3 Clinical Pharmacology Serious Adverse Events
Forest reported no SAEs from Group 3A studies (0/207) and three SAEs from Group 3B studies (1.1%, 3/280). The Group 3B SAEs were MI in a subject with renal insufficiency, respiratory failure in a subject with pronounced emphysema and renal insufficiency, and adenocarcinoma diagnosed in an AIDS patient (NDA vol. 265, p.276-7, Response to Reviewer questions 5/15/03).

4.5.4 Clinical Pharmacology Discontinuations for Adverse Events
Forest reported that 4.8% (10/207) of Group 3A subjects and 2.9% (8/280) of Group B subjects discontinued for AEs; aside from ataxia, there did not appear to be clusters of similar events leading to discontinuation from these trials. Five group 3A subjects (11, 16, 33, 34, 36) discontinued for ataxia, all from one study, 9704 (NDA vol. 104, pp. 68-70). Some of these subjects also reported other AEs such as impaired concentration, and dizziness. Study 9704 assessed the food interaction of the test formulation, a new film tablet, and compared the bioavailability of the new film tablet to a reference formulation in healthy elderly males and females. The subjects were divided into two groups. The first group received a single dose of test formulation (20mg) while fasting, followed by multiple doses of the test formulation (10mg, 20mg). The second group received a single dose of the test formulation (20mg) following a standard meal, followed by multiple doses of the reference formulation (10mg, 20mg). Two dropouts were from the first treatment group and three from the second treatment group. Three dropouts were males and two were females. These events resolved in all cases, in one case on the day of withdrawal and in the other cases within 2 to 5 days (one did not note the time to improvement). There was little other information provided about these events.

4.5.5 Clinical Pharmacology Treatment Emergent Adverse Events
Forest reported that 71% (34/48) of memantine exposed subjects in single dose Group 3A studies reported one or more AEs (SU vol. 1.11, p.306). Dizziness (35%, 17/48), headache (23%, 11/48), fatigue (17%, 8/48), somnolence (10%, 5/48), concentration

impaired (8%, 4/48) and ataxia (6%, 3/48) were the AEs reported by at least 5% of subjects from these trials (SU Panel 50, vol. 1.11, p.307).

Forest reported that 65% (103/159) of memantine exposed subjects in multiple dose Group 3A studies reported one or more AEs (SU vol. 1.11, p.307). Fatigue (32%, 51/159), headache (27%, 43/159), dizziness (18%, 29/159), somnolence (16%, 25/159), mouth dry (7%, 11/159), agitation (6.3%, 10/159), nausea (6%, 9/159) and concentration impaired (6%, 9/159) were the AEs reported by at least 5% of subjects from these trials (SU table 12.2.2b).

I read through SU Table 12.2.2, which summarized all AEs from Group 3A studies and there were no events suggestive of renal failure, hepatic failure, rhabdomyolysis, pancreatitis, or serious skin reactions. Below I summarize selected AEs from the Group 3A studies.

Face edema

9402-1-8 This 66 year old female had an AE of face edema and the AE data set included the verbatim term "eyelid edema" for this event. This AE resolved the same day, was not serious, did not lead to discontinuation, and required no treatment. This subject did not report any AEs related to allergy or breathing difficulty.

Hepatic Enzymes increased

9704-1-37 This 59 year old female had an AE of hepatic enzymes increased. The lab data set noted a baseline SGPT of 5 that increased to 39 (ULN=30) and returned to 9. There were no associated increases in SGOT, GGT, ALP, or bilirubin.

Anemia

9702-1-12 This 59 year old male had a baseline Hgb of 14.3g/dL and HCT of 45% that decreased to 10.7g/dL and 34%, respectively. WBC count was 5.1 at baseline and increased to 5.2 while the platelet count was 135 at baseline and increased to 316. There were no abnormally increased bilirubin or LDH results. This event was reported as resolved, was not considered serious, and did not lead to discontinuation.

9702-1-18 This 55 year old female had a baseline Hgb of 13.4g/dL and HCT of 39% that decreased to 10.6g/dL and 31%, respectively. The comment section of the AE data set noted that the drop was due to blood loss but did not explain and no bleeding AEs were reported. WBC was 4.8 at baseline and decreased to 3.8 while baseline platelet count was 212 and it increased to 230. The comment section reported that the values were clearly increased 3 weeks later but the data set did not include these results. There were no abnormally increased bilirubin or LDH results. This event was reported as resolved, was not considered serious, and did not lead to discontinuation.

Leucopenia

9201-1-2 This 23 year old male had an AE of leucopenia. The comment section of the data set noted a relative lymphocytosis. Baseline WBC count was 4, which was followed by WBC counts of 3.8, and 4.1. There were no remarkable changes in Hgb, HCT, or platelet count. The data set had no outcome recorded for this event, it was considered non-serious, and did not lead to discontinuation.

Forest did not provide a complete list of AEs from Group 3B studies. They commented that some Group 3B studies did not capture AE data. For the studies that included AE data, Forest summarized the most commonly reported AEs (at least 10%). The commonly reported AEs were similar to AEs reported in other studies.

4.5.6 Clinical Pharmacology, Lab Data
Aside from a mean increase in platelets (15.1), there were no remarkable laboratory mean changes for the single dose Group 3A studies. No memantine subjects in Group 3A single dose studies met laboratory potentially clinically significant outlier criteria.

Aside from a mean increase in platelets (7.1), there were no remarkable laboratory mean changes for the multiple dose Group 3A studies. Two memantine subjects in multiple dose group 3A studies met potentially clinically significant criteria for low hemoglobin (10.6g/dl, and 10.7g/dL), two for low hematocrit (0.28, and 0.31) and two for high potassium (5.5mmol/L and 6.0mmol/L). One memantine subject had a low platelet count of 8,000 that appeared to be a lab error since the platelet count the next day was 310,000 (SU tables 12.4.2b and 12.4.1).

Forest did not provide a lab data summary for Group 3B studies.

4.5.7 Clinical Pharmacology, Vital Sign Data
Forest reported a mean decrease in systolic BP (-9.9mmHg) and diastolic BP (-0.9 mmHg) and a slight increase in pulse (0.9 bpm) in the single dose Group 3A studies. One subject in these studies had a decrease in systolic BP from 140mm Hg to 88mmHg that returned to 107mmHg at the next measurement, five and a half hours later. A second subject had an increase in systolic BP from 148mmHg at baseline to 221mmHg. Forest reported that the systolic blood pressure for this subject returned to normal at follow up (SU vol. 1.11, p.308).

Forest reported mean decreases in systolic BP (-4.2mm Hg), diastolic BP (-2.8mm Hg) and pulse (-0.2bpm) in the group 3A multiple dose studies (SU table 12.3.2b). No blood pressure outliers were identified but Forest reported that three subjects had met potentially clinically significant criteria for decreases in pulse (all three decreased to 48bpm).

When asked for data supporting the proposed labeling claim that memantine does not cause orthostatic blood pressure changes, Forest referenced two clinical pharmacology trials, IE1801 and HUK-610/5P. Both studies were Group 3B studies. Forest noted that supine and standing blood pressures were captured during both studies. Forest was unable to describe the methodology used to collect blood pressures in these trials, specifically the duration of time subjects were supine and the time between capture of supine and standing blood pressure. In study IE1801, at 4 hours post dose, the measurement closest to T_{max}, for each dose studied there appeared to be mean increases in systolic and diastolic blood pressure and pulse when comparing standing to supine measurements. In study HUK-610/5P, an iv study, there did not appear to be consistent differences between supine and standing blood pressures, but mean standing pulse was increased compared to mean supine pulse for all time points and in both the placebo and memantine phases. Forest reported that four subjects (one placebo, one 30mg, and two 40mg) experienced dizziness on standing between three and five hours of the start of infusion, lasting 1 to 2 minutes, and not associated with blood pressure changes (July 3, 2003 submission, Response to reviewer questions).

Forest did not provide a summary analysis of vital sign data for the Group 3B studies.

4.5.8 Clinical Pharmacology, ECG data
Forest submitted no clinical pharmacology studies specifically designed to evaluate the effect of memantine on cardiac repolarization. Forest summarized the ECG data for the 88 memantine subjects in Group 3A studies that had baseline and end of study ECGs. The mean change from baseline for QTcB was -6.5msec and no subjects had a QTcB≥500msec (SU tables 12.5.1, 12.5.3).

4.6 Phase II/III Studies, Other Studies Safety
4.6.1 Deaths
Forest reports that 75 memantine-treated subjects (3.3%, 75/2,297) from Group 1 and 2 trials died (SU, vol. 1.11, p.212). I include a complete listing of all reported Group 1 and 2 trials memantine deaths as an appendix to this review. Forest presented the number of patients who died within 30 days of last dose by treatment for Group 1 studies. Forest did not specify the period of time since last dose for the deaths from Group 2 trials.

Deaths Group 1 trials
Forest reports 51 deaths (2.9%, 51/1,748) within 30 days of last exposure in memantine subjects enrolled in Group 1 studies.

Deaths Group 1 Dementia Placebo Controlled Trials
Mortality risk was similar in the memantine and placebo treatment groups from Group 1 dementia placebo controlled trials. Eighteen memantine subjects (1.9%, 18/940) and 21 placebo subjects (2.3%, 21/922) enrolled in Group 1 dementia placebo controlled trials died within 30 days of last exposure. The mortality rate was slightly higher among placebo subjects (5.5/100 patient-years, 21/381) compared to memantine subjects (4.6/100 patient-years, 18/389) in these studies (SU, vol. 1.11, p.212).

The following table lists the causes of death by body system and preferred term and stratified by dementia type. The cause specific mortality risks were similar for the memantine and placebo treated groups. I provide clinical descriptions for selected memantine deaths in a section below.

FDA TABLE 5 Group 1 dementia placebo controlled study deaths by body system and preferred term and stratified by dementia type

Body System Preferred Term	**Alzheimer's Dementia**		**Vascular Dementia**	
	Memantine	Placebo	Memantine	Placebo
	N=396	N=394	N=544	N=528
Body as a Whole	**0**	**0**	**1 (0.2%)**	**0**
Sudden Death	0	0	1 (0.2%)	0
Cardiovascular Disorders	**2 (0.5%)**	**0**	**0**	**0**
Cardiac Failure	2 (0.5%)	0	0	0
Centr and Periph Nerv Sys	**0**	**1 (0.3%)**	**4 (0.7%)**	**5 (0.9%)**
Cerebral Hemorrhage	0	0	1 (0.2%)	1 (0.2%)
Cerebrovascular disorder	0	1 (0.3%)	1 (0.2%)	3 (0.6%)
Coma	0	0	2 (0.4%)	2 (0.4%)
Quadraplegia	0	0	0	1 (0.2%)
GI System Disorders	**0**	**0**	**2 (0.4%)**	**1 (0.2%)**
Diarrhea	0	0	1 (0.2%)	0
GI disorder NOS	0	0	1 (0.2%)	0
Hematemesis	0	0	0	1 (0.2%)
Heart Rate/Rhythm disorder	**0**	**0**	**3 (0.6%)**	**2 (0.4%)**
Cardiac Arrest	0	0	3 (0.6%)	2 (0.4%)
Myo Endo Pericardial & Valve Disorders	**3 (0.8%)**	**2 (0.5%)**	**0**	**0**
Myocardial infarction	3 (0.8%)	2 (0.5%)	0	0
Neoplasm	**0**	**2 (0.5%)**	**1 (0.2%)**	**1 (0.2%)**
Carcinoma	0	0	0	1 (0.2%)
Metastasis NOS	0	0	1 (0.2%)	0
Thyroid neoplasm malignant	0	1 (0.3%)	0	0
Pulmonary Carcinoma	0	1 (0.3%)	0	0
Psychiatric disorder	**0**	**2 (1.0%)**	**0**	**0**
Alzheimer's disease	0	2 (1.0%)	0	0
Respiratory system disorder	**1 (0.5%)**	**1 (0.5%)**	**5 (0.9%)**	**5 (0.9%)**
Apnea	0	0	2 (0.4%)	2 (0.4%)
Bronchitis	0	0	1 (0.2%)	1 (0.2%)
Pneumonia	1 (0.5%)	1 (0.5%)	2 (0.4%)	2 (0.4%)
Vascular disorders	**0**	**0**	**0**	**2 (0.4%)**
Aneurysm ruptured	0	0	0	1 (0.2%)
Embolism Pulmonary	0	0	0	1 (0.2%)

Adapted from SU table 4.2.1A. * 3 placebo and 2 memantine patients had 2 causes of death each and 1 placebo and 1 memantine patient had 3 causes of death each.

Deaths Group 1 Dementia Open Label Extension Trials
Forest reported thirty-two deaths (3.7%, 32/856) within 30 days of last exposure to memantine in dementia open-label extension studies. The mortality rate in the dementia open-label extensions (7.9/100 person-years, 32/407 person years) was similar to the mortality rate observed in the placebo (5.5/100 patient-years, 21/381) and memantine subjects (4.6/100 patient-years, 18/389) during the Group 1 dementia placebo controlled trials (see above). The mortality risk for the subgroup that received memantine for the first time during an extension trial was 3.8% (16/417) compared to 3.6% (16/439) for those who received memantine in the previous controlled trial.

The following table lists the causes of death by body system and preferred term and stratified by treatment for Group 1 dementia open label extension trials. I provide clinical descriptions for selected memantine deaths in a section below.

FDA TABLE 6 Group 1 dementia open-label study deaths by body system and preferred term and stratified by treatment

Body System Preferred Term	**Placebo- Memantine** N=417	**Memantine-Memantine** N=439
Body as a Whole	**3 (0.7%)**	**1 (0.2%)**
Condition Aggravated	1 (0.2%)	0
Inflicted Injury	1 (0.2%)	0
Sepsis	1 (0.2%)	0
Sudden death	0	1 (0.2%)
Cardiovascular disorders	**1 (0.2%)**	**3 (0.7%)**
Cardiac failure	1 (0.2%)	2 (0.5%)
Hypertension	0	1 (0.2%)
Centr and Periph Nerv Sys	**3 (0.7%)**	**4 (0.9%)**
Cerebral Hemorrhage	1 (0.2%)	1 (0.2%)
Cerebrovascular disorder	2 (0.5%)	3 (0.7%)
Heart rate/rhythm disorders	**1 (0.2%)**	**0**
Cardiac arrest	1 (0.2%)	0
Metabolic/Nutrition disorders	**0**	**1 (0.2%)**
Dehydration	0	1 (0.2%)
Myo Endo Pericardial & Valve Disorders	**1 (0.2%)**	**3 (0.7%)**
Myocardial Infarction	1 (0.2%)	3 (0.7%)
Neoplasm	**1 (0.2%)**	**0**
Carcinoma	1 (0.2%)	0
Psychiatric disorder	**0**	**1 (0.2%)**
Anorexia	0	1 (0.2%)
Somnolence	0	1 (0.2%)
Respiratory system disorder	**7 (1.7%)**	**5 (1.1%)**
Pneumonia	6 (1.4%)	3 (0.7%)
Bronchitis	0	1 (0.2%)
Respiratory disorder	1 (0.2%)	0
Respiratory insufficiency	0	1 (0.2%)
Urinary System disorder	**1 (0.2%)**	**0**
Urinary tract infection	1 (0.2%)	0
Vascular disorder	**0**	**1 (0.2%)**
Aneurysm ruptured	0	1 (0.2%)

Adapted from SU table 4.2.2. Three subjects had 2 causes of death each and one subject had 3 causes of death.

Deaths Group 1 Neuropathic Pain Trials
Forest reported one memantine death (0.3%, 1/391) from a neuropathic pain study.

Deaths Group 1 Dementia Trials, Clinical Descriptions
I found no clusters of unexpected causes of death in the Group 1 safety information provide by Forest. Forest reported no deaths attributable to hepatic failure, renal failure, serious skin reactions, hematologic dyscrasias, pancreatitis, or rhabdomyolysis.

I used narrative summaries, electronic data sets, CRFs and information provided in the NDA to summarize selected Group 1 memantine deaths below. I selected the most common causes of death for memantine subjects.

Pneumonia
Respiratory system disorders were listed as a cause of death for 18 memantine treated subjects in Group 1 dementia studies and the most common respiratory cause of death was pneumonia (n=12). In the placebo controlled trials the risk for dying from pneumonia was similar for the memantine (0.3%, 3/939) and placebo (0.3%, 3/922) treated groups. I read the narrative summaries for the twelve-memantine subjects who died and had pneumonia listed as the cause of death. Ten subjects who died of pneumonia were males and two were females and the age range was 71-90 years. The narratives and CRFs generally included little information about these events. Forest reported that the patients died from pneumonia but did not provide supportive data such as physical exam, laboratory, and X-ray results. Using the submitted electronic lab data sets, I determined that none of these subjects had a low leukocyte counts prior to these events.

Cerebrovascular disorder
Central and Peripheral Nervous system disorders were listed as the cause of death for 11 memantine subjects in Group 1 dementia trials and cerebrovascular disorder was the most common cause of death from this body system group (n=6). In the Group 1 dementia placebo controlled trials, the risk dying from cerebrovascular disorder was higher among the placebo subjects (0.4%, 4/922) than among memantine subjects (0.1%, 1/939). I read the narratives and CRFs for the six-memantine subjects who died and had cerebrovascular disorder listed as the cause of death. Five of these events occurred in males and one in a female and the age range was 62 to 83 years. The narratives generally used verbatim terms such as stroke and cerebrovascular accident to describe the events and did not provide additional details. One narrative (9202-00658) did provide the results from a CT scan that documented a fresh basal ganglia infarction.

Myocardial Infarction
Seven memantine treated subjects from Group 1 dementia studies died and had myocardial infarction listed as the cause of death. In the dementia placebo controlled trials, 3 memantine (0.3%, 3/939) and 2 placebo subjects (0.2%, 2/922) died and had myocardial infarction listed as the cause of death. I read the narratives and CRFs for the seven memantine subjects that died of MIs and found that none of the narratives included information (ECGs, cardiac enzymes, etc.) to support the diagnoses. Four of the deaths occurred following hospitalization, and in that setting the diagnosis is presumably

accurate. In the remaining three cases, the patient either died suddenly (9202-00843) or Forest provided no details about the events leading to death (9408-00388, MEM-MD-02-9206) to allow an assessment of the cause of death.

Cardiac Failure
Five memantine treated subjects from Group 1 dementia studies died and had cardiac failure listed as a cause of death. In the dementia placebo controlled trials, 2 memantine (0.2%, 2/939) and 0 placebo subjects (0/922) died and had cardiac failure listed as a cause of death. I read the narratives and CRFs for the five memantine subjects that died of cardiac failure and found that in four cases the subjects had preexisting histories of cardiac insufficiency or CHF. In the remaining case (9202-00153), the subject had cardiac failure and unspecified carcinomatosis listed as causes of death. This subject also experienced increases in liver enzymes and total bilirubin prior to death but the sponsor noted that these lab abnormalities initially arose during the double blind period when this subject was treated with placebo.

Death Group 1 Neuropathic Pain Trials, Clinical Description
One memantine treated subject from a peripheral neuropathy study died within 30 days of last exposure. Subject 100094, a 78-year-old female with a history of coronary artery disease, had myocardial infarction reported as the cause of death.

Deaths Group 2 Studies
Forest reported that the mortality risk among memantine subjects in Group 2 studies was 4.4% (24/549). This mortality risk is greater than the risk observed in Group 1 studies. Forest felt the difference in risk was likely due to underlying differences in the studied populations. Forest explained that all of these deaths were from two studies (MRZ90001-9406, MRZ9001-8801). MRZ9001-9406 was a 14-month trial in subjects with spasticity, and MRZ9001-8801 was a 6-month trial in hospitalized subjects with organic brain syndrome (average age 79 years). Forest commented that these populations were "extremely ill" (NDA vol. 265, p.197).

The data from the Group 2 studies do not allow for accurate exploration of cause specific mortality due to missing data. Four subjects had missing causes of death and 3 subjects had "death" listed as the cause of death. The most common listed causes of death in this group were cardiac failure (n=10), and pneumonia (n=4). No other cause was listed for more than 2 patients. Forest did not report any Group 2 deaths due to hepatic failure, renal failure, serious skin reactions, rhabdomyolysis, pancreatitis, or hematologic dyscrasias.

Deaths Ongoing Studies
Forest reported in the SU that 35 subjects (0.77%, 35/4,537) from ongoing studies died through 9/2002 (SU vol. 1.11, p.220). Forest did not report any deaths from ongoing studies due to hepatic failure, renal failure, serious skin reactions, rhabdomyolysis, pancreatitis, or hematologic dyscrasias. I include a list of deaths from ongoing studies as an appendix to this review.

Deaths Post Marketing Reports
In their SU submission, Forest reported one death identified from a post marketing report: An 81 year old female with Alzheimer's disease experienced cachexia, hyperthyroidism, shock, and ulcerative colitis on day 639 of treatment. The outcome was death (SU vol. 1.11, p.339).

In a separately submitted line listing of post marketing reports, Forest identified another post marketing report with an outcome of death: a 63 year old female who died with a diagnosis of epidermal necrolysis (July 9, 2003 submission).

During the review of the memantine NDA, Forest submitted a post marketing report of hepatic failure that resulted in death. This case is from France (initial report 4/21/03, follow-up 4/30/03). An 83 year old male treated with prazepam, piracetam, zopiclone, ginkgo, irbesartan, tamulosin, and memantine (approximately 25 days) was admitted to a hospital for a fall and worsening state, and was diagnosed with fulminant hepatitis. Galantamine was discontinued about one month before this event. A CT scan and liver serologies (hepatitis A, B, and C) were reportedly normal. CPK was 879, ALT 106. During hospitalization the patient fell and developed rhabdomyolysis. The hospitalization was further complicated by development of disseminated intravascular coagulation, coma, and left foot ischemia and the patient subsequently died. A post mortem liver biopsy revealed "a large injury of sinusoidal dilation in the centrovascular area with congestive intracellular cholestasis and intracanular and macrovesicular steatosis." The reporter noted that "some drugs could induce this type of injury, but most of the time, it is due to cardiac insufficiency." This patient apparently did not have recognized cardiac insufficiency at the time of the event.

4.6.2 Serious Adverse Events
I include a listing of all SAEs reported during Group 1 dementia trials as an attachment to this review.

Group 1 Dementia Placebo Controlled Trials
Forest reported that the SAE risk was higher in the placebo treated group (14.6%, 135/922) than in the memantine treated group (13.5%, 127/940) in the Group 1 placebo controlled dementia trials. The SAE rate in the memantine group was 32.7/100PY (127/389PY) compared to 35.5/100PY (135/381PY) in the placebo group (SU vol. 1.11, p.224).

No memantine treated subjects had a SAE due to hepatic failure, renal failure, rhabdomyolysis, or pancreatitis. Memantine subject 00181, an 83-year-old female, had a SAE that was listed as skin ulceration. The narrative for this event described a decubitus ulcer of the left leg that subsequently resolved without interruption of memantine. Memantine subject 9202-0649 had an SAE of anemia with a positive test for occult blood in her stool. She was treated with iron, the anemia resolved, and she continued in the study.

The following table provides the SAEs occurring in at least 3 memantine subjects and at least twice as frequently compared to placebo.

FDA TABLE 7: SAEs occurring in at least 3 memantine subjects and twice as frequently when compared to placebo, Group 1 placebo controlled dementia trials

Preferred Term	Memantine (n=940)	Placebo (n=922)
Cardiac Failure	0.7% (7)	0.2% (2)
Thrombophlebitis deep	0.6% (6)	0
Dyspnea	0.5% (5)	0.2% (2)
Transient Ischemic Attack	0.5% (5)	0.1% (1)
Constipation	0.4% (4)	0.1% (1)
Dehydration	0.4% (4)	0.1% (1)
Malaise	0.4% (4)	0.2% (2)
Breast neoplasm malignant	0.3% (3)	0.1% (1)
Chest pain	0.3% (3)	0
Heart disorder	0.3% (3)	0
Hemiplegia	0.3% (3)	0
Sepsis	0.3% (3)	0

From Forest Panel 27, SU vol. 1.11, p. 225.

I reviewed the heart disorder events to determine the nature of the AEs that this preferred term subsumed. All three memantine patients with heart disorder SAEs (9202-00591, 9408-00506, and 9048-00012) had pacemaker insertions (two described as replacement and one as planned insertion). None of the three patients had AEs suggestive of new onset or worsening arrhythmia, bradycardia, or syncope during the trials.

Group 1 Dementia Open label Extension Trials
Forest reported that 17.4% (149/856) of subjects in the dementia open label extension trials experienced an SAE. The SAE rate in the dementia open label extension trials, 36.6/100PY, was similar to the rate observed in the memantine group during the placebo controlled trials (32.7/100PY). The SAE risk observed during the open label trials for subjects who received placebo in the controlled trials and then received memantine during the extension (16.8%, 79/417) was similar to the SAE risk for patients who previously received memantine in the controlled trials (18%, 79/439).

The SAEs occurring in more than one percent of patients in the dementia open label extension trials were cerebrovascular disorder (1.8%), pneumonia (1.6%), TIA (1.3%), fall (1.2%), bronchitis (1.1%) and inflicted injury (1.1%).

Since Inflicted injury SAEs were common in the dementia placebo controlled trials (reported by 1.7% (16/922) of placebo subjects and 1.1% (10/940) of memantine subjects) and open label extensions (reported by 1.1% of open label subjects) I reviewed the inflicted injury SAEs to determine the nature of the AEs that this preferred term subsumed. I found that nine subjects from dementia open label trials had SAEs coded to the term inflicted injury. In eight cases, inflicted injury was the term used to subsume the injury following a fall. In three of these eight cases, the patients also had AEs of fall recorded while in the other five cases, only inflicted injury was captured as an AE and the fall event, while present in the CRF, was not reported as a separate AE. The inflicted

injury event not obviously associated with a fall occurred in an 81 year old female (9202-00134) who developed dizziness, somnolence, nausea and agitation, which was treated with thioridazine, and subsequently suffered a head injury, mechanism not described. This subject's condition deteriorated and she died seven days later.

I reviewed the listing of all SAEs occurring in dementia open label trials and there were no events suggestive of acute liver failure, rhabdomyolysis, or pancreatitis. There was one reported for each of the following events: jaundice, anemia, rash, blindness, creatinine increased, and hepatitis. I reviewed the narratives, CRFs, and data sets for these events and summarize the cases below.

Jaundice

9202-00257 This 67-year-old male developed an SAE described as obstructive jaundice. Lab results included GGT 646, ALP 492, Bilirubin 3.7, SGOT 346, and SGPT 731. The patient's CRF noted that he had an ultrasound that demonstrated gallstones and was awaiting an ERCP. The CRF subsequently noted that the gallstones were removed and that he recovered.

Anemia

9202-00089 This 84 year old male was hospitalized for transfusion with a hemoglobin of 7.9g/dL. I reviewed the lab data sets and found that this event was isolated to the red blood cell line (WBC and platelet counts remained normal). The CRF reported colon cancer but there was no other information provided about this diagnosis. Forest reported that the colon cancer and long term aspirin and naproxen use likely contributed to this event (Response to reviewer questions, 5/15/03).

Rash

9202-00764 This 76-year-old female had an SAE of rash and the narrative described the occurrence of herpes zoster.

Blindness

9202-00078 A 64 year old male developed blindness, headache, and abnormal gait after 199 days on drug. The subject was scheduled for a head CT but no other information was provided. Forest noted that the subject had an abnormal baseline ophthalmologic exam (bilateral decreased visual acuity, pseudophakia OS, cataract OD) and they were seeking additional information about this event (Response to reviewer questions, 5/15/03).

Creatinine Increased

9206-00047 An 84 year old male who received memantine in a controlled trial and its extension developed increased creatinine after 147 days of memantine. The subject was discontinued from the trial for confusion (SAE) and increased creatinine (not considered serious). The lab data set demonstrated a baseline creatinine of 1.9mg/dL and a creatinine of 2.2mg/dL at the time of discontinuation.

Hepatitis

9408-00185 A 72 year old male discontinued from an open label trial for hepatitis. The event was identified after 257 days of memantine treatment. This diagnosis was made by the investigator, apparently based on labs that were not included in the CRF. Memantine and other concomitant medications (acetylsalicylate lysine, trimetazidine, piretanide, pentoxifylline, bisoprolol, amlodipine, ramipril, and alprazolam) were discontinued. Follow-up liver related lab tests drawn one week later were normal.

Group 1 Neuropathic Pain Trial SAEs

In the placebo controlled neuropathic pain trials, the SAE risk for the memantine group was 4.1% (16/391) compared to 3.4% (5/149) in the placebo group. The SAE risk for the

memantine 20mg/day group was 2.9% (5/171) compared to 5% (11/220) in the memantine 40mg/day group (NDA table 4.4.5).

I reviewed the SAE narratives for the memantine subjects in the neuropathic pain trials. There were no events suggestive of renal failure, hepatic failure, hematologic dyscrasias, rhabdomyolysis, pancreatitis, or serious skin reactions. Abdominal pain was the only SAE reported by more than one memantine subject (n=2) in these studies.

Group 2 SAEs

Forest reported that 4.9% (27/549) of subjects in group 2 studies had SAEs. Forest acknowledged the low frequency of SAEs compared to the group 1 studies and attributed the lower frequency to the less stringent reporting requirements with group 2 studies. I read through the listing of SAEs from group 2 studies (NDA table 4.6.6). There were no events suggestive of renal failure, hepatic failure, hematologic dyscrasias, rhabdomyolysis, pancreatitis, or serious skin reactions.

Ongoing Studies

Forest reported that there were 345 patients with SAEs from ongoing studies being conducted by Forest, Merz, Suntory, and Allergan through 9/02 (SU vol. 1.11, p.229). Some of the SAEs are from double blind placebo controlled trials where the treatment blind has not yet been broken.

Forest provided narratives from their ongoing studies for patients who experienced SAEs. While they listed patients and SAEs from studies being conducted by Merz, Suntory and Allergan, they did not provide narratives for these patients. I reviewed the narratives for SAEs from the ongoing Forest studies. Forest did not report any events suggestive of serious skin reactions or rhabdomyolysis from their ongoing studies. Forest identified four patients with SAEs of renal failure, one with kidney dysfunction, one with anemia, three with pancreatitis and two with hepatic-related SAEs. I summarize those events below.

Renal SAEs

MEM-MD-01 179112 An 83 year old male, with blinded treatment assignment had an SAE of kidney dysfunction. The narrative summarized an event of obstructive uropathy secondary to benign prostatic hyperplasia.

MEM-MD-01 319101 An 85 year old female, with blinded treatment assignment, had an SAE of renal failure. The narrative described an episode of pre-renal azotemia that occurred in a patient with pseudomembranous colitis and pneumonia.

MEM-MD-06-A 099002 A 60 year old female with blinded treatment assignment and a history of diabetes mellitus, chronic renal insufficiency, hypertension, and nephrosclerosis had an SAE of renal failure. This patient experienced an increase in blood pressure (253/213 mmHg) that was associated with labs indicating acute renal failure (not further described). She was treated with IV medications (not specified) and hydration and improved.

MEM-MD-06-B 259001 A 73-year-old male with a history of diabetes, hypertension and cerebrovascular disease, received memantine during an open label trial and developed acute renal failure. This patient was admitted for atrial fibrillation and had a creatinine of 2.2mg/dL. His renal function worsened with his creatinine increasing to 4.4 mg/dL. His condition deteriorated and he died with the cause of death listed as cardiac arrest secondary to myocardial infarction, pericarditis, and acute renal failure. Forest felt that the subject's underlying medical conditions and concomitant medications (lisinopril, triamterene

hydrochlorthiazide) were the most likely etiology of this subject's acute renal failure (Response to Reviewer Questions 5/15/03).
MEM-MD-10 189021 An 88 year old female with a history of hypertension, elevated cholesterol, and renal failure was receiving blinded therapy and developed pneumonia and renal failure and died. The cause of death was pneumonia and ARDS and there were no additional details about the renal failure.

Anemia SAE

MEM-MD-01 319119 An 88 year old female with blinded treatment assignment had a hemoglobin of 7.5g/dL. This subject, who was taking warfarin, fell and sustained a large hematoma. Warfarin treatment was stopped and the patient was transfused.

Pancreatitis SAEs

MEM-MD-06-A 029015 This 40-year-old male with blinded treatment assignment and a history of diabetes mellitus and elevated triglycerides developed acute pancreatitis. He was treated with gemfibrozil, glipizide, pantoprazole and an increased dosage of atorvastatin and improved.
MEM-MD-06-B 099006 This 76 year old male with a history of pancreatitis, cholelithiasis, diabetes, diabetic neuropathy, duodenal ulcer, and anemia had an SAE of pancreatitis. This patient received blinded therapy in MD-06A and open label memantine in MD-06B. He was hospitalized for epigastric pain and was diagnosed with pancreatitis (lipase 7,561, amylase 1,577). An ultrasound showed a thickened gall bladder and multiple stones. A cholecystectomy was planned pending resolution of the pancreatitis. This patient had an EGD demonstrated two duodenal ulcers one with adherent clot. He underwent surgery (unspecified) and electrocautery. The pancreatitis resolved and the patient continued in the study.
ME-MD-06B 209005 This 55 year old female with diabetes mellitus and diabetic neuropathy was receiving open label memantine and was hospitalized for abdominal pain, nausea, and vomiting. She was diagnosed with cholecystitis and biliary pancreatitis resulting from cholelithiasis. She underwent a laparoscopic cholecystectomy and the event was considered resolved. She discontinued from the study.

Hepatic SAEs

MEM-MD-06-B 049016 This 64 year old male with a history of diabetes mellitus, diabetic neuropathy, cryptogenic cirrhosis and portal hypertension had an SAE of cirrhosis biliary. This condition was present prior to initiation of memantine treatment.
MEM-MD-10 119009 This 79 year old male received blinded medication for 31 days and was seen by his primary care physician for cough, poor oral intake, and two episodes of syncope. He was subsequently found to have an AST of 103, an ALT of 177, and an ALP of 336 with a PSA of 10. The impression was possible prostate cancer with liver metastases. The subject was discontinued. The primary care physician did not provide additional information but the sponsor documented that after stopping memantine the subject had an AST of 15, an ALT of 11 and an ALP of 138.

Post Marketing Reports Serious Adverse Events

Forest included the following five post marketing reports in their SU that appeared to meet the regulatory criteria for SAEs: hypotension during anesthesia; vertigo and nausea; psychosis; agitation, hallucinations and CVA (SU vol. 1.11, p.339).

In a separate line listing, Forest identified 24 serious post marketing reports and a listing of 13 additional reports where the seriousness was not specified. The line listing included two reports of epidermal necrolysis and a single report for each of the following events: aplastic anemia, vasculitis allergic, and hepatic enzymes increased (July 9, 2003 submission).

During the review cycle, Forest forwarded a report of a SAE from a Japanese clinical trial with the terms encephalopathy, EEG abnormal, cognitive disorder, and convulsions NOS. I summarize that report below.

An 82 year old male with Alzheimer's disease, hypertension, diabetes, diabetic retinopathy, cardiac hypertrophy, prostatic hyperplasia and herpes zoster completed four weeks of placebo treatment in a controlled memantine study. The narrative states that he first experienced a convulsion while receiving placebo (lasting 5-6 seconds). During the open label phase, he developed acute encephalopathy with symptoms of bilateral convulsions, abnormal EEG, and abnormal cognitive function. While taking memantine 20mg each morning, he experienced a seizure described as "trembling of the whole body from morning until 3:00 pm". Four days later he had a similar event that lasted from 7:30am to 9:30am. On the next day he had a similar event from 7:20 am to 9:00am. He was hospitalized and was noted to provide poor responses to questions and had head CT and MRI scans that indicated diffuse encephalopathy, bilateral atrophy of the hippocampus and ischemic changes to the parenchyma. No comparison was made to previous scan results. During an EEG, seizures (21 times during 12 minutes) with tremors were recorded. Additional reported EEG findings included a basal rhythm of alpha rhythm of 30μv, 10Hz predominantly observed in C-P-O, sporadic delta waves in Fp-F-C-P-O and a theta waves frequently in all leads. The tremors were described as right hand grasping and right forearm rhythmic movements at 7Hz. The narrative noted that sometimes similar tremors were noted on the left side. The hospitalization was complicated by pneumonia. The investigator described the events observed during hospitalization as acute encephalitis, with paroxysmal bilateral convulsions (or myoclonus). Memantine was stopped. An EEG one day after memantine discontinuation showed increased delta waves, which was improved by the following day. After hospital discharge, the narrative noted that the tremors and abnormal cognitive function were resolved and the EEG was improved. At this time, the investigator noted that the EEG and clinical course did not indicate epileptic seizure but instead, possible temporal worsening of extrapyramidal symptoms.

4.6.3 Discontinuations for Adverse Events

Group 1 Dementia Placebo Controlled Trials

Forest reported that the discontinuation due to AE risk was similar for the placebo treated group (11.5%, 106/922) and the memantine treated group (10.1%, 95/940) in the Group 1 placebo controlled dementia trials (SU vol. 1.11, p.251). The discontinuation due to AE rate in the memantine group was 24.4/100PY (95/389PY) compared to 27.8/100PY (106/381PY) in the placebo group.

The following table includes the AEs leading to discontinuation that occurred in at least three memantine subjects and at least twice as frequently compared to placebo.

FDA TABLE 8. AEs Leading to Discontinuation That Occurred in at Least Three Memantine Subjects and at Least Twice as Frequently Compared to Placebo, Group 1 Dementia Placebo Controlled Trials

AE leading to Discontinuation	Memantine (n=940)	Placebo (n=922)
Dehydration	0.4% (4)	0
Nausea	0.3% (3)	0
Diarrhea	0.3% (3)	0.1% (1)
Personality disorder	0.3% (3)	0.1% (1)
Asthenia	0.3% (3)	0.1% (1)
Urinary Tract Infection	0.3% (3)	0.1% (1)

From Forest Panel 31, SU vol. 1.11, p.252

I reviewed the narratives for the four memantine subjects who discontinued for dehydration (9605-028-0214, MEM-MD-02-2096, MEM-MD-02 2383, MEM-MD-02 2473). At the time of discontinuation, dehydration was diagnosed along with infections in three of the subjects and with dysphagia and poor intake resulting in a feeding tube placement in the fourth subject.

No memantine treated subjects discontinued from Group 1 dementia placebo controlled trials for events suggestive of hepatic failure, renal failure, rhabdomyolysis, pancreatitis, or serious rash. One subject discontinued for anemia, one for increasing BUN and creatinine. Those cases are summarized below.

Anemia

MEM-MD-02 037 2383 This 79-year-old female had only baseline lab values and her baseline hemoglobin was 11.3g/dL with a hematocrit of 33%. Baseline WBC count was 6.6 with a platelet count of 207. She was hospitalized for sepsis, arthralgia, anemia (extent not described) and atelectasis. She subsequently developed dehydration, a urinary tract infection, increased confusion and asthenia. She discontinued from the study for all of these events and was transferred to a nursing home. The anemia was reported as resolved.

Increased BUN/Creatinine

9202/00273 This 88 year old male with a history of hypertension and angina had a screening BUN/Cr of 27.5mg/dL/1.5mg/dL. Prior to his first memantine dose his BUN/Cr had increased to 31.7mg/dL/1.8mg/dL. After 90 days of memantine treatment his BUN/Cr was 36.4mg/dL/2mg/dL, despite increased oral fluid intake. The subject was discontinued from the study and the narrative and data sets did not include additional lab results.

The discontinuation due to AE risks for Alzheimer's disease subjects did not appear to be meaningfully different when compared to the discontinuation due to AE risks for vascular dementia subjects (SU vol. 1.11, Panel 32, p.253).

Open Label Dementia Trials

Forest reported that 10.7% (92/856) of subjects enrolled in open label dementia trials discontinued for adverse events. The discontinuation for adverse event rate in open label dementia trials (22.6/100PY; 92/407PY) was similar to the discontinuation due to AE -rates observed in the memantine (24.4/100PY) and placebo (27.8/100PY) groups in the group 1 placebo controlled dementia trials. The discontinuation due to AE risk for subjects who received placebo during the preceding placebo controlled trial (9.8%, 41/417) was similar to the risk in those who received memantine in the preceding controlled trial (11.6%, 51/439).

Cerebrovascular disorder (1.2%, 10/856) and pneumonia (1.2%, 10/856) were the only AEs leading discontinuation reported for more than 1% of dementia open label study subjects.

I reviewed the table of discontinuations due to AEs for the open label dementia trials (NDA Table 5.2.2) to look for infrequent events of particular significance. No subjects discontinued for events suggestive for liver failure, serious rash rhabdomyolysis, or pancreatitis. One subject discontinued for hepatitis (9408-00185, also an SAE, see above) and one for hepatic function abnormal (9202-00657). One subject discontinued for anemia (9408-00075), one for renal function abnormal (9202-00375) and one for creatinine increased (9206-00047, also an SAE, see above). I summarize the non-serious discontinuations for these AEs of interest below.

Abnormal Liver Function Tests

9202-00657 An 83 year old male discontinued from a trial for abnormal liver function tests. The CRF documented that the subject was consuming alcohol at the time of the abnormal test results. The subject was instructed to abstain from alcohol and the CRF commented that the subject subsequently improved. The subject had a normal bilirubin (0.6), SGOT (29) and SGPT (36) at visit 1. The last on-drug bilirubin was 1.5, (1.9, one week later) with an SGOT 88 (74, one week later), and SGPT 67 (58 one week later).

Anemia

9408-00075 A 79-year-old female discontinued from a trial after developing anemia due to GI bleed that was attributed to NSAID (piroxicam) use. Her hemoglobin was low (11.3g/dL) at the first visit and did not substantially change throughout the study. The CRF commented that the anemia was beginning to resolve following discontinuation from the study.

Renal Function Abnormal

9202- 00375 A 90-year-old male with a history of hypertension developed abnormal renal function and discontinued from the study. The CRF commented that the patient had abnormal blood tests throughout the study showing gradual age-related renal deterioration. The subject's baseline creatinine was 2.1mg/dL and increased to 2.9mg/dL (last on drug) and was 2.6mg/dL approximately one month later. BUN at baseline was 37mg/dL and increased to 55mg/dL (last on drug) and was 47mg/dL approximately one month later.

Group 1 Neuropathic Pain Trials

In the placebo controlled neuropathic pain trials, the discontinuation due to AE risk for memantine group was 12.5% (49/391) compared to 12.1% (18/149) in the placebo group. The discontinuation due to AE risk for the memantine 20mg/day group was 7% (12/171) compared to 16.8% (37/220) in the memantine 40mg/day group (NDA table 5.2.5).

I reviewed Forest's listing to look for AEs leading to discontinuation more frequently among memantine subjects and with evidence of dose response. Dizziness led to discontinuation of 5.9% (32/391) of memantine subjects and 1.3% (2/149) of placebo subjects. Most of the dizziness leading to discontinuation occurred in the 40mg memantine group (10%, 20/220) with one 20mg subject (0.6%, 1/171) discontinuing for dizziness (NDA table 5.2.5). There was also some suggestion of dose response for discontinuations due to nausea with 2.3% (5/220) of the memantine 40mg group, 1.2% (2/171) of the memantine 20mg group, and 1.3% (2/149) of the placebo group discontinuing for nausea.

I reviewed the discontinuations due to AEs listing for the memantine subjects in the neuropathic pain trials to look for infrequent events of particular importance. There were no discontinuations for events suggestive of renal failure, hepatic failure, hematological dyscrasias, rhabdomyolysis, pancreatitis, or serious skin reactions. One memantine subject discontinued for bilirubinemia (NTI 9801-00074) and one for photosensitivity reaction (NTI 9801-00320). I summarize those cases below.

Bilirubinemia

NTI 9801-00074 A 53 year old male who received treatment with memantine for 56 days, developed elevated bilirubin. This subject had an elevated alkaline phosphatase at screening (179) with normal bilirubin (0.6), AST (23), and ALT (24). At week 2, the alkaline phosphatase increased (207) while the bilirubin (0.6), AST (22), and ALT (20) remained normal. At week 4, the alkaline phosphatase (216) and bilirubin (2.1, repeat 2.4) were elevated while the AST was 29 and ALT was 25. The subject discontinued

from the trial and follow up labs approximately 1 month later found alkaline phosphatase 160, bilirubin 0.6, AST 22, and ALT 19. (Study report NTI 9801, Appendix 111.2, NDA vol. 239).

Photosensitivity

NTI 9801-00329 A 33 year old male developed sweating, parasthesias of the lips, photosensitivity of the eyes, tremors, slurred speech, dizziness and nausea with all events resolving the same day except dizziness and nausea (resolved 2 days later).

Group 2 Studies

Forest reported that 10.9% (60/549) of memantine subjects and 1.7% (3/173) of placebo subjects discontinued from Group 2 studies (NDA table 5.1.6). Cardiac failure (memantine 1.5%, 8/549, placebo 0/173), dizziness (memantine 3.6%, 20/549; placebo 1.2%, 2/173) and agitation (memantine 1.1%, 6/549; placebo 0/173) were the only AEs leading to discontinuation in at least 1% of memantine subjects and at least twice as frequently compared to placebo. No memantine treated subjects in these studies discontinued for AEs suggestive of renal failure, hepatic failure, hematological dyscrasias, rhabdomyolysis, pancreatitis, or serious skin reactions.

Ongoing Studies

Forest did not summarize the discontinuations for AEs from ongoing studies.

4.6.4 Treatment Emergent AEs

Group 1 Dementia Placebo Controlled Trials

In Group 1 dementia trials, the proportion of memantine treated subjects with at least one AE (70.4%, 662/940) was similar to the proportion of placebo subjects with at least one AE (67.7%, 624/922). The rate of subjects with one or more AEs in the memantine group (170/100PY, 662/389PY) was similar to the rate in the placebo treated group (164/100PY, 624/381PY).

Forest presented a table summarizing AEs reported for at least 2% of memantine subjects and greater than placebo (NDA Panel 35, p.233) and I summarized those data below. I highlighted events that were reported in at least double the percentage of memantine subjects compared to placebo subjects.

FDA TABLE 9 Treatment Emergent AEs in ≥2% of Memantine Patients and at a Higher Rate than Placebo Patients- Double Blind Placebo Controlled Dementia Studies

Preferred Term	Memantine (n=940)	Placebo (n=922)
Dizziness	6.8% (64)	5.3% (49)
Confusion	6.2% (58)	4.6% (42)
Headache	5.7% (54)	3.4% (31)
Constipation	5.3% (50)	3% (28)
Urinary Incontinence	4.4% (41)	3.9% (36)
Coughing	3.9% (37)	3.4% (31)
Hypertension	3.5% (33)	2.2% (20)
Gait abnormal	3% (28)	2.7% (25)
Somnolence	3% (28)	2.5% (23)
Vomiting	3% (28)	2.3% (21)
Back pain	2.6% (24)	2.3% (21)
Hallucination	2.6% (24)	1.6% (15)
Pain	2.6% (24)	0.9% (8)

Anxiety	2.4% (23)	1.6% (15)
Edema Peripheral	2.4% (23)	1.6% (15)
Fatigue	2.4% (23)	1.3% (5)
Anorexia	2.2% (21)	1.8% (17)
Dyspnea	2% (19)	1% (9)

From Forest Panel 35, NDA vol. 265, p.233.

I reviewed the investigator terms subsumed by the preferred term pain for the memantine treated subjects. The preferred term pain subsumed a variety of investigator terms including pain in an extremity, sore mouth due to dentures, and generalized aches. There did not appear to be a cluster of distinct or related events among the AEs coded to the preferred term pain.

Since there was an excess risk of dyspnea in the memantine treated subjects and since this term refers to a symptom rather than a diagnosis, I examined these AEs further to look for a unique event responsible for this AE. I identified the 19 memantine treated subjects who experienced dyspnea. I then used the AE data set to identify associated AEs occurring around the same time as the dyspnea AE (within 1 week). In seven cases the subjects with dyspnea also had an AE of cough or fever and in some of these cases the subject was diagnosed with bronchitis, pneumonia, or influenza symptoms. Malaise, confusion, worsening allergies, chest pain and fatigue were reported on the same day as dyspnea in six cases. For the remaining six cases, dyspnea was reported without other AEs and in most of these cases the events were non-serious, did not lead to discontinuation and resolved within a matter of days. I saw a similar distribution of concomitant AEs among the placebo subjects with dyspnea AEs.

When considering only the Alzheimer's dementia trials, the following events occurred in at least 2% of memantine subjects and more often than compared to placebo (highlighted events were reported in at least double the percentage of memantine subjects compared to placebo subjects).

FDA TABLE 10 Treatment Emergent AEs in ≥2% of Memantine Patients and at a Higher Rate than Placebo Patients- Double Blind Placebo Controlled Alzheimer Dementia Studies

Preferred Term	**Memantine (n=396)**	**Placebo (n=394)**
Urinary Incontinence	6.3% (25)	5.6% (22)
Fall	6.1% (24)	5.8% (23)
Dizziness	5.8% (23)	5.3% (21)
Headache	**5.6% (22)**	**2% (8)**
Confusion	5.3% (21)	3% (12)
Insomnia	4.8% (19)	4.1% (16)
Anorexia	4% (16)	2.8% (11)
Hallucination	4% (16)	2.5% (10)
Prostatic disorder*	**3.8% (5)**	**0**
Vomiting	3.8% (15)	2.5% (10)
Constipation	3.5% (14)	3.3% (13)
Depression	3.5% (14)	3% (12)
Edema peripheral	3.5% (14)	2.5% (10)
Hypertension	3.5% (14)	2.3% (9)
Somnolence	3.5% (14)	3.3% (13)

Coughing	3.3% (13)	3% (12)
Gait abnormal	3% (12)	1.5% (6)
Fatigue	2.8% (11)	2% (8)
Back pain	2.5% (10)	2% (8)
Pain	2.3% (9)	0.3% (1)
Abdominal Pain	2% (8)	1.5% (6)
Arthralgia	2% (8)	1.5% (6)
Cardiac Failure	2% (8)	0
Micturition frequency	2% (8)	1% (4)
Rash	2% (8)	1.3% (5)

From Forest SU Table 6.1.1A

*Uses the number of males in the denominator of the risk calculation

I read through the entire list of AEs from Group 1 Dementia Placebo Controlled Trials and found no events in memantine treated subjects suggestive of hepatic failure, renal failure, rhabdomyolysis, pancreatitis, or serious skin reactions.

There were several liver-related lab abnormalities identified as AEs in Group 1 Dementia Placebo Controlled Trials. I identified the memantine treated subjects with these events and then summarized the events using the lab data sets, AE data sets, concomitant medication data sets, and narratives and CRFs (for SAEs and events leading to discontinuation).

Four memantine-treated subjects (9202-00049, 9202-00147, 9403-00072, 9605-00100) had AEs of bilirubinemia, with or without other liver-related lab AEs, compared to one placebo subject. Those events are summarized below.

Subject 9202-00049 (AE bilirubinemia) had a bilirubin of 1.5mg/dL that exceeded the lab ULN (1.2mg/dL) but that was not associated with increases in transaminases.

Subject 9202-00147 (AEs bilirubinemia increased GGT, increased ALP) had a treatment emergent bilirubin of 2.1mg/dL along with an increased GGT of 466 and an ALP of 1,247 with normal SGOT and SGPT. These abnormal lab values occurred in a setting of worsening CHF, which led to discontinuation from the trial. The subject died nine days after discontinuation and the cause of death was CHF.

Subject 9403-00072 (AEs bilirubinemia, increased ALP) had a treatment emergent bilirubin of 2.2mg/dL and ALP of 363 that was not associated with increases in GGT, SGOT or SGPT.

Subject 9605-00100 (AEs bilirubinemia, increased ALP, increased GGT, increased SGOT and SGPT) had a bilirubin of 1.3mg/dL that exceeded the ULN (1.2mg/dL) along with increased GGT of 77, increased SGOT of 172, increased SGPT of 169 and an ALP of 174. The subject fractured her pelvis just prior to these lab results and subsequently withdrew consent. There were no follow-up lab results.

Two memantine-treated subjects (9202-00654, 9408-00229) had AEs of hepatic enzymes increased compared to none with placebo. Those events are summarized below.

Subject 9202-00654 (AEs hepatic enzymes increased, hepatic function abnormal) had an elevated ALP (406) and GGT (174) at baseline. Approximately one month later, while taking memantine, the ALP and GGT were decreasing while the SGOT (79) and SGPT (101) were elevated. The SGOT and SGPT declined while the ALP and GGT increased again. Throughout the study, the bilirubin was normal (highest recorded 0.5mg/dL).

Subject 9408-00229 (AEs hepatic enzymes increased, GGT increased) had an increased ALP (291) at baseline with no other liver related abnormalities. During the study, the subject had increases in GGT (54), SGOT (76) and SGPT (52). At the last visit these labs were normal. This subject's highest recorded bilirubin was at baseline (0.9mg/dL).

Eight memantine-treated subjects (9202-00147, 9202-00573, 9403-00082, 9408-00229, 9408-00257, 9605-00027, 9605-00100, 9605-00298) had AEs of increased GGT, with or without other liver-related lab AEs, compared to six placebo subjects. Below I summarize the GGT increased AEs not previously discussed.

Subject 9202-00573 (AE increased GGT) had an elevated GGT of 143 that was not associated with increases in transaminases or bilirubin.

Subject 9403-00082 (AEs increased GGT, increased SGOT, increased SGPT, and increased ALP) had an increased GGT (99) and ALP (266) at baseline. One month later, GGT was 76 with ALP 256, SGOT 27, and SGPT 29. At the last visit, GGT was 113, ALP was 449, SGOT was 43 and SGPT was 71. The subject completed the trial. Bilirubin was normal throughout the study and there were no concomitant medications recorded.

Subject 9408-00257 (AE GGT increased) experienced increases in GGT (566) and ALP (407) and a single increased SGPT of 71 (ULN30) and SGOT of 36 (ULN 30). Bilirubin was normal throughout the study and the transaminases were normal at end of study.

Subject 9605-00027 (AEs GGT increased, ALP increased) This subject had normal labs at baseline and the only other labs 3 months later included GGT 89, ALP 132, SGOT 34, and SGPT 35. Bilirubin was normal during the study. This subject discontinued from the trial after experiencing a fall and myoclonic jerks.

Subject 9605-00298 (AEs GGT increased, ALP increased) This subject had normal labs while treated with memantine and had an elevated ALP (195) and GGT (128) twenty-four days after stopping memantine, and after starting phenytoin.

Three memantine-treated subjects (9202-00465, 9202-00005, 9202-00654) had AEs of hepatic function abnormal compared to six placebo subjects. Below I summarize the hepatic function abnormal AEs not previously discussed.

Subject 9202-00465 (AE hepatic function abnormal) had an elevated ALP (316) during the trial without associated increases in GGT, SGOT, SGPT, or bilirubin.

Subject 9202-00005 (AE hepatic function abnormal) had normal liver related labs at baseline and after approximately seven months of memantine treatment developed increased ALP (748), GGT (261), SGOT (58) and SGPT (114). Bilirubin was normal (0.6mg/dL). Approximately one week prior to these lab results, the subject was diagnosed with a UTI and began treatment with amoxicillin/clavulanate and acetaminophen. These lab abnormalities resolved without interruption of memantine.

Four memantine-treated subjects (9403-00082, 9403-00133, 9605-00100, 9605-00324) had SGOT increased AEs compared to five placebo subjects. Below I summarize the SGOT increased AEs not previously discussed.

Subject 9403-00133 (AEs SGOT increased, SGPT increased) had normal liver related lab results at baseline. After approximately two and a half months of treatment and at end of study, this subject had elevated SGOT (83) and SGPT (84) results, while GGT, ALP, and bilirubin were normal. Follow up SGOT (19) and SGPT (12) approximately two weeks after stopping memantine were normal.

Subject 9605-00324 (AE SGOT increased) a single elevated SGOT of 48 (ULN 36) and SGPT of 42 (ULN 37) during the study and these abnormalities resolved by the end of the study.

Four memantine-treated subjects (9403-00082, 9403-00133, 9408-00205, 9605-00100) had SGPT increased AEs compared to six placebo subjects. Below I summarize the SGPT increased AEs not previously discussed.

Subject 9408-00205 (AE SGPT increased) had a SGPT of 41 (ULN 39) and a SGOT of 37 (ULN 39) at baseline. This subject experienced increased SGPT (highest 52) and SGOT (highest 41). ALP, GGT, and bilirubin were normal throughout the study.

Nine memantine-treated subjects (9202-00147, 9202-00463, 9403-00072, 9403-00082, 9408-00330, 9408-00506, 9605-00027, 9605-00100, 9605-00298) had ALP increased

AEs compared to 5 placebo subjects. Below I summarize the ALP increased AEs not previously discussed.

Subjects 9202-00463, 9408-00330, and 9408-00506 all had on treatment increases in ALP (subject 9408-00330 also had an elevated ALP at baseline) and none were associated with increased GGT, suggesting non-liver related increases in ALP.

Seven memantine subjects had AEs of anemia compared to nine placebo subjects. I summarize the anemia events in memantine treated subjects below.

9202-00120 This 71 year old female had a Hgb at baseline of 10.9g/dL that decreased to 10.3g/dL on the day of her first memantine dose. After two weeks of memantine, her Hgb was 9.9g/dL. This anemia was not associated with thrombocytopenia or leucopenia. She was treated with iron sulfate and her Hgb increased to 14.5g/dL with continued memantine treatment. She completed the study.

9202-00649 SAE, summarized above.

9605-00028 This 88 year old female had an AE of anemia that did not lead to discontinuation. The lab data set included only results from this subject's last study visit and at that time the hemoglobin was 12.6g/dL. Forest noted that the subject's other study lab values were hemolyzed. Labs drawn during the study period but not part of the safety database included a hemoglobin of 12.5mg/dL, and two months later a hemoglobin of 11.4mg/dL.Following recognition of the anemia AE, this subject had a hemoglobin of 12.6mg/dL (Addition data from response to reviewer question dated 7/3/03).

MEM-MD-02 29216 This 77 year old female developed difficulty walking which led to discontinuation from the study (after 33 days of memantine). Fifteen days after discontinuation she was hospitalized for dehydration, renal insufficiency, sepsis, and hypernatremia. One month after discontinuing she was hospitalized due to overall deconditioning, suspected UTI, and deep venous thrombosis. The investigator also noted anemia as an AE during this admission but provided no laboratory results to support the diagnosis. Physical exam noted a right breast mass suspicious for cancer, but no surgery was performed. She was discharged to a long term care facility.

MEM-MD-02 209215 This 89 year old female with a history of anemia treated with ferrous sulfate, had AEs of anemia and leucopenia . This subject had a baseline hemoglobin of 11.2g/dL, HCT 35%, WBC 4.2, PLT 222. She was hospitalized for right sided congestive heart failure and had a hemoglobin of 11.7g/dL, HCT 34.9%, and a WBC count of 4.5. The subject's caregiver stopped giving the study medication and two days later, the subject was admitted after being found unconscious on the floor. Hospital records noted anemia and leucopenia but Forest could find no lab values to corroborate these findings. Three days after hospitalization, the subject's WBC count was 9.5. (Addition data from response to reviewer question dated 7/3/03).

MEM-MD-02 379222 This 83 year old male had an AE of anemia that was not serious, did not lead to discontinuation, and required no action. This subject had a baseline hemoglobin of 14g/dL, HCT 43%, WBC count 6.8, PLT 196; On 4/5/02, the date of the anemia AE, this subject had a hemoglobin of 12.5g/dL, HCT 38%, WBC count 5.2, and PLT 202.

MEM-MD-02 379236 This 79 year old female, had a baseline hemoglobin of 11.3mg/dL, HCT 33%, WBC count 6.6, PLT 207. This subject had a recorded AE of anemia; however, the anemia was not quantified and occurred in the setting of sepsis and UTI. This subject discontinued from the study and the anemia was reported as resolved two weeks after discontinuation.

Group 1 Dementia Open Label Trials

Forest reported that 71% (604/856) of subjects enrolled in open label dementia trials experienced one or more adverse events (NDA vol. 265, p.236). The rate of subjects experiencing one or more AEs in open label dementia trials (148/100PY; 604/407PY) was similar to the AE rates observed in the memantine (170/100PY) and placebo (164/100PY) groups in the group 1 placebo controlled dementia trials. The AE risk for subjects who received placebo during the preceding placebo controlled trial (72%, 301/417) was similar to the risk in those who received memantine in the preceding controlled trial (69%, 303/439).

Using Forest's table 6.1.2, I summarized the AEs occurring in at least 2% of patients from open label dementia trials. I present the risks stratified by those who received memantine and those who received placebo in the preceding double blind clinical trial.

FDA TABLE 11 Treatment Emergent AEs Reported by ≥2% of Treated Population, Open Label Dementia Trials, by Previous Treatment

Adverse Event	Placebo-Memantine N=417	Memantine-Memantine N=439	Total N=856
Agitation	7.2% (30)	6.6% (29)	6.9% (59)
Urinary tract infection	5.5% (23)	5.7% (25)	5.6% (48)
Fall	5.5% (23)	5.2% (23)	5.4% (46)
Inflicted Injury	4.3% (18)	6.2% (27)	5.3% (45)
Dizziness	7.2% (30)	3.2% (14)	5.1% (44)
Bronchitis	3.8% (16)	5.7% (25)	4.8% (41)
Confusion	5% (21)	4.3% (19)	4.7% (40)
Headache	4.8% (20)	3.2% (14)	4.0% (34)
Cataract	2.4% (10)	5.2% (23)	3.9% (33)
TIA	3.8% (16)	3.6% (16)	3.7% (32)
Influenza symptoms	3.8% (16)	3.4% (15)	3.6% (31)
Urinary incontinence	3.4% (14)	3.6% (16)	3.5% (30)
Insomnia	3.1% (13)	3.9% (17)	3.5% (30)
Depression	3.1% (13)	2.7% (12)	2.9% (25)
Coughing	2.6% (11)	3.2% (14)	2.9% (25)
Vomiting	3.1% (13)	2.7% (12)	2.9% (25)
Diarrhea	3.8% (16)	1.8% (8)	2.8% (24)
Somnolence	3.1% (13)	2.5% (11)	2.8% (24)
Vision abnormal*	2.9% (12)	2.7% (12)	2.8% (24)
Cerebrovascular disorder	1.9% (8)	3.4% (15)	2.7% (23)
Gait abnormal	3.8% (16)	1.4% (6)	2.6% (22)
Constipation	2.6% (11)	2.3% (10)	2.5% (21)
Hypertension	2.4% (10)	2.5% (11)	2.5% (21)
Arthralgia	2.6% (11)	1.8% (8)	2.2% (19)
Dyspnea	2.2% (9)	2.3% (10)	2.2% (19)
Aggressive reaction	1.4% (6)	2.5% (11)	2.0% (17)

*Included a number of verbatim terms but most commonly blurred vision and decreased visual acuity.

I read through the entire list of AEs from these trials and found no events in memantine treated subjects suggestive of hepatic failure, renal failure, rhabdomyolysis, pancreatitis, or serious skin reactions. Below I summarize selected AEs from the Open label dementia studies.

GGT increased

9605-00345- 65-year-old female who got memantine during the double blind trial had normal bilirubin, GGT, AST, ALT and ALP throughout. During the open label extension, the subject experienced increased GGT to 159, ALP 127 (up from 95), SGOT 30 (up from 15) and SGPT 76 (up from 22). The only other AE listed for this subject was urinary frequency. This subject withdrew from the study at the time of the abnormal results and the reason listed was consent withdrawn.

9408-00148- 79-year-old male treated with memantine during the double blind study had normal bilirubin, GGT, TA and ALP throughout. On the last visit of extension this subject had an elevated GGT (92). The highest recorded bilirubin for this subject was 0.7mg/dL and the highest ALP was 218 (ULN 277). SGOT and SGPT were normal throughout this subject's treatment with memantine.

Hepatic enzymes increased

9408-00221 This 75 year old female subject who received placebo during the double blind study experienced an increased ALP (highest 387) and GGT (highest 92) that were most abnormal on the last visit of the double blind study/start of the extension. These abnormalities gradually returned toward normal during the extension and while the subject received memantine. This subject had a slightly elevated SGPT at the last visit of the extension (34, ULN 30). Bilirubin and SGOT were normal throughout the double blind and extension phases. This subject experienced no other liver-related AEs and no other AEs within one month of this event.

Hepatic Function Abnormal

9408-00251 This 81-year-old male subject had elevated GGT (147), SGOT (72) and SGPT (113) at the baseline visit of the double blind trial and was randomized to placebo. He experienced increases in GGT (highest 171), SGOT (highest 107) and SGPT (highest 138) with the highest increases at the last visit of the double blind study/start of the extension. These abnormalities improved while the subject was treated with memantine and on the last visit of the extension trial/date of last memantine dose, the GGT was 130, SGOT was 27 and SGPT was 33. This subject had normal bilirubin results throughout the double blind and extension trials.

9605-00024 This 71 year old female subject had normal liver related lab tests throughout the double blind and extension phases and on the last day of the extension phase had elevated ALP (127), GGT (139), SGOT (44), SGPT (40). Bilirubin at the time of these other abnormalities was 0.4mg/dL. This subject had no other liver related abnormalities and follow up was to be with the subject's primary care physician.

Jaundice

9202-00257 This subject had an SAE of jaundice due to cholelithiasis and the event was summarized above.

SGOT increased

9408-00324 This 76 year old female subject had an abnormal GGT at baseline (59) and received placebo during the double blind phase. The GGT increased during the study period and was highest at the second to last visit of the extension phase (153). This subject had normal SGOT throughout and SGPT was slightly increased during the double blind phase (31, ULN 30) and the highest value (51) was at the last visit approximately ten days after stopping memantine. These abnormalities were not associated with increases in ALP or bilirubin. This subject had no other liver related AEs. (Note the investigator term for the event was abnormal transaminase, which was coded to SGOT increased even though the SGOT was normal and it was the SGPT that was increased).

Thrombocytopenia

9202-00319 This 66 year old male subject had a platelet count of 111,000 at baseline. At the completion of the extension phase the platelet count was 78,000. This was repeated 16 days later, off memantine, and was 68,000. Two weeks later, it was 83,000. This abnormality was not associated with a low WBC count or hemoglobin. This subject had no bleeding related AEs reported around the time of the thrombocytopenia AE. This subject was taking multiple medications including quinine.

Leucopenia

9605-00031 This 71 year old female subject had a baseline WBC count of 6.5. She was randomized to placebo and during the double blind phase had a WBC was 6. Three days after starting the extension, her WBC count was 2.8 (66% neutrophils). Ten days later the WBC count was 3.6. Three months later (last available lab) her WBC count was 2.8 (70% neutrophils). The subject discontinued from the trial at this time and the reason given was patient request. These findings were not associated with decreases in hemoglobin or platelets. This subject was treated with multiple concomitant medications including fluoxetine, donepezil, trazodone, haloperidol, chloral hydrate, and aspirin.

Pulmonary Fibrosis

9202-00247 This 70-year-old male subject had an AE coded to the preferred term of pulmonary fibrosis. This subject received placebo during the controlled trial phase. During the extension phase, the subject developed consolidation in the right lung base (event coded to pulmonary fibrosis) and associated tachypnea. Thirteen days after the onset of this AE, the patient died suddenly and the CRF noted ischemic heart disease as the cause of death.

Group 1 Neuropathic Pain Trials

Forest reported that 76% (297/391) of memantine treated subjects and 75% (111/149) of placebo subjects in Group 1 neuropathic pain trials experienced one or more AE (NDA vol. 265, p.237). In the memantine group, 68% (116/171) of subjects randomized to 20mg/day experienced one or more AEs compared to 82% (181/220) of subjects randomized to 40mg/day. In the table below, I summarize AEs from Group 1 neuropathic pain trials. The table includes events occurring in at least 1% of memantine subjects, ≥1.5 times more frequently compared to placebo, and with evidence of dose response, that is a higher risk in the 40mg/day group compared to the 20mg/day group (Source: NDA Table 6.1.5).

FDA TABLE 12 Treatment Emergent AEs Reported by ≥1% of Memantine Treated Population, Group 1 Neuropathic Pain Trials, AEs occurring ≥1.5 times more Frequently among Memantine Subjects and with Evidence of Dose Response

AE	Memantine 20mg (n=171)	Memantine 40mg (n=220)	Memantine total (n=391)	Placebo (n=149)
Dizziness	9.9% (17)	32.7% (72)	22.8% (89)	11.4% (17)
URI	5.3% (9)	6.4% (14)	5.9% (23)	4% (6)
Parasthesia	4.1% (7)	6.8% (15)	5.6% (22)	1.3% (2)
Inflicted Injury	2.9% (5)	4.1% (9)	3.6% (14)	1.3% (2)
Constipation	2.9% (5)	3.6% (8)	3.3% (13)	1.3% (2)
Pain	1.8% (3)	4.1% (9)	3.1% (12)	1.3% (2)
Confusion	1.2% (2)	3.2% (7)	2.3% (9)	0.7% (1)
Concentration imp	1.8% (3)	2.3% (5)	2% (8)	0.7% (1)
Depression	0.6% (1)	3.2% (7)	2% (8)	0.7% (1)
Skin ulceration	0.6% (1)	2.3% (5)	1.5% (6)	0.7% (1)
Fever	1.2% (2)	1.4% (3)	1.3% (5)	0.7% (1)
Sweating increased	0	2.3% (5)	1.3% (5)	0.7% (1)
Syncope	0.6% (1)	1.4% (3)	1% (4)	0.7% (1)

I read through the entire list of AEs from the neuropathic pain trials and found no events in memantine treated subjects suggestive of hepatic failure, renal failure, rhabdomyolysis, pancreatitis, or serious skin reactions. Below I summarize selected AEs in memantine subjects not discussed in previous sections of this review.

Transaminase elevations

Subjects 9801-087, 9801-088, 9801-101, and 9801-156 had AEs of SGOT elevation, SGPT elevation, or both. None of these events were associated with increases in bilirubin. The highest increase in this group was approximately 3 times upper limit of normal (subject 9801-156 had an ALT of 128) and three of these subjects had mild elevations at baseline.

Renal AEs

Subjects 9801-094 and 9801-561 had AEs of NPN (creatinine) increased and subject 9801-022 had an AE of renal function abnormal. Subject 9801-094 developed elevated creatinine (lab result not reported) while hospitalized for treatment on myocardial infarction and cardiogenic shock (treatment included diuretics). This subject died during the hospitalization. Subject 9801-561 had a baseline creatinine of 1.8mg/dL and BUN of 31mg/dL that increased to 2.9mg/dL and 80mg/dL, respectively (week 8, last on drug). One month later the creatinine was 2.1mg/dL and the BUN was 39mg/dL. Subject 9801-022 had a baseline creatinine of 1.4mg/dL and BUN of 35mg/dL and the highest on drug creatinine was 1.8mg/dL (last on drug) and BUN was 41mg/dL (last on drug). Five days after stopping memantine this subject's creatinine was 1.5mg/dL and BUN was 33mg/dL.

Group 2 AEs

Forest reported that 23% (127/549) of memantine subjects in Group 2 studies had AEs compared to 13% (22/173) of placebo patients. Forest acknowledged that Group 2 studies had less stringent reporting requirements (included only events believed possibly or definitely due to study drug), which could impact the validity of these comparisons. I read through the listing of AEs from Group 2 studies (NDA table 6.1.6). Dizziness (memantine 8.2%, 45/549, placebo 3.5%, 6/173), and headache (memantine 2.6%, 14/549, placebo 0.6%, 1/173) were the only AEs occurring in at least 2% of memantine subjects and at least twice as frequently compared to placebo subjects. There were no events suggestive of renal failure, hepatic failure, hematologic dyscrasias, rhabdomyolysis, pancreatitis, or serious skin reactions.

4.6.5 Laboratory Data

Forest analyzed lab data by identifying subjects with outlier results and by examining mean changes at end of study compared to baseline. Forest's outlier analyses looked at the percentage of subjects who had treatment emergent potentially clinically significant (PCS) results. I include Forest's PCS criteria for lab results as an attachment to this review.

Lab Mean Changes

Group 1 Dementia Placebo Controlled Trials

The most notable difference between treatment groups from Forest's analysis of the mean changes from baseline for lab results was an increase in ALP among memantine subjects (7.37) compared to a slight decrease for placebo treated subjects (-0.12). For the remainder of the lab analytes, the mean changes were generally small and similar in both groups. I summarize the lab mean change from baseline results in the table below.

FDA TABLE 13 Lab Mean Change at End of Study Compared to Baseline, Group 1 Dementia Placebo Controlled Trials

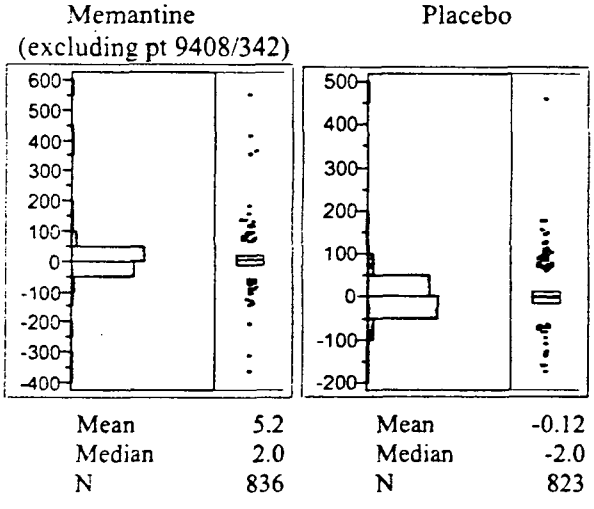
	Mean Change from Baseline	
Parameter	Memantine (n)	Placebo (n)
Hemoglobin (g/dL)	-0.01 (833)	-0.04 (819)
Hematocrit (%)	0 (811)	0 (797)
RBC count (10**12/L)	0.02 (829)	-0.01 (816)
WBC count (G/L)	0.02 (833)	0 (818)

Platelet count (G/L)	0.02 (742)	4.46 (730)
Neutrophils (%)	-0.2 (701)	0.23 (684)
Eosinophils (%)	0.07 (701)	0.1 (684)
Chloride (mmol/L)	-0.6 (188)	-0.3 (183)
LDH (U/L)	2.2 (186)	-5.4 (182)
AST (U/L)	0.11 (836)	0.71 (822)
ALT (U/L)	0.65 (836)	1.58 (822)
GGT (IU/L)	2.72 (649)	1.41 (638)
ALP (U/L)	7.37 (837)	-0.12 (823)
Total Bilirubin (umol/L)	-0.19 (786)	-0.07 (771)
Blood Urea Nitrogen (mmol/L)	0.16 (650)	0.19 (638)
Creatinine (umol/L)	2.38 (838)	1.61 (823)
Uric Acid (mmol/L)	0.01 (788)	0 (772)
Total Protein (g/L)	-0.14 (650)	-0.49 (638)
Albumin (g/L)	-0.54 (650)	-0.56 (638)
Glucose (mmol/L)	0.05 (839)	0.2 (819)
Total Cholesterol (mmol/L)	-0.07 (788)	-0.1 (772)
Sodium (mmol/L)	-0.02 (788)	-0.22 (771)
Potassium (mmol/L)	-0.02 (785)	-0.03 (768)
Calcium (mmol/L)	-0.02 (301)	-0.02 (298)

From SU Table 8.4.1

Using the SU lab data sets, I examined the changes from baseline for ALP to characterize the nature of the difference between treatment groups. I plotted the distributions of changes from baseline and found one memantine subject with a very large ALP increase (1,796). After excluding this subject (to allow more comparable graphs), I plotted the distributions of the ALP changes from baseline and they are included below.

Distribution of ALP changes from baseline, Group 1 Placebo Controlled Dementia Trials



It appeared that five memantine outliers (four in the above graph and one excluded) were responsible for a large part of the difference in mean ALP changes from baseline between the treatment groups. In fact, when I excluded the five extreme memantine outliers and the one extreme placebo outlier, the mean ALP change from baseline in the memantine group was 3.2 compared to -0.7 in the placebo.

I reviewed available data for the five memantine subjects with extreme ALP outliers. There did not appear to be a cluster of similar events. I summarize that information below.

Subject 9408-00342 This 84 year old female had normal total bilirubin, AST and ALT at baseline and an elevated ALP of 326 (ULN 277). ALP increased to 1,035 and 2,122 during the study and the subject was diagnosed with a hepatic neoplasm and subsequently died.

Subject 9202-00005 had normal liver related labs at baseline (ALP 188) and after approximately seven months of memantine treatment developed increased ALP (748), GGT (261), SGOT (58) and SGPT (114). Bilirubin was normal (0.6mg/dL). Approximately one week prior to these lab results, the subject was diagnosed with a UTI and began treatment with amoxicillin/clavulanate and acetaminophen. These lab abnormalities resolved without interruption of memantine.

Subject 9202-00147 had a treatment emergent ALP of 1,247 along with an increased GGT of 466 and a bilirubin of 2.1mg/dL with normal SGOT and SGPT. These abnormal lab values occurred in a setting of worsening CHF, which led to discontinuation from the trial. The subject died nine days after discontinuation and the cause of death was CHF.

Subject 9202-00147 This 76 year old female had an ALP of 234 at baseline. Her ALT increased to 648 and she was hospitalized for gall bladder pain. She was diagnosed with cholelithiaisis and the CRF mentioned that surgery was planned but it was not clear if this subject underwent a cholecystectomy. She continued on memantine and at end of study, her ALP was 246.

Subject 9202-00147 This 86 year old female with a history of Paget's disease had a baseline ALP of 943 that increased to a high of 1,452 and was 1,308 at end of study.

Group 1 Double Blind Placebo Controlled Neuropathic Pain Studies

Forest summarized the mean lab results by study week and by treatment group for study NTI 9801 in tables 25 and 26 (NDA vol.236, pp.304-307). This study in diabetics with peripheral neuropathy included two memantine dose groups (20mg, 40mg) and therefore allows a dose-response analysis. There did not appear to be meaningful differences among the treatment groups. I provide selected results of that analysis in the table below.

FDA TABLE 14 Mean Lab Results by Study Week and Treatment Group, Study NTI 9801

	Treatment Group		
Parameter	Placebo (n)	Memantine 20mg (n)	Memantine 40mg (n)
ALP (IU/L)			
Baseline	93.8 (77)	99.2 (159)	95.5 (153)
Week 8	93.6 (69)	100.5 (145)	97.2 (128)
Week 12	95.6 (67)	97.4 (141)	93.1 (119)
Total Bilirubin (mg/dL)			
Baseline	0.6 (77)	0.6 (159)	0.5 (153)
Week 8	0.5 (69)	0.5 (145)	0.5 (128)
Week 12	0.5 (67)	0.5 (141)	0.5 (119)
BUN (mg/dL)			
Baseline	17.6 (77)	17.7 (159)	17.5 (153)
Week 8	17.6 (69)	18.5 (145)	18.1 (128)
Week 12	17.5 (67)	18.8 (141)	18.3 (119)
Calcium (mg/dL)			
Baseline	9.3 (76)	9.3 (159)	9.3 (153)
Week 8	9.3 (69)	9.3 (145)	9.3 (128)
Week 12	9.3 (67)	9.3 (141)	9.3 (119)
Cholesterol (mg/dL)			
Baseline	198.5 (77)	205.2 (159)	197.7 (153)
Week 8	196.2 (69)	198.7 (145)	196.1 (128)