Safety Review of Clinical Data

Application Information:

NDA 20-796

Sponsor: Orion Corporation; Espoo, Finland
Submission Date: October 24, 1997
Resubmission: January 2, 1998

Generic Name (Code Name): Entacapone (OR-611)

Proposed Trade Name: Comtan®

Drug Characteristics:

Pharmacologic Category: catechol-O-methyltransferase (COMT) inhibitor

Proposed Indication: adjunct to levodopa/dopa decarboxylase inhibitor therapy for Parkinsons disease

Dosage Form: Oral film-coated tablet - 200mg

Proposed Dosing: One tablet with each dose of levodopa/dopa decarboxylase Inhibitor up to a maximum of 2000mg per day

Safety Review Conducted By: /S/
Michael J. Sevka, M.D.

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1.0 MATERIALS AND ABBREVIATIONS USED IN THE REVIEW

a) NDA 20-796 on paper, dated October 24, 1997; resubmitted January 2, 1998

b) Correspondence – submission of narratives for SAEs not attributed to entacapone, on paper, December 14, 1998

c) Electronic data sets submitted on CD-ROM as SAS transport files for trial –44 dated, May 6, 1998

d) Safety Update, on paper, dated May 15, 1998

e) Correspondence - response to request for summaries of certain PK studies, on paper, dated May 20, 1998

f) Correspondence – response to request for desk copies for selected trials, on paper, dated August 3, 1998

g) Correspondence – response to request CRF tabulation decoding document, on paper, dated August 5, 1998

h) Correspondence - response to request for clarification regarding AE glossary, on paper, dated August 11, 1998

i) Correspondence - response to request for several clarifications and additional information, on paper, dated September 10, 1998

j) Correspondence – response to request for several clarifications, on paper, October 1. 1998

k) Correspondence - response to request for AE glossary combining NDA and safety update, on paper, dated October 7, 1998

l) Fax correspondence - response to clarify Table 3.7 of the safety update, on paper, dated October 20, 1998

m) Correspondence – response to clarify indices of CRFs for enumeration of deaths and dropouts due to adverse events, on paper, dated November 4, 1998

ABBREVIATIONS USED IN THE REVIEW:

AE/AEs – adverse events
COMT – catechol-O-methyltransferase
CR – controlled-release
CRF/CRFs – case report forms
CSR/CSRs – clinical study report
DDC – dopa decarboxylase
DDCI –dopa decarboxylase inhibitor
DB – double blind
IND – investigational new drug
ISS – integrated summary of safety
ISE – integrated summary of efficacy
MAO – monoamine oxidase
NDA – new drug application
RCT – randomized controlled trials
SAE/SAEs – serious adverse events

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2.0 BACKGROUND

2.1 General Comments

Entacapone is a reversible peripherally acting inhibitor of catechol-O-methyltransferase (COMT) being developed as an adjuvant to the combination of levodopa and dopa decarboxylase inhibitor (DDCI) for the treatment of Parkinson's disease.

The sponsor seeks marketing approval for 200mg tablets administered in total daily doses of 2000mg or less. The sponsor has appointed Target Research Associates, Scotch Plains, NJ as their representative for US marketing approval.

At the time of NDA filing, entacapone was not approved in any country. Therefore, no post-marketing safety experience was available at that time. Application had been submitted to the EMEA in April 1997 for the centralized registration procedure and to Estonia, Iceland, Switzerland and New Zealand in June-August 1997. On September 22, 1997, the Committee for Proprietary Medicinal Products issued Marketing Authorization for Comtan™.

During the review of this NDA, there have been several actions taken against the only COMT inhibitor approved for the treatment of Parkinson's disease, tolcapone (Tasmar). These actions have been in response to the identification of at least 3 reports of acute liver failure in patients taking tolcapone. The EMEA has recommended the suspension of marketing approval for tolcapone and in the US the sponsor (Roche) has revised the product labeling to include a black box warning about liver failure and informed consent for patients prescribed this medication.

2.2 Summary of Preclinical Pharmacology and Toxicology

Entacapone is an inhibitor of catechol-O-methyltransferase (COMT) developed for the treatment of Parkinson's disease in combination with levodopa and a DDCI (eg carbidopa or benserazide). Entacapone reduces the metabolism of levodopa to 3-O-methyldopa (3-OMD) in peripheral tissues and thereby, in combination with carbidopa, is purported to improve the bioavailability of levodopa to the brain. **Attachment 1** reproduces the sponsor's Figure 1, which shows the metabolic pathways for levodopa and dopamine in the peripheral tissues and the brain. COMT is a catecholamine metabolizing enzyme present in the peripheral tissues and the brain with highest activity in the liver and kidney. COMT exists in two forms - S-COMT (soluble COMT) and MB-COMT (membrane bound COMT). Both forms are intracellular enzymes. COMT catalyses the transfer of the methyl group from S-adenosyl-L-methionine to a hydroxyl group of an acceptor catechol substrate. The sponsor lists the following as some substrates of COMT: dopamine, noradrenaline, adrenaline, DOPA, DOPAC (3,4-dihydroxyphenylacetic acid), catechol estrogens, triphenols, flavonoids, dobutamine, isoprenaline (isoproterenol), rimiterol, methyldopa, benzerazide, carbidopa. Entacapone inhibites oxidative phosphorylation in rat liver mitochondria at IC50 58μM compared to tolcopone (IC50 2.6μM) and dinitrophenol (IC50 12.5μM).

Acute toxicity in rats and mice is similar with oral LD50 >2g/kg. The sponsor declared the oral no toxic effect level (NTEL) of 65 mg/kg/day after 13 weeks exposure in rat and 45mg/kg/day after 13 weeks exposure in dog. In the 52 week oral study the NTEL was 90m/kg/day in rat and 80m/kg/day in dog. In the 28 day study, hyaline bodies were observed on microscopy of the kidneys of all male rats at the highest dose level (600mg/kg/day). In the 104-week carcinogenicity study in rats the accumulation of α2μ-globulin in male kidneys was associated with increased hyaline bodies in the proximal tubules. In the 52 week study in rats, examination

of the kidneys showed increased incidence of chronic progressive nephropathy and an increased incidence of chronic myocarditis at the 400mg/kg/day dose level in males. In several studies rats and dogs in the high-dose groups developed slight anemia which was more prominent in males with white cells not consistently affected. Since entacapone can chelate iron, the sponsor has suggested the anemia may be related to the chelating property of entacapone. In dogs, dark coloured feces and yellow-orange urine were observed and similar to that observed in rats. Combination toxicity studies where triple therapy with levodopa, DDC inhibitor and entacapone were given to rats and cynomolgus monkeys. The highest dose (120mg/kg/day orally) produced behavioral changes attributed to increased dopamine brain levels and bone marrow smear from rats in the 13 week study were regarded as normal for both red and white blood cells.

Carcinogenicity: The major finding in 104-week study in rats showed an increased number of adenomas and carcinomas in the kidneys of males related to the male rat specific protein, $\alpha 2\mu$-globulin, which is not found in humans or female rats.

2.3 Summary of Human Pharmacokinetics

Entacapone is a nitrocatechol derivative which exists as a trans (E) and cis (Z) isomer with the drug substance specifications stipulating that not more than 0.5% of the Z-isomer be present. Entacapone does not exhibit optical isomerism. Some isomerization to the Z-isomer occurs in humans representing only of the combined AUCs. The Z-isomer exhibits a similar profile of COMT inhibition and has similar pharmacokinetics to that of the E-isomer.

Entacapone is rapidly absorbed with a Tmax range of 0.9-1.4 hours in Parkinson's patients when co-administered with levodopa/DDC inhibitor. Bioavailablity was in healthy volunteers following administration of 200mg without co-administration of levodopa/DDC inhibitor with first pass metabolism most likely reducing bioavailability. E and Z-isomers are approximately bound to plasma proteins, respectively, mostly albumin. The half-life is hours based on the beta elimination phase. Entacapone is extensively metabolized by two major pathways - isomerization to the Z-isomer and glucuronidation followed by additional glucuronidation of the Z-isomer. Urinary excretion of entacapone and the Z-isomer accounts for only approximately 13% of an oral dose suggesting biliary excretion also occurs. Entacapone pharmacokinetics do not appear to be effected by gender, age or renal impairment. However moderate to severe hepatic impairment increases bioavailability by 2 fold which led the sponsor to recommend that entacapone be given with every other levodopa dose. Entacapone in doses higher than 200mg are associated with reductions in carbidopa AUCs, presumably due to a reduction in carbidopa absorption.

2.4 Safety Issues Identified in Proposed Labeling

Within the sponsor's submitted proposed labeling, the sponsor identified "demonstrated hypersensitivity to the drug or its ingredients" as the only contraindication to entacapone use.

Warnings
In the *Warnings* section of the labeling, the sponsor states that entacapone enhances the effects of levodopa and warns that it may be necessary to adjust the dose of levodopa during the first weeks following the initiation of entacapone in order to reduce levodopa related adverse effects (ex *dyskinesias, nausea, vomiting, and hallucinations*).

Precautions

In the *Precautions* section of the labeling, the sponsor discusses the potential for entacapone to interfere with the metabolism of catechol structured compounds. Specifically, the sponsor states that prescribers should monitor patients treated concomitantly with entacapone and rimiterole, isoproterenol, epinephrine, norepinephrine, dopamine, dobutamine, alpha-methyldopa, and apomorphine. The sponsor mentions the potential for intensified sympathomimetic effects and adrenergic reactions when these medications are combined with entacapone.

Also in the *Precautions* section the sponsor comments on consideration of dose adjustments in hepatic-impaired and renal-impaired patients.

In the *Information for Patients* section, the sponsor suggests the following:

- cautioning patients not to change the prescribed dosage regimen of levodopa and entacapone and not to add any additional antiparkinsonian medication without first consulting the physician,
- cautioning patients to notify the physician if abnormal involuntary movements appear or get worse during treatment since adjustment of levodopa dosage may be needed,
- informing those patients taking entacapone that they may experience a change in the color of their urine described as brownish-orange.

The sponsor states that no special laboratory tests are needed during treatment with entacapone.

In the *drug interactions* section the sponsor comments:

- that single doses of entacapone exceeding 400mg may decrease carbidopa bioavailability,
- that no drug interactions were observed with imipramine, moclobemide, selegiline, and other antiparkinsonian drugs,
- that entacapone should not be given in combination with non-selective MAO inhibitors or combination of selective MAO-inhibitors,
- that clinical experience is limited regarding the use of entacapone with MAO-inbibitors, tricyclic antidepressants, and catechol-structured drugs that are metabolized by COMT so that patients should be carefully monitored when entacapone is administered with these drugs.

Adverse Events

In the *Adverse Events* section of the proposed entacapone labeling, the sponsor listed the following common adverse events that occurred more often with entacapone than placebo and considered to be related to the use of entacapone: *dyskinesias* (29%), *nausea* (15%), *abnormal urine* (13%), *diarrhea* (10%), and *abdominal pain* (9%). The sponsor proposed including a table (Table 2) which lists AEs occurring in 3% of patients and more often in patients treated with entacapone than placebo from the double blind RCTs. The information from that table is reproduced in the following table.

Adverse Events Table 2 from the sponsor's proposed labeling

SYSTEM ORGAN CLASS Preferred Term (WHO classification)	Entacapone (n=406) % of patients	Placebo (n=296) % of patients
BODY AS A WHOLE- GENERAL DISORDERS		
Pain	6.4	5.4
Fatigue	6.2	4.4
Back Pain	4.4	3.0
Sweating Increased	3.7	2.7
CENTRAL & PERIPHERAL SYSTEM DISORDERS		
Dyskinesias	28.8	14.9
Dizziness	9.9	7.4
GASTROINTESTINAL SYSTEM DISORDERS		
Nausea	14.5	7.4
Diarrhea	10.1	3.7
Abdominal Pain	9.1	4.1
Constipation	5.9	3.7
Mouth Dry	4.2	0.3
PSYCHIATRIC DISORDERS		
Hallucination	4.2	3.7
RESPIRATORY SYSTEM DISORDERS		
Upper Respiratory Tract Infection	3.4	3.4
SECONDARY TERMS- EVENTS		
Fall	4.9	3.7
URINARY SYSTEM DISORDERS		
Urine Abnormal	13.1	0

The sponsor noted that the most frequent AEs related to the use of entacapone (i.e. – *dyskinesia, nausea*) parrallelled the increase in dopaminergic activity and occurred in the beginning treatment and that reduction of levodopa dosage usually decreased the severity and frequency of these events. The sponsor states that the other major class of AEs reported are gastrointestinal including *nausea, abdominal pain, diarrhea, constipation* and *vomiting.*

The sponsor noted that the incidence of *dyskinesia, nausea*, and or *abdominal pain* appeared to be increased with high daily doses of entacapone (≥1600 mg/day).

The sponsor states in proposed labeling that *diarrhea* (2%) and *vomiting* (1%), and increased dopaminergic effects including *dyskinesia* and *nausea* (1-2%) were the most common adverse events leading to discontinuation of entacapone treated patients.

The sponsor also proposes listing in alphabetical order, AEs reported in at least 1% of patients in clinical studies with entacapone.

Overdose

In the *Overdose* section of the label, the sponsor states that no cases of either accidental or intentional overdose have been reported with entacapone. The sponsor also states that the highest dose given to man has been 2400mg per day and that the highest plasma concentration in man was 14.1µg/ml. The sponsor states that management of entacapone overdose is symptomatic and that there is no known antidote. The sponsor advises hospitalization with general supportive care, gastric lavage and repeated doses of charcoal, and also advises that interaction with catechol-structured drugs should be kept in mind and that there is no experience with dialysis or hemoperfusion which are not likely to be of benefit because entacapone is highly protein bound.

Dosage and Administration

The sponsor states that the recommended dose is one 200mg tablet with each dose of levodopa/DCC inhibitor up to 10 times per day and that clinical experience is limited with doses over 1600mg per day. The sponsor states that entacapone has no antiparkinsonian effect of its own, that it can be administered with immediate-release and sustained-release levodopa/DDC inhibitor preparations, and that levodopa dose may need adjustment during the first few days or weeks to reduce dopaminergic side effects. The sponsor also states that there is no need to adjust dosage in patients with moderate to severe renal impairment but that for patients with moderate to severe hepatic impairment it may be necessary to extend the interval between entacapone dosing or to alternate entacapone with every other levodopa dose.

3.0 REVIEW METHODS

The responsibilities for the safety review were divided among several members of the Division's Safety Review Team. James F. Knudsen, M.D. conducted the safety data quality assessment in preparation of the 45 day NDA filing meeting. Dr Knudsen indicated that he verified data accuracy by comparing the line listings, narratives and information in the CSRs for the pivotal controlled studies for deaths, SAEs and dropouts in the ISS. Gerard Boehm, MD conducted and wrote the reviews for dropouts and liver data analysis, which are included as their respective sections of this document. Dr Boehm also conducted the person-time calculations, summarized the clinical course of dropouts due to diarrhea, prepared the narratives for patients who were hemoglobin outliers and aided in the editing of the final document. Dr Boehm indicated that he also conducted an audit of the CRF for the new dropouts submitted in the 4 month safety update by comparing the content of the narratives for dropouts due to AEs to data tabulations and the content of the CRFs. The remainder of the safety review including the 4 month safety update and the audit for new deaths in the 4 month safety update was conducted by the author of this document.

To evaluate the accuracy of patient accounting and disposition, the content of selected tables from the ISS and 4 month safety update were compared to one another and to the content reported in the CSRs for the 3 pivotal trials and the CSR synopses for the Phase I and II trials. Additionally, content of death narratives for patients reported in the 4 month safety update was compared to content of CRFs and data tabulations of the safety update. To evaluate the sponsor's AE coding, all verbatim AE terms were examined for mapping appropriateness to subsumed preferred AE terms using an overall verbatim glossary which combined terms from the original NDA and 4 month safety upadate. Particular attention was focused on terms associated with enhancement of levodopa effects and other clinically important events not covered in the regulatory definition of a SAE.

4.0 REVIEW FINDINGS

4.1 Audit Findings and AE Coding

Dr. Knudsen concluded that the completeness and quality of the safety data were adequate but noted that only narratives for SAEs which investigators attributed to entacapone had been submitted, prompting a request to the sponsor for submission of narratives for all SAEs. According to Dr Knudsen, he verified the accuracy of data by comparing the line listings, narratives and information in the CSR for the pivotal controlled studies for deaths, SAEs and dropouts in the ISS and noted congruency between narrative summaries and listings/tabulations.

Dr. Boehm also concluded that the accuracy of data for dropouts from the 4 month safety update was adequate, showing congruency between available CRFs, tabulations and narratives.

My audit of data for deaths in the 4 month safety update also showed adequate congruency between CRFs and tabulations except for 2 patients (-62: #1911; -73: #1304) whose complete CRFs were not submitted to the safety update and whose death cause could not be verified.

In general, the data are presented in the standard format of an NDA, with an ISE, ISS and CSR for each completed human clinical trial and interim reports for several ongoing studies. Information is provided in navigable format with tables of contents, summaries, body with tables and charts, and appended data. Typographical errors were frequent and sometimes were present in important tables of exposure, necessitating requests for clarification or corrected versions. Occasional inconsistencies were noted between in-text tables and post-text reference tables. For example, the sponsor provided their specific SAE risk estimates for open-label trials in two different locations in the ISS (in-text Table 8.29 and post-text Table 33); the in-text table cites higher risks for several events compared to the post-text table. The sponsor did not provide an explanation for these apparent inconsistencies. The sponsor did not submit the narratives for discontinuations due to AEs from phase I & II trials in the NDA despite listing them in the table of contents of Attachment C of the ISS (vol. 77 p.8-202).

In addition to the investigator identified AEs, the sponsor reported that abnormal tests (e.g. laboratory, ECGs, vital signs) not associated with a previous condition or symptom and for which action was taken with the study drug, were defined as AEs. AEs were mapped according to the WHO coding system. The sponsor points out that some use of reported terms may vary between investigator (e.g. hyperkinesia vs dyskinesia in -33 Nordic study since they are both preferred terms). Additionally, uncommon terms may have no appropriate term and may be mapped to several different preferred terms. The sponsor indicates that no attempt has been made to reclassify or recombine various combinations of similar events for the ISS. Instead AEs are used for pooled analyses as they appear in the clinical study report. The sponsor also indicates that during phase III trials, AEs were collected on a continuous AE sheet in the CRFs instead of individual sheets for each study visit and that this resulted in loss of data regarding duration of certain unspecified AEs.

Examination of the AE glossary for the NDA, shows that in some instances reported events which appear to be similar have been mapped to different preferred terms. Reported terms containing phrases such as "dizziness when standing up," "lightheaded upon standing up," "orthostatic dizziness," "symptomatic orthostatic light-headedness" were mapped to *dizziness*, while "orthostatic hypotension" and "postural hypotension," were mapped to *hypotension postural.* A

few other other verbatim terms suggestive of hypotension were mapped to *vertigo* or *hypotonia*. "Syncope," "fainting," "black-out" and "collapse" were mapped to *syncope*. Some verbatim terms such as "broken hip", "fractured rib", and "broken left clavicle" were mapped to *bone disorder* and some terms such as "black eye secondary to a fall," "bruised right knee from a fall," "fall - bruised right hip" were mapped to *purpura*, while some other falls were mapped to *pathological fracture* or *ataxia*, so that additional falls, broken bones and orthostatic events may have been missed. With this diversity of mapping, fall, fracture and orthostatic event rates may be underestimated. Additionally, it was noted that *tremors* were mapped to two preferred terms, *tremor* and *condition aggravated*.

Since the 4 month safety update added a considerable amount of additional safety data, an AE glossary combining verbatim and mapping terms for AEs from the NDA and the safety update was requested from the sponsor. Examination of the combined glossary shows similar mapping patterns as that for the NDA.

In addition to the coding problems noted above, there were inconsistencies in the grouping of terms. In the safety update SAE presentation (post-text table 13), confusion is included under both the Central and Peripheral Nervous system group and the Psychiatric event group. The frequencies for this same event differ between the groups (higher in the Psychiatric event group). Additionally, syncope was grouped to *cardiovascular events* as well as *autonomic nervous system disorders*.

4.2 Entacapone Clinical Development Program

4.2.1 General Comments

The trial numbering system for this NDA consists of the numbers 2939 or 29390 followed by 2 digits. Throughout the NDA, individual trials are identified by the last 2 digits preceded by a hyphen (eg -44).

The sponsor states that several Phase I and II studies (-01/03, -02, -04, -05, -06, -08, -09, -18) were conducted before the implementation of GCP by the EC (July 1, 1991) but followed the guidelines of national authorities and the amended declaration of Helsinki. Entacapone development in the US was carried out in 6 trials (-12, -16, -28, -31, -44, -54, -61) under IND 37,771.

4.2.2 NDA Cut-Off Dates

- October 31, 1996 for general safety data,
- April 30, 1997 for SAEs and dropouts due to AEs,
- May 31, 1997 for deaths.

4.2.3 Four Month Safety Update Cut-Off Dates

- October 31, 1997 for general safety data and dropouts,
- February 28, 1998 for SAEs and deaths.

4.2.4 Description of Trials in the NDA

The sponsor submitted safety data from 51 trials in the NDA ISS. Six additional trials (-41, -62, -63, -65, -69, -73) were ongoing in Parkinson's patients as of October 31, 1996, and had no interim report submitted to the NDA. **Attachment 2** of this review reproduces the following sponsor's tabulations for reference:

a) ISS Table 5.1 (Vol 76 p268) which groups the 51 studies by study type, and

b) un-numbered tabulation (Vol. 76 p237) which briefly describes these trials and identifies their locations in the NDA.

The following 6 trials from the NDA provide long-term safety data in Parkinson's patients:

a) 3 double-blind, randomized, parallel-group, placebo controlled trials:
-44 (US/Canada - 6 month duration; completed; 103-entacapone; 102 -placebo),
-33 (Nordic - 6 month duration – completed; 85-entacapone; 86-placebo),
-52 (Finland - 1 year duration - 6 month interim report in ISS; 218-entacapone; 108-placebo)

b) 3 uncontrolled, open-label trials, each up to 3 years in duration with 1 year interim safety reports in ISS:
-34 (Nordic), 132 patients,
-54 (US/Canada), 169 patients,
-61 (US), 24 patients.

Of the 6 trials mentioned above, four (-34, -52, -54, -61) were still ongoing at the time of NDA submission but had interim reports submitted in the ISS so that only -33 and –44 had completed CSRs.

The remaining trials contributing safety data to the NDA included:
a) 10 multi-dose studies of 1-8 weeks duration in Parkinson's patients;
b) 8 single-dose studies in Parkinson's patients;
c) 27 single dose or multi-dose studies of 10 or fewer days duration in healthy volunteers.

4.2.5 Description of Information in the 4 Month Safety Update

The sponsor has not submitted CSRs for the additional trial data included in the 4 month safety update.

The following Phase III trials had interim reports submitted to the original NDA and had additional data included as part of the safety update:
-52 – completed 1 year data - 218-entacapone, 108-placebo;
-34 - (132 patients) open-label ongoing;
-54 - (170 patients) open-label ongoing;
-61 - (24 patients) open-label ongoing.

The following trials were not included in the original NDA but contributed safety data that was combined with the ISS data in the safety update:
-63 – Phase III; completed; 24 week; parallel; 197- entacapone; 104-placebo;
-41 – Phase II; completed; single dose; placebo controlled; cross-over; 15 patients;
-76 – Phase I; completed; 6 day; multi-dose; open-label; PK; 12 healthy volunteers;
-62 - Phase III; ongoing open-label; 226 patients;
-73 – Phase III; ongoing open-label; 186 patients.

The following trials contribute only deaths, SAEs and AE dropouts to the safety update;
-65 – ongoing new RCT;
-69 - ongoing open-label.

4.2.6 Entacapone Doses, Concomitant Medications, Levodopa Formulations in the Development Program

Doses: Across the development program, entacapone was generally administered orally as 200mg or 100mg tablets but only 200mg scored tablets were used in the Phase III trials in the NDA. In Parkinson's patients, the highest daily dose given was 2400mg administered as 400mg six times a day for 14 days combined with levodopa/carbidopa to 15 patients who started the 400mg arm of a cross-over study which tested placebo vs 3 active dose levels (-28). Entacapone was also administered intravenously as single 20-25mg doses to 44 healthy volunteers and 34 patients with renal or hepatic impairment (-01/03, -06, -19, -57, -58). In healthy volunteers, the highest single oral dose administered was 800mg to 26 volunteers across 3 studies (-01/03, -15A, -22) and the highest multiple dose was 800mg TID (2400mg/day) for 7 days to 8 volunteers who completed the trial (-20). During the RCTs and the open-label trials, the highest total daily dose administered was 2000mg.

Concomitant Medications: In general, concomitant use of other antiparkinsonism drugs was allowed across trials. Studies conducted outside the US allowed use of levodopa/benzerazide combinations so that the combined safety database from the Phase III DB and open trials in the original NDA contains approximately 29% (211/731) of the experience with levodopa/benserazide preparations alone and 2.4% (18/731) with both levodopa/benserazide and levodopa/carbidopa preparations.

Levodopa Formulations: Of the 3 pivitol trials of safety and efficacy, use of controlled-release (CR) levodopa was permitted only in study -52. At the time of randomization during study -52, 66% (144/218) of entacapone exposed patients and 76% (82/108) of placebo exposed patients took CR levodopa or CR levodopa and standard preparations of levodopa. This means that at randomization across the 3 placebo controlled trials, CR levodopa preparations were used in 36% (143/406) entacapone exposed patients and 28% (82/296) placebo exposed patients. In the NDA, safety data are combined from entacapone treated patients using standard or controlled-release levodopa preparations.

4.2.7 Description of RCT design

I prepared the following table comparing the design and entry criteria of the 3 RCTs that were included in the NDA ISS.

COMPARISION OF PIVOTAL TRIALS – DESIGN AND ENTRY CRITERIA			
	-44 (US/Canada)	-33 (Nordic)	-52 (Finland)
Study Design			
Parallel group	Yes	Yes	Yes
Placebo controlled	Yes	Yes	Yes
Double-blind	Yes	Yes	Yes
Multicenter	Yes	Yes	Yes
Randomized (Entacapone:Placebo)	1:1	1:1	2:1
Study duration	6 months	6 months	12 months (6 month interim report
Study periods	2-4 week run-in on stable levodopa dose without entacapone; 6 month DB period with stable levodopa dose; 4 week staggered washout period	2-4 week run-in on stable levodopa dose without entacapone; 6 month DB period with stable levodopa dose (first morning dose was to be kept constant if dosing adjustments were necessary); 2 week post-DB withdrawal	2-4 week screen on stable levodopa dose without entacapone; 12 month DB period with stable levodopa dose for the last 3 months; 2 week post-DB withdrawal
Primary Efficacy Parameter	Proportion of daily ON time while awake according to home diaries	Mean daily ON time and duration of ON time after first morning dose (both from home diaries)	Motor score of UPDRS (Sum of Part III)
Other anti-Parkinsons drugs permitted	amantadine, anticholinergics, selegiline, dopamine agonists	amantadine, anticholinergics, selegiline, dopamine agonists	amantadine, anticholinergics, selegiline, dopamine agonists
Inclusion Criteria			
Disease Severity	levodopa-responsive idiopathic Parkinsons with motor fluctuations and Hoehn/Yahr stage 1.5-4.0 defined in OFF stage	Levodopa-responsive idiopathic Parkinsons with motor fluctuations and Hoehn/Yahr stage 1.5-4 during ON stage with average ON time less than 4 hours	Levodopa-responsive idiopathic Parkinsons needing enhancement or smoothing of levodopa effects
Age	≥30 years but <90 years in Canadian centers	not specified	30-80 years
Levodopa dose	4-10 doses per day with stable levodopa treatment	4-10 doses per day with constant dose during DB period	2-10 doses per day on stable treatment for at least one month before randomization
Levodopa preparations CR = controlled release	CR levodopa NOT permitted; Benserazide not administered	CR levodopa NOT permitted; Benserazide permitted	standard or CR levodopa permitted Benserazide permitted
Table continued below			

COMPARISION OF PIVOTAL TRIALS –DESIGN AND ENTRY CRITERIA (CONTINUED)			
Exclusion Criteria			
Dementia or neurologic disease interfering with patient evaluation	Yes	Yes	Yes
Major psychiatric disorders (eg severe depression)	Yes	Yes	Yes
Severe cardiac, renal, pulmonary, hepatic, GI disorders, other major concurrent disorders	Yes	Yes	Yes
Lack of adequate capacity for effective participation	Yes	Yes	
Use of MAO-A or non-selective MAO inhibitors within one month	Yes	Yes	Yes
Use of catechol-structured drugs within one month	Yes	Yes	Yes
Use of any experimental drug within one month	Yes	Yes	Yes
Other exclusionary criteria	1) Use, within one month, of alpha-methyldopa, reserpine, or drugs with antidopaminergic action (other than neuroleptics or neuroleptic antiemetics); Use within 6 months of neuroleptics including neuroleptic antiemetics 2) Use, within one month, of apomorphine, nomifensine, clozapine, domperidone or ondansetron 3) Prior treatment in Phase II with entacapone	1) Use, within one month, of alpha-methyldopa, reserpine, neuroleptics including neuroleptic antiemetics or other drugs with antidopaminergic action 2) Use, within one month, of apomorphine or nomifensine	1) Use, within one month, of alpha-methyldopa, reserpine, neuroleptics including neuroleptic antiemetics except sulpiride, thioridazine, melperone and resperidone for nights) and except occasional use of metoclopramide; Use within one month of other drugs with antidopaminergic action 2) Use, within one month, of nomifensine 3) Diseases which limit patient movement (eg arthritis) 4) Recent history of alcohol or drug abuse

4.3 Subject Exposure

The extent of patient/volunteer exposure to entacapone and placebo is displayed in ISS text Tables 5.2-5.14 and post-text Table 12. Significant tables are reproduced in **Attachments 3 (ISS) and 4 (Safety Update)** for reference.

Comparison of patient exposures to entacapone and/or placebo in the in-text Table 5.1 (Grouping of Studies and Patient Enumeration) to post-text Table 12 (patient disposition) and to synopses of each CSR, shows that patient accounting by the sponsor was inconsistent across these 3 data displays with approximately 10 patients, exposed to entacapone or placebo, accounted for differently, across all trials in the NDA. An additional 28 PD patients in single dose crossover trials (-08; -18) are listed on Table 12 as exposed to placebo, yet these were open-label trials where entacapone treatment was compared to no treatment rather than placebo, so that placebo exposure may be over estimated in Phase II single dose trials.

ISS Table 5.2 shows that 1415 subjects/patients were exposed to entacapone but does not account for multiple exposures. Table 5.4 shows that 1150 unique individuals were exposed to at least 1 dose in 1 trial after accounting for 177 (from 85 patients) and 148 (from 148 patients) multiple enrollments of patients entering Phase II to Phase III trials and from DB Phase III to open label trials, respectively. The sponsor reports in Table 5.5 that the 1150 entacapone exposures result in 567 person-years for entacapone; and the 536 placebo exposures result in 184 person-years for placebo. In order to verify these figures, we estimated the person time using information from Tables 5.7 and 5.8. we attributed the full duration of an interval to patients completing each time interval and half of the duration of the interval to subjects who dropped out during the interval. Person-time was then summed across all of the intervals to arrive at a total person-time estimate. Using this method, there were approximately 561 person-years of exposure to entacapone and 178 person-years of exposure to placebo.

In Table 3.4 on p. 21 of the safety update, the sponsor reported that 366 new, unique individuals were exposed during the safety update period. They reported a total of 1516 unique individuals exposed to entacapone through the safety update cutoff and stated that the updated person time exposure was 1271 person-years. Using the same method described in the previous paragraph, and the exposure data provided in the safety update, we calculated an overall person-time exposure to entacapone that matched the person-time reported by the sponsor.

4.3.1 Exposure by Duration

In Table 3.7 (p. 23) of the safety update, which provided exposure by duration through the safety update cutoff, the sponsor reported that a total of 451 subjects were exposed for at least 24 weeks and that 118 subjects were exposed for at least 52 weeks in RCTs. Also in that same table, the sponsor reported that a total of 613 subjects were exposed for at least 24 weeks and 379 subjects were exposed for at least 52 weeks in extension trials through the safety update cutoff.

4.3.2 Exposure by Dose

In Table 3.11 on (p. 28) of the safety update, the sponsor provided the overall exposure by dose in the RCTs through the safety update cutoff. The highest percentage of subjects were exposed to a mean daily dose of 800-1000mg (n=267, 44%). Roughly 10% (62/603) were exposed to a mean daily dose ≥1600mg in these studies. Table 3.12 provided the overall exposure by dose for the extension trials. The sponsor reported that the highest percentage of subjects were exposed to a mean daily dose of 800-1000mg (n=341, 46%) and 11% (n=84) were exposed to a mean daily dose ≥1600mg.

4.3.3 Exposure by Dose and Duration

Using Tables 3.11 and 3.12 (pp. 27 and 28) of the safety update, I reviewed the exposure by dose and duration for the controlled trials and extensions. In the RCTs the sponsor reported that 47 subjects were exposed to a mean daily dose of ≥1600mg for at least 24 weeks and that 4 subjects were exposed for at least 52 weeks. In the extension trials, the sponsor reported that 62 subjects were exposed to a mean daily dose of ≥1600mg for at least 24 weeks and that 37 subjects were exposed for at least 52 weeks.

4.4 Deaths

The sponsor identified a total of 29 deaths in the NDA and safety update. The sponsor used several different cutoff dates in reporting deaths. Thirteen deaths occurred as of the NDA cutoff date and were reported in the NDA ISS. The sponsor included information in the ISS for 7 additional deaths that occurred between the NDA cutoff date and 5/31/97. The safety update described 9 deaths in addition to those reported in the ISS. I have read the narratives for all 29 deaths reported in the NDA and safety update. It is difficult to attribute clear causality of entacapone to any case. The majority of narratives remain silent regarding availability of autopsy reports and many have vague descriptions of the terminal event without clinical information such as VS, lab values, other medications, physical findings or X-ray findings around the time of the terminal event, which might support the probable cause of death. Five deaths on entacapone were associated with pneumonia.

4.4.1 Mortality Rate Estimates

The sponsor reported a total of 13 deaths (9 entacapone, 4 placebo) in the development program through the NDA cutoff date (10/31/96). On p. 49 of the safety update, the sponsor reports 12 additional entacapone deaths (no additional placebo deaths) through the safety update cutoff. They also report 4 additional deaths through 2/98 (3 entacapone, 1 code-locked). Therefore, there were a total of 29 deaths in the development program (24 on entacapone, 4 on placebo, 1 unknown). The sponsor did not specifically mention the time interval between the last dose and death in the narrative summaries for many of the deaths. Two of the deaths from the safety update (-34 #2110, and –65 #0302) were noted to have occurred more than 30 days after last dose. For the remainder of this mortality review, rates are calculated assuming that the remaining deaths reported by the sponsor occurred within 30 days of last dose. Additional information regarding the interval between last dose and death should be requested from the sponsor to assure that this assumption is correct. From in-text Table 8.2, p. 113 of the ISS, as of the NDA cutoff date the sponsor reports that for the RCTs and extensions, the mortality rate for entacapone exposed subjects was 15.8/1000PY (9/567 person-years). As stated above, the sponsor reported 10 additional deaths in patients exposed to entacapone since the NDA cutoff date that were within 30 days of last exposure. Counting 9 entacapone deaths from the NDA and the 10 within 30 days of last exposure from the safety update and using the total entacapone exposure estimate from the safety update, yields a mortality rate of 14.9/1000PY (19/1271 person-years) for the development program through the safety update cutoff.

4.4.1.1 RCTs

Through the safety update, the sponsor reported 3 deaths in entacapone exposed subjects in RCTs and 4 placebo deaths. The mortality risks through the safety update cutoff were 0.5% (3/603) for entacapone and 1% (4/400) for placebo. Using the sponsor's exposure Table 3.7 on p.23 of the safety update and the methods described above, we estimated the updated exposure in the RCTs to be 374 person-years for entacapone. Using the information from Table 3.9 on p. 26, we estimated the updated placebo exposure to be 242 person-years. Using these exposure estimates,

the mortality rates through the safety update for the RCTs are 8.0/1000PY (3/374 person-years) for entacapone and 16.5/1000PY (4/242 person-years) for placebo.

4.4.1.2 Extension Studies

Through the safety update, the sponsor reported 18 open label deaths (16 assumed to be within 30 days of last exposure). The mortality risk for extension trials is 2.2% (16/738). Using the method described above and the information from sponsor's Table 3.7 on p. 23, we estimated the person-time exposure in extension trials through the safety update to be 897 person years. Using this exposure estimate, the mortality rate for extension trials is 17.8/1000PY (16/897 person-years).

4.4.2 Review of Death Narratives

4.4.2.1 NDA Death Narratives

The sponsor reports a total of 20 deaths as of May 31, 1997 with 13 of these occurring before the NDA cut-off date of October 31, 1996 and the other 7 occurring through May 31, 1997. No deaths were reported from trials -33 or -44 or from phase I and II studies.

Below are synopses for the 19 of 20 patients with narratives submitted in the NDA. An identical narrative was submitted for 2 patients. The correct 20th patient was identified in the death table of the NDA and the correct narrative was submitted in the safety update. For these 19 patients: all were 59 years of age or older; 3 were 6 days to 3 weeks from the last dose (#1, 16, 18 below); 4 were on placebo (#10-13 below); 2 had malignacies (#5, 9 below); 2 had aspirations with pneumonia (#2, 4); 1 experienced cardiopulmonary arrest when vomiting during an upper GI procedure (#3); 1 had probable sepsis following surgeries related to burns (#6); 1 was a possible MI having been hospitalized for angina 2 weeks earlier (#14 below); and 5 had vague descriptions of death - Parkinsons disease with ThXII fracture with paresis (#7), complications of pneumonia as reported by his wife (#8), found dead at home due to Parkinsons disease (#15), died during sleep with history of CHD and prior MI (#17), progressive weakness and loss of weight due to cardiac insufficiency, hypertension, Parkinsons disease, and constipation (#19).

1) Study 2939052 - Pt # 0301: 71 yo M - died about 3 weeks after discontinuing entacapone (800mg/day) following 196 days of treatment during double-blind period; reportedly died of septic shock after developing pneumonia and experiencing an MI following surgery for prosthetic repair of an abdominal aortic aneurysm; other meds - levodopa, selegiline, bromocriptine, and isosorbide.

2) Study 2939052 - Pt # 1610: 76 yo M - after 165 days of entacapone (800mg/day) treatment during double-blind period, hospitalized for vomiting, burning sternal pain and breathing difficulty; had a history of swallowing difficulties, epigastric pain, hiatus hernia and cardiac infarction; developed infiltrate on chest x-ray on Day 166 and given antibiotic for aspiration pneumonia, rapidly worsened, failed resuscitation and died; other meds - levodopa, sucralfate.

3) Study 2939054 - Pt # 285: 75 yo F - after 388 days of open-label entacapone (1000mg/d) treatment, hospitalized for severe vomiting; thought to have either ileus or early bowel obstruction based on abdominal x-ray findings; underwent upper-GI exam when she vomited and experienced cardiorespiratory arrest; died about 36 hours after further medical and neurological deterioration; death reported as probably due to be caused by hypoxic encephalopathy and cardiopulmonary collapse; other meds - levodopa.

4) Study 2939054 - Pt # 184: 60 yo F - after 303 days of open-label entacapone (1600mg/d) treatment, was hospitalized for respiratory problems and died 5 days later reportedly due to

aspiration pneumonia; had a history of dysphagia secondary to Parkinson's disease; other meds - levodopa, bromocriptine, clindamycin, fluconazole, digoxin.

5) Study 2939054 - Pt # 012: 63 yo M - diagnosed with metastatic adenocarcinoma of the lung after about 4 months treatment with open-label entacapone (1200mg/d) treatment; underwent chemotherapy; died on entacapone after 477 days of treatment with entacapone; other meds - levodopa.

6) Study 2939034 - Pt # 4303: 69 yo M - hospitalized, under the influence of alcohol and during open-label entacapone (1200mg/d) treatment, for burns sustained while bathing; subsequent confusion and anxiety led to a reduction in levodopa and entacapone doses; the burn injury required skin transplants, antibiotics and antimycotics; following establishment of a sigmoidal stoma on Day 320, the patient died on Day 323 reportedly with signs of septic shock; other meds - levodopa

7) Study 2939034 - Pt # 2113: 78 yo F - on Day 347 of open-label entacapone (600mg/d) treatment hospitalized for Th XII vertebral fracture with paresis and died on Day 463 with Parkinson's disease reported as the cause of death; no autopsy; no further information received.

8) Study 2939034 - Pt # 4204: 76 yo M - as reported by the patients wife, died due to complications of pneumonia on Day 475 of open-label entacapone (1200mg/d) treatment.

9) Study 2939034 - Pt # 4702: 59 yo F - hospitalized after about 7 months of entacapone (1000mg/d) treatment, for generalized seizure when CT revealed intracerebral tumor which was a glioblastoma; died about 3 months after tumor detection; other meds - levodopa, bromocriptine.

10) Study 2939052 - Pt # 0206: 76 yo M - after 31 days **placebo** treatment, hospitalized due to stomach pain and slight chronic anemia; died reportedly of sepsis one month after gastrectomy for gastric carcinoma; other meds - levodopa.

11) Study 2939052 - Pt # 0802: 65 yo F - after 24 days **placebo** treatment discontinued due to mild palpitation, moderate chest pain, moderate fatigue and suspected leukemia; was found dead 18 days after discontinuing study treatment with autopsy verification of oxazepam and temazepam intoxication; other meds - levodopa, piperidine, temazepam.

12) Study 2939052 - Pt # 0906: 66 yo M - after 138 days of **placebo** treatment, hospitalized for metastatic esophageal carcinoma and died the same day he underwent surgery with the cause of death reported to be esophageal carcinoma; other meds - levodopa, selegiline, pergolide.

13) Study 2939052 - Pt # 1254: 70 yo M- after 168 days of **placebo** treatment, hospitalized due worsening heart failure and 2 days later experienced parietal brain infarction with probable re-in infarction and death 7 days later; other meds - levodopa, selegiline

14) Study 2939052 - Pt # 2006: 64 yo F - after 355 days of entacapone (400mg/d) treatment during double blind period, died because of suspected acute myocardial infarction; had complained of anginal pain the night before and taken nitroglycerine; had past history of angina and had been hospitalized 2 weeks earlier due to unstable angina; other meds - nitroglycerin.

15) Study 2939061 - Pt # 413: 65 yo F - after 524 days of open-label entacapone (1200mg/d) treatment was found dead at home; death certificate lists Parkinson's disease as cause; no

autopsy; was seen in clinic 1 month earlier and had a reduction in Sinemet dose due to increased falling, dyskinesia and freezing.

16) Study 2939034 - Pt # 4402: 78 yo M - after 830 days of open-label entacapone (1000mg/d) treatment and 2 weeks after study drug discontinuation due to hallucinations, died reportedly due to pneumonia and urosepsis; other meds - Cinacef for UTI

17) Study 2939062 - Pt #0456: 72 yo M - after 90 days of open-label entacapone (1000mg/d) treatment and 1 year of unspecified treatment in a double-blind study, died in his sleep; history CHD and previous MI.

18) Study 2939062 - Pt #1911: 72 yo M - after 26 days of open-label entacapone (800mg/d) treatment, died 6 days after discontinuing study drug; pneumonia reportedly assessed as cause of death; no autopsy.

19) Study 2939073 - Pt #2451: 66 yo M - after 135 days of open-label entacapone (1800mg/d) treatment and 6 months of unspecified treatment in double-blind study, died with the cause of death on the death certificate listed as left cardiac insufficiency, arterial hypertension, Parkinson's disease and constipation; before death had experienced progressive weakness, weight loss and constipation.

20) Study 2939065 - Pt #0302: 74 yo M - the narrative provided for this subject is identical to that for subject 19 above. Corrected narrative in the 4 month safety update.

4.4.2.2 Safety Update Death Narratives

The safety update provides narratives on for 16 patients but some are for the same patient reported in the NDA so that 9 additional deaths and a correct narrative for patient 0302 from RCT -65 reported in the original NDA. Therefore narratives provided for 29 deaths in the NDA and safety update. For the 10 deaths below: all were 62 years of age or older, 4 occurred at least 12 to 38 days after entacapone was discontinued (#1, 4, 6, 10 below); 3 were associated with sepsis or septic shock (#3, 5, 7 below); 1 was associated with ARDS following surgery (#2 below); 1 was associated with GI carcinoma (#8 below); 1 was possibly associated with MI but post-mortem is pending (#9 below).

1) -034 - Pt # 2110 76 yo F- treated with 600mg/day during open extension after having previously been on entacapone for 6 months during DB; hospitalized for contractures 851 days after start of study; patient could not swallow and entacapone discontinued; died in health center of arrhythmia 40 days after entacapone discontinued and 975 days after study start.

2) -034 - Pt # 1404 - 78 yo M- treated with 1000mg/day during open extension after having previously been on entacapone for 6 months during DB; hospitalized after 2 years and 3.5 months in study for due to acute GI hemorrhage; underwent surgery for duodenal diverticula after which he reportedly developed ARDS and died after 10 days.

3) -034 - Pt # 4706 - 72 yo M- treated with 1200mg/day during open extension after having previously been on entacapone for 6 months during DB; hospitalized 1 year and 10 months because of back pain and spinal necrosis (ThXII and LII); bilateral kidney tumors found; died 3 months later reportedly due to sepsis and nephrosis.

4) -062 - Pt # 1208 - 73 yo M- treated with 800mg/day during open extension after having previously been on entacapone for 12 months during DB; 8 months into the study fractured his

hip, developed pneumonia 4 weeks later and study drug was stopped; 3 days later underwent surgery for colloidal cyst in 3rd ventricle of the brain and sustained a brain infarction 9 days after the operation, dying reportedly of heart failure 10 days later.

5) -062 - Pt # 1251 - 83 yo M- treated with 600mg/day during open extension after having previously been on entacapone for 12 months during DB; hospitalized after 1 year in study due to confusion and worsening general condition when pneumonia and staphylococcus epidermidis sepsis were diagnosed with patient dying 12 days later.

6) -073 - Pt # 2761 - 81 yo M- treated with 1200mg/day during open extension after having previously been on entacapone for 6 months during DB; hospitalized for fractured hip 7 months into study when he experienced cardiac arrest due to spontaneous airway detachment; entacapone was discontinued with the arrest and patient died 3 weeks later reportedly of pneumonia.

7) -073 - Pt # 1304 -62 yo M- treated with 600mg/day during open extension after having previously been on entacapone for 6 months during DB; past medical history of urinary infection and orthostatic dysregulation; after 187 days in study experienced sudden arrest and was resuscitated but remained comatose dying 1 day later reportedly of septic shock; no autopsy

8) -065/69 - Pt # 2110 - 76 yo M- participated in double-blind study (code still not broken); hospitalized for acute abdominal pain 5 months into study and found to have bowel obstruction secondary to carcinoma and underwent unsuccessful partial gastrectomy; 8 weeks after completing DB study he entered the extension study at 800mg/ day; died after 5 months in extension.

9) -069 - Pt # 2651 - 68 yo M- treated with 800mg/day during open extension after having been in DB study for 6 months (code still not broken); had history of LVH; died suddenly after 2 months in study reportedly due to MI; post-mortem exam is pending

10) -065 - Pt # 0302 - 74 yo M- (corrected narrative from original NDA submission) participated in double-blind study (code still not broken); had 2 year history of angina; 3 days after completeing DB phase experienced unstable angina leading to CABG followed by MI and middle cerebral artery stroke and death 38 days after stopping study treatment.

4.5 Overall Profile of Dropouts

In the sponsor's presentations describing dropouts, they provided the risks for each of the reasons leading to discontinuation for the controlled trials (entacapone v. placebo) and for the extensions. Discontinuing subjects were assigned one reason leading to dropout. In some instances, the sponsor presented deaths separately from AEs leading to discontinuation. The sponsor did not provide a complete explanation for the types of events included in the *other* category, but did comment that this group included some subjects with a lack of clinical response to drug.

4.5.1 Controlled Trials

The sponsor reported on p. 37 of the safety update that in the controlled trials the risk for dropout was higher for entacapone exposed (17.6%, 106/603) compared to placebo exposed subjects (13.0%, 52/400). The sponsor provided the reasons leading to dropout for entacapone exposed subjects in the post-text Table 4 of the safety update. In the controlled trials, 13.8% (83/603) of those exposed to entacapone discontinued for *adverse events* (excluding deaths) compared to 7.8% (31/400) of placebo exposed. The other reasons leading to withdrawal of entacapone subjects were *protocol violation* (0.7%, 4/603), *non-compliance* (1.0%, 6/603), *intercurrent*

illness (0.2%, 1/603), *death* (0.5%, 3/603), *other* (1.3%, 8/603), and *lost to follow up* (0.2%, 1/603). The sponsor provided an update of the reasons leading to discontinuation for placebo exposed subjects in the safety update in post-text table 5. The reasons other than adverse event leading to discontinuation for the placebo group were *protocol violation* (0.5%, 2/400), *non-compliance* (0.5%, 2/400), *death* (0.8%, 3/400), and *other* (3.3%, 13/400).

4.5.2 Extension Trials

On page 37 of the safety update, the sponsor noted that in the extension trials, 29.5% (218/738) of those enrolled dropped out. From this group, the greatest risk associated with discontinuation was for *adverse event*. From the sponsor's post-text table 4 in the safety update, 14.6% (108/738) of those enrolled in extension trials discontinued for AEs (excluding deaths). The sponsor reported that 0.1% (1/738) dropped out for *protocol violation*, 0.4% (3/738) for *non-compliance*, 0.8% (6/738) for *loss to follow up*, 6.6% (49/738) for *subject wish*, 0.4% (3/738) for *intercurrent illness*, 2.0% for *death* (15/738), and 4.5% (33/738) for *other*.

4.6 Discontinuations Due to AEs

For the presentation of discontinuations due to AEs, the sponsor provided all of the AEs leading to discontinuation of an individual. There are instances where a subject has more than 1 AE leading to dropout.

4.6.1 Controlled Trials

In-text Table 5.2 (Safety update p.38), presents the discontinuation due to AE risks by study categories through the safety update cutoff. Following the addition of the safety update data, the risk of discontinuation due to AE (including deaths) was 14.3% (86/603) for entacapone subjects and 8.5% (34/400) in placebo subjects (RR=1.7). This represented a slight increase in the percentage of discontinuations due to AEs compared to the NDA (10.3%, 42/406) with little change in the placebo dropouts due to AEs (8.1%, 24/296).

In the safety update, the sponsor presented additional data from trial -52, an RCT that was ongoing at the time of the NDA cutoff and from trial -63, the only new controlled trial included in the safety update submission. There were no meaningful changes in the discontinuation risks for trial -52 when comparing the safety update to the NDA presentation. When viewed alone, trial -63 appeared to have a higher risk for discontinuation due to AEs (19.8%, 39/197) compared to the other controlled trials (7-12%). The placebo AE dropout risk for trial -63 was 9.6% (10/104) yielding a relative risk for discontinuation of 2.1(19.8/9.6), which is also higher than the relative risks seen with the other controlled trials (1.7). The number of levodopa doses per day was similar for -63 and the other RCTs (entacapone- 5.5±1.9; placebo- 5.6±1.9 for -63 vs entacapone- 4.2±1.4 – 6.1±1.9; placebo- 4.3±1.5 – 6.3±1.7 across the other RCTs).

The following table is derived from information included in in-text Table 5.3 on p. 39 of the safety update. It includes the most common adverse events leading to discontinuation from the NDA RCTs, and following the addition of the information from the safety update (Overall).

Summary of the most common adverse events leading to discontinuation from controlled trials				
EVENT	NDA		OVERALL	
	Entacapone(n=406)	Placebo(n=396)	Entacapone(n=603)	Placebo(n=400)
	% (n)	% (n)	% (n)	% (n)
Diarrhea	2.2 (9)	0	1.7 (10)	0
Dyskinesia/hyperkinesia	1.7 (7)	0.7 (2)	1.5 (9)	0.8 (3)
Abdominal pain	1.2 (5)	0.3 (1)	1.3 (8)	0.3 (1)
Psychiatric	0.7 (3)	1.0 (3)	2.0 (12)	1.0 (4)
Nausea	0.5 (2)	0.7 (2)	1.5 (9)	0.5 (2)

There were 2 additional events leading to dropout that are not included in the above table but which demonstrated increases in frequency following the addition of the safety update data. Hallucinations, which did not lead to any discontinuations from the controlled trials in the NDA, led to dropout of 5 entacapone subjects (0.8%) and no placebo subjects after the addition of the safety update data. Notably, there were 6 events leading to discontinuation listed as hypokinesia in entacapone exposed subjects from controlled trials in the safety update and none in the NDA. Hypokinesia was also described more often in the placebo subjects in the safety update and therefore the relative risk for discontinuation was <1. There were no other AEs leading to discontinuation that had notable changes in risk when comparing the NDA presentation to the safety update presentation.

Because all of the diarrhea cases leading to dropout occurred in entacapone exposed subjects and none in placebo exposed subjects, these cases were reviewed. Eleven cases were identified using the dropout narratives. The cases are described in the following table. In each case diarrhea was the only reason for discontinuation except #108 who also had abdominal pain and vomiting and #506 who also had anorexia and paroniria.

Study/PID	Days on treatment prior to dropout	Comments
-33/#1310	64	77 year old male on 1400mg, symptoms resolved upon discontinuation
-33/#1406	55	63 year old male on 1200mg, symptoms resolved upon discontinuation
-52/#108	33	59 year old female on 600mg, symptoms resolved upon discontinuation
-52/#207	56	73 year old female on 600mg, narrative suggests + re-challenge
-52/#308	46	60 year old male on 600mg, symptoms resolved upon discontinuation
-52/#1106	91	45 year old male on 600mg, symptoms resolved upon discontinuation
-52/1304	147	59 year old male on 800mg, symptoms resolved upon discontinuation
-52/#1452	40	56 year old female on 1000mg, + re-challenge
-52/#1861	95	61 year old male on 1000mg, symptoms resolved upon discontinuation
-63/#506	24	61 year old female on 400mg, symptoms resolved upon discontinuation
-63/#2754	126	56 year old female on 1000mg, symptoms resolved upon discontinuation

In summary, these cases demonstrate that exposure to entacapone was associated with increased risk of discontinuing due to diarrhea. The information did not appear to suggest a dose response relationship for discontinuation due to diarrhea and all subjects were on the drug at least 24 days month prior to discontinuing. Symptoms resolved in all cases upon discontinuation of entacapone and two cases appear to be examples of positive re-challenges.

Dr Boehm reviewed the narrative summaries for entacapone exposed subjects discontinuing from controlled trials (n=42 in the NDA and n=44 in the safety update) and reported there were no events leading to discontinuation that were suspicious for aplastic anemia, acute renal failure, liver failure, hepatocellular injury, rhabdomyolysis, or Stevens Johnson syndrome.

4.6.1.1 Discontinuations Due To AEs By Gender

The sponsor provided entacapone exposed discontinuations due to adverse events by gender but did not do the same for the placebo exposed subjects from the RCTs. Therefore, these data could not be evaluated for evidence of variation attributable to drug by gender.

4.6.2 Extension Trials

In In-text Table 5.4 in the safety update (p.40), the sponsor reports that 16.7% (123/738) of those enrolled in extension trials discontinued for adverse events. Following the addition of the data for the uncontrolled trials from the safety update, there were no meaningful changes in the discontinuation due to AE risk when comparing the NDA to the overall data (16.7% v. 13.8%). Through the safety update cutoff, the AEs leading to discontinuation of more than 1% from uncontrolled studies included psychiatric events (3.6%, n=27), death (2.0%, n=15), diarrhea (1.2%, n=9), and dyskinesia/hyperkinesia (1.1%, n=8).

Dr Boehm read the narrative summaries provided by the sponsor for subjects discontinuing for adverse events (n=45 in the NDA, n=78 in the safety update) and reported there were no events suggestive of renal failure, liver failure, hepatocellular injury, aplastic anemia, rhabdomyolysis or Stevens Johnson Syndrome. Several narratives described psychiatric events including confusion, delusions, and hallucinations, some of which resulted in hospitalizations and or required medication. Subject 2939034 #4607 dropped out for low WBC counts (lowest reported was 2.9) and it is unclear from the summary if this abnormality resolved upon discontinuation. Subject 2939034 #3403 discontinued for decreased platelets (lowest=84,000) and 20 days after stopping entacapone, the platelet count was 100,000. The sponsor reported that subject 2939054 #345 discontinued for *dermatitis* but did not provide details about this event. The sponsor reported that subject 2939062 #0408 developed symmetrical upper and lower extremity weakness with sensory symptoms 10 months into the study that was diagnosed as neuritis. She was treated with immunoglobulins and steroids and her symptoms resolved after 3months. In addition, 5 subjects withdrew from these extension trials for muscle cramps. From information included in the narratives, the onset of cramping ranged from after 3 doses to several years after first dose. A majority of the reports specifically mentioned leg cramps. Not all narratives included information about resolution of cramping after discontinuation. Explanations for the cramping (ex. electrolyte abnormalities) were not identified.

4.7 Serious Adverse Events (SAEs)

The sponsor classified the SAEs into one of several categories (i.e. death, hospitalizations, life threatening, permanently disabling, cancer, and overdose). The sponsor did not indicate what criteria they used to classify events as life threatening or permanently disabling.

In the 4 month safety update, the sponsor indicated that when they identified a patient meeting criteria for a serious adverse event, their description included up to 3 symptoms. They did not describe the criteria they used to select which 3 symptoms were reported in cases where the SAE was associated with more than 3 symptoms. This raises concern about incomplete descriptions for some of the serious adverse events. The comment regarding limiting the number of symptoms per report that were classified was not present in the ISS of the original NDA. Presumably the same approach was used for the NDA.

4.7.1 SAEs From RCTs

In the ISS In text Table 8.27, the sponsor summarized the RCT SAEs by type, outcome, and action taken. The majority of SAEs in the RCTs were hospitalizations, reportedly resolved and there were few fatalities. The sponsor has not summarized or characterized the nature of the hospitalizations. The following table summarizes the categories, outcomes, and actions taken for RCT SAEs through the NDA cutoff. The sponsor did not update this information in the 4 month safety update.

SAE Characteristics – RCTs –33, -44, -52 (From ISS In-Text Table 8.27)		
	Entacapone %	Placebo %
SAE – type		
Hospitalizations	90	76
Disability/incapacity	6	8
Cancer	2	3
Fatality	2	11
Outcome		
Resolved/Improved	87	82
Unchanged	9	5
Deterioration	1	0
Death	2	11
Unknown	0	3
Action Taken		
No Action Taken	68	55
Dose Reduced	9	5
Dosing Interrupted	9	18
Discontinuations	12	16
Unknown	2	5

APPEARS THIS WAY ON ORIGINAL

In the overall database for RCTs, the sponsor reports 181 SAEs for entacapone and 87 SAEs for placebo treated patients were received as of the safety update cutoff (p.54 Safety update). The sponsor does not indicate the number of unique individuals who experienced one or more SAE. Instead, they calculated risk by dividing the number of SAEs by the number enrolled in the RCTs, and estimated 30.0% (181/603) entacapone and 21.8% (87/400) of placebo treated patients experienced an SAE (RR=1.4).

The following table is derived from information contained in the sponsor's In text Table 6.11 from the safety update. It contains information about the SAEs incidence by body systems for the RCTs from the NDA, and following the addition of the data from the safety update (Overall). In calculating these risks, the sponsor divided the number of SAEs for each system by the number exposed. Therefore, this is a ratio of SAEs to the number exposed rather than the risk for individuals experiencing an event.

Ratio of the number of SAEs to number exposed to Entacapone ≥ 1.5% by Body Systems (From safety update Table 6.11)				
	NDA		Overall (%)	
	Entacapone (n=406)	Placebo (n=296)	Entacapone (n=603)	Placebo (n=400)
	% (n)	% (n)	% (n)	% (n)
CNS/PNS	6.9 (28)	4.4 (13)	6.3 (38)	6.0 (24)
GI	5.9 (24)	0.3 (1)	4.5 (27)	0.8 (3)
Body as a Whole	5.4 (22)	5.1 (15)	4.6 (28)	4.3 (17)
Psychiatric	2.7 (11)	1.4 (4)	3.2 (19)	1.5 (6)
Respiratory	2.7 (11)	0.3 (1)	2.5 (15)	0.3 (1)
Musculoskeletal	2.0 (8)	1.4 (4)	1.5 (9)	2.3 (9)
Secondary Terms	1.5 (6)	0.7 (2)	1.5 (9)	1.0 (4)

In comparing the risk of SAEs in the NDA database as calculated by the sponsor to the new overall database (in-text Table 6.11), there has been very little change in the relative risk for any body system. Only 3 have increases - psychiatric disorders increased from 1.9 to 2.1 (entacapone risk – 2.7% to 3.2%); vision disorders 1.7 to 3.3 reflecting reports in only 4 more patients on entacapone (entacapone risk - 0.5% to 1.0%); and heart rate and rhythm from 0.7 to 1.4 reflecting reports in only 2 more patients on entacapone (entacapone risk - 0.5% to 0.7%).

The next table is derived from information included in the sponsor's post-text Table 12 from the safety update. It compares the number of specific SAEs from RCTs by treatment, for the NDA and following the addition of the information from the safety update (Overall). Again, the sponsor used the number of SAEs in the numerator of these risk calculations rather than the number of unique individuals experiencing the event.

Ratio of the number of SAEs to number exposed to Entacapone ≥ 1.0% and greater than placebo (from safety update post-text Table 12)				
Event	NDA		Overall	
	Entacapone (n=406)	Placebo (n=296)	Entacapone (n=603)	Placebo (n=400)
	% (n)	% (n)	% (n)	% (n)
Nausea	1.7 (7)	0.3 (1)	1.3 (8)	0.3 (1)
Dyskinesia	1.5 (6)	0.7 (2)	1.2 (7)	0.8 (3)
Bone disorder	1.5 (6)	0.3 (1)	1.2 (7)	1.3 (5)
Pneumonia	1.0 (4)	0	0.8 (5)	0
Fall	1.2 (5)	0.7 (2)	1.2 (7)	1.0 (4)
Hallucination	0.2 (1)	0.7 (2)	1.2 (7)	1.0 (4)

Not included in the above table but also notable is that the relative risk for confusion increased from 1.7 in the NDA to 2.3 in the safety update. (entacapone risk - 0.5% to 0.7%)

Because of the excess of SAEs labeled as nausea in the above table, we identified the 8 cases of SAEs in which nausea was included as a descriptor (-33 #3401; -44 #266, #330, -52 #1802, #2003, #552, #158, –63 #3253; SAE report #s 949, 9421, 9523, 9642, 96138, 9555, 9544, 96163). All 8 patients were hospitalized with other concomitant events – 1 had diarrhea/vomiting/gallstone diagnosis resolving spontaneously; 1 chest pain/dizziness resolving spontaneously; 3 appeared to have orthostatic-like events which responded to entacapone reduction or anti-hypertensive reduction; 1 had fatigue/vomiting resolving the next day with 2 day entacapone interruption. All six of these subjects continued in study. The seventh patient was admitted with fatigue/pain in lower extremities but also was noted to have anemia and alkaline

phosphatase elevations; she discontinued study and is described in the section on liver findings. The last subject was hospitalized for weight loss (noted as the most important event), akinesia and nausea and discontinued from the study.

SAEs by Age, Gender and Entacapone Dose
The sponsor's presentation did not allow for evaluation of variation attributable to drug with respect to age or gender nor did it allow for a dose response analysis.

4.7.2 SAEs From Open-Label Studies

The sponsor reports there were 488 SAEs reported in 324 reports in the 738 exposed patients (66%) in the overall database for uncontrolled studies (p.56 Safety update). Again, the sponsor did not report the number of unique individuals in whom one or more SAE was reported and computes risk as was described above for the RCTs. From open-label studies the majority of SAEs were hospitalizations. As with the RCT data, the sponsor has not summarized or characterized the nature of these hospitalizations. The following table summarizes the SAE types, outcomes, and actions taken for the NDA data. The information in this table was not updated in the safety update.

SAE Characteristics – Open-label Trials –54, -34, -61 (ISS Text Table 8.30)	
	Entacapone %
SAE – type	
Hospitalizations	88
Disability/incapacity	1
Cancer	5
Fatality	5
Unknown	1
Outcome	
Resolved/Improved	74
Unchanged	17
Deterioration	1
Death	5
Unknown	3
Action Taken	
No Action Taken	69
Dose Reduced	3
Dosing Interrupted	12
Discontinuations	13
Unknown	3

As in the RCT SAE presentations, the sponsor provides the number of SAEs divided by the number exposed in the open-label trials. The following table identifies the body systems where the number of SAEs divided by the number exposed patients was at least 1.5% for extension trial data from the NDA, and following the addition of the safety update data (Overall).

Ratio of the number of SAEs to number exposed to Entacapone ≥ 1.5% by Body Systems (From safety update Table 6.12)		
	NDA (n=325)	Overall (n=738)
	% (n)	% (n)
Psychiatric	11.7 (38)	9.6 (71)
Body as a Whole	11.4 (37)	11.2 (83)
CNS /PNS	7.4 (24)	12.2 (90)
GI	6.5 (21)	4.6 (34)
Musculoskeletal	5.5 (18)	6.2 (46)
Respiratory	4.0 (13)	3.7 (27)
Neoplasms	3.1 (10)	2.3 (17)
Secondary Terms – includes Fall	2.5 (8)	4.3 (32)
Reproductive, male	1.8 (6)	1.6 (12)
Heart Rate/Rhythm	1.5 (5)	1.2 (9)
Platelet, bleeding, clotting	1.5 (5)	0.7 (5)
Urinary System disorders	1.2 (4)	1.8 (13)
Cardiovascular disorders, general	0.3 (1)	1.6 (12)

The following table is derived from information presented in the sponsor's Post text table 13 from the safety update. It identifies specific SAEs with 1.8% or more reports per total exposed patients from the NDA, and after the addition of the information from the safety update. Notable on this table is the appearance of 2 psychiatric terms, *hallucinations* and *confusion,* which were not identified as common SAEs in the RCTs. Among the *condition aggravated* group are 13 pallidotomies that were listed in the ISS. The sponsor did not identify the number of pallidotomies in the safety update.

Ratio of the number of SAEs to the number exposed to entacapone ≥1.8% (From post-text Table 13, safety update)		
Event	NDA (n=325)	Overall (n=738)
	% (n)	% (n)
Condition aggravated	4.6 (15)	3.3 (24)
Hallucinations	1.5 (5)	2.7 (20)
Chest pain	2.2 (7)	2.3 (17)
Parkinsons aggravated	2.5 (8)	4.6 (34)
Confusion	2.5 (8)	1.5 (11)
Bone Disorder	2.2(7)	3.5 (26)
Death	2.2 (7)	2.4 (18)
Pneumonia	1.8 (6)	1.4 (10)
Abdominal pain	1.5 (5)	0.9 (7)
Dyskinesia	0.9 (3)	1.8 (13)

4.7.3 Narratives for SAEs

Two subjects from study -44 (#364; #003) are listed among the SAE narratives (ISS Attachment D-2; p-8-261/2) but no narrative is provided for them (ISS p8-261/262 - ENT9446-fever; ENT956-no SAE listed). All available narratives for SAEs in entacapone treated patients in the NDA (241) and 4 month safety update (221) were read. There were no SAEs suggestive of renal failure, hepatic failure, aplastic anemia, rhabdomyolysis or Stevens Johnson syndrome. There were two SAEs with increased hepatic enzymes. Report ENT9674; pt 1802 described a case of enzyme elevation which reportedly normalized with continued entacapone treatment. Report ENT 97112; pt 2005 described a case of increased alkaline phosphatase and GGT which requires further follow up. Both of these cases are addressed in greater detail in the liver data review section below. It is difficult to attribute any SAEs directly to entacapone treatment.

Approximately 47 SAE, initial and follow-up reports reported after the cutoff date for the 4 month safety update do not have narratives nor are there narratives for 31 SAEs from studies that are not yet unblinded. Only a few narratives have clinical information such VS, laboratory results, physical or X-ray findings included, making assessment difficult. Narratives for the more common events such as *Parkinsons aggravated, dyskinesia, and abdominal pain* do not all describe if these events reoccur after entacapone has been discontinued and some narratives do not describe levodopa or entacapone doses. There are several SAEs that require additional follow up by the sponsor. These cases are listed in the recommendations section.

4.8 Common AEs Regardless of Severity

4.8.1 NDA Common AEs from RCTs (-44; -33, -52)

The safety profile from –44 study reflects entacapone use with only standard levodopa/carbidopa preparations, since use of controlled-release levodopa/carbidopa preparations and levodopa/benserazide were not permitted in -44 but were permitted in –33 and –52 and controlled-release preparations were permitted in –52.

The table below compares patient AEs across NDA RCTs. From this table it is apparent that the ratio of AEs to number of randomized patients is higher in -44 than -33 or -52 suggesting that there may be a difference between trials in AE detection, patient population or trial execution.

COMPARISON OF ADVERSE EVENTS IN PIVOTAL TRIALS

	-44		-33		-52 (6 month report)	
Number of Patients	E*	P*	E*	P*	E*	P*
Randomized	103	102	85	86	218	108
Safety Evaluated	103	102	85	86	218	108
Adverse Events						
Total Number of Patients with AEs	97	91	64	45	174	72
% of Patients with AEs	94	89	75	52	80	67
Total Number of AEs	560	385	163	111	405	158
Ratio of AEs to No. of Randomized Patients	5.44	3.77	1.92	1.29	1.86	1.46

* E=Entacapone; P=Placebo

Further, when comparing the reporting rates of AEs across the three pivotal trials definite differences in the incidence of certain AEs are noted, sometimes with an increase in relative risk. The table below shows some notable examples. The preferred term, *postural hypotension*, is reported primarily in the European trials and that *"syncope" and "fall"* are reported primarily in the US/Canadian trial. *"Bone disorder"*, the mapping term for fractures (not shown in the table below), is reported more uniformly (1.2%-1.9% on entacapone) across trials. The sponsor does not comment on any relationship between fractures and falling or experiencing hypotension while on entacapone compared to placebo.

Comparison of Risk of Common AEs in RCTs						
	-44		-33		-52 (6 month report)	
Preferred Term	E* N (%)	P* n (%)	E* n (%)	P* N (%)	E* n (%)	P* n (%)
Dyskinesia	55 (53.4)	34 (33.3)	7 (8.2)	1 (1.2)	55 (25.2)	9 (8.3)
Parkinsons Aggravated	36 (35.0)	36 (35.3)	1 (1.2)	0 (0.0)	21 (9.6)	11 (10.2)
Dizziness	24 (23.3)	14 (13.7)	8 (9.4)	4 (4.7)	8 (3.7)	4 (3.7)
Hyperkinesia	0 (0.0)	0 (0.0)	8 (9.4)	3 (3.5)	3 (1.4)	1 (0.9)
Hallucination	10 (9.7)	4 (3.9)	1 (1.2)	5 (5.8)	6 (2.8)	2 (1.9)
Paroniria	8 (7.8)	3 (2.9)	1 (1.2)	0 (0.0)	0 (0.0)	1 (0.9)
Fall	16 (15.5)	10 (9.8)	(0.0)	0 (0.0)	4 (1.8)	1 (0.9)
Syncope	3 (2.9)	2 (2.0)	(0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Hypotension Postural	1 (1.0)	2 (2.0)	4 (4.7)	2 (2.3)	4 (1.8)	6 (5.6)
* E=Entacapone: P=Placebo (From ISS Table 18)						

When the data from the three DB controlled trials are combined, the most common AEs with incidence greater than 5% and greater than placebo are: *dyskinesia (28.8%), nausea (14.5%), abnormal urine (13.1%), diarrhea (10.1%), dizziness (9.9%), abdominal pain (9.1%), pain (6.4%), fatigue (6.2%), constipation (5.9%)* (ISS Table 8.3). The sponsor indicates that abnormal urine refers to the discoloration caused by the color of entacapone.

When the data from the three DB controlled trials are combined, the overall incidence of AEs suggests that the following body systems are more commonly affected by entacapone (>10%) compared to placebo (ISS Table 8.1):

CNS (46.6% vs 40.9%),
GI (39.9% vs 23.0%),
Urinary (17.2 % vs 7.4%).

In table R55, the sponsor provided an analysis which compared the AE risks for the entire trial to the risks observed during the stable dosing period for study –44. There were few notable differences when viewing the event risks in this manner. A comparison of risk during the titration period to the stable period might be more informative. The following table includes the sponsor's analysis by treatment period.

Percent of Patients Reporting AEs in Study –44				
	Weeks 1-24		Weeks 9-24 (Stable Dosing Period)	
	Entacapone % (n=103)	Placebo % (n=102)	Entacapone % (n=95)	Placebo % (n=97)
Dyskinesia	53.4	33.3	42.1	25.8
Urine Abnormal	31.1	0	32.6	0
Dizziness	23.3	13.7	17.9	11.3
Nausea	16.5	5.9	14.7	4.1
Falls	15.5	9.8	10.5	6.2
Constipation	13.6	4.9	11.6	5.2
Hallucinations	9.7	3.9	8.4	4.1
Sweating Increased	8.7	3.9	3.2	3.1
Back Pain	8.7	3.9	9.5	4.1
Paroniria	7.8	2.9	6.3	2.1
Abdominal Pain	7.8	2.0	6.3	2.1
Dyspnea	7.8	1.0	5.3	1.0
Fatigue	7.8	4.9	7.4	4.1

Ataxia	6.8	1.0	5.3	1.0
Diarrhea	6.8	3.9	5.3	1.0
Purpura	6.8	2.9	5.3	3.1
Asthenia	6.8	2.9	5.3	3.1
Paresthesia	5.8	2.0	5.3	2.1
Anxiety	5.8	2.9	5.3	3.1
Speech Disorder	5.8	2.0	4.2	2.1
(From CSR-44 Table R55)				

In CSR Table 56, the sponsor presents AEs occurring at different dose levels of entacapone in at least 10% of patients in study 44 and in Table 57 presents a similar table for placebo but is very abbreviated compared to the table for entacapone. The table below was constructed for those AEs for which placebo comparison was presented in Table 57. Some AEs such as dyskinesia, dizziness, nausea, falls and pain seem to increase with dose in the entacapone group while little or no dose increase is seen in the placebo group; but caution must be used in interpreting these data since randomization was to treatment and not to dose level.

Dose Relationship of AEs Over Weeks 1-24
Study – 44

	Entacapone (n=103)			Placebo (n=102)		
	(% of patients) 600-800mg /day n=25	(% of patients) 1000-1400mg /day n=54	(% of patients) 1600-2000mg /day n=24	(% of patients) 3-4 doses/day n=29	(% of patients) 5-7 doses/day n=47	(% of patients) 8-10 doses/day n=26
Dyskinesia	36	54	71	21	38	38
Dizziness	24	15	42	17	15	8
PD Aggravated	16	41	42	31	38	35
Nausea	12	15	25	7	6	4
Constipation	12	11	25	7	4	4
Tremor	12	4	4	7	13	15
Hallucination	4	15	4	7	2	4
Diarrhea	4	4	17	7	2	4
Falls	4	19	21	10	11	8
Pain	4	11	21	14	9	4
(From CSR-44 Tables R56, 57)						

Adverse Events by Age

In sponsor's in-text ISS Table 8.10, they provided the risks for the common adverse events (>5%) by treatment, and stratified by age (<65, and ≥65) for the RCTs. Using these data, I calculated the relative risks for these common events and compared them for the 2 age groups to look for evidence of variation in risk by age. Diarrhea had the greatest difference in relative risk when comparing age groups (3.5 for <65 compared to 1.8 for ≥65).

Adverse Events by Gender

In the sponsor's in-text ISS Table 8.11, they presented the risks for the common adverse events (>5%) by treatment, and stratified by gender for the RCTs. Using these data, I calculated the relative risks for these common events and compared them for the 2 gender groups to look for evidence of variation in risk by gender. While males had higher relative risks for diarrhea (4.1 vs 1.9) and abdominal pain (4.4 vs 1.5), females had higher relative risks for nausea (2.6 vs 1.4) and falls (3.2 vs <1).

Adverse Events by Weight

I calculated the relative risk for the events in the table below and note that patients less than 65 kg in weight may be at higher risk for these events.

Relative Risk (from ISS in-text Table 8.12)				Percent of patients					
				Entacapone n=406			Placebo n=296		
	<65kg	65-84 kg	85 kg	<65kg n=120	65-84 kg n=211	85 kg n=70	<65kg n=94	65-84 kg n=137	85 kg n=65
Nausea	4.3	1.1	1.9	22.5	10.0	14.3	5.3	8.8	7.7
Fall	4.8	0.6	0.9	10.0	2.8	2.9	2.1	5.1	3.1
Back Pain	6.8	1.0	0.7	7.5	2.8	4.3	1.1	2.9	6.2
Pain	4.6	1.0	0.9	5.0	6.6	8.6	1.1	6.6	9.2

4.8.2 NDA Common AEs in Long-Term Open Extension Trials (-54, -34, -61)

The most common AEs during the open-label extensions *were dyskinesia (31%), nausea (12%), Parkinsons aggravated (27%), insomnia (12%), pain (11%) and dizziness (10%) and similar in risk to DB except Parkinsons aggravated which was 14% in the entacapone group during DB.* (from In-text Table 8.17)

4.8.3 Common AEs in 4 Month Safety Update

The risk for AEs is similar between the overall database and that of the NDA for both double-blind and open-label trials for AEs over 5% in the overall in the double-blind database.

4.9 Laboratory Data

This section reviews the sponsor's analyses for hematologic, chemistry, and urine testing laboratory data. The liver related chemistry test result analyses are discussed separately in a liver data analysis section below.

There were differences in the lab testing procedures for the different studies. In studies –52 and –44, laboratory samples were analyzed in 1 central lab, but for study –33 they were analyzed at each separate study center. Therefore, in study -33 not all analytes were assayed if a particular center did not routinely run a specific analyte. The largest number of analytes were measured in studies –44, -54 and –61.

Because of inter-center variation of methods and reference values, the sponsor felt that pooling of mean change data from the RCTs was not appropriate (p.125, ISS). Therefore, the mean change from baseline analyses were presented separately for each controlled trial. For their analysis of outliers, the sponsor presented the pooled results. **Attachment 5** reproduces tables showing mean change from baseline data for the RCTs.

4.9.1 Hematological lab results

4.9.1.1 Mean change from baseline in the RCTs

In the safety update, the sponsor presented the mean change from baseline data for lab test results in Table 7.1 and 7.2, on pp. 59-60. This table presents the mean change at the end point of the study compared to the baseline. Lab data are presented separately for each of the RCTs for the reasons described above. The data for studies –33 and –44 remain unchanged from the NDA presentation. The data for study –52 are the updated results following the addition data from the safety update. The data from study –63 was presented for the first time in the safety update. I summarized the mean change data for selected hematological tests in the following table.

Mean change from baseline for hematological tests collected during RCTs, through the safety update								
Parameter	-33		-44		-52		-63	
	E (n=85)	P (n=86)	E (n=103)	P (n=102)	E (n=218)	P (n=108)	E (n=197)	P (n=104)
Hemoglobin (g/L)	-0.45	-0.10	-1.65	-0.85	0.30	0.60	-0.15	-0.15
Hematocrit (%)	-0.60	-0.05	-0.25	0.05	-0.70	-0.50	-0.40	-0.25
MCV (fl)					-0.15	-0.45		
WBC (10E9/L)	-0.30	0.05	-0.15	-0.10	-0.02	0.10	-0.05	-0.05
Platelets (10E9/L)	-5.95	-1.30	-2.60	-4.85	-1.85	-3.55	7.35	17.15

According to the sponsor's Tables 7.1 and 7.2, none of the differences listed above achieved statistical significance.

4.9.1.2 Outlier analysis in the RCTs

The sponsor identified outliers for hematological test results in Table 7.3 on page 61 of the safety update. The sponsor stated that their criteria for outlier were from FDA guidance documents. The following table presents the data from sponsor's Table 7.3.

Parameter	RCT		RCT		EXT	
	% (n)		% (n)		% (n)	
	NDA		Overall		NDA	Overall
	E(n=406)	P(n=296)	E(n=603)	P(n=400)	(n=325)	(n=738)
Hemoglobin (decreased ≥2g/dL)	1.5 (6)	0.3(1)	1.8 (9)	0.7 (2)	5.8 (19)	5.8 (41)
WBC (drop to ≤2.8x10^9/L)	1.8 (7)	0.7 (2)	1.7 (10)	0.8 (3)	1.9 (6)	2.1 (14)
Platelets (drop to≤75,000)	0	0.3 (1)	0.2 (1)	0.5 (2)	0.3 (1)	0.3 (2)
Platelets (increased to >700,000)	0	0	0.2 (1)	0.5 (3)	0.3 (1)	0.3 (2)

This table shows an excess risk for drop in hemoglobin and WBCs in entacapone subjects in RCTs. Because of the excess risk for drop in hemoglobin in entacapone subjects, Dr Boehm identified the 6 individuals from the NDA RCTs with hemoglobin outliers using attachment E from the ISS (Lab listings for subjects with clinically significant results in the NDA) and reviewed the lab data for these subjects. In addition, I reviewed the SAE and dropout narratives that were available for these subjects. Summaries of the available information for those subjects are presented below.

Study-44 Subject#25 This 63 year old male entered the study with a baseline hemoglobin of 13.9 g/dl and experienced a decline to 11.2 g/dl by week 26. WBC and platelets were not affected. This patient did experience an SAE (hospitalized for vertebral osteomyelitis) but the narrative did not mention diagnosis or treatment of anemia. The patient continued in the study.

Study-44 Subject#111 This 75 year old male entered the study with a baseline hemoglobin of 13.3g/dl and experienced a decline to 10.4g/dl by week 28. WBC and platelets were not affected. This patient did experience a SAE (hospitalized for pneumonia) but the narrative did not mention diagnosis or treatment of anemia. This subject continued in the study.

Study-44 Subject 266 This 73 year old female entered the study with a hemoglobin of 13.5g/dl and experienced a decline to 10.6g/dl by week 28. WBC and platelets were not affected. This subject did experience an SAE (hospitalized for nausea, and vomiting and diagnosed with gallstones) but the narrative did not mention diagnosis or treatment of anemia.

Study-44 Subject#5 This 65 year old female entered the study with a baseline hemoglobin of 12.7g/dl and experienced a decline to 9.6g/dl by week 28. WBC and platelets were not affected. During the study she was diagnosed with iron deficiency anemia but this did not result in an SAE or discontinuation. On p. 128

of the ISS, the sponsor mentioned that this subject continued into extension –54 and her hemoglobin ranged between 10.1g/dl and 12.5g/dl. The sponsor did not mention if this subject was treated for the anemia.
Study-52 Subject#754 This 66 year old male entered the study with a baseline hemoglobin of 139g/L and experienced a decline to 118 g/L after 6 months in the study. WBC and platelets were not affected. This subject did experience an SAE (hospitalized and discontinued for painful muscle cramps and diagnosed with spinal compression fractures) but the narrative did not mention the diagnosis or treatment of anemia.
Study-52 Subject#1951 This 74 year old female entered the study with a baseline hemoglobin of 130g/L and in approximately 2 weeks had dropped to 117g/L. WBC and platelets were not affected. No additional labs were provided until 2 months later and at that time her hemoglobin was 116g/L (off entacapone). This subject had discontinued the study after 23 days for dyskinesia.

4.9.2 Chemistry Clinical Laboratory Monitoring -44

Chemistry laboratory testing was performed at screening visit, baseline visit and each subsequent study visit through week 26 except Visit 2 (week 2) and was optional for the last visit (week 28) following the double-blind placebo controlled washout period. Serum iron, TIBC, UTIBC, TSH, T4, and cholesterol were obtained only at baseline and at week 24.

4.9.2.1 Chemistry Mean change from baseline analyses

Statistically significant differences between study treatments were noted sporadically for the mean change from baseline over time for the analytes listed in the table below (See **Attachment 5** for CSR Table 18.1.1). The sponsor does not indicate in Table 18.1.1 what units of measurement were used in calculating these changes

Statistically significant differences between study treatments for mean change from baseline Study –44

(from CSR Post-text Table 18.1.1)		Week 4	Week 8	Week 16	Week 24
Potassium	Entacapone				-0.01
	Placebo				-0.09
Calcium	Entacapone	-0.03			
	Placebo	-0.01			
Phosphorous	Entacapone	-0.04			
	Placebo	0.02			
Creatinine	Entacapone		3.20	2.22	
	Placebo		0.73	0.98	
Glucose	Entacapone				0.32
	Placebo				-0.01
Albumin	Entacapone		-0.60		
	Placebo		-0.35		
Serum Iron #	Entacapone				-0.90
	Placebo				0.27

measured only at baseline and 24 weeks
N.B. statistically significant differences all at $p<0.05$

Statistically significant differences within the entacapone group were noted for mean change from baseline over time and are presented in the table below (See **Attachment 5** for CSR Table 18.1.1).

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Statistically significant differences within the entacapone group for mean change from baseline Study –44				
(from CSR Post-text Table 18.1.1)	Week 4	Week 8	Week 16	Week 24
Calcium reduction	–0.03	–0.04	–0.02	
Phosphorus reduction	–0.04			
Creatinine increase		3.20	2.22	2.56
TSH increase				0.37
T4 reduction				–4.38
Blood glucose increase				0.32
Albumin reduction		–0.60		
Total protein reduction	–1.08	–1.17	–0.91	
Uric acid reduction	–15.7	–10.6	–16.6	– 18.0
TIBC reduction				–1.89
# Measured only at baseline and 24 weeks N.B. statistically significant differences all at p<0.05 or lower				

For the placebo group, statistically significant differences were noted within the placebo group for mean change from baseline for potassium at week 24, calcium at weeks 8 and 16, total bilirubin at week 4, BUN at week 16, and urine pH at week 24.

4.9.2.2 Chemistry Outlier Analyses

The sponsor presents in CSR Tables 18.39.1 and 18.40.1 the percent of patients who had newly occurring low or high laboratory values at one or more visits. Results for analytes, where the incidence is about 3% more for entacapone compared to placebo, are reproduced in the table below. The sponsor does not mention if any subject discontinued the trial for changes seen in total iron, TIBC, calcium, glucose, albumin or total protein. Phosphorous values do not appear to have changed.

Incidence of LOW Laboratory Values – Percent of Patients in Study –44						
	Entacapone (%) n=103			Placebo (%) n=102		
Parameter	Newly Occurring Weeks 1-24	At Week 24	At Week 28	Newly Occurring Weeks 1-24	At Week 24	At Week 28
Potassium	5.9	1.1	1.2	2.0	-	1.2
Calcium	22.5	6.7	6.1	8.9	3.3	3.5
Glucose	9.8	-	1.2	5.9	1.1	2.4
Albumin	4.9	2.2	1.2	1.0	-	-
Total Protein	4.9	-	-	1.0	-	1.2
Serum Iron	4.1	5.6	-	1.0	1.1	-
TIBC	12.4	20.2	-	5.2	12.2	-

The Jump database for study -44 was examined for entacapone treated patients with abnormal BUN, creatinine, calcium, phosphorus, Na and K. Although age and gender defined normal limits were used in this trial, estimates for multiples above ULN used the most conservative estimate (ie the lowest for the adult age group). No trends for analyte changes were noted for calcium, phosphorous, platelets, BUN, creatinine, Na, and K.

4.9.3 Chemistry Lab Results from Study -52

Between treatment groups, statistically significant differences in mean change from baseline at 6 months, were noted for increase in total protein and phosphorous. Additionally, within the entacapone group, but not between entacapone and placebo, small but statistically significant

differences, in mean change from baseline at 6 months, were noted for increase in Ca, phosphorous and total protein and decrease in Na, uric acid and albumin. (CSR Tables R25, R26)

4.9.4 Chemistry Lab Results from study -33

Between treatment groups, a statistically significant difference was noted, for mean change from baseline to week 24, in the entacapone treated patients for an increase in creatinine. Statistically significant differences were also noted within the entacapone group, for change from baseline to week 24, for a decrease in and alkaline phosphatase (12% mean change) and an increase in creatinine (6.4% mean change). (CSR Tables R33, R35)

4.9.5 Chemistry Clinical Laboratory Assessments in 4 Month Safety Update

The chemistry clinically significant abnormalities presented show no obvious increase in frequency between the NDA and overall database (In-Text Table 7.3).

4.10 Vital Signs

For the RCTs vital signs were to be collected using Korotkoff I and V sounds measured to an accuracy of 2 mmHg in –33 and –44 but 5 mmHg in –52 and –63. Trial –63 also could use and automatic measuring device. They were to be taken after 2 minutes supine and immediately upon standing. It is not clear from the protocols or CRFs that vital signs were to be taken before or after entacapone administration. Therefore, as for ECG measuremnts, it is possible that many if not all measurements were obtained upon patient arrival when entacapone serum concentrations were at their nadir. The sponsor should be asked to identify Phase I and II trials where serial vital signs were measured after entacapone administration and examine effects on vital signs by comparing baseline to each post-administration time point to describe the effects over a dosing interval.

4.10.1 Vital Signs for -44

For changes from baseline for supine or standing SBP (Tables 16.1.3/4) or DBP (Tables 16.2.3/4) or HR (Tables 16.4.3/4), there were no statistically significant differences between entacapone and placebo for each study visit.

For the difference between treatments for supine minus standing (i.e.- orthostasis):

- SBP: no statistically significant differences for the mean of weeks 2-24 or for each visit; although there was an othrostatic trend for entacapone to show about a 4-5mmHg greater drop than placebo for weeks 2 (p=0.1010) and 4 (p=0.0958) (Table 16.3.1).
- DBP: no statistically significant differences for the mean of weeks 2-24 or for each visit; although there was an orthostatic trend for entacapone to show a greater drop than placebo for the overall mean of weeks 2-24 (p=0.0785) and about a 2-3mmHg drop for week 2 (p=0.0519) (Table 16.3.3)
- HR: no statistically significant differences for the mean of weeks 2-24 or for each visit (Table 16.3.5).

Analyses were not conducted for changes from baseline between treatments for differences in supine minus standing SBP, DBP or HR; nor were analyses conducted to examine effect of entacapone dose on VS.

According to CSR Tables 16.3.2 and 16.3.4 the number and proportion of patients with orthostatic changes of >30mmHg in SBP or DBP were tabulated by week. Although the body of the CSR mentions the use of >15mmHg for DBP, Table 16.3.4 lists >30mmHg. It is unclear if this is a typographical error. For SBP at baseline 9 (8.7%) patients randomized to entacapone and 4 (3.9%) patients randomized to placebo were orthostatic by the >30mmHg definition; and across

the double-blind period 4-12 (3.9-11.7%) patients randomized to entacapone and 2-7 (2-6.9%) patients randomized to placebo met the orthostatic criterion during any one study visit. For DBP at baseline no patient randomized to entacapone and 2 (2.0%) patients randomized to placebo were orthostatic by the >30mmHg definition; and across the double-blind period 1 (1.0%) randomized to entacapone and 1-10 (1.0-9.8%) randomized to placebo were orthostatic during any one study visit. From these tables it is not clear how many patients were orthostatic during more than one study visit. No discussion of these tables is presented in the CSR and no comment is made regarding what proportion may have been symptomatic, required levodopa dose adjustment, or experienced a fall, broken bone, bruise, other injury, or SAE in conjunction with the orthostatic period. No information is provided concerning reversal of orthostasis with levodopa dose adjustment or during entacapone discontinuation in the double-blind staggered withdrawal period.

One patient (#321) treated with entacapone discontinued the study due to increased hypotension, light-headedness and dizziness which disappeared following study discontinuation; and another (#364) treated with entacapone discontinued due to SAE of palpitations which disappeared with study drug withdrawal and felt "pins and needles" in his hands and forearms confirmed by EMG to be carpal tunnel syndrome.

The sponsor concludes that "the mean standing blood pressure was slightly but statistically significantly lower on entacapone than on placebo" and that "there was a slight tendency to orthostatic hypotension similarly in both treatment groups; SBP decreased from standing to supine position by about 10mmHg."

4.10.2 Vital Sign Results from Study -52

There was a clear tendency towards orthostasis for SBP of about 20mgHg at baseline and at 6 months. There were statistically significant differences between treatments at the 2-4 dose stratum for supine to standing SBP at 0.5 months and for DBP at 6 months.

4.10.3 Vital Sign Results from Study -33

There were no differences between mean supine minus standing blood pressure or heart rate between the 2 treatment groups.

4.10.4 Vital Signs in 4 Month Safety Update

Clinically significant abnormalities are presented showing no obvious increase in the frequency of between the NDA and the overall database (In-Text Table 8.1).

4.11 ECGs

4.11.1 ECGs for -44

ECGs were recorded at screening visit, baseline visit and each subsequent study visit. Standard 12-lead ECGs were to be taken with paper speed 50mm/s and interpreted at the site with abnormal changes and conduction intervals (PR, QRS, QTc) recorded on the CRF. It is not clear from the CSR, study protocol or CRF if ECG measurements should be conducted at a specified time relative to the time of administration of the study drug and test dose of levodopa. This suggests that some unknown portion of these data may have been collected before entacapone administration (i.e. entacapone nadir) and levodopa test, and may not have captured an immediate effect of entacapone on ECGs.

No statistically significant differences were noted between entacapone and placebo for mean PR, QRS, or QTc intervals or for mean changes from baseline to each post-baseline study visit. No

outlier analysis is provided and no analysis or discussion is provided of ECG changes in patients who may have had newly emergent changes while on drug but reverted to normal following entacapone discontinuation during the placebo controlled double-blind withdrawal period. ECG events are described in 5 patients (#45, #109, #123, #130, #181) which were reported as AEs. Assessment of entacapone causality for each of these descriptions is difficult because information is lacking about either the presence of the abnormality at baseline, or its disappearance post study, or the role of concommitant drugs or conditions. The sponsor states that none of the ECG abnormalities reported for patients treated with entacapone resulted in discontinuation or were reported as SAEs.

4.11.2 ECG Results from Study -52

There were 3 reports of ECG changes reported as AEs, in entacapone treated patients - 1 for atrial arrhythmia, 1 ventricular arrhythmia and 1 atrial fibrillation.

4.11.3 ECG Results from Study -33

CSR sites no reports of ECG changes regarded as AEs.

4.11.4 ECGs in 4 Month Safety Update

No further conduction time data were collected so that only incidence of abnormalities are compared between NDA and overall with incidence on entacapone the same as placebo for both NDA (E: 18.3% vs P: 19.7%) and overall (E: 14.1% vs P: 15.5%) in the controlled clinical trials (In-Text Table 9.1).

4.12 Liver Data Analyses

4.12.1 RCTs

On p. 124 of the ISS, the sponsor states that all subjects underwent testing, including chemistry, at least once prior to entering the studies. In their presentation of lab results, the major comparison of lab data was conducted between the 4 controlled long-term studies with at least 24 weeks of follow-up time (-44, -33, -52,-63). The liver related tests varied slightly among the 4 RCTs included in the NDA. The following table lists the liver related tests conducted by study.

Liver related chemistry tests by study for RCTs

Study Number	Tests
-33	ALT, AST, GGT, Alkaline phosphatase
-44	ALT, AST, GGT, alkaline phosphatase, total bilirubin, direct bilirubin
-52	ALT, AST, GGT, alkaline phosphatase, total bilirubin, direct bilirubin
-63	ALT, AST, GGT, alkaline phosphatase

The scheduling for testing was identified using the individual study reports (vols. 122, 136, 144). In study –33, liver testing was done at screening, weeks 0, 4,8,16,24, and post-study (week 26). For study –44, chemistry testing was done at screening, weeks 0,4,8,16,24,26 and again at week 28 if there were abnormalities at week 26. In study -52, chemistry testing was conducted at screening and at months 0,0.5,3,6,9, 12, and 12.5 (post-study). The safety update did not include a study report for study –63 to allow review of the testing schedule. The listings of lab results suggests that testing was done at screening, baseline, ½ month, 1 ½ months, 3 months, 6 months, 9 months, 12 months and post study.

4.12.2 Mean change from baseline analysis for RCT liver testing results

For mean change from baseline analysis the sponsor presented data in tables 7.1 and 7.2 that compared end-point to baseline lab results for each of the individual studies (safety update, pp.

59-60). They did not pool the lab data across studies for this analysis and the sponsor explained that this was because of inter-center variation in methods and reference values (p. 125, ISS). The numbers for each treatment in the following tables represent the number treated and do not equal the number tested in all cases.

Mean change from baseline for liver chemistry tests collected during RCTs, through the safety update

Parameter	-33		-44		-52		-63	
	E (n=85)	P (n=86)	E (n=102)	P (n=102)	E (n=218)	P (n=108)	E (n=197)	P (n=104)
AST (U/L)	0.10	-1.35	0.55	0.30	-1.15	0.65	-0.10	-0.10
ALT (U/L)	-0.35	-2.35	0.90	1.55	-0.65	0.20	-0.95	-0.45
GGT (U/L)	-1.90	-2.55	0.75	-0.20	-3.10	0.60	0.65	1.00
Alk phos (U/L)	-17.90	-4.95	-2.00	1.30	-18.90	-7.05	-2.85	5.80
Total bili (μmol/L) (mg/dl)	na	na	-0.60 -0.05	-0.05 0.0	-0.20	-0.15	0.0	0.05

For these studies, the changes from baseline were generally small and were similar for the entacapone and placebo exposed groups. The results demonstrate decreases in alkaline phosphatase that were more pronounced for those exposed to entacapone and that were present in all four studies.

4.12.3 Outlier analysis

In the safety update, the sponsor presented an outlier analysis for chemistry results (Table 7.4, p.63). Their presentation provided results from the controlled trials (for entacapone and placebo) and the results from the extension trials. The table also separated the NDA results from the updated results. For those with normal results at baseline, the sponsor identified the subjects developing outliers exceeding 3x ULN for AST, ALT, GGT, and alkaline phosphatase. For total bilirubin, the sponsor identified any values exceeding 2.0mg/dl using conventional units or 34.2 μmol/dl using SI units. The outliers for liver related chemistry tests are summarized in the following table.

Outliers for liver related chemistry tests (>3xULN or >2.0 for bilirubin), phase III entacapone trials, through the safety update

Parameter	RCTs		EXT		Placebo	
	NDA n=406	Overall n=603	NDA n=325	Overall n=738	NDA n=296	Overall n=400
Total bilirubin	0.3%	0.2%	0	0.2%	0	0
AST	0.3%	0.3%	0	0.2%	0.7%	0.3%
ALT	0.5%	0.5%	0	0.2%	0.8%	0.6%
GGT	0	0.4%	0.3%	0.3%	0.4%	0*
Alkaline Phosphatase	0	0	0	0	0.4%	0*

* The sponsor did not explain why the overall percentage was being reported as zero.

Using the sponsor's criteria, there were few outliers identified in the NDA database and little difference between entacapone and placebo outlier percentages.

4.12.4 Subjects with liver related chemistry result abnormalities from phase III trials

The sponsor did not identify any subjects who withdrew from a study for liver related chemistry abnormalities in the NDA or the safety update. On p. 129 of the ISS, the sponsor identified a single patient from the NDA database with significant increases in multiple liver related chemistry results. That case is summarized below.

Subject #1802, Study-52 This 71-year-old female developed increases the following parameters: AST 252, ALT 349, GGT 621 and alkaline phosphatase 1067. She was hospitalized for icterus and diagnosed with cholelithiasis. The sponsor stated that the enzyme levels returned to normal and that the subject continued in the trial.

In the safety update, the sponsor identified the 4 subjects with elevations (>3x ULN) in liver related chemistry tests (pp. 64-5). Those cases are summarized in the following paragraphs.

Subject #1606, Study-52 This 53-year-old male had an ALT result of 155U/L, six months after starting entacapone. No other lab results were mentioned. The sponsor reported that the subject continued in the study had a normal ALT 1 month later. The patient continued into an open label study without any new liver related chemistry abnormalities.

Subject #2703, Study-63 This 36-year-old male had the following elevations: AST 56U/L, ALT 72U/L at 4 months after first exposure to entacapone. At six months the AST was 30U/L and the ALT 31U/L (both slightly above ULN). The patient continued into the open label study and the highest AST has been 88U/L and the highest ALT has been 93U/L. At the time of the cutoff, the patient was continuing in the extension.

Subject #1210, Study-62 This 44-year-old female who had completed the controlled trial and was continuing in the extension had sporadic elevations in ALT and AST three months after the initiation of entacapone in this study (highest AST 63U/L, highest ALT 150U/L). These enzymes normalized on subsequent visits and the sponsor reported that this subject continued in the study.

Subject #2202, Study-73 This 75-year-old female had a normal AST and ALT until month 4 of this study. At that time, the AST was 62U/L and the ALT was 50U/L. These enzymes were lower, but still above the ULN at study months 6 and 9 (AST19U/L, ALT 24U/L and AST 23U/L, ALT 25U/L respectively). The subject continued in the study

In addition to the cases noted above, a review of serious adverse event narratives and dropout narratives identified two additional patients with potentially liver related chemistry abnormalities. Those cases are summarized below.

Subject #3401, Study-33 This 68-year-old female developed nausea, tiredness, and pain in her lower extremities at week 4 of the study. At that time, the alkaline phosphatase was elevated at 369U/L. In addition, her AST had increased to 50U/L (from 21U/L at the prior visit) and GGT increased to 48U/L (9U/L at the prior visit) although both were still within normal limits. She was hospitalized, diagnosed with anemia (hemoglobin 10.9 g/100ml) and begun on iron replacement therapy. She discontinued from the study and the sponsor noted that 1-month later, her alkaline phosphatase remained elevated (343U/L). No additional liver related chemistry results were reported in the narrative summary.

Subject #2005 Study-62 This 68-year-old male was classed as chest pain, fever, abdominal pain; had been in the open study for 6 months (previously treated with entacapone for 12 months). He was hospitalized at 7 months with increased alkaline phosphatase (936 U/l), GGT (306 U/l), and ESR (81mm/h). Following discharge, this subject was re-hospitalized 5 days later with chest pain, left eye pain and fever and the sponsor noted that the C-reactive protein, ESR and alk phos remained elevated and mentioned a hyperplastic bone marrow; further follow up of this case is needed.

4.12.5 Subjects with liver related chemistry result abnormalities from phase I and II trials

On p. 131 of the ISS, the sponsor identified the patients with lab abnormalities from phase I and II trials. From this list, 3 patients were identified with liver related chemistry result abnormalities. Those events are summarized in the following paragraphs.

Subject #7, Study –55 This 48-year-old male had the following lab results at baseline: ALT 26U/L, AST 54U/L (ULN=50U/L), GGT 15U/L, alkaline phosphatase 156U/L. After 1 week of entacapone, 600mg/day, he had the following lab results: ALT 299U/L, AST 96U/L, alkaline phosphatase 208U/L, and GGT 53U/L.

He continued in the study and was crossed over to placebo. His lab values on placebo were ALT 266U/L, AST 82U/L. The sponsor commented that later on in the follow up period the transaminases returned to normal (did not mention how long, or the actual results). He was subsequently diagnosed with CMV hepatitis based upon changes in CMV antibody titers.

Subject #17, Study –04 This 22-year-old male had abnormal transaminases on day 1, prior to beginning entacapone (ALT 116U/L, AST 252U/L). The next day, labs were repeated and the subject was also noted to have an elevated CPK of 7930U/L (ULN 200U/L). The sponsor reported that these abnormalities were resolving during the study but had not normalized by day 4 and therefore, the subject was discontinued. The sponsor hypothesized that the abnormalities were due to either heavy athletic training or an acute infection.

Subject #4, Study-71 This 26-year-old female developed increased transaminase values (ALT 150U/L, AST 120U/L) 1 week after two single dose administrations of entacapone, 200mg, separated by 1 week. The sponsor reported that by 2 weeks, the results had normalized. The sponsor attributed the findings to a concomitant medication (Nizax, an H_2 blocker).

The sponsor did not identify any cases of acute hepatic failure in the NDA or safety update databases. A review of death, SAE, and dropout narratives did not identify any cases of acute hepatic failure. The sponsor did identify several entacapone patients with elevations in hepatic enzymes. In some cases the abnormality predated the exposure or the reason for the elevations was provided. For the remaining cases, the exact relationship between entacapone exposure and enzyme elevation is not clear.

4.13 Overdose and Excessive Dose Experience

4.13.1 Preclinical Animal Data

The sponsor sites the LD_{50} in mice and rats to be ≥2000mg/kg with acute toxicity manifesting as piloerection, salivation, hypoactivity, and orange-yellow urine. Ataxia and tonic convulsions were reported in the late stage of toxicity with the lethal plasma entacapone concentration of 130µg/ml.

4.13.2 Clinical Overdose Experience

The sponsor states that no patients experienced entacapone overdose during clinical trials. However, 2 patients were reported as levodopa overdoses (up to 18 tablets) resulting in hospitalization but there is no certainty that these patients took entacapone concomitantly as part of the overdose, although the possibility could not be excluded. One of these patients experienced hallucinations and delusions; the other experienced paleness, depression, confusion, reduced assertiveness and talkativeness. These events resolved when these patients were treated with their prescribed drug regimens. In the overdose section of the submission the sponsor did not describe their hospital courses further nor identify the two patients or the studies they were in, nor indicate if they were withdrawn.

4.13.3 Plasma Drug Concentrations

Across clinical trials, the highest individual plasma concentration measured in humans was 14.1 µg/ml after a single 800mg dose with average peak concentrations of 7.3 µg/ml. Following 200mg dose the average peak concentrations were between 0.8-1.9 µg/ml.

4.13.4 Highest Exposures in Human Clinical Trials

Across clinical trials, the highest daily entacapone dose administered was in trial -28 and was 2400mg/day (400mg 6 times per day) for 14 days to 15 of 25 randomized PD patients. The other 10 patients took only 4 or 5 doses per day. The 25 patients were randomized to treatment sequence in this trial, which was of complete crossover design without washout, using 4 dosing

arms: placebo, 100mg, 200mg, and 400mg. Patients were seen at the end of each 2 week period and underwent pharmacokinetic and pharmacodynamic testing with a levodopa challenge.

Deaths, Serious AEs, Dropouts: There were no deaths reported in study -28 and only 1 serious AE. Patient #29 experienced rapid onset of severe back pain, nausea and vomiting, requiring 2 days of hospitalization for treatment of renal stones which were detected by IVP. He was on Day 1 of the 100mg dose level (Period 2) and had completed the 200mg dose level. He was not withdrawn from study. Four other patients withdrew due to AEs. Patient #1 withdrew due to anxiety and worsening parkinsonian symptoms at the 100mg dose level (Period 2) after 6 doses and having completed the 200mg dose level. This patient is also listed as having post-treatment orthostatic hypotension (CSR-Appen V-Table 19.7: Vol 96, p 428) and hypertension as a concurrent illness (CSR-Appen V-Table 1.1: Vol 96, p 200). Patient #24 withdrew due to nausea and vomiting at the 400mg dose level (Period 2) after a few days and having completed the placebo arm. The remaining 2 withdrawals were exposed only to placebo.

Common AEs: Common AEs were recorded on each testing day, recording AEs for the previous 2 weeks of treatment. The most common new AEs were - dystonia, dyskinesia, dizziness, abnormal dreaming, sleep disorders, diarrhea, constipation, nausea, and fatigue.

Labs: Laboratory testing was conducted at the end of each 2 week period. Mean SGOT and direct bilirubin values for the 400mg dose level both showed small but statistically significant increases compared to placebo (27.0 ±18.5 vs 20.0 ±5.4, p=0.02 and 0.21±0.19 vs 0.12±0.09, p=0.02, respectively). These changes were caused predominantly by SGOT elevations in 2 patients (to 95 U/l in Pt 43 and 52 U/l in Pt 47) and direct bilirubin elevation in 1 patient (to 0.8 mg/dl - Pt 47) but all 3 values normalized at study end, 7-14 days after the last dose of entacapone. Total bilirubin, GGT, and alkaline phosphatase were normal for these 2 patients. SGPT was not measured.

Vital Signs: Serial vital signs were obtained for a least 4 hours during each testing session. No statistically significant differences were noted between treatment groups for maximal increases, decreases or maximal changes in supine and standing SBP, DBP or heart rate. Similar numbers of patients across treatment groups had post-treatment orthostatic hypotension (7, 6, 6, 5 for placebo, 100mg, 200mg, and 400mg, respectively).

ECGs: According to the final study protocol, serial ECGs were to be obtained on each testing day (levodopa challenge test day) at baseline and hourly for 4 hours; then bi-hourly until the end of the session. No mention of the results of these ECGs is included in the clinical study report. CRFs for this study have no space allotted for recording ECG data.

4.13.5 Overdose Management

Management is symptomatic recognizing that the beta half-life is 0.4-0.7 hours. Hospitalization is advised with general supportive care. There is no known antidote. Immediate gastric lavage may reduce absorption. There is no experience with hemodialysis or hemoperfusion but these are unlikely to be of benefit since entacapone is 97-98% bound to plasma proteins, mainly albumin. The potential consequences of drug interactions should be kept in mind particularly with catechol-structured drugs.

4.14 Special Safety Study

Study -25: "The effect of entacapone on the metabolism of intravenous isoprenaline and adrenaline and the synergistic effect on the hemodynamics." The purpose of this trial was to examine entacapone effects on plasma concentrations of isoprenaline and adrenaline and their hemodynamic effects, since COMT participates in their metabolism. This study was designed as a 2 period complete crossover trial with 7 day washout where each of 12 healthy subjects (age range – 21-32 years) was to randomly assigned to treatment sequence with placebo or entacapone 400mg. Levodopa/carbidopa were not administered concomitantly. Each period also consisted of 2 days of treatment, one each with isoprenaline or adrenaline administered in random sequence as

20 minute IV infusion, by IV pump, with 4 serially increasing dose levels at 5 minute intervals. Each infusion was to start 30 minutes after entacapone or placebo administration. Serial supine hemodynamic measurements were made before starting the infusion, at the end of each infusion dose level, and for 40 minutes after the completion of the infusion. Serial plasma blood samples were obtained for drug levels and selected metabolites, at baseline and for approximately 1 hour after starting the infusion. **This study was terminated prematurely after 2 subjects were withdrawn due to ventricular extrasystoles**. At the end of his adrenaline infusion, subject #7 while treated with entacapone experienced ventricular extrasystoles, followed by a short run of bigeminy and finally ventricular tachycardia at 120 bpm. He was successfully treated with 2mg IV propranolol. This subject is noted to have the highest plasma adrenaline concentration (6.3 nmol/l - CSR-Appendix 2-Table 10: Vol 118, p 140) at the end of his infusion, compared to any subject at any time point whether pretreated with entacapone or placebo. His plasma entacapone concentration at infusion end was 867 ng/ml and not exceptionally high relative to those of some other subjects, 2 of which had concentrations >2000 ng/ml. The CSR is silent regarding arrhythmia during the placebo period for Subject #7. Subject #3, treated with entacapone and isoprenaline, also experienced ventricular extrasystoles which increased in frequency and necessitated the discontinuation of his infusion after 12 minutes and after which ventricular bigeminy lasting about 30 seconds was noted. His extrasystoles disappeared without treatment. His plasma isoprenaline plasma concentrations were among the lowest but his entacapone concentration was 2330 ng/ml. Subject #3 was later rechallenged with IV isoprenaline in the absence of entacapone and reportedly experienced identical arrhythmias. Since the study was prematurely stopped, statistical analysis of data was modified and conducted as a parallel group design, not including cross-over data from the few patients who crossed-over or data from patient #3 who was withdrawn. A statistically significant difference in greater mean maximal heart rate with entacapone compared to placebo ($p=0.0496$) was observed only with isoprenaline but not with adrenaline nor for blood pressure or plasma concentrations of isoprenaline, adrenaline or noradrenaline; but these non-statistically significant findings need to be interpreted cautiously since the modified statistical plan may have made detection of differences more difficult.

5.0 CONCLUSIONS AND RECOMMENDATIONS

The safety review of NDA 20-796 as submitted to date, shows no affirmative evidence that should preclude approval but the following information should be requested of and submitted by the sponsor to complete the review.

Additional examination of data is needed for the following:

1) In trial 44 we noted an excess of cases of dyspnea in patients exposed to entacapone compared to placebo. Each case of dyspnea across the NDA needs to be examined and summarized describing the event and the clinical course.

2) In the ISS and the safety update we noted and excess of entacapone exposed patients compared to placebo exposed patients who had normal white cell counts at baseline who met outlier criteria for decrease in counts. Each case needs to be examined and summarized describing extent of decrease, time to onset, dose response, resolution upon discontinuation, positive rechallenges, and any additional available laboratory results (eg bone marrow results).

3) In the ISS and the safety update we noted and excess of entacapone exposed patients compared to placebo exposed patients who had normal hemoglobin values at baseline who met outlier criteria for decrease in measurement. Each case needs to be examined and summarized describing extent of decrease, time to onset, dose response, resolution upon discontinuation, and positive rechallenge. For these patients, the examination should also describe the results of any other pertinent testing such as serum iron concentration, TIBC, ferritin, reticulocyte counts, and red cell indicies.

4) We note that the narratives for *death* inconsistently describe the interval between death and the administration of the last dose. For both the placebo and entacapone exposed patients please provide a listing of this interval in days.

5) We noted that the glossary for mapping adverse events classified certain potentially related verbatim terms to more than one hierarchical term. We identified verbatim terms which appeared to describe injury sustained following falls but were mapped to several different preferred hierarchical terms such as *falls*, *bone disorder*, *pathological fractures*, *skin disorder*, *arthropathy*, *purpura*,, *joint dislocation* and *other* traumatic events,). This may have resulted in an underestimation of fall risk. The sponsor should identify all events that describe *fall* or any injury resulting from *fall* and map them to a single preferred term (eg *fall events*) and recalculate event rates on active treatment versus placebo for RCTs and recalculate risk in extension studies. This reexamination should include an analysis for evidence of dose response.

6) In our review of verbatim coding, we noted that adverse events that were potentially due to orthostasis were mapped to more than one hierarchical term. The sponsor should identify all events suggestive of orthostasis (eg *dizziness*, *vertigo*, *syncope*, *hypotension*, *hypotension postural*, *lightheadedness*) and map them to a single preferred term (eg *orthostatic events*) and recalculate event rates on active treatment versus placebo for RCTs and recalculate risk in extension studies. This reexamination of event coding should cover all body systems since we also noted that some these hierarchical terms were mapped to more than one body system (eg syncope was mapped to autonomic nervous system and cardiovascular disorders). This reexamination should include an analysis for evidence of dose response.

7) The sponsor did not submit the narratives for discontinuations due to AEs from phase I & II trials in the NDA despite listing them in the table of contents of Attachment C of the ISS (vol. 77 p.8-202). These narratives should be submitted.

8) The SAE narratives summarized below require further work up by the sponsor (SAE report #/ study #/ patient #):

Narratives from the Original NDA

ENT9510 -34 #3403 classed as thrombocytopenia, epistaxis; need baseline data prior to DB exposure, F/U laboratory data and outcome after entacapone discontinuation.

ENT963 -54 #41 classed as pulmonary fibrosis; patient hospitalized after 353 days exposure for scar tissue removal from left lung; need to know if SAE was present prior to entacapone exposure, pathology results, past medical history and outcome with continued entacapone exposure.

ENT95128 -52 #1001 classed as pulmonary fibrosis; detected on X-ray when hospitalized after 211 days in study for chest pain and gastritis symptoms, pergolide was discontinued,

rehospitalized, "pleuritis" had not resolved, need follow-up on resolution with continued entacapone exposure.

ENT949 -33 #3401 classed as nausea, fatigue, pain; hospitalized, anemia and LFT elevations noted, need F/U regarding LFTs elevations, reason for discontinuation, and results of other lab abnormalities and results of any rechallenge with entacapone.

ENT9658 -52 #106 classed as hemoptysis; in study for 286 days when hospitalized for hemoptysis and dyspnea, need F/U on reoccurrence with continued entacapone exposure.

ENT9673 -52 #255 – classed as back pain; hospitalized for back surgery and discontinued study, need reason for discontinuation.

ENT9446 #003-fever; ENT956 #364-no SAE listed) - these subjects from study are listed among the SAE narratives (ISS Attachment D-2; p-8-261/2) but no narrative is provided for them (ISS p8-261/262).

Narratives From the 4 Month Safety Update

ENT9780 -44 #2206 - classed as pleurisy; hospitalized due to breathing difficulties, pleurisy diagnosed and pergolide discontinued, need outcome on continued exposure to entacapone.

ENT9758 -62 #1954 classed as coughing and weight decrease; previously treated with entacapone for 12 months; after 5 months in the open study pleural fluid was detected on chest X-ray; bromcriptine which had been administered for 9 years was discontinued; need information about resolution with continued entacapone treatment.

ENT9697 -62 #152 – classed as vomiting; vomited on the second day of exposure to entacapone and again on rechallenge but tolerated third rechallenge, would apprectiate further outcome information.

ENT97112/ ENT97118 -62 #2005 - classed as chest pain, fever, abdominal pain; in open study for 6 months, hospitalized at 7 months with increassed alkaline phosphatase (936 IU/l), GGT (306 IU/l), and ESR (81mm/h); previously treated with entacapone for 12 months; rehospitalized 5 days later with chest pain, left shoulder pain, left eye pain and fever; C-reactive protein elevated, ESR and alk phos still elevated; hyperplastic bone marrow and leucemic transformation noted; outcome needed.

ENT96186 -73 #1558 - classed as stupor, hallucination, fatigue; treated with placebo during DB study; in open study 79 days when hospitalized; bilirubin was 1.24 mg/dl; need reason for discontinuation and other labs results including LFTs summarized.

ENT9750 -73 #1562 - classed as hypokinesia; on entacapone for 50-80 days and became akinetic, discontinued after 101 days and became hyperkinetic again, event considered definite, would appreciate further event description and outcome information.

ENT9787 -73 #1566 - classed as gait abnormal and pruritus; on entacapone for 170 days when hospitalized for walking difficulties and fluctuations, also reported itching of unknown origin, need LTF results and reason for discontinuation.

9) The following dropout narratives need further work up by the sponsor.

Subject 2939034 #4607 dropped out for low WBC counts (lowest reported was 2.9) and it is unclear from the summary if this abnormality resolved upon discontinuation.

Subject 2939054 #345 discontinued for *dermatitis* but no details about this event are provided.

10) It is not clear from CSRs or protocols for RCTs when vital sign and ECG measurements were to be obtained relative to entacapone administration at clinic visits so that many measurements may have been obtained before entacapone administration when serum concentrations were at their nadir. The sponsor should identify Phase I and II trials where vital signs and ECGs were measured at baseline and serially after entacapone administration and describe entacapone effects on these parameters over a dosing interval by comparing baseline to each post-administration time point.

11) It is not clear from Table 18.1.1 for RCT –44 or table 15.1.1 for RCT –33 what units of measurement were used in reporting changes in laboratory values. The sponsor should be asked for this information.

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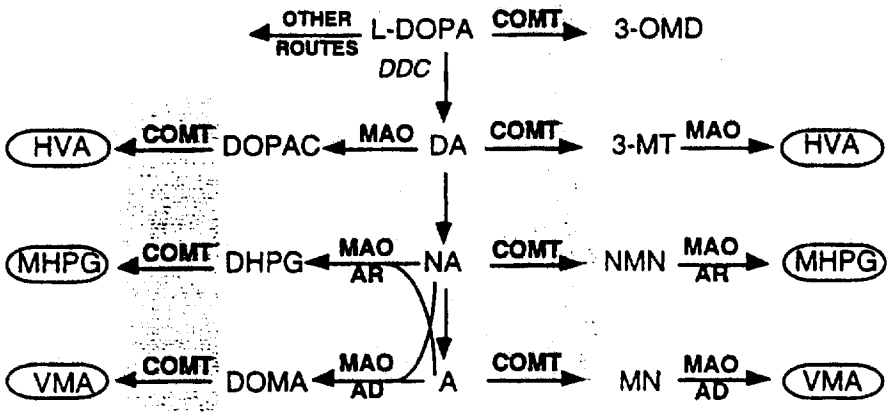
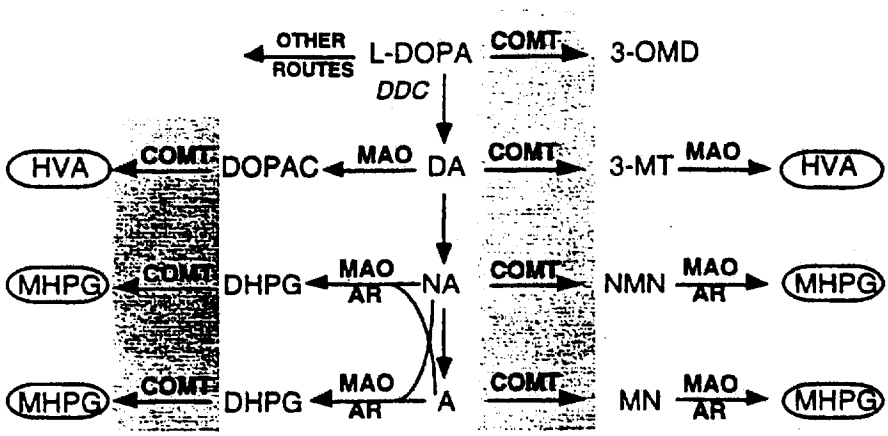
Attachment 1

Figure 1

METABOLISM OF L-DOPA AND DA IN THE CENTRAL NERVOUS SYSTEM



METABOLISM OF L-DOPA AND DA IN PERIPHERAL TISSUES



Note to the peripheral metabolism: Relative high proportion of catecholamines are sulphoconjugated in the liver by phenolsulphotransferase.

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Attachment 2

44 pages
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Attachment 4

13 pages
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Attachment 5

12 pages
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Review of Clinical Data

Safety Team Leader Review of the Entacapone NDA

NDA:	**20-796**
Sponsor:	**Orion**
Drug:	**Entacapone**
Route of Administration:	**Oral**
Reviewer:	**Greg Burkhart, M.D., M.S.**
Review Completion Date:	**December 16, 1998**

/S/ 12/16/98

The entacapone NDA was submitted to the FDA on January 2, 1998. Dr Sevka conducted the primary safety review of the NDA and the 120-day safety update assisted by Drs. Boehm and Knudsen. Dr. Sevka reached the conclusion that there was no affirmative evidence of entacapone-associated risk that would preclude its approval, but recommended clarifying several issues before marketing.

An additional relevant finding from the review that deserves some comment was the absence of evidence suggesting that entacapone could cause hepatocellular injury. In RCTs, patients assigned to entacapone did not have any greater risk for increases in liver enzymes than patients on placebo, and across the NDA and safety update, there were no cases of liver necrosis or liver failure. Entacapone's capacity to cause hepatocellular damage is particularly important given the strong signal for liver failure resulting in death that has resulted from the post-marketing experience with tolcapone, the first COMT inhibitor that was approved in early 1998.

In the tolcapone NDA, there was also a dose-related increase in the risk of elevated liver enzymes (above 3 times the upper limit of normal), but no clinical evidence of liver dysfunction. Tolcapone labeling has now been revised to include a black box warning describing the risk for liver failure, and its use has also been restricted to patients failing other adjunctive therapy. In addition to liver failure, its labeling has also been revised to describe cases of rhabdomyolysis and NMS that have been reported in association with tolcapone use.

In an effort to take an *approval* action with entacapone, we spoke with the sponsor following tolcapone's re-labeling and after Dr. Sevka had identified the major safety issues requiring additional follow-up before entacapone could be approved. We asked the sponsor to provide a second safety update that added the missing narratives from the 120-day safety update. We also asked for a systematic review of entacapone's capacity to

cause liver dysfunction, anemia, rhabdomyolysis or the NMS syndrome. Finally, since entacapone had been approved in Europe after the NDA was submitted, we asked for a description of this post-marketing experience. The sponsor responded to these requests with a December 7, 1998 submission. I have now completed the review of this submission as well as Dr. Sevka's review, and will summarize the safety experience with entacapone to date.

Extent of exposure in the development program

Based upon the data in the most recent update, there have now been 1773 patients exposed to at least one dose of entacapone providing about 1823 person-years of use. About 760 patients have had exposure to entacapone that was at least 52 weeks in length.

The sponsor has recommended a daily dose of up to 2000 mgs in their proposed labeling, but I don't think they will have enough experience at higher doses to justify that recommendation. In fact, based upon the data in the 120 day safety update (I don't think the sponsor updated the duration of use by daily dose data in the most recent submission), there appears to be little experience above 1600 mg per day. However, since the sponsor examined the extent of use by computing the mean daily dose, the use at higher doses may be underestimated if there was a trend to higher doses with longer-term use. Computing person-years by daily dose and duration would allow for a more exact characterization of this experience.

Comparative safety experience in the RCTs

Mortality

As pointed by Dr. Sevka on page 18 of his review, the mortality rate on placebo was slightly greater than that for entacapone. However, since the sponsor did not describe the time since the last dose for all the RCT deaths and therefore not allowing for computation of rates based upon deaths within a selected period from last use (i.e., 30 or 7 days), we are not certain that the comparison is valid.

Patient Discontinuation

The overall dropout risk was greater on entacapone than placebo (17.6% vs 13.0%) with the difference increasing when focusing on dropouts attributed to AE occurrence (14.3% vs 8.5%; page 23 of Sevka's review). AEs that were most strongly attributable to entacapone use were diarrhea (some of which resulting in hospitalization), abdominal pain (frequently with diarrhea), nausea (also reporting along with abdominal pain and diarrhea), dyskinesia and hallucination.

Serious AE Risk

There probably was an excess risk of all-cause serious AEs in the RCTs, but the sponsor has used the total number of events in the numerator rather than the number of patients with at least one serious AE. This problem also applies to individual events, but the clinical nature of the serious events is generally similar to that as observed with patient discontinuation. Some additional work will be necessary for selected events to describe serious AE risk in labeling.

Laboratory Findings

As already noted, there was no evidence that entacapone caused an increase in liver enzymes either when considering change from baseline or in an outlier analysis.

Since entacapone is purportedly a chelator, its effects on hematological parameters are of special interest. Overall the findings are somewhat difficult to interpret. When examining mean changes from baseline, there was a decline in serum iron from baseline. However, the TIBC, if any thing decreased and there did not seem to be much of an effect on ferritin. On the other hand, patients assigned entacapone did seem to have a greater risk for hemoglobin decreases of 2 grams or more. Of the 603 patients assigned entacapone in the RCTs, 9 (1.5%) had a greater than 2 gram drop in hemoglobin compared 2 of 400 on placebo (0.5%). In Table 10 on page 16 of volume 11 from the December 7 submission, the sponsor shows that there were statistically significant decreases in both the hematocrit and RBC counts in the RCTs. As shown in Table 12, there may also have been a dose response for decreased hematocrit.

On page 34 of Dr. Sevka's review, clinical summaries are provided for the 6 patients identified with at least a 2 gram drop in hemoglobin in the RCTs that were in the NDA. While the clinical information was somewhat limited (no data for serum iron, TIBC or ferritin), none of the patients had concurrent abnormalities in any other hematological cell line and none of these patients appeared to have been treated for anemia or discontinued entacapone because of it. Whether hemoglobin continues to decline with longer-term follow-up and use is not clear. In the sponsor's recent submission, they acknowledge the inconsistent effects, but have concluded that entacapone is unlikely to cause any clinically significant changes. In my opinion, I don't think we have enough information to interpret whether these changes are or are not significant.

Entacapone was also associated with leukopenia. (white counts decreased to less than 2800). The risk was 1.7% (10/603) in patients assigned entacapone and 0.8% (3/400) in patients assigned placebo. We were unable to identify the clinical summaries for these patients so we do not know the outcome. However, there were no patients in the NDA who had agranulocytosis or aplastic anemia as a reason for discontinuation or hospitalization.

Overall AE occurrence

Dr Sevka's review summarizes overall AE occurrence starting on page 31. In my opinion, the most important finding is in the table at the top of page 33. This table summarizes additional analyzes conducted by the review team on the effect of baseline body weight on AE risk. The table shows relative risks (drug/placebo) for patients grouped by baseline body weight using study 33, study 44 and study 52 data (the RCTs in the NDA). The findings are striking in that the events most strongly associated with entacapone appear to be greater than placebo only in patients who were less than 65 kg weight at baseline. (While diarrhea is not shown in this table, patients with body weights less than 65 were at more risk for its occurrence; the effect however, was not as persuasive as for the events shown.)

I find the effect on falls particularly alarming since falls in the elderly can have significant morbidity and mortality. Based upon the findings in these 3 RCTS, 8% of patients less than 65 kg had a fall that was attributable to entacapone (placebo risk was 2.1% in patients with baseline weights less than 65 kg). While there is generally a dose-response between increasing daily dose and several events including falling, it would be of interest to conduct a dose response analysis by body weight. Clarifying the effect of body weight on efficacy may also be of interest.

Dr. Sevka et al also discovered that falls have been classified with several terms; fractures, purpura, falling, joint dislocation, etc, and the coding of falls and perhaps syncope seems to vary by study. Given these concerns, I don't thing we have an accurate picture of the extent and consequences of falling in the NDA.

Coding problems also appear to an issue for events suggestive of orthostasis. As outlined by Dr. Sevka, the analysis of the blood pressure data was for the most part inconclusive regarding entacapone capacity to cause orthostasis, and BP measurements were probably not timed to dose.

Clinical Review of Deaths, AE Dropouts and Serious Events

The most recent safety update brought the total number of deaths on entacapone to 35 giving a death rate of about 2 deaths per 100 PYs of use. While the sponsor did not describe the relationship between death and last dose, there were no unusual AEs associated with death. There were, however, at least 2 deaths that occurred in post-operative period following repair of a hip fracture resulting from falls.

The total number of serious AEs increased from 738 in the 120-day safety update to 903 in the most recent. The number of patients having at least one serious AE was not provided by the sponsor either overall or for individual events. Based upon my review of the additional events and Dr. Sevka et al's review of the NDA and safety update, there were no cases of agranulocytosis, aplastic anemia, hemolytic anemia, serious skin rash

liver failure or any other unusual event. Clinical review of the AE dropouts was also unrevealing.

Special Studies

On page 27 of Dr. Sevka's review, he describes a special study of entacapone with isoproterinol and epinephrine. The study was prematurely terminated because of cardiac AEs. These events were not well described in the submission.

Post-marketing Experience

According to the sponsor, there have been no reports of any post-marketing events although use has been limited. I am aware, however, of a communication from the French FDA equivalent to FDA personnel that a case of rhabdomyolysis had occurred in a French patient taking entacapone.

Discussion

Entacapone does not appear to cause hepatocellular injury at least to the extent observed in the tolcapone NDA where there was a clear increase in the risk of clinical significant increases and a dose response. Of course, one could never prove that there isn't a very small effect, but it seems likely that entacapone has much less capacity to cause hepatocellular damage than tolcapone. Whether this translates to a reduced risk for liver failure is unknowable, but certainly possible. It is generally believed that most drugs that have been associated with liver failure have also had the capacity to cause an observable increase in liver enzymes. Thus, the capacity to cause an increase in liver enzymes is believed to be a sensitive indicator of drugs likely to cause significant harm so negative findings would seem to be important at least given current beliefs. (The predictive value is low, however, since there are many drugs than increase liver enzymes that have not been associated with liver failure.)

In my opinion, the most striking affirmative finding in the entacapone NDA is the effect of body weight on the occurrence of several AEs. In fact, there was little risk of dyskinesia, falls, hallucination, diarrhea in patients with a body weight of 65 kg or greater. This suggests to me that patients with body weight less than 65 kg may require lower doses, or, if the risk is shown to be great enough, should be strongly warned about using the drug. One problem with recommending a lower dose in labeling is the absence of well-designed studies that evaluated doses less than 200 mg. If the additional analyzes described below result in defining significant morbidity and mortality for patients less than 65 kg, and the drug works for patients with patients with body weights greater than 65 kg, perhaps a warning would suffice.

The clinical relevance of entacapone's purported action as a chelator is difficult to evaluate without long-term comparative data on the incidence of anemia, particularly that secondary to iron deficiency. While there were some findings suggesting an effect on

serum iron with a decrease in hamatocrit and RBC counts, and an increase in the percentage of patients with a drop in hemoglobin, we should still be mindful of other mechanisms. For example, while there was no evidence of hemolysis, there also was no systematic work-up in the NDA.

The labels for both tolcapone and entacapone include a warning for using non-selective MAO inhibitors but allow the use of selegiline. The concern about concomitant use of MAO inhibitors and COMT inhibitors relates to the metabolism of any co-administered catecholamine. Since the entacapone NDA included at least 400 patients who were using selegiline, a separate analysis of patients who also had exposure to a catecholamine would be of interest.

Conclusion

While I believe that the application is likely to be approvable, I think additional work is needed particularly regarding the degree of serious morbidity and mortality attributable to entacapone in patients who weight less than 65 kg.

Questions for the sponsor

1) Compute the exact time at 1600, 1800, and 2000 mg per day.
2) Compute the mortality rates for the RCTs using deaths within 30 days and then again for deaths within 7 days of last use.
3) In the RCTs, reclassify AEs that are associated with falls. First focus on all falls, falls resulting in hospitalization and then falls resulting in fractures. Re-analyze the RCT data focusing on these outcomes separately for each study and then across all RCTs.
4) Conduct a similar review of events that could represent orthostatic hypotension or syncope. Include a separate category that consists of only patients who had objective findings of confirmed BP changes consistent with orthostasis. For syncope, include a separate category for patients with reported loss of consciousness.
5) Evaluate the effect of body weight on patient risk for diarrhea, falls, hallucinations, dyskinesia, syncope, orthostasis, etc. by stratifying patients in groups according to baseline body weight. Consider the effects of age, gender and concomitant medication on the findings.
6) Using the same body weight grouping as in the above analyzes, re-analyze the efficacy data by group.
7) Did any study collect blood pressure data to evaluate patients for orthostasis where the BP measurements were carefully timed to dose?
8) Provide narratives for patients having leukopenia separately for patients in the RCTs and then in uncontrolled experience.
9) For patients who had greater than a 2-gram drop in hemoglobin in the RCTs, provide patient narratives that include other lab data (serum iron, TIBC, ferritin, RBC indices, etc) and longitudinal follow-up.
10) In the most recent update of serious events (see table 9b in volume 1), why does the total for some events decline with the update. For example, there are 14 chest pains in

data thorough October 31, 1998 but there were a total of 17 through the 120-day update.

11) Develop a list of catecholamine drugs whose metabolism is likely to be affected by co-administration of inhibitors of COMT and MAO. For the patients, taking selegiline and entacapone in the NDA identify those patients who had any of the catecholamine co-administered. For any patient exposure, please describe any AE occurrence associated with this use.
12) Did the urinalysis data, include a check for blood? If so, please describe results.
13) Were the narratives for patients having a serious AE in phase 1 or 2 studies provided in the NDA?
14) Was there any ECG data that was timed to dose?
15) It is our understanding that there has been a case of rhabdomyolysis reported in France. Is this true?
16) Dr. Sevka also lists a number of patients for whom he would like additional follow-up although it is unlikely to be than helpful.

Cc
HFD-120/Katz/Burkhart