

SEP 3 1999

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS (OCPB)  
REVIEW**

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**NDA: 20-796****Submission Dates:**  
April 16, 1999

**Generic Name:** Entacapone  
**Brand Name:** COMTAN  
**Indications:** Parkinson's disease (adjunct therapy with levodopa/carbidopa)  
**Strength(s):** 200 mg Tablets  
**Formulation:** Film Coated Tablets for Oral Administration.  
**Sponsor:** Orion Corporation  
Espoo, Finland  
**Subject:** Re-submission (Formulations Link)  
**Reviewer:** Sayed Al-Habet, Ph.D.  
**Date of Review:** July 14, 1999

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**Background:**

This NDA was reviewed by the Office of Clinical Pharmacology and Biopharmaceutics on November 10, 1998 and December 23, 1998. One of the main concerns was that formulation 55 (to be marketed) was not bioequivalent to formulation 54 (formulation used in most of Phase III study). In the pivotal BE study (#293071), the AUC was within the [redacted] but not the Cmax [redacted]. Due to the high inter- and intra-subject variability in the absorption of entacapone, the sponsor requested the Agency to accept the AUC data alone instead of Cmax to establish the bioequivalence link.

In the approvable letter dated December 31, 1998 the sponsor was requested to provide additional justification to support the acceptance of formulation 55. In addition, the sponsor was requested to adopt the dissolution methodology and specification set by the Agency. Furthermore, the sponsor was requested to provide an *in vitro* evaluation of the CYP P450 isozymes responsible for any oxidation pathways for entacapone. On April 16th, 1999, the sponsor submitted a response to the above requests with some justification for the acceptance of formulation 55. The main justification provided by the

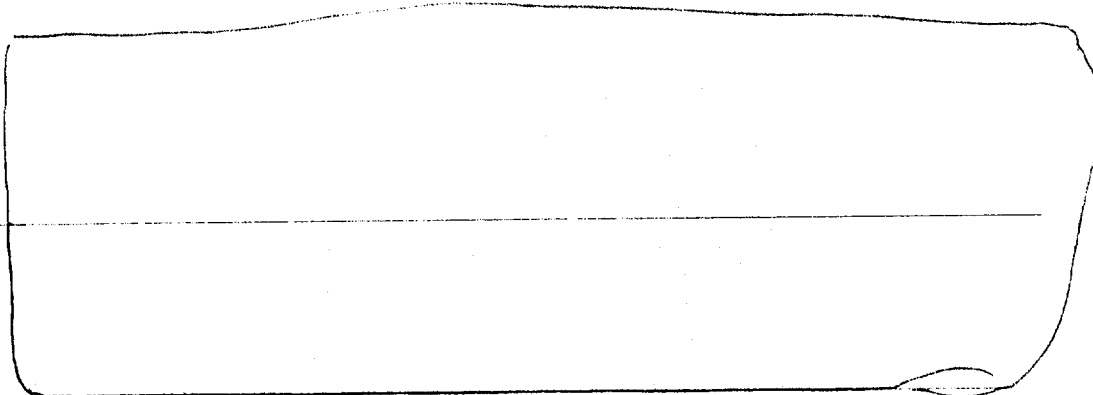
sponsor was that the Cmax is less important than AUC in relation to safety and efficacy of entacapone. The sponsor indicated that the efficacy is related to exposure (i.e., AUC) rather than Cmax. In addition, considering entacapone a highly variable drug, the sponsor requested the Agency to consider [redacted]

Based on the sponsor's response, the newly submitted data as well as the original data were carefully reviewed and extensively analyzed by the Office of Clinical Pharmacology and Biopharmaceutics. The focus of our review and analysis was on the bioequivalence issue related to formulation 54 and 55, the clinical pharmacology of the drug, and the PK/PD relationship with special emphasis on the entacapone and levodopa Cmax. The following observations are integrated from the original review dated November 10, 1998 and the new analysis and evaluation of the data provided in the current resubmission (April 16, 1999).

### **I) Formulation Issues:**

#### **A: Cmax of Entacapone Relative to Bioequivalence:**

1. The individual Cmax data for the replicate design bioequivalence study #293060 are shown in Attachments 1-3. From these data it can be concluded that there was no systematic bias when the same batch (T59-04) was administered twice to the same subjects (Attachments 1 and 2). However, there was a wide inter-subject variability when the two different batches (U03-03 and U04-03) were administered to the same subjects (Attachments 1 and 3).



### B. Entacapone Cmax Relative to Levodopa:

1. The Cmax and AUC of entacapone increase proportionally with dose up 800 mg (Attachment 5)
2. The Tmax of entacapone is about [redacted] regardless of the dose (Attachment 6)
3. The COMT maximum inhibition (Imax) occurs at the same time as entacapone Cmax, i.e., at [redacted]
4. The levodopa Cmax occurs at the same time of entacapone Cmax, i.e., at [redacted] (Attachment 8). However, the levodopa Cmax did not increase as entacapone doses increased from 50 to 400 mg (Attachments 8 and 9). The relationship between entacapone Cmax and levodopa Cmax was unclear as shown in Attachments 10-12. This was negative relationship in study #26 (Attachment 10), U shape in study #02 (Attachment 11) and convex in study # 22 (Attachment 12). Moreover, levodopa mean AUC was about [redacted] after 200mg and 400 mg doses of entacapone compared to control (levodopa/carbidopa), respectively (study #293902). This is probably of clinical importance in which only the exposure is changed with increasing the dose. Moreover, Attachment 13 shows the scatter plot for individual entacapone plasma concentration and levodopa plasma concentration at all doses, including placebo, in 22 subjects from study #26. This suggests that there is little or no (may be slightly negative) relationship between entacapone and levodopa plasma levels.


### C. Entacapone Cmax Relative COMT Inhibition:

There was a good correlation between the maximum inhibition of COMT (Imax) and entacapone Cmax (Attachment 14).



### D. Entacapone Cmax Relative 3-OMD Formation:

The formation of levodopa inactive metabolite, 3-OMD, starts to plateau at approximately the same time as entacapone and levodopa Cmax (Attachment 15). The decrease in the metabolite formation is dose dependent and is associated with entacapone and levodopa Cmax (Attachments 16-17)


**E: Cmax of Entacapone Relative to Efficacy:**

1. In a placebo controlled single doses study #293926 in patients with Parkinson's disease, the maximum efficacy as defined by the lowest UPDRS score occurred at about 1.5 h which correspond roughly to the time of Cmax of entacapone and levodopa (Attachment 18).  
  
Please note the wide scale of entacapone Cmax and the narrow scale of UPDRS score in Attachment 19.
2. Moreover, Attachment 20 shows the relationship between individual plasma concentration of entacapone and UPDRS scores at all doses, including placebo, from study #293926. The relationship is widely scattered, with no consistent pattern. Attachment 21, shows this relationship for the mean data. This suggests that there is no relationship between entacapone plasma levels and UPDRS scores.
3. The relationship between levodopa plasma levels and UPDRS scores is shown in Attachment 22. From this scattered plot it can be seen that the maximum benefit (lowest score) occurs at a levodopa plasma concentration of about 1000 ng/ml. The effect starts to plateau after 2000 ng/ml. Thus, no additional benefits may occur by increasing levodopa plasma level beyond 2000 ng/ml.

**F: Cmax Relative to Dyskinesia:**

Similarly and in the same study #293926, dyskinesia scores were worse at  after entacapone and levodopa/carbidopa administration (Attachment 23). This again corresponds well with the Cmax of entacapone and levodopa. However, Attachment 24 shows the relationship between mean entacapone Cmax and mean dyskinesia scores from two studies, #293902 and #293926. The relationship is unclear as dyskinesia is worse at the lower concentration of approximately  compared to the higher concentrations. Similarly, a wide scattered plot for individual entacapone plasma levels and dyskinesia scores at all doses, including, placebo, from study # 293926 is shown in Attachment 25. The plot for the mean data is shown in Attachment 26. Furthermore, the relationship between dyskinesia scores and levodopa plasma levels is much more scattered than for the plasma levels of entacapone (Attachment 27). From this data it can be concluded that there is no clear relationship between dyskinesia and entacapone or levodopa plasma levels.

**G: AEs Relative to Formulation 54 and 55:**

From April 16, 1999 resubmission, some of the AEs data from  presented in Table 5 (volume 17, page 9) are plotted as shown in Attachment 28. It can be seen from this plot that formulation 54 is associated with a slightly higher % of patients with AEs than formulation 55. It should be noted that

the sponsor has selected 84 patients from each study. The selection criteria used by the sponsor should be carefully evaluated by the safety team of this NDA.

Furthermore, it was noted that the bioavailability of formulation 55 was [redacted] than that of formulation 54. In all Phase III studies, only 200 mg formulation was administered as a single dose. It should be noted that there is no safety data available after a single dose higher than 200 mg. Therefore, we do not know the consequences of the [redacted] in bioavailability relevant to the safety of formulation 55.

## II) Dissolution Issues

The sponsor has accepted the following dissolution methodology and specification:

Apparatus II:	USP (Paddles)
Speed:	[redacted]
Medium:	[redacted]
Sampling times:	[redacted]
Specification:	Not less than [redacted]

[redacted]

It should be noted that, the statements included in the updated label (pages 2 and 10, see Attachments 30 and 31) relative to entacapone metabolism and drug interactions are acceptable to the Office of Clinical Pharmacology and Biopharmaceutics.

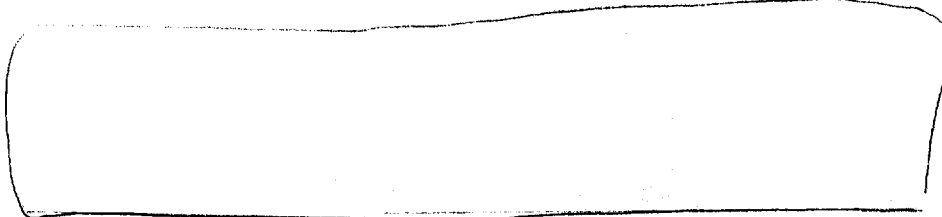
[redacted]



### B. Clinical Pharmacology Issues:

6. It appears that there is little or no relationship between entacapone and levodopa plasma levels. The levodopa C<sub>max</sub> occurs at the same time of entacapone C<sub>max</sub> which is about [redacted]. However, levodopa C<sub>max</sub> did not increase as entacapone doses increased from 50 to 400 mg. Our extensive PK/PD analysis reveals that the relationship between entacapone C<sub>max</sub> and levodopa C<sub>max</sub> was unclear; a negative relationship in study #26, U shape in study #02, and concave in study # 22. The plot for individual entacapone plasma concentration and levodopa plasma concentration at all doses, including placebo, in 22 subjects from study #26 was widely scattered. In some situations, we note that levodopa plasma levels after placebo (i.e., levodopa/carbidopa and placebo) is higher than when levodopa/carbidopa were co-administered with entacapone. This raises some concern as to whether there is a real benefit by further increase in either entacapone dose beyond [redacted] and/or concentrations above [redacted]. In addition, the selected 200 mg dose of entacapone raises some questions and may need to be reevaluated. The sponsor is encouraged to provide some explanation.
7. Our extensive data analysis suggests that there is no relationship between entacapone plasma levels and UPDRS scores.
8. From our PK/PD analysis we concluded that the maximum benefit based on the lowest UPDRS scores occurs at a levodopa plasma concentration of about 1000 ng/mL which corresponds to entacapone dose of 100 mg. Little or no additional benefit (or lowering the UPDRS scores) occurs at levodopa plasma concentration beyond [redacted].
9. Dyskinesia scores were worse at the time of entacapone and levodopa C<sub>max</sub> which is about [redacted] after entacapone and levodopa/carbidopa administration. This again corresponds well with the C<sub>max</sub> of entacapone and levodopa. However, considering the entire data, there is no clear relationship between dyskinesia scores and levodopa or entacapone plasma levels. The plots of the individual plasma concentrations for entacapone or levodopa in relation to dyskinesia are widely scattered.
10. Based on the data from [redacted] the AEs associated with the two formulations appears to be similar.

11. In terms of drug interactions and metabolism, the sponsor's responses to the Agency questions are acceptable. In addition, the statements included in the updated label (Attached pages 2 and 10) relative to entacapone metabolism and drug interactions are acceptable to the Office of Clinical Pharmacology and Biopharmaceutics.
12. The sponsor has accepted the following dissolution methodology and specification.



**Recommendation:**

Based on the pivotal BE study # 71, the two formulations (54 and 55) are NOT bioequivalent. However, based on our extensive PK/PD data analysis and the limited clinical data submitted to us, it appears that there is no obvious clinical difference to us between the two formulations. In addition, based on the data from [redacted]

[redacted] the AEs associated with the two formulations appears to be similar. Therefore, the Office of Clinical Pharmacology and Biopharmaceutics has no objection if the medical division approves formulation 55 based on this review and the extensive clinical data submitted and reviewed by the division. Please convey comments 1-12 to the sponsor.

Reviewed by:

[redacted] /S/ Aug 18, 1999

Sayed Al-Habet, Ph.D.  
Office of Clinical Pharmacology and Biopharmaceutics  
Division of Pharmaceutical Evaluation I

RD/FT initialed by Raman Baweja, Ph.D.

[redacted] /S/ 9/3/99.

cc: NDA # 20-796 (Orig.), HFD-120, HFD-860 (Al-Habet, Baweja, Mehta), HFD-19 (FOI), and Drug files (Biopharm File, CDR).

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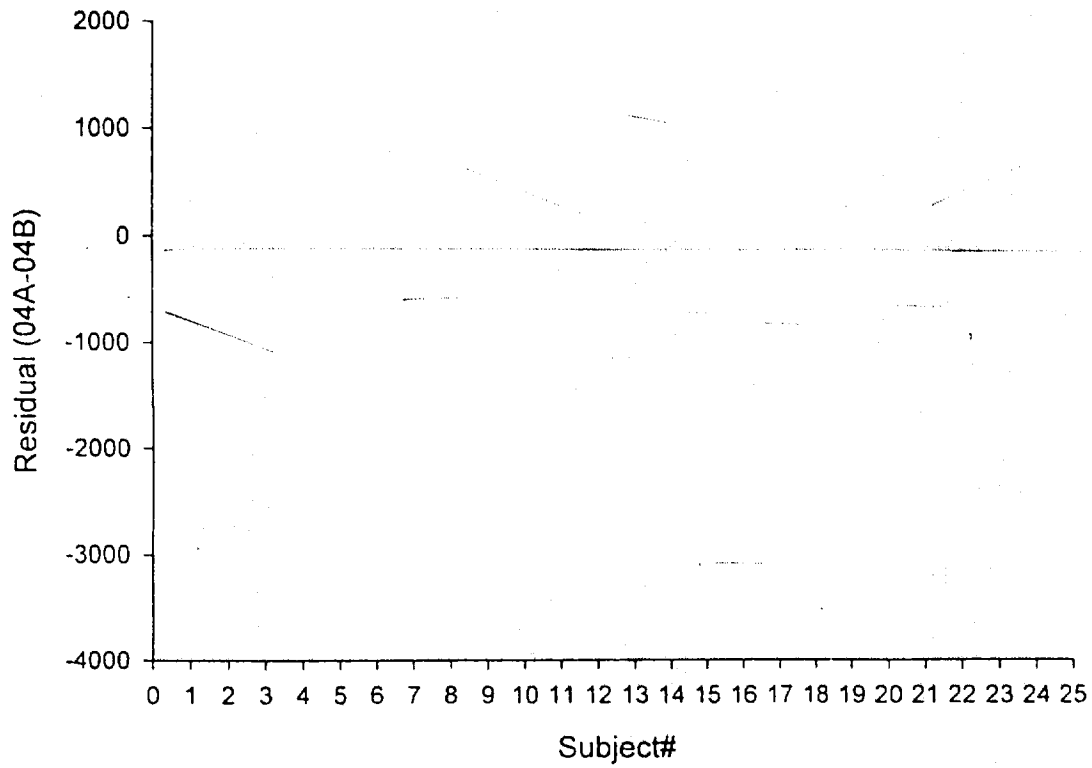
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Individual Cmax From Replicate Study #60 For Comtan (NDA-20-796)								
Subject#	T50.04A	T50.04B	Bias (A-B)	% (Bias)	U03-03	U04-03	Bias (U03-U04)	Bias (%)
1								
3								
5								
6								
7								
8								
10								
12								
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Mean	1415	1379			1317	1418		
SD	641	729			583	534		
%CV	45	53			44	38		
n	19	19			19	19		



2

Residual Plot For Cmax of Replicate Study #60  
(Cmax for 04A-Cmax of 04B)

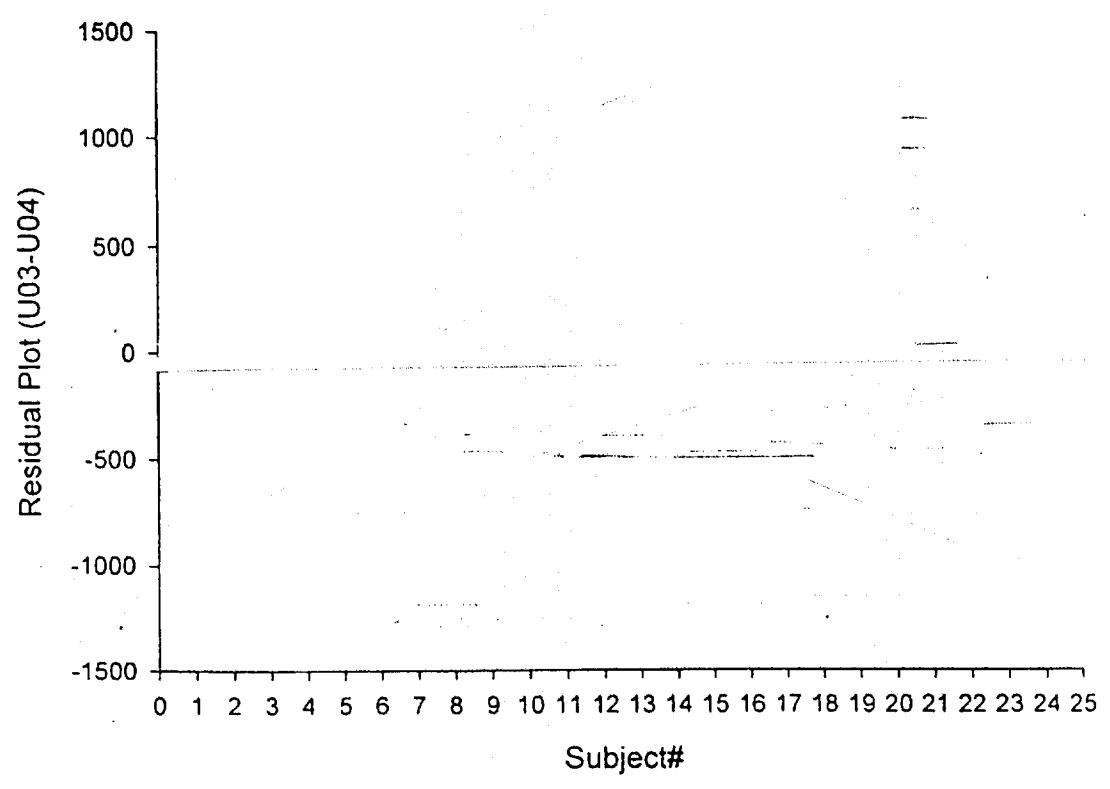


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### Residual Plot For Cmax (Formulation U03-U04) (Study # 60)



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WJ

4-i

4-i

Summary of the 9 BE Studies For Entacapone (COMTAN)  
(NDA #20-796)  
(July 13, 1999)

Study#	Formulations	Cmax	90%CI	AUC	90%CI	Remarks
39 Single Dose n=24 11/91	R: 12-S01-08 (100 mg) T: 03-T59-04 (200 mg)	1393 ± 521 [redacted] 1298 ± 656 [redacted]	0.71, 1.15	1531 ± 388 [redacted] 1505 ± 517 [redacted] (0-8 h)	0.90, 1.06	Failed for low Cmax
23 Single Dose n=12 1/93	T1: 12-P02-02 (100 mg) T 2: 12-R02-07 (100 mg) T 3: 12-S01-08 (100mg)	895 ± 115 [redacted] 717 ± 87 [redacted] 748 ± 91 [redacted]	Not Reported	730 ± 110 [redacted] 709 ± 127 [redacted] 628 ± 65 [redacted] (0-∞)	Not Reported	1. No reference <sup>c</sup> formulation 2. 90% CI not reported
24 Single Dose n=12 5/93	R: 12-S01-08 (100 mg) T 1: 03-S02-02 (200 mg) T 2: 03-S03-02 (200 mg)	Not reported (Only plasma profiles)	Not Reported	Not reported (Only plasma profiles)	Not Reported	AUC, CMax and CI90% data were not reported  No conclusions can be made!!

4-ii

4-ii

36 Single Dose n=12 6/93	R: 12-S01-08 (100 mg) T 1: 03-T07-02 (200 mg) T 2: 03-T13-02 (200 mg)	1416 ± 434 [redacted] 1775 ± 831 [redacted] 1629 ± 650 [redacted]	0.96,1.55 (For T07) 0.86,1.44 (For T13)	1640 ± 413 [redacted] 1685 ± 288 [redacted] 1547 ± 360 [redacted] (0-∞)	0.93,1.12 (For T07) 0.85,1.04 (For T13)	Failed for <b>high</b> Cmax
32 Single Dose n=21 8/93	R: 12-S01-08 (100 mg) T: 12-S02-04 (100 mg)	864 ± 110 [redacted] 792 ± 83 [redacted]	0.75,1.09	705 ± 47 [redacted] 658 ± 34 (n=19) [redacted] (0-∞)	0.87,0.99	Failed for <b>low</b> Cmax
50 Single Dose n=24 7/29/94	R: 03-T59-04 (200 mg) T 1: 03-U01-03 (200 mg) T 2: 03-U02-03 (200 mg)	1970 ± 1170 [redacted] 1510 ± 689 [redacted] 1660 ± 904 [redacted]	0.66,1.04 (For U01-03) 0.66,1.15 (For U02-03)	1660 ± 342 [redacted] 1600 ± 306 [redacted] 1610 ± 373 [redacted] (0-8 h)	0.90,1.03 (For U01-03) 90,1.04 (For U02-03)	Failed for <b>low</b> Cmax
42 Single Dose n=23 9/94	R: 12-S01-08 (100 mg) T: 03-T68-02 (200 mg)	1654 ± 743 [redacted] 1508 ± 896 [redacted]	0.76,1.07	1604 ± 430 [redacted] 1523 ± 432 [redacted] (0-8 h)	0.88,1.02	Failed for <b>low</b> Cmax

4-iii

4-iii

60 <b>Replicate</b> Single Dose n=19 4/4/95	R: 03-T59-04A (200 mg) R: 03-T59-04B (200 mg) T 1: 03-U03-03 (200 mg) T 2: 03-U04-03 (200 mg)	1415 ± 641 [redacted] 1379 ± 729 [redacted] 1317 ± 583 [redacted] 1418 ± 534 [redacted]	0.77,1.27 (03 vs 04B) 0.84,1.39 (U04 vs 04B)	1439 ± 306 [redacted] 1420 ± 368 [redacted] 1432 ± 410 [redacted] 1396 ± 331 [redacted] (0-8 h)	0.92,1.10 (03 vs 04B) 0.90,1.10 (04 vs 04B)	Failed for <b>high</b> Cmax
71 Single Dose n=23 11/28/96	R: 03-U04-03 (200 mg) T: XF001-02 (200 mg)	1353 ± 571 [redacted] 1636 ± 787 [redacted]	0.989,1.403	1607 ± 478 [redacted] 1630 ± 520 [redacted] 0-8 h)	0.966,1.061	Failed for <b>high</b> Cmax

**Overall Conclusions:**

1. Failing is only with Cmax. High or low (no consistent patterns).
2. Cmax is consistently more variable than AUC. Overall, the %CV for Cmax is about 45% and of the AUC is about 25%.
3. The determination of the AUC is inconsistent. In some studies is 0-8h and in others 0-∞.
4. Variability in Cmax appears to be lower for 100 mg formulations than the 200 mg formulations.
5. In all BE studies, entacapone was administered **alone** and not with levodopa/carbidopa.

22 pages

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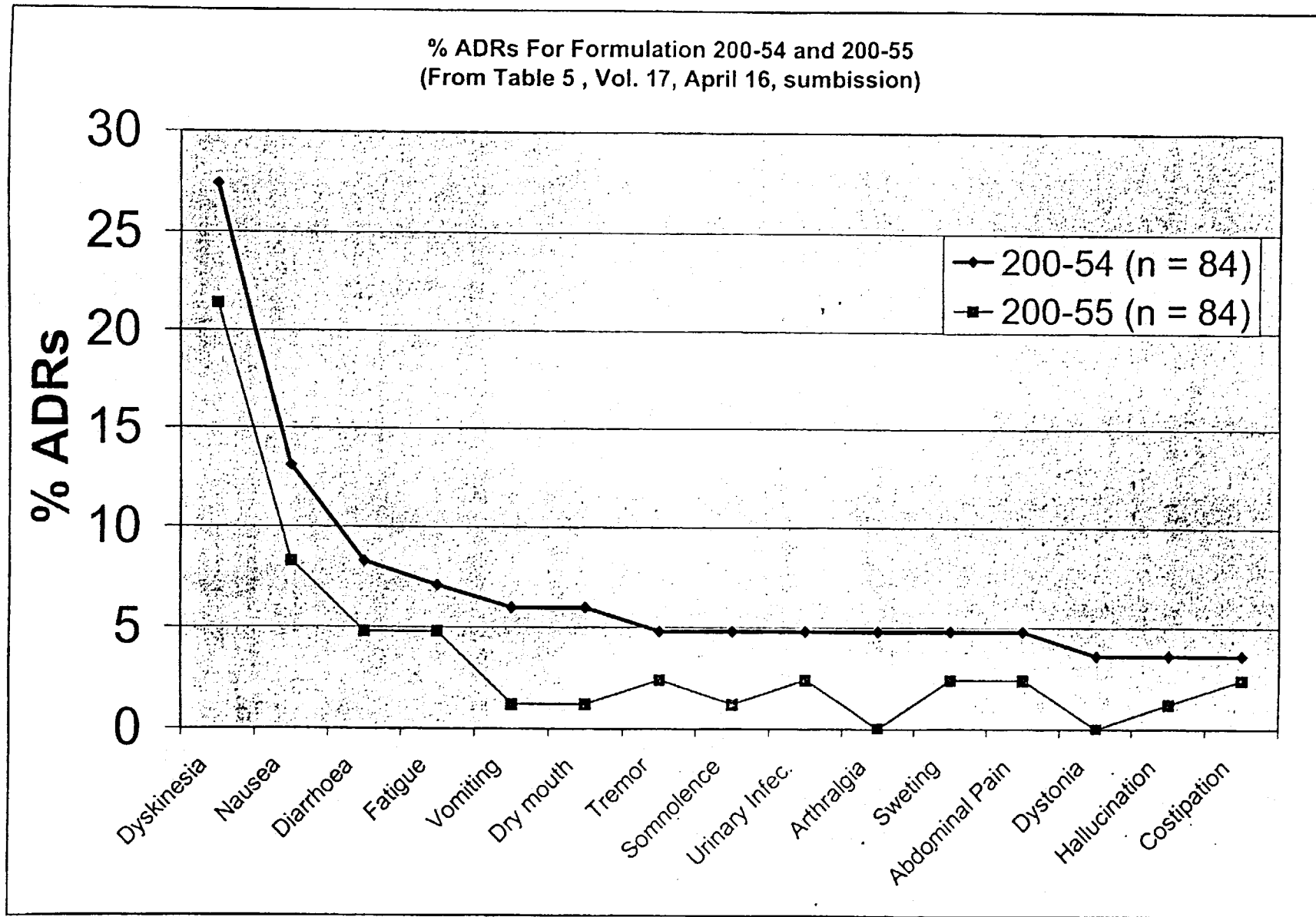
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COMTAN (NDA # 20-796)

28

May 17, 1999



Sheet 1

File: %ADRS

**TABLE 1.** Comparison of inhibitory potencies of entacapone and CYP-specific reference inhibitors on CYP-catalyzed model reactions in human liver microsomes *in vitro*

	Measured	Calculated
	IC <sub>50</sub> (μM)	K <sub>i</sub> (μM)*
<b>Ethoxyresorufin O-deethylase (CYP1A2)</b>		
Entacapone	>1000	>300
Fluvoxamine	0.045	0.004
<b>Coumarin 7-hydroxylase (CYP2A6)</b>		
Entacapone	321	3.2
Methoxsalen	0.7	0.02
<b>Tolbutamide (methyl)hydroxylase (CYP2C9)</b>		
Entacapone	3.5, 4.0, 4.4	1
Sulphaphenazole	4.1	1
<b>Mephenytoin 4'-hydroxylase (CYP2C19)</b>		
Entacapone	212	35
Omeprazole	67	11
<b>Dextromethorphan O-demethylase (CYP2D6)</b>		
Entacapone	>1000	>40
Quinidine	0.41	0.02
<b>Chlorzoxazone 6-hydroxylase (CYP2E1)</b>		
Entacapone	>1000	>450
Pyridine	4.7	1
<b>Testosterone 6β-hydroxylase (CYP3A)</b>		
Entacapone	435	40
Ketoconazole	0.34	0.03

\* K<sub>i</sub> calculated by using mean K<sub>m</sub> values obtained from the literature.



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**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
REVIEW (VOLUME 1 of 2)**

**NDA: 20-796**

**Submission Dates:**

January 2, 1998

October 1, 1998

**Generic Name:** Entacapone  
**Brand Name:** COMTAN  
**Strength(s):** 200 mg Tablets  
**Formulation:** Film Coated Tablets for Oral Administration.  
**Sponsor:** Orion Corporation  
Espoo, Finland  
**Type of Submission:** NDA (NME)  
**Reviewer:** Sayed Al-Habet, Ph.D.  
**Date of Review:** October 28, 1998

**SYNOPSIS:**

COMTAN (entacapone) is a reversible catechol-O-methyltransferase (COMT) inhibitor. COMT converts levodopa to 3-O-methyldopa (3-OMD). Thus, the inhibition of COMT will increase levodopa levels in peripheral tissues. Levodopa combined with a peripherally acting dopa decarboxylase (DDC) inhibitor such as carbidopa or benserazide is the most effective and widely used antiparkinsonian medication. When the enzyme DDC is blocked, the enzyme COMT compensates by degrading levodopa into 3-OMD in the periphery. Entacapone acts peripherally and does not pass the blood-brain barrier at therapeutic concentrations. By blocking COMT in the periphery, entacapone decreases the peripheral metabolism of levodopa, increasing its availability in the circulation. Thus a greater proportion of levodopa will consequently reach the striatum, for conversion by DDC to dopamine. Only a small proportion of levodopa is metabolized by COMT in the brain (Attachments 1 and 2).

Since entacapone does not have any inherent antiparkinsonian activity as a sole agent, it is being proposed to be used as adjunct to levodopa/DDC inhibitor therapy in the treatment of Parkinson's disease. The sponsor is proposing to market COMTAN as a single 200 mg tablet for oral administration. The proposed dose is one 200 mg tablet administered concomitantly with each levodopa/DDC inhibitor dose up to 10 times daily. The focus of this NDA is on the parent drug, entacapone, levodopa, and 3-OMD.

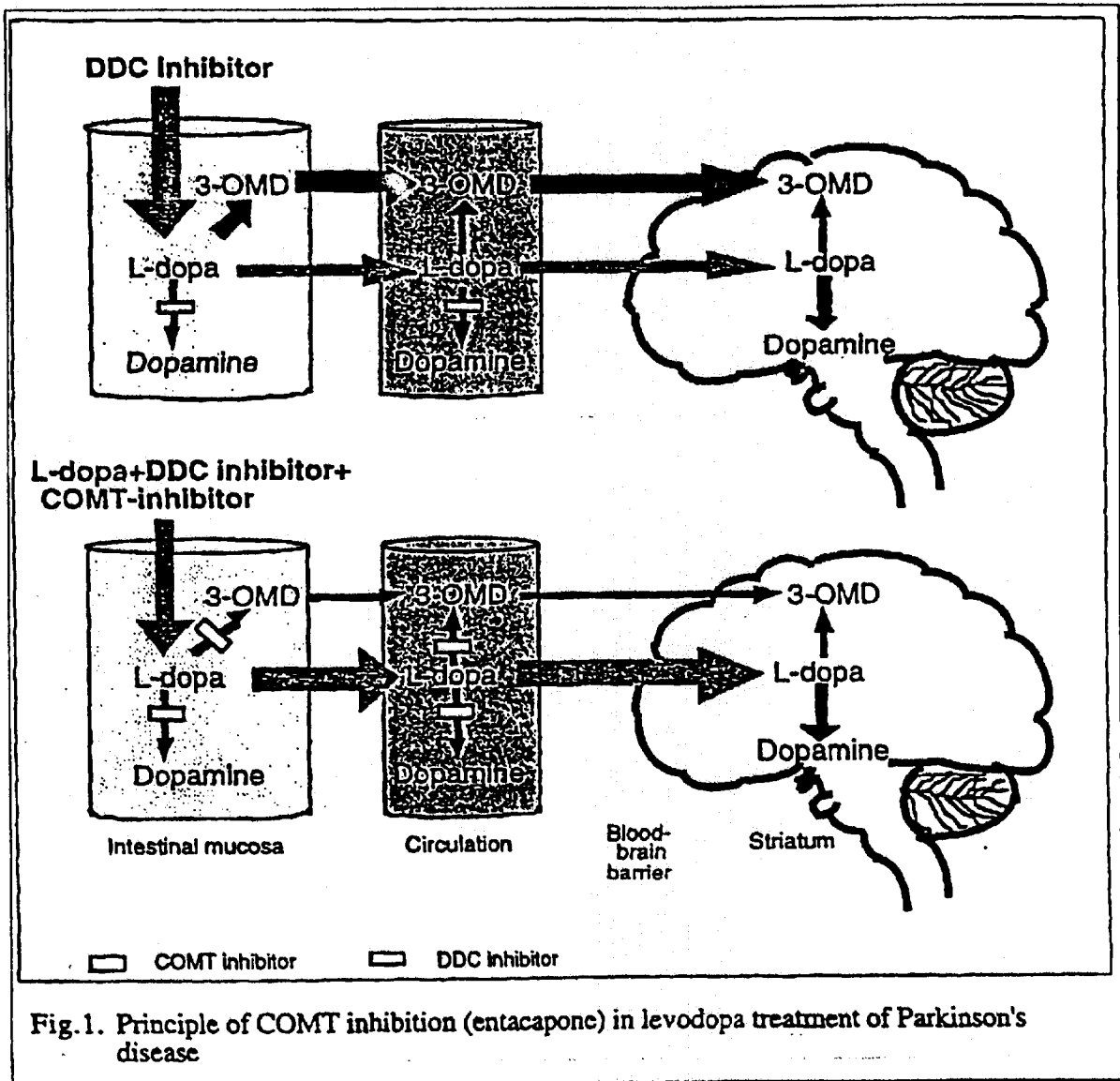
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**Relevant Abbreviations:**

AD	Aldehyde dehydrogenase
AR	Aldehyde reductase
DA	Dopamine
DHPG (DOPEG)	3,4-dihydroxyphenylethylene glycol
DOPAC	3,4-dihydroxyphenylacetic acid
HVA	Homovanillic acid
L-Dopa	levodopa
MAO	Monoamine oxidase
MHPG (MOPEG)	3-methoxy-4-hydroxyphenylethylene glycol
MN	Metanephrine
NA	Noradrenaline
NMN	Normetanephrine

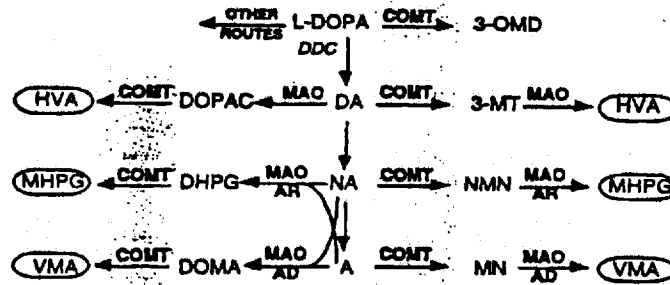
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Attachment 1

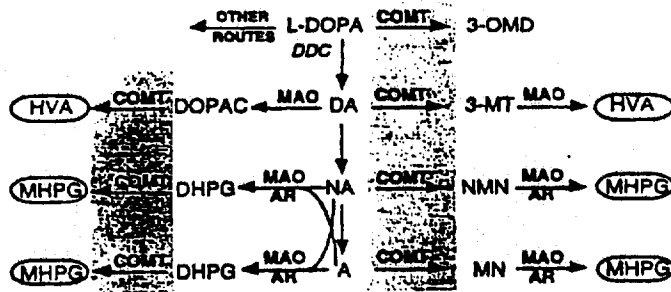


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METABOLISM OF L-DOPA AND DA IN THE CENTRAL NERVOUS SYSTEM



METABOLISM OF L-DOPA AND DA IN PERIPHERAL TISSUES



Note to the peripheral metabolism: Relative high proportion of catecholamines are sulphocojugated in the liver by phenol sulphotransferase.

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## RECOMMENDATION:

Based on the information submitted to us, this NDA is ACCEPTABLE to the Office of Clinical Pharmacology and Biopharmaceutics.

The Medical Division should consider the incorporation of some or all of the Comments related to labeling. The sponsor is requested to adopt the dissolution methodology and specification, as outlined in Comment # 1 to the sponsor.

## COMMENTS TO THE CLINICAL DIVISION

(See also respective summary sections):

The Comments and the observations listed below are for the Medical Division's consideration. The Medical Division may convey all or part of these Comments to the sponsor and/or be incorporated in the label. Some of these comments are based on the limited data that were submitted to the Office of Clinical Pharmacology and Biopharmaceutics in this NDA. These Comments should be carefully assessed by the Safety and Efficacy team of this NDA relative to the large data base submitted to the Clinical Division.

1. Overall, the sponsor has performed an extensive program to characterize the clinical pharmacology and pharmacokinetics of this drug.
2. Overall, levodopa mean AUC was about [redacted] after 200mg and 400 mg doses of entacapone compared to control (levodopa/carbidopa), respectively. This appears to be irrespective of levodopa/carbidopa formulations (i.e., Sinemet IR or CR tablets). However, it should be noted that there was no change in C<sub>max</sub> or T<sub>max</sub> of levodopa with dose. This is probably of clinical importance in which only the exposure is changed with increasing the dose. Some of the side effects such as dyskinesia are more associated with C<sub>max</sub> than AUC.
3. It appears that there is little or no separation among entacapone doses and some of the clinical responses, especially relative to the "ON time" data (Attachments 3-5). These observations are based on the limited data submitted to us and on the following two main studies:
  - i. Study # 293926: This was a dose finding study in 22 patients. The entacapone tested doses were: placebo, 50, 100, 200 and 400 mg. In this study the 200 mg dose was found to produce the optimum "ON time" response (Attachment 3)
  - ii. From study # 293926 there was no separation among doses in terms of "modified total motor scores" as shown in Attachment 5 and dyskinesia

scores (Attachment 6). However, in terms of recovery, the separation was more apparent at 200 mg and 400 mg doses compared to placebo.

- iii. Study # 293930: Based on the above study (#293926), the 200 mg dose was selected for 4 weeks treatment in 26 patients. Overall, the total duration of "ON time" was about 30 minutes longer for Sinemet and entacapone compared to control (Sinemet alone) or placebo (levodopa/placebo). See Attachment 4.

4. The mean C<sub>max</sub> of entacapone and levodopa, but not the AUC, was approximately [redacted] in elderly than young subjects. No formal gender study has been conducted by the sponsor.
5. In liver impairment patients, the C<sub>max</sub> and AUC were doubled compared to healthy subjects. Dose adjustment in liver impairment by prolonging the dosing intervals is necessary and should be based on individual patient. Further, levodopa/carbidopa were not administered in this study.
6. A single dose was used in all special population studies and some of the drug interaction studies. Therefore, the effects after multiple doses of long term therapy, especially in patients with liver impairment are unknown. Again, levodopa/carbidopa were not administered in this study. Thus, the data from these studies are of little clinical significance since entacapone must be given with levodopa/carbidopa and the level of levodopa must be determined to establish the PK/PD in these populations.
7. All drug interaction studies focused mainly on the PD interactions and with MAO inhibitors. It is important to note that in all drug interaction studies (except selegiline), levodopa/carbidopa was not administered. Therefore, the clinical significance of these interactions are unknown, particularly after multiple doses of each drug and long term therapy with levodopa/DDC inhibitor and entacapone. These drug interaction studies are: selegiline, moclobemide (an MAO inhibitor marketed in Europe), imipramine, isoprenaline and adrenaline. No drug interactions have been noted with selegiline and imipramine.

The only clinically significant drug interaction that have been noted in these studies is that associated with the increase in the heart rate when entacapone/levodopa/carbidopa were co-administered with intravenous isoprenaline and adrenaline. The clinical and the practical significance of this interaction is in the emergency situations and in those patients on isoprenaline and/or adrenaline inhalers. The inhibition of COMT by entacapone may reduce the first pass effect of isoprenaline and adrenaline in the lungs and increase their levels in the circulation. Therefore, caution should be exercised when entacapone is given with isoprenaline, adrenaline and other related drugs. This should be stated in the label with a list of related drugs with potential interactions with COMT

inhibitor, entacapone.

8. Another noticeable drug interaction was the effect of moclobemide, an MAO inhibitor marketed in Europe, on endogenous catecholamine metabolites: 3,4-dihydroxyphenylethylene glycol (DHPG), 3,4-dihydroxyphenylacetic acid (DOPAC), and 3-methoxy-4-hydroxyphenylethylene glycol (MHPG). Overall, the plasma levels of these metabolites were about [redacted] when moclobemide was co-administered with entacapone compared to entacapone alone. It should be noted that these metabolites are also levodopa metabolites (see Attachment 2). This suggests that moclobemide may also affect the metabolism of levodopa. However, as indicated above, levodopa/carbidopa was not administered in this study. Therefore, the effect of moclobemide on the fate of levodopa is unknown, especially after long term therapy.
9. The plasma levels of levodopa were always about [redacted] after Madopar (levodopa/benserazide) than Sinemet (levodopa/carbidopa). It should be noted that benserazide is another DDC inhibitor marketed in Europe. This observation should be stated in the label.
10. It appears that entacapone reduces the secretion of the growth hormone by about [redacted] compared to the placebo (study # 293909). However, levodopa/carbidopa causes [redacted] to [redacted] in the Cmax and AUC of growth hormone compared to placebo. The co-administration of entacapone with levodopa/carbidopa was not associated with further increase in growth hormone. In this study, the levodopa/carbidopa doses were 300/75 mg given as a single dose that is different from the recommended dose of 100/25 mg TID.
11. The effect of entacapone on prolactin data seems to be negligible. However, levodopa/carbidopa with entacapone treatment reduces [redacted] to placebo (study # 293909). Similar to growth hormone, the co-administration of entacapone with levodopa/carbidopa was not associated with further decrease in prolactin secretion.
12. In the Precaution/Drug interaction Section: The following statement should be included:  
[redacted]
13. Entacapone PK of entacapone appears to be linear up to 800 mg dose when co-administered with levodopa/carbidopa (see summary, Attachment 7). However, in one study (#293909) when entacapone was concomitantly administered with levodopa/carbidopa, the mean Cmax and AUC of entacapone were [redacted]



[redacted] compared to control. In this study, the levodopa/carbidopa doses were 300/75 mg given as a single dose that is different from the recommended dose of 100/25 mg TID.

14.

[redacted]

15. This drug could be given up to 10 times daily. Thus, compliance is an issue in the elderly population and could be associated with safety and efficacy problems.

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## COMMENTS TO LABELLING:

These Comments are also for the Clinical Division consideration, but specifically on labeling. For completeness, some of these Comments have appeared in the previous Section. In addition, some of these comments have been addressed by the sponsor in the label, but have not been strongly emphasized.

1. Dose adjustment in liver impairment patients is necessary and should be individualized. Since there is only one tablet strength, this can be achieved by prolongation of dosing interval.
2. In the Precaution/Drug Interaction Section: The following statement should be included:

[Redacted]

3. In the Precaution/Drug Interaction Section: The following statement should be included:

[Redacted]

4. In the Precaution/Drug Interaction Section: The following statement should be included:

[Redacted]

5. In the Precaution/Drug Interaction Section: The following statement should be included:

[Redacted]

6. In the Precaution/Drug Interaction Section: The following statement should be included:

[Redacted]

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**COMMENTS TO THE SPONSOR:**

1. The sponsor is requested to adopt the following dissolution methodology.

Apparatus II:	USP (Paddles)
Speed:	[REDACTED]
Medium:	[REDACTED]
Sampling times:	[REDACTED]
Specifications:	Not less than [REDACTED]

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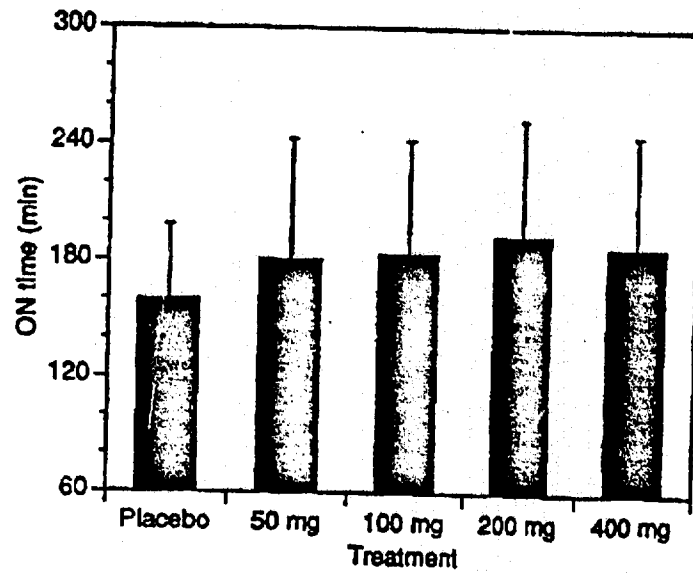
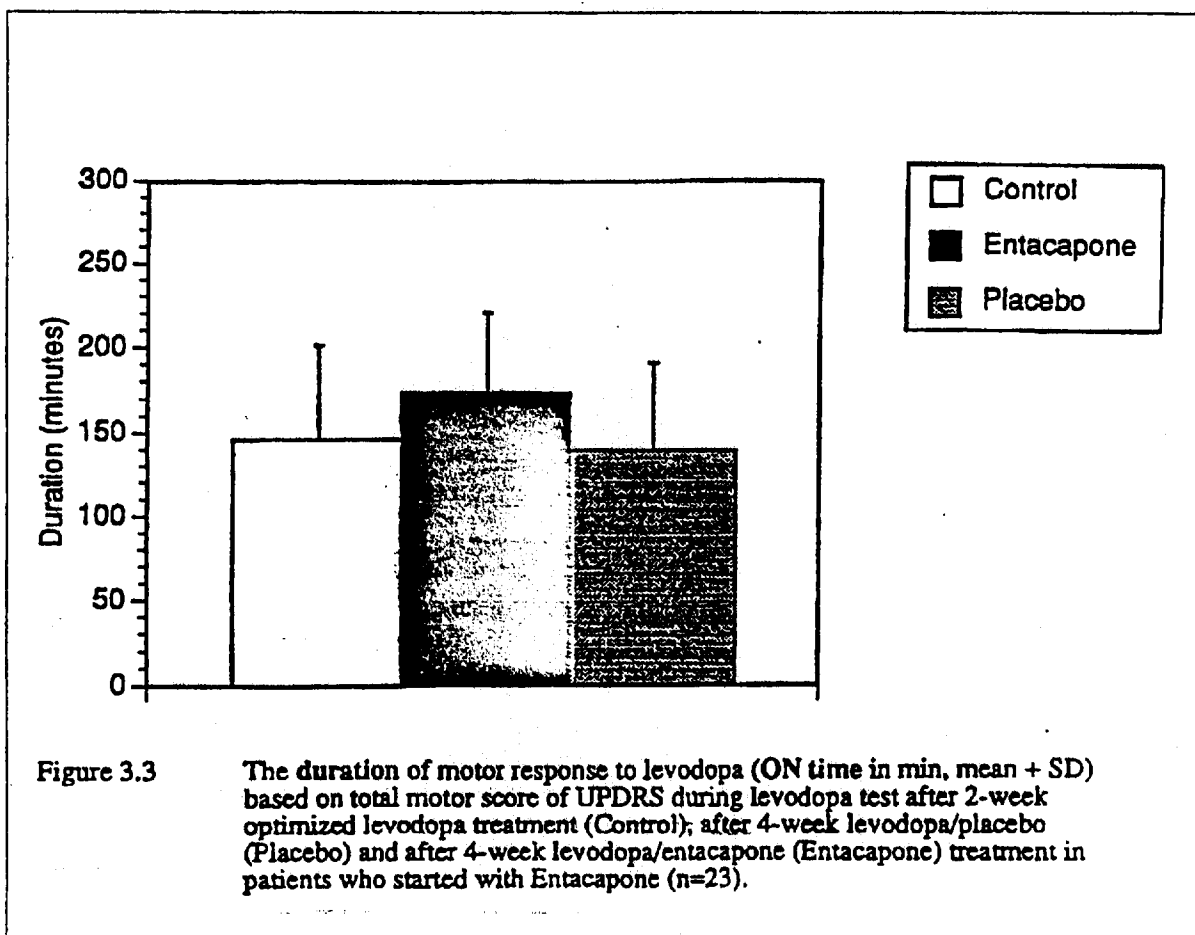


Figure 1.2 Mean ON time (duration of clinical response, min) based on modified total motor score of UPDRS (levodopa test) after placebo or different doses of entacapone administered with an individual single oral dose of levodopa/DCI (mean+SD, N=19)

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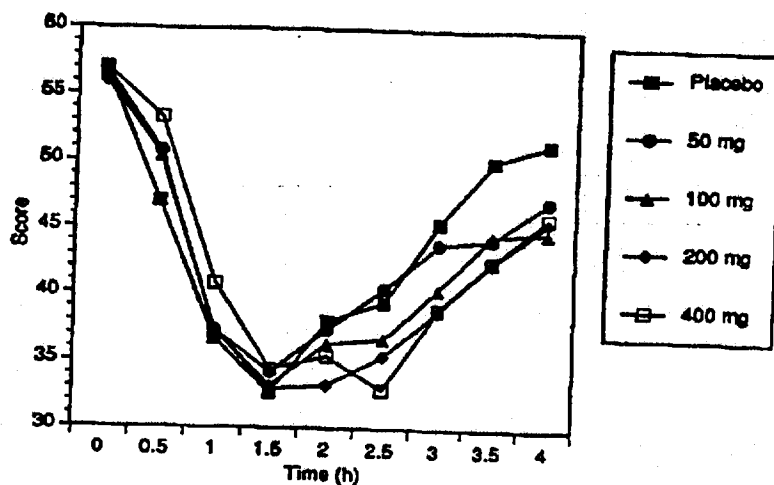
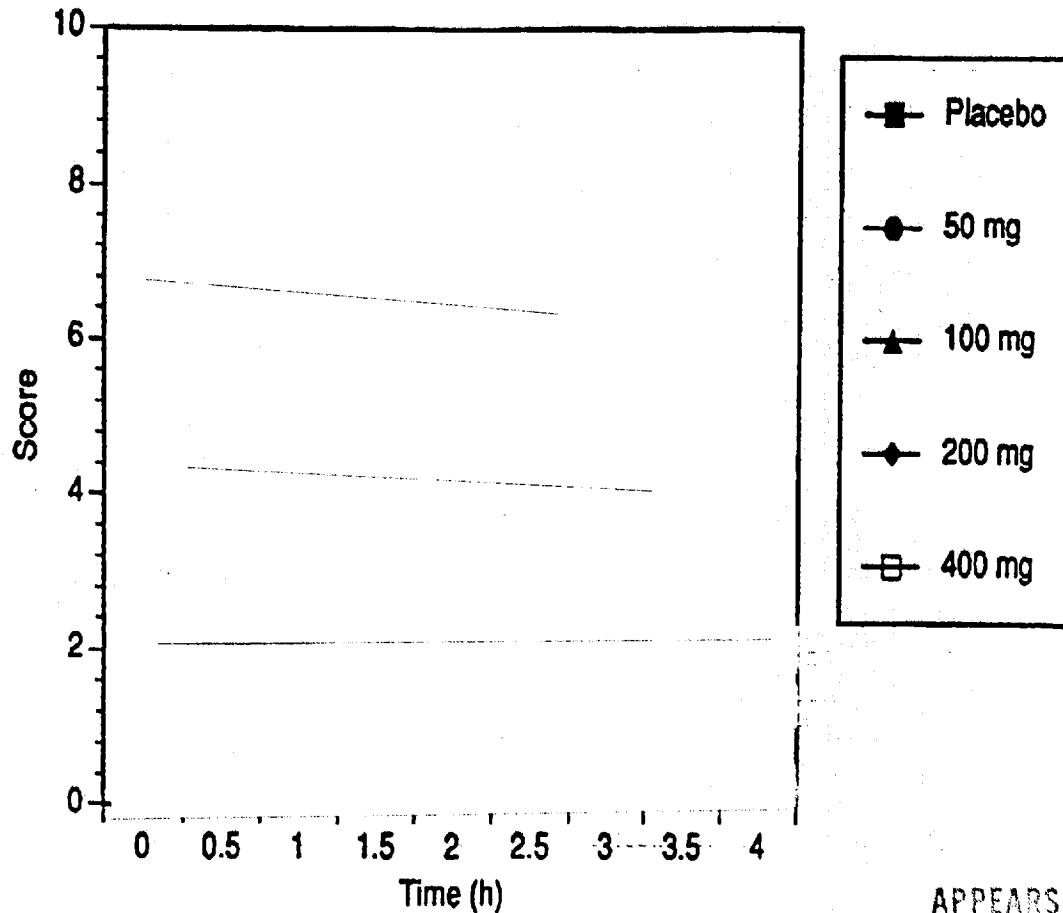


Figure 1.1 Mean modified total motor scores of UPDRS (levodopa test) after placebo or different doses of entacapone administered with an individual single oral dose of levodopa/DCI. Some patients were still ON after 4 hours. Number of patients contributing to the means varies from 19 at baseline to between 9 and 15 at 4 hours.

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Figure 2.1 Mean dyskinesia score after placebo or different doses of entacapone administered with an individual single oral dose of levodopa/DCI (N=19)

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(VOLUME 1 OF 2)**

**(VOLUME 1)**

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**BIOAVAILABILITY AND EFFECT OF FOOD:**

Comparison Between Sinemet CR "Depot" and Standard Sinemet (Study # 293927)  
Bioequivalence of 200 mg tablets (Study # 2939071)  
Absolute Bioavailability: 2 X 100 mg tablets, 200 mg oral solution and IV solution (Study # 293919)

**PHARMACOKINETICS (MULTIPLE DOSE)**

Single escalating doses: 5, 25, 50, 100, 200, 400, 800 mg (Study # 293901/293903)  
Single escalating doses: 50, 100, 200, and 400 mg (Study # 293902)  
Single escalating doses: 100, 200, 400, and 800 mg with Sinemet CR (Study # 293922)  
Multiple dose: 100 mg TID, 200 mg TID, and 400 mg TID X 10 days (study # 293904)  
Multiple dose: 200 mg X 7 days with levodopa/benserazide (study # 293914)

**PLASMA PROTEIN BINDING**

Study # CR95031210228

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## **SPECIAL POPULATIONS**

Hepatic Impairment: Single Dose, 200 mg (Study # 2939058)

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## **DRUG INTERACTIONS:**

Effect of Selegiline and Madopar-Benserazide (Study # 2939035)

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## **VOLUME 2**

### **METABOLISM AND ELIMINATION**

Identification of Metabolites in Urine (Study # CR90032870017)

<sup>13</sup>C-Entacapone IV and unlabelled PO, urine and plasma data (Study # 293906)

Species comparison study: <sup>13</sup>C-Entacapone PO in animals and unlabelled PO in human (Study # BF96411210009)

### **CLINICAL RESPONSES AND PHARMACODYNAMICS**

(see also other individual studies)

Dose Finding, Escalating Doses of 0, 50, 100, 200, and 400 mg, Motor Responses and PK/PD data (Study # 293926)

Clinical Effects, 200 mg Dose X 4 weeks, Double Blind-Crossover Study (Study # 293930)

200 mg Dose X 2 weeks of Entacapone With Levodopa/Benserazide, Clinical Responses and PK (Study # 293929)

Effect of Entacapone on Growth Hormone and Prolactin secretion, Single Dose (Study # 293909)

#### **APPENDIX II:**

(Dosage Form Formulations-Drug Substance and Drug Product)

#### **APPENDIX III:**

(Dissolution Methodology, Specification and Bioequivalence links)

#### **APPENDIX IV:**

(Analytical Methodology)

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## BACKGROUND

COMTAN (entacapone) is a selective, peripherally acting, and reversible catechol-O-methyltransferase (COMT) inhibitor. Levodopa is combined with a peripherally acting levodopa/dopa decarboxylase (DDC) inhibitor such as carbidopa. This combination is the most effective and widely used antiparkinsonian medication. When the enzyme DDC is blocked, the enzyme COMT compensates by degrading levodopa into 3-O-methyldopa (3-OMD) in the periphery. When entacapone is added to the mixture, COMT is blocked peripherally and the degradation of Levodopa to 3-OMD is reduced leading to the increase of Levodopa in the circulation and its availability to cross the blood brain barrier (Attachments 1 and 2). Entacapone does not cross the blood brain barrier.

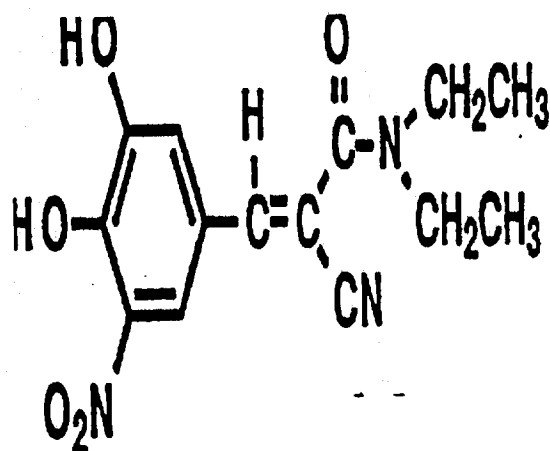
Entacapone has nitrocatechol structure. Since entacapone does not have any inherent antiparkinsonian activity as a sole agent, it is proposed to be used as an adjunct to levodopa/dopa decarboxylase (DDC) inhibitor therapy.

### Physico-Chemical Properties:

Entacapone exists in two stereoisomeric forms: the (E) or trans-isomer and the (Z) or Cis-isomer. The chemical structure (see below) of entacapone molecule precludes the possibility of optical isomerism (chirality).

Entacapone is practically insoluble in water and sparingly soluble in methanol and ethanol. The  $pK_a$  of the drug is approximately 4.5 and the molecular weight is 305.28.

### Structural Formula:



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**Chemical Formula:**

The chemical name is (*E*)-2-cyano-*N,N*-diethyl-3-(3,4-dihydroxy-5-nitrophenyl) propamide. It has an empirical formula of  $C_{14}H_{15}N_3O_5$  and a molecular weight of 305.28.

**Indications and Usage:**

COMTAN is indicated for the treatment of signs and symptoms of Parkinson's disease as an addition to levodopa/DDC inhibitor treatment.

**How Supplied:**

COMTAN (entacapone) will be available as a single-unit film-coated tablet preparation. Each tablet contains 200 mg of the active ingredient, entacapone. The tablet will be oval-shaped and brownish-orange in color.

**Proposed Dosage and Administration:**

The recommended dose of COMTAN is one 200 mg tablet administered concomitantly with each levodopa/DDC inhibitor dose up to 10 times daily. The maximum daily dose is 2000 mg. The clinical experience with daily doses over 1600 mg is limited. There is no need to adjust the dose in elderly patients. COMTAN can be used with both immediate-release and sustained-release levodopa/DDC inhibitor preparations.

**Manufacturer and Manufacturing Site:**

The finished drug product of COMTAN tablets, will be manufactured by Orion Pharmaceuticals, Finland, and the packaging and labeling of the finished product will be carried out by Novartis Pharmaceuticals Corporation, USA.

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## **SUMMARY REVIEW OF PHARMACOKINETICS AND BIOAVAILABILITY**

### **Introduction:**

Entacapone (Comtan) is a peripherally acting catechol-O-methyltransferase (COMT) inhibitor. It is indicated in the treatment of signs and symptoms of Parkinson's disease as adjunct drug to levodopa/dopa decarboxylase inhibitor-DDC (e.g., carbidopa and benserazide) treatment.

COMT is responsible for the metabolism and inactivation of catecholamines, their hydroxylated metabolites, catechol estrogens, and other catechols (Attachments 1 and 2). Exogenous levodopa is a substrate of COMT and is converted mainly to 3-O-methyldopa (3-OMD), which has a half life of approximately 15 hours. 3-OMD is therapeutically ineffective. During combined levodopa/DDC inhibitor therapy, COMT is also degrading peripheral levodopa to 3-OMD as reflected by increased plasma levels of 3-OMD. The inhibition of COMT activity is, therefore, a promising strategy for decreasing the degradation of levodopa, enhancing its striatal availability and therapeutic effect in Parkinson's disease.

Entacapone is a reversible inhibitor of soluble COMT activity in human erythrocytes which, according to animal studies, reflected well with the extent of inhibition in other peripheral tissues. It is highly selective to COMT and acts predominantly in the periphery.

A total of 35 studies were conducted to evaluate the clinical pharmacology and pharmacokinetics of levodopa/DDC/entacapone treatment regimen. These studies focus mainly on the PK/PD of levodopa, 3-OMD and the parent drug entacapone. Additional studies were performed in small patient populations to establish the dose response relationship relative to motor scores and ON Time scores. Other pharmacokinetics studies were conducted namely: metabolism, effect of food, drug interactions, age, gender, hepatic and renal impairments. In almost all studies, the plasma levels of levodopa, 3-OMD, entacapone and COMT were measured to determine the PK/PD relationship.

## Pharmacokinetics (Dose Proportionality and Multiple Dose of Entacapone)

### A: Pharmacokinetics of Entacapone

1. Considering the inter- and intra-subject variability in the data and the assay, the AUCs of entacapone appear to be dose proportional up to 800 mg single doses of entacapone with fixed dose of levodopa/carbidopa. The Cmax of entacapone also appears to increase with the dose (Attachments 7 and 8). The same trend was also seen for entacapone metabolite, z-isomer.
2. There was no evidence of drug accumulation after 10 days of multiple dosing.
3. However, in one study (#293909) the presence of levodopa/carbidopa appears to markedly affect the PK of entacapone. When entacapone was concomitantly administered with levodopa/carbidopa, the mean Cmax and AUC of entacapone were reduced by about [redacted] compared to control. A similar trend, but to [redacted] was also seen for entacapone z-isomer Cmax and AUC. In this study, the levodopa/carbidopa doses were 300/75 mg given as a single dose that is different from the recommended dose of 100/25 mg TID.

### B: Effect of Entacapone on Levodopa:

1. Overall, levodopa mean AUC was [redacted] at 200 mg and 400 mg doses of entacapone compared to control, respectively (Attachment 9). This appears to be irrespective of levodopa/carbidopa formulations (i.e., Sinemet IR or CR tablets). It should be noted that there was no change in Cmax or Tmax of levodopa with dose. This is probably of clinical importance in which only the exposure is changed with increasing the dose. Some of the side effects such as dyskinesia are more associated with Cmax than AUC.
2. The plasma levels of levodopa were always about [redacted] after Madopar (levodopa/benserazide) than Sinemet (levodopa/carbidopa). It should be noted that benserazide is another DDC inhibitor marketed in Europe. This observation should be stated in the label.
3. At doses greater than 200 mg of entacapone, there was some disproportionate increase in the AUC of Levodopa as entacapone dose increases.
4. Overall, the half life of levodopa [redacted] after multiple doses of entacapone.

5. As expected, the AUC of levodopa major metabolite, 3-OMD, decrease proportionally with increasing doses of entacapone (Attachment 10), and this corresponded well with the increased % inhibition of COMT enzyme (Attachment 11). There was a strong inverse relationship [redacted] between % inhibition of COMT and entacapone log dose (Attachment 12). Similar to levodopa, and as expected, the level of 3-OMD was about [redacted] relative to control at 400 mg dose level.

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Attachment 7

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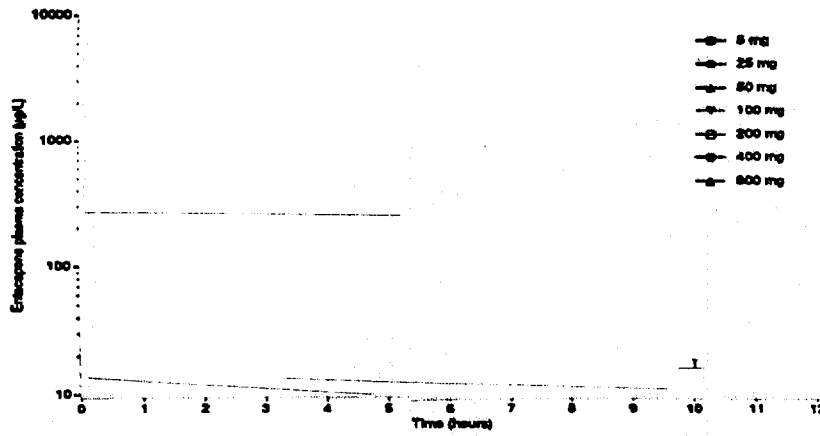


Figure 1. The plasma concentrations of entacapone in 12 healthy volunteers following oral administration of single increasing doses of entacapone (mean  $\pm$  SEM) [1]

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Attachment 8

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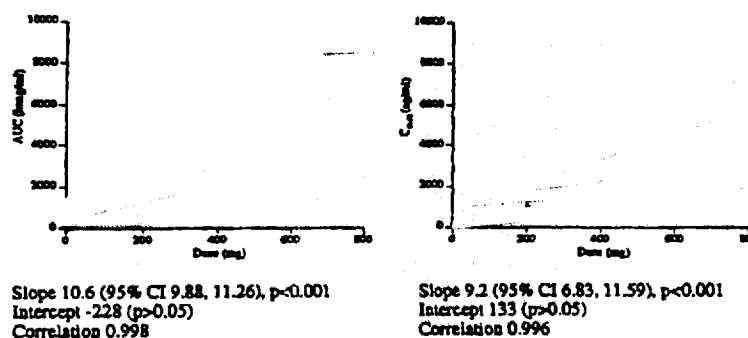


Figure 8. Relationship between dose and AUC, and between dose and  $C_{max}$  of entacapone after oral administration of single doses ranging from 5 to 800 mg to 12 healthy volunteers (mean  $\pm$  SD).

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Attachment 9

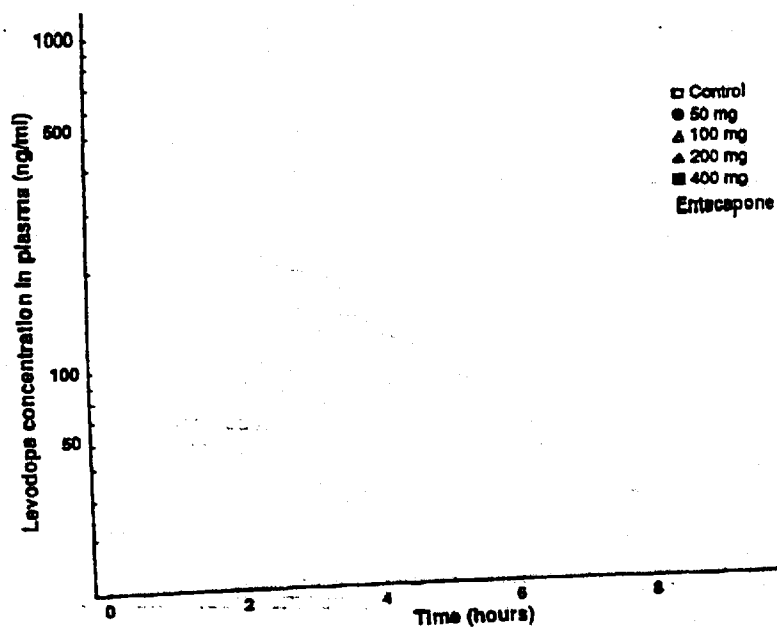


Figure 4. Mean ( $\pm$ SEM) plasma concentration of levodopa after a concomitant administration of levodopa/carbidopa (100/25 mg) and increasing single doses of entacapone in healthy volunteers (N=12) [2]

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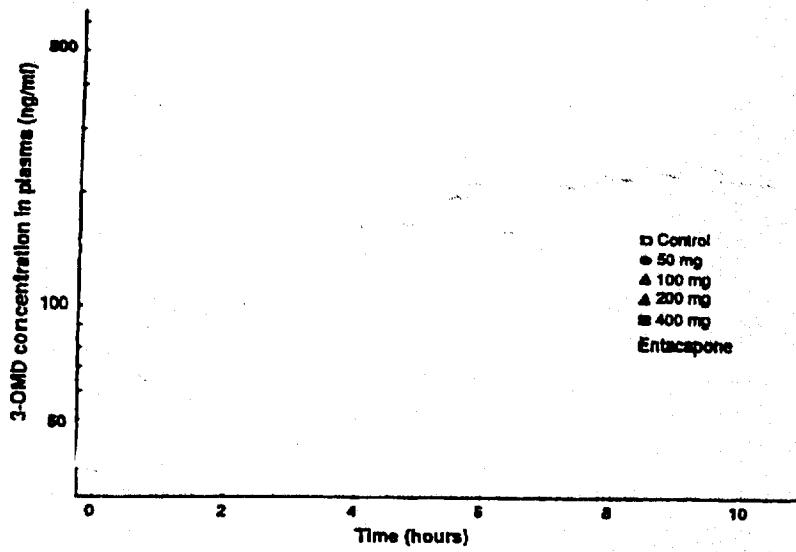


Figure 5. Mean AUC levels of 3-O-methyldopa (3-OMD) after increasing single doses of entacapone in combination with levodopa/carbidopa (100/25 mg) in healthy volunteers (2)

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Attachment 11

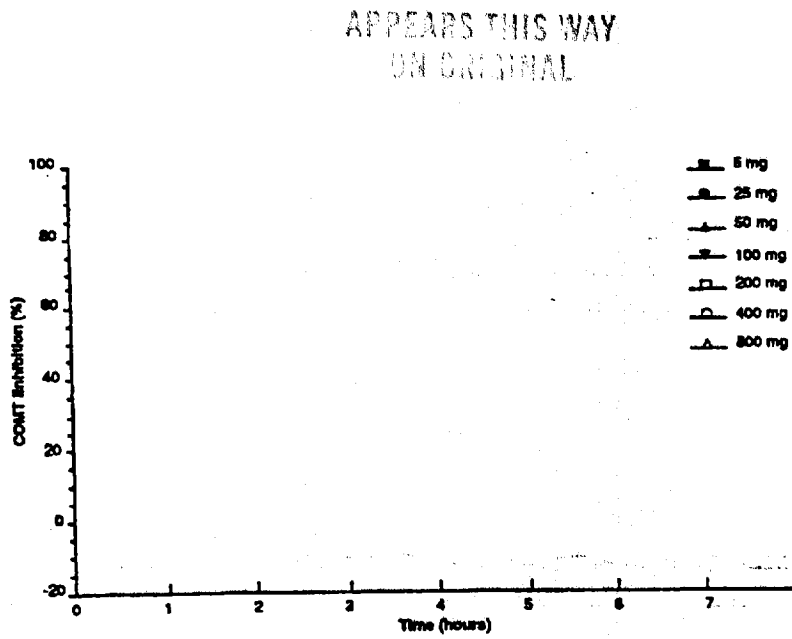
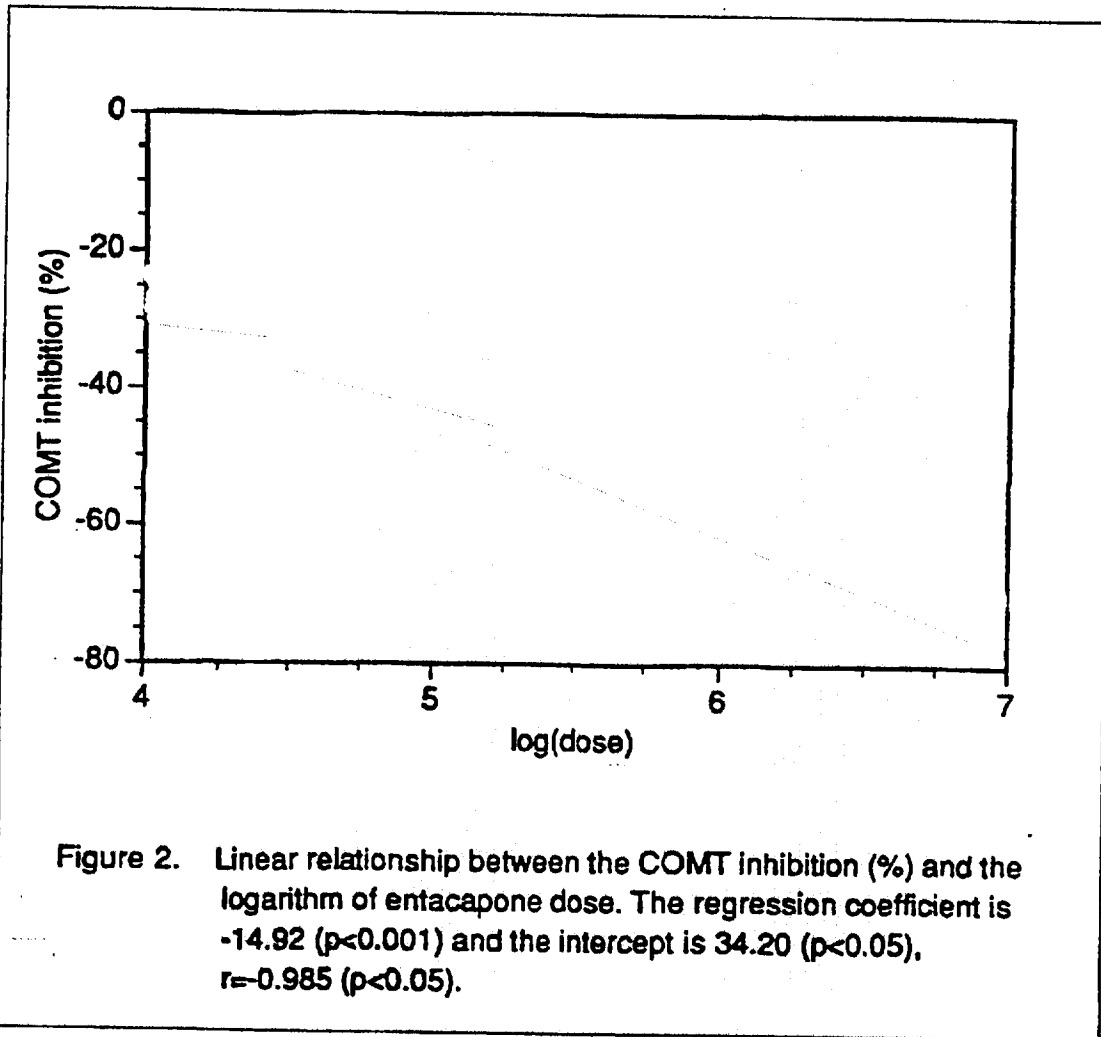


Figure 3. Mean inhibition of erythrocyte soluble COMT activity after increasing single doses of entacapone in healthy volunteers [1]

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Attachment 12



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### Distribution and Clearance:

1. The binding of entacapone to human plasma proteins is about 98% at a plasma concentration of [redacted]. It should be noted that no binding displacement was found in either direction between entacapone and the following tested highly bound drugs: warfarin, salicylic acid, phenylbutazone, and diazepam.
2. The half life of entacapone is [redacted].
3. Following IV administration, entacapone total body clearance is approximately [redacted] mL/min and the volume of distribution is approximately [redacted].

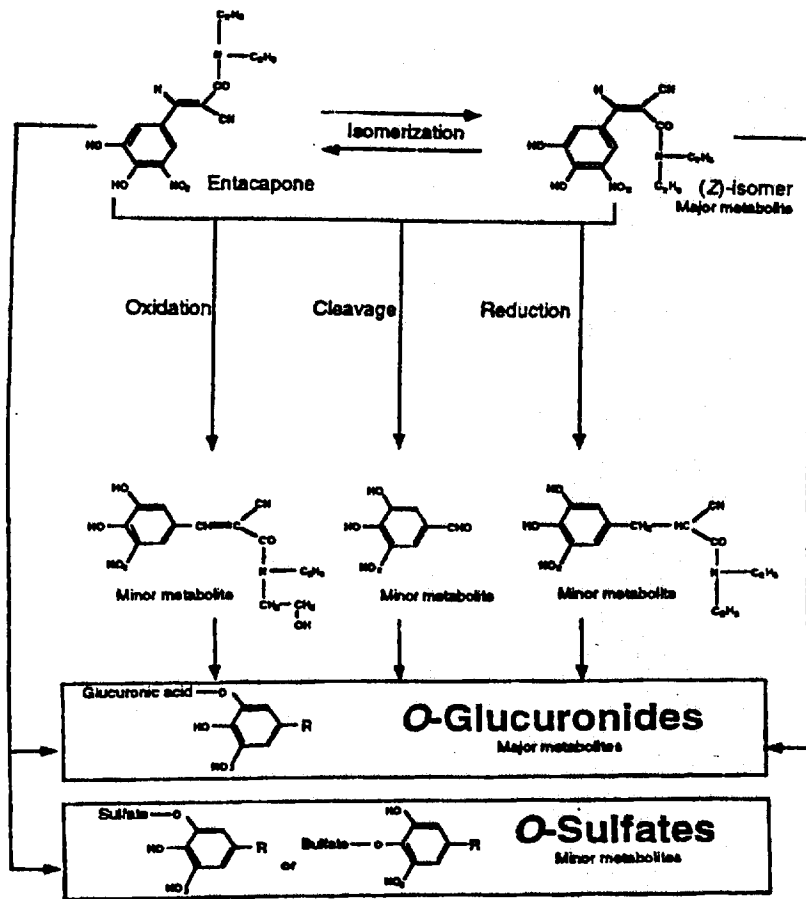
### Effect of Food:

Food does not appear to affect the absorption and the bioavailability of entacapone.

### Metabolism:

1. The proposed metabolic pathways for entacapone are shown in Attachments 13 and 14.
2. About [redacted] of the dose was excreted in urine within [redacted] after oral administration. The drug undergoes an isomerization step for conversion from "trans" to "cis" forms (Phase I reaction) prior to glucuronidation (Phase II conjugation reactions).
3. The free parent drug and the [redacted] of all metabolites in urine. Glucuronides represent about [redacted] of the parent drug and about [redacted] of the z-isomer in urine. Thus, [redacted] represents the combined (free and conjugated) metabolites of the parent and z-isomer in urine. No study was conducted to identify the responsible isozymes.
4. In the Precaution/Drug Interaction Section: The following statement should be included:

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Figure 3. The metabolic pathways of entacapone in humans.

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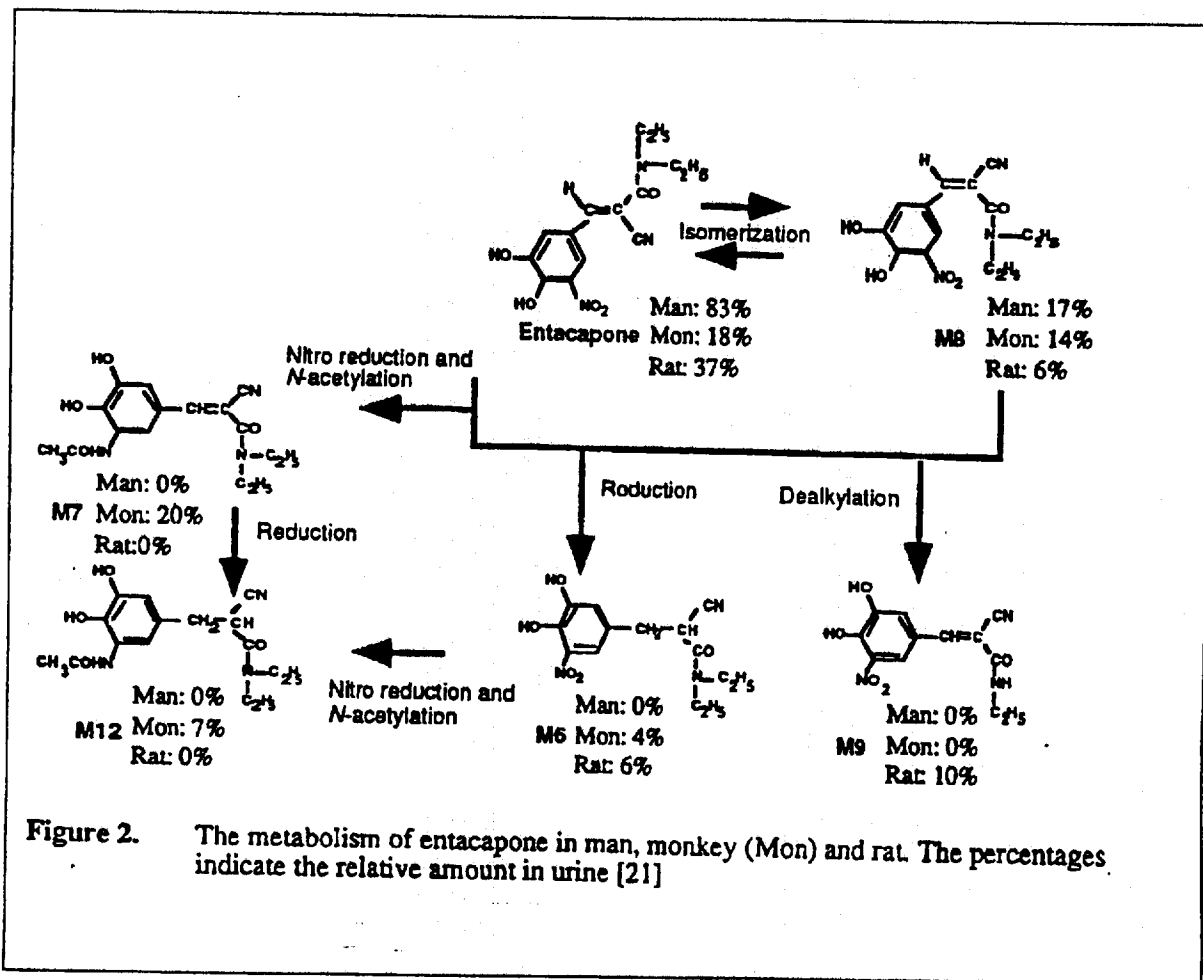


Figure 2. The metabolism of entacapone in man, monkey (Mon) and rat. The percentages indicate the relative amount in urine [21]

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## **Drug Interactions:**

All drug interaction studies that were conducted in this NDA were related mainly to the pharmacodynamic interactions associated with those drugs that affect the CNS, those that are commonly administered drugs in Parkinson's disease, and/or the hemodynamic profiles and partly on the pharmacokinetics interactions. It is important to note that in all these studies (except selegiline), levodopa/carbidopa was not administered. Therefore, the data from these studies may be of little value since entacapone must be given with levodopa/carbidopa. These studies include:

### **Selegiline:**

The objective of this study was to investigate the effect of selegiline on the PK and PD of levodopa/benserazide and entacapone. In this study, 12 patients (7M/5F) stabilized on levodopa/benserazide for about one month were enrolled. It was placebo controlled, crossover, with regard of selegiline/placebo treatments; 200 mg dose of entacapone administered concomitantly with each dose of levodopa/benserazide (200/50 mg) for 14 days, and 10 mg single dose of selegiline or placebo.

### **Moclobemide:**

Moclobemide is an MAO inhibitor marketed in Europe. The objective of this study was to investigate the possible synergistic effect of entacapone and moclobemide on the hemodynamics and catecholamine metabolism. This was a placebo-controlled, crossover study with single 200 mg dose of entacapone and 150 mg of moclobemide in 12 healthy male subjects.

### **Imipramine:**

The objective of this study was to investigate the effect of imipramine on the PK and PD of entacapone. This was a placebo controlled, crossover study with 200 mg single dose of entacapone and 25 mg dose of imipramine given to 12 healthy female subjects.

### **Isoprenaline and Adrenaline:**

The objective of this study was to investigate the effect of entacapone on the metabolism of isoprenaline (marketed in Europe) after intravenous infusion. This was a crossover design, placebo controlled study with single 400 mg dose entacapone in 12 healthy subjects. Isoprenaline or adrenaline infusions were started 30 minutes after entacapone administration. Four dose levels of infusions were given with each dose level for 5 minutes. Thus, the total duration of infusion is 20 minutes. The dose levels given were 1.5, 3, 6, and 12 ug/min for adrenaline and 0.5, 1, 1.5 and 2 ug/min for isoprenaline.



### Results of Interaction Studies:

As indicated above, levodopa/carbidopa was not administered in these studies (except for selegiline).

1. In selegiline and imipramine studies, no significant effects were noted on the PK and/or the PD of entacapone.
2. Another noticeable drug interaction was the effect of moclobemide, an MAO inhibitor marketed in Europe, on endogenous catecholamine metabolites: 3,4-dihydroxyphenylethylene glycol (DHPG), 3,4-dihydroxyphenylacetic acid (DOPAC), and 3-methoxy-4-hydroxyphenylethylene glycol (MHPG). Overall, the plasma levels of these metabolites were about [redacted] when moclobemide was co-administered with entacapone compared to entacapone alone. It should be noted that these metabolites are also levodopa metabolites (see Attachment 2). This suggests that moclobemide may also affect the metabolism of levodopa. However, as indicated above, levodopa/carbidopa was not administered in this study. Therefore, the effect of moclobemide on the fate of levodopa is unknown, especially after long term therapy.
3. In terms of entacapone/isoprenaline/adrenaline interactions study, there were significant changes in heart rates when entacapone was given with isoprenaline or adrenaline compared to placebo. The mean maximal changes in heart rate during infusion and elimination rate [redacted] were [redacted] higher when isoprenaline and adrenaline were co-administered with entacapone compared to placebo, respectively. The mean data were 26.9 beats/min, [redacted] beats/minute, when isoprenaline was co-administered with placebo and 39.5 beats/minute [redacted] when isoprenaline was co-administered with entacapone. The mean data for adrenaline were 13.8 beats/min, [redacted] when adrenaline was co-administered with placebo and 25.1 beats/minute [redacted] when adrenaline was co-administered with entacapone.

This was a hemodynamic study to investigate the effect of entacapone on the metabolism of isoprenaline and adrenaline. The former drug is marketed in Europe. COMT is responsible for the metabolism of isoprenaline and adrenaline. Intravenous isoprenaline or adrenaline are usually given in emergency situations. The relevance of this study can also be extended to those patients on isoprenaline or adrenaline inhalers who are also taking entacapone-levodopa/carbidopa combination. The inhibition of COMT by entacapone may increase the level of isoprenaline and adrenaline by increasing their systemic bioavailability from the lungs. Based on the limited data from this study, it appears that entacapone may potentiate the cardiovascular effects of isoprenaline and

adrenaline. Therefore, caution should be exercised when entacapone is given with isoprenaline, adrenaline and other related drugs. Further study would be of interest in a larger group of subjects after IV administration of isoprenaline and adrenaline and in another group using inhalers of these two medications.

### **Special Population Studies:**

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#### ***Hepatic Impairment:***

A single oral 200 mg dose study was conducted in ten hepatic impaired patients and ten healthy subjects. In this study there was about 2 fold increase in the AUC and C<sub>max</sub> of entacapone and its z-isomer in liver impairment patients compared to normals. In terms of urine data, there was a dramatic, about [ ] increase in entacapone amount and the percentage of dose excreted in urine in liver impairment patients compared to healthy subjects. A similar trend, but to lesser extent, was also noted for z-isomer metabolites. The effect could be even higher after multiple dose administration. Nevertheless, based on the data from this study, dose adjustment is necessary in liver impairment patients. This could be performed on the basis of individual patient needs by increasing the dosing interval.

#### ***Renal Impairment:***

A single oral 200 mg dose study was conducted in 10 renally impaired patients and ten healthy subjects. There was no difference in the AUCs of entacapone or its z-isomer between the groups. It should be noted that the C<sub>max</sub> in the Moderate group was about twice higher than the Severe group and similarly about [ ] than healthy subjects. It should be noted that renal elimination of this drug is not the major route of elimination. Thus, based on the data from this study, dose adjustment is not necessary in renal impaired patients. However, the study was conducted after a single dose and the effects are unknown after multiple doses and long term therapy in this group of patients.

#### ***Age and Gender Effects:***

After a single 200 mg dose in 15 healthy young (20-24 years) and 16 healthy elderly (64-76 years) subjects, the data clearly demonstrate that there were no PK or PD differences between the groups. Again, multiple dose study is more appropriate in elderly, the target patient population, who will be taking this drug for long term therapy.

#### **Pharmacodynamics:**

1. There were PK/PD relationship between entacapone dose and/or concentration and the

plasma levels of levodopa, 3-OMD, and COMT which are shown in Attachments 7-12. It should be noted that, the maximum response for levodopa, 3-OMD, and COMT corresponds well with entacapone plasma Cmax. The data shown in these attachments are as expected from the enzyme inhibition kinetics.

2. It appears that entacapone reduces the secretion of the growth hormone by about 50% compared to the placebo (study # 293909). However, levodopa/carbidopa causes about [redacted] in the Cmax and AUC of growth hormone compared to placebo. The co-administration of entacapone with levodopa/carbidopa was not associated with further increase in growth hormone.
3. The effect of entacapone on prolactin data seems to be negligible. However, levodopa/carbidopa with entacapone treatment reduces Cmin [redacted] relative to placebo (study # 293909). Similar to growth hormone, the co-administration of entacapone with levodopa/carbidopa was not associated with further decrease in prolactin secretion.

### **Clinical Response (see also Comments to Clinical Division):**

In several clinical pharmacology studies, clinical responses were conducted to assess the motor functions in small patient population (n= 20-25). Two main placebo controlled studies were conducted, one at single entacapone doses of 50, 100, 200 and 400 mg concurrently with levodopa/DDC inhibitors (study # 293926) and another a 4 week study at 200 mg entacapone doses given up to 10 times daily concurrently with levodopa/DDC inhibitors (study # 293930).

Overall, there were some statistically significant data compared to placebo and among doses. However, the clinical significance of these data remains to be established by the efficacy team in the large clinical studies. Overall, there were little or no relationship between entacapone doses and the following clinical responses.

- i. ON time modified total score: Overall, the total duration of "ON time" was about 30 minutes longer at 200mg and 400 mg doses compared to control (levodopa/carbidopa alone) and placebo (levodopa/carbidopa with placebo). See Attachments 3 and 4.
- ii. Mean modified total motor scores: As shown in Attachment 5, there was no separation among doses. However, the recovery appears to be slower at 200 mg and 400 mg doses compared to placebo.
- iii. Dyskinesia scores: Similar to motor scores, there was no separation among doses. However, the recovery was more rapid after placebo compared to 200 mg and 400

mg doses (Attachment 6).

- iv. Starting time of clinical response.
- v. Magnitude of clinical response.
- vi. Tapping test scores.
- vii. Walking test scores.

APPEARS THIS WAY  
ON ORIGINAL

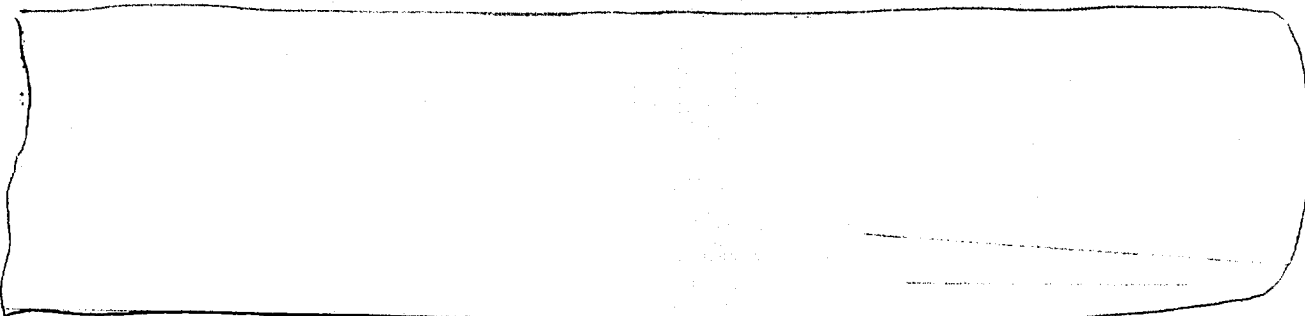
**Safety:**

Based on the limited data that have been reviewed from Clinical Pharmacology and Biopharmaceutics studies, the drug appears to be relatively safe. The common ADRs are dyskinesia and orthostatic hypotension.

**Formulation Links:**

APPEARS THIS WAY  
ON ORIGINAL

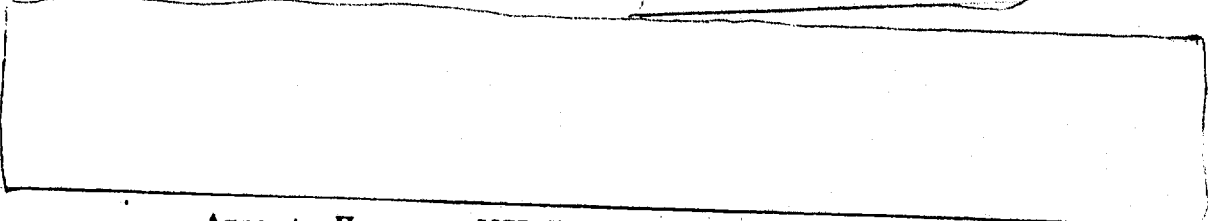
Only 200 mg tablet strength will be marketed for this drug. Bioequivalence studies were not required in this NDA, because there were no major formulation changes during the clinical program. In early Phase I and II studies the 100 mg tablets were used. In later Phase I and II studies and all Phase III studies entacapone 200 mg tablet was used. In addition, in tolerability, safety and dose-response studies, other tablet strengths (5, 25, and 50 mg) were used. The difference between the composition of the 200 mg tablet (formulation # 200-54) used in the major Phase III studies and the to-be-marketed formulation # 200-55 which was also used in Phase III clinical studies, is in the presence or absence of red iron oxide and small difference in the amount of yellow iron oxide



**Dissolution:**

Only 200 mg strength tablet is the proposed to be marketed for this drug [redacted] # XF001-02, formulation # 200-55). The sponsor would like to adopt the following dissolution methodology (Appendix III):

Apparatus II: USP (Paddles)  
Speed: [redacted]  
Medium: [redacted]  
Sampling times: [redacted]  
Specifications: Not less than [redacted]



Apparatus II: USP (Paddles)  
Speed: [redacted]  
Medium: [redacted]  
Sampling times: [redacted]  
Specifications: Not less than [redacted]

ClinPharm/Biopharm Briefing on: November 4, 1998.

Reviewed by:

[redacted] /S/

November 9, 1998

Sayed Al-Habet, Ph.D.  
Office of Clinical Pharmacology and Biopharmaceutics  
Division of Pharmaceutical Evaluation I

RD/FT initialed by Raman Baweja, Ph.D.

[redacted] /S/ 11/10/98

cc: NDA # 20-796 (Orig.), HFD-120, HFD-860 (Al-Habet, Baweja, Mehta), HFD-19 (FOI), and Drug files (Barbara Murphy, CDR).