CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 020796

Trade Name: COMTAN TABLETS 200 MG.

Generic Name: ENTACAPONE

Sponsor: ORION COPORATION

Approval Date: 12/30/99

INDICATION(s): AS AN ADJUNCT TO LEVODOPA/CARBIDOPA TO TREAT PATIENTS WITH IDIOPATHIC PARKINSON'S DISEASE WHO EXPERIENCE THE SIGNS AND SYMPTOMS OF END OF DOSE "WEARING-OFF".

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
ADDENDUM TO STUDY REPORT
NDA 20-796
Comtan (entacapone)

Sponsor: Target Research Associates, Scotch Plains, NJ for Orion Corporation, Espoo, Finland
Reviewer: Paul Roney
Date: August 6, 1999

Background

As part of their initial NDA submission, the sponsors submitted a two year carcinogenicity assay in mice. In this study, the mice were given 0, 0, 20, 100, 600 mg/kg/day by gavage. High mortality was observed at the high doses in males and females. Only the high and mid-dose female groups and the high dose male group were examined histopathologically. In addition, only one of the two control groups was examined. No significant histophatology findings were observed at 100 mg/kg. Dr. Steele reviewed this study in his NDA review (see Appendix 1). He expressed concern about the adequacy of the doses used. He noted that a 13 week dose range finding study (in which mice were given 20, 200, 300 (raised to 600 mg/kg during week 8), and 400 mg/kg) provided no useful toxicity information for carcinogenicity study dosage selection. A very limited histopathological analysis of a few tissues revealed no significant findings and no effects were noted on body weight. The carcinogenicity study was submitted to the Executive CAC committee on November 24, 1998. In their recommendations, the committee stated:

> **Demonstration of an adequate, negative study in the mouse is essential to appropriately assess the human carcinogenic risk of entacapone. The validity of the mouse carcinogenicity study was questionable because of inadequate survival at the HD, the large spread in dose (based on nominal dose) between the HD and MD, the absence of data to support the MD as an appropriate "back-up" dose, and the absence of a full histopathological analyses, particularly MD males. For the study to be considered acceptable, the committee recommends that the sponsor should provide evidence of saturation of absorption of entacapone based on systemic exposure to entacapone and its major metabolites at the MD of 100 mg/kg/day in a short dose-ranging study, and complete the histopathological analyses of all animals.**

In his review of Comtan, Dr. Steele recommended against approval based on the lack of an adequate mouse carcinogenicity study. In her review of the NDA review, Dr. Fitzgerald, the Pharmacology Team Leader, stated that the application was approvable provided that sponsor undertook studies to validate the mouse carcinogenicity study during the early Phase 4 period. Her reasons for not requiring the complete information prior to approval were based on the demonstrated clinical efficacy of Comtam and the fact that Comtan would be the only drug acting by this mechanism of action which would be widely available. In the action letter sent to the company on December 31, 1998, the FDA stated:

...we request that you initiate studies as soon as possible in an attempt to validate the mouse study: We would prefer that the results of these studies be submitted as a

component of your response to this action letter; however, as an alternative, we ask that you make a commitment for submission of the results in Phase 4. These studies should include the following: 1) a study that provides evidence of saturation of absorption of Comtan, based on systemic exposure to Comtan and its major metabolites, at the middle dose of 100 mg/kg and 2) a complete histopathological analysis of all animals in the mouse carcinogenicity study. Alternatively, you could elect to try to demonstrate in a 3-month study that 100 mg/kg is at least one half of the maximum tolerated dose.

If you fail to validate the mouse study it will be necessary for you to then commit to conducting a Phase 4 repeat bioassay, or possibly an alternative mouse assay.

In their response of April 16, 1999, the sponsor submitted data suggesting that the 100 mg/kg dose was approximately the half the MTD on a AUC basis and that the mortality of the high dose male mice was not excessive. Dr. Roney reviewed these data in his memo of May 24, 1999 (Appendix 2). In this memo, he concluded that the available data did not support saturation of absorption for Comtan at 600 mg/kg. In addition, based on criteria used by the CAC and the Office of Science and Technology Policy, the mortality in the high dose males was unacceptably high. Dr. Roney noted that requested histopathology data had not been submitted. The histopathology data were submitted on May 24, 1999 and received by the FDA on May 25, 1999. This report reviews the results of these low dose groups.

Review

Dr Steele's review of the original carcinogenicity is included as Appendix 1. Dr Steele examined mortality, body weight changes, food consumption, gross pathology, organ weight, and the available histopathology data (1 set of controls, high dose (600 mg/kg) males and middle and high dose females (100 and 600 mg/kg, respectively)). In his review, the primary toxicologic effect was early mortality in the 600 mg/kg groups. No treatment-related cause of death was established to account for the early deaths. In addition, no treatment related effects were observed on body weight, food consumption, organ weights or gross necropsy.

In the present submission, it is stated that the methods were identical to those used in the original study. A complete list of tissues examined histopathologically is provided below. In general, there was good agreement between the results of the two studies. This suggests that the pathological evaluation method was similar in both analyses. The results of the re-evaluation can be combined with the results of the original study.

The incidence of tumors in the 20 mg/kg male group was increased (45 vs 38 and 35 tumors for the two control groups). This increase can be primarily attributed to an increase in the number of benign neoplasms in the low dose males (26 vs 20 and 17 for controls), although there was a slight increase in malignant neoplasms (19 vs 18 and 18 for controls). On the other hand, the number of tumors in the 100 mg/kg group was lower than control values (28 vs 38 and 35 for controls). This suggests that there is no association between exposure of comtan to male mice and incidence of tumor development. There was a small increased in the incidence of malignant tumors in low dose females (23 vs 20 and 17 for controls); this was similar to the number of malignant tumors in 100 mg/kg females (22).

There were sporadic increases in tumor rates at isolated sites, but none of the increases were significant using the Fishers Exact Test. In addition, no apparent dose response relationship was observed between incidence of tumors and dose. A complete of list of tumor findings is presented in Table 1. The new data is highlighted in **Bold**.

The type, group distribution, and incidence of necropsy findings did not provide substantial evidence of a treatment-related effect. The only finding which a pattern of occurrence suggesting a potential treatment relationship was terminal lung congestion.

	0 mg/kg	0 mg/kg	20 mg/kg	100 mg/kg	600 mg/kg
Males	1/50	2/50	0/59	0/50	11/50
Females	1/50	1/50	1/50	3/50	21/50

The sponsor did not comment on this finding and its possible relationship to treatment. However, this type of finding is generally considered somewhat nonspecific in decedent animals. A listing of histopathological finding in which one or more of the results were significantly increased or appeared somewhat higher is provided in Table 2.

Conclusion

This submission is part of an attempt to validate the mouse carcinogenicity study. In the action letter, the FDA stated that in order to validate the study, it would be necessary to demonstrate that either (1) absorption was saturated at doses above 100 mg/kg or (2) 100 mg/kg is an appropriate back up dose (ie, about half the MTD). In a previous submission, the sponsor failed to demonstrate that absorption of Comtan occurred at doses higher than 100 mg/kg. In this submission, 100 mg/kg did not cause any noticeable histopathological alterations. No significant increases in neoplastic, or non-neoplastic alterations were observed. In addition, the results of a 13 week range finding study suggested that mice can tolerate doses as high as 400 mg/kg for 13 weeks. Thus, 100 mg/kg appears to be less the half the maximum tolerated dose. As a result, the mouse carcinogenicity study has not been validated.

/S/

Paul L. Roney, Ph.D.

cc: / Division File, HFD-120
/ G. Fitzgerald, Ph.D.
/ T. Wheelous
/ P. Roney, Ph.D.

Signed /S/ 9/21/98

Addendum 1

Histopathology Inventory for Mouse Carcinogenicity Study (NDA 20-796)

Study	1353
Species	Mouse
Adrenals	✓
Aorta	✓
Bone Marrow smear	
Bone (femur)	
Brain	✓
Cecum	✓
Cervix	
Colon	✓
Duodenum	✓
Epididymis	✓
Esophagus	✓
Eye	✓
Fallopian tube	
Gall bladder	✓
Gross lesions	✓
Harderian gland	
Heart	✓
Hyphophysis	
Ileum	✓
Injection site	
Jejunum	✓
Kidneys	✓
Lachrymal gland	
Larynx	
Liver	✓
Lungs	✓
Lymph nodes, cervical	
Lymph nodes mandibular	✓
Lymph nodes, mesenteric	✓
Mammary Gland	✓
Nasal cavity	
Optic nerves	✓
Ovaries	✓
Pancreas	✓
Parathyroid	✓
Peripheral nerve	
Pharynx	
Pituitary	✓
Prostate	✓
Rectum	✓
Salivary gland	
Sciatic nerve	✓
Seminal vesicles	✓
Skeletal muscle	✓
Skin	✓
Spinal cord	✓
Spleen	✓
Sternum	✓
Stomach	✓
Testes	✓
Thymus	✓
Thyroid	✓
Tongue	✓
Trachea	✓
Urinary bladder	✓
Uterus	✓
Vagina	✓
Zymbal gland	

Table 1. Incidence of Neoplastic Lesions in Comtan Mouse Carcinogenicity Study

Tumors Findings	Males					Females				
	0 mg/kg	0 mg/kg	20 mg/kg	100 mg/kg	600 mg/kg	0 mg/kg	0 mg/kg	20 mg/kg	100 mg/kg	600 mg/kg
Animals with Tumors	30/50	28/50	32/50	22/50	16/50	24/50	25/50	28/50	24/50	7/50
Animals with Single Tumors	23/50	22/50	21/50	16/50	13/50	16/50	22/50	24/50	17/50	6/50
Animals with Multiple Tumors	7/50	6/50	11/50	6/50	3/50	8/50	3/50	4/50	7/50	1/50
Animals with Benign Tumors	17/50	15/50	19/50	12/50	9/50	10/50	10/50	9/50	8/50	2/50
Animals with Malignant Tumors	17/50	16/50	16/50	11/50	8/50	18/50	17/50	23/50	20/50	6/50
Total Tumors	38	35	45	28	19	33	28	32	31	8
Total Benign Tumors	20	17	26	16	10	13	11	9	9	2
Total Malignant Tumors	18	18	19	12	9	20	17	23	22	6
Abdomen: Osteosarcoma	-	0/1	-	1/1	-	-	-	-	-	-
Adrenal: Pheochromocytoma	0/49	0/50	0/48	0/49	0/49	0/49	0/50	1/50	1/50	0/49
Adrenal: Spindle Cell Adenoma	0/49	1/50	0/48	0/49	0/49	0/49	1/50	0/50	0/50	0/49
Brain: Astrocytoma	0/50	1/50	0/49	0/50	0/50	1/50	1/50	0/50	0/50	0/50
Cervix: Leiomyoma	-	-	-	-	-	-	-	1/1	-	-
Colon: Adenocarcinoma	0/50	0/50	0/49	0/50	0/50	0/50	0/50	0/50	1/50	0/50
Harderian Gland: Adenoma	1/2	0/1	2/2	-	-	1/1	-	-	-	-
Kidney: Adenoma	1/50	0/50	1/50	1/50	0/50	1/50	0/50	0/50	0/50	0/50
Kidney: Carcinoma	0/50	1/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50
Liver: Hepatocellular Adenoma	11/50	6/50	8/49	5/50	7/50	1/50	0/50	0/50	0/50	1/50
Liver: Hemangioma	0/50	0/50	1/49	0/50	0/50	0/50	0/50	0/50	0/50	0/50
Lung: Alveolar/Bronchiolar Adenoma	4/50	8/50	7/49	4/50	1/50	3/50	2/50	1/50	3/50	0/50
Lung: Alveolar/Bronchiolar Carcinoma	6/50	7/50	7/49	2/50	3/50	2/50	2/50	4/50	3/50	2/50
Lymphoreticular/Hemopoietic Tissue: Histiocytic Sarcoma	0/3	0/1	1/6	0/1	0/1	2/7	0/6	2/9	0/7	0/2

Tumors Findings	Males					Females				
	0 mg/kg	0 mg/kg	20 mg/kg	100 mg/kg	600 mg/kg	0 mg/kg	0 mg/kg	20 mg/kg	100 mg/kg	600 mg/kg
Lymphoreticular/Hemopoietic Tissue: Granulocytic Leukemia	0/3	0/1	0/6	0/1	1/1	0/7	0/6	0/9	0/7	0/2
Lymphoreticular/Hemopoietic Tissue: Lymphoma	3/3	1/1	5/6	1/1	0/1	5/7	6/6	7/9	7/7	2/2
Mammary Gland: Carcinoma Multiple	0/50	0/50	0/49	0/50	0/50	1/50	0/50	0/50	0/50	0/50
Mammary Gland: Carcinoma	0/50	0/50	0/49	0/50	0/50	0/50	4/50	5/50	0/50	0/50
Mammary Gland: Adenoma	0/50	0/50	0/49	0/50	0/50	0/50	0/50	1/50	1/50	0/50
Ovary: Adenoma	-	-	-	-	-	0/50	1/50	0/50	0/50	0/50
Ovary: Carcinoma	-	-	-	-	-	1/50	0/50	0/50	0/50	0/50
Ovary: Granulosa Cell Tumor	-	-	-	-	-	0/50	0/50	0/50	1/50	0/50
Pituitary Gland: Adenoma	0/48	0/46	0/46	1/47	0/46	1/49	0/50	0/50	0/47	0/47
Salivary Gland: Carcinoma	0/50	0/50	0/49	0/50	0/50	1/49	0/50	0/50	0/50	0/50
Skin and Subcutis: Sarcoma	0/50	0/50	0/49	1/50	1/50	2/50	1/50	2/50	1/50	0/50
Spinal Cord: Astrocytoma	0/50	1/50	0/49	0/50	0/50	0/50	0/50	0/49	0/50	0/50
Spleen: Hemangioma	1/50	0/50	0/49	0/50	1/50	0/50	0/50	0/50	1/50	1/50
Stomach: Squamous Cell Carcinoma	0/50	0/50	0/49	1/50	0/50	0/49	0/50	0/50	0/50	0/50
Testis: Interstitial Cell Adenoma	2/50	1/50	5/49	3/50	1/50	-	-	-	-	-
Testis: Hemangioma	0/50	0/50	0/49	2/50	0/50	-	-	-	-	-
Thymus: Sarcoma	0/49	0/47	0/46	0/43	1/46	0/48	0/48	0/50	0/47	0/49
Thyroid Gland: Follicular Adenoma	0/50	0/49	2/44	0/49	0/50	0/50	0/49	0/50	0/49	0/49
Urinary Bladder: Transitional Cell Adenoma	0/50	0/50	0/49	0/50	0/50	1/50	0/50	0/50	0/50	0/50

Tumors Findings	Males					Females				
	0 mg/kg	0 mg/kg	20 mg/kg	100 mg/kg	600 mg/kg	0 mg/kg	0 mg/kg	20 mg/kg	100 mg/kg	600 mg/kg
Urinary Bladder: Hemangiopericytoma	0/50	0/50	0/49	0/50	0/50	0/50	0/50	1/50	0/50	1/49
Uterus: Leiomyoma	-	-	-	-	-	3/50	5/50	4/50	2/50	0/50
Uterus: Hemangioma	-	-	-	-	-	0/50	1/50	0/50	1/50	0/50
Uterus: Leiomyosarcoma	-	-	-	-	-	3/50	1/50	2/50	6/50	1/50
Vagina: Leiomyoma	-	-	-	-	-	1/50	1/50	0/50	0/50	0/50
Vagina: Adenoma	-	-	-	-	-	1/50	0/50	0/50	0/50	0/50
Vascular System: Hemangiosarcoma	3/3	2/2	-	-	1/1	2/2	-	-	2/2	-

Table 2. Incidence of Non-Neoplastic Lesions in Comtan Mouse Carcinogenicity Study

Histopathology Findings	Males					Females				
	0 mg/kg	0 mg/kg	20 mg/kg	100 mg/kg	600 mg/kg	0 mg/kg	0 mg/kg	20 mg/kg	100 mg/kg	600 mg/kg
Brain: Focal Mineralization	13/50	14/50	16/49	19/50	8/50	8/50	7/50	5/50	6/50	2/50
Brain: Status spongiosis	0/50	0/50	0/50	0/50	0/50	0/50	0/50	6/50*	1/50	0/50
Heart: Epicarditis	2/50	1/50	0/49	5/50	0/50	2/50	0/50	1/50	1/50	0/50
Ileum: Amyloid	3/50	5/50	10/49	1/49	2/50	2/50	2/50	3/50	3/50	6/50
Jejunum: Amyloid	0/50	2/50	5/49	1/50	0/50	0/50	2/50	1/50	2/50	3/50
Kidney: Lymphocytic infiltration	0/50	1/50	1/50	3/50	0/50	0/50	5/50	6/50*	5/50	1/50
Lung: Terminal hemorrhage	1/50	1/50	3/49	6/50	6/50	3/50	1/50	1/50	0/50	5/50
Lung: Terminal congestion	1/50	2/50	0/49	0/50	11/50*	1/50	1/50	1/50	3/50	21/50*