3 pages
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LABELING

RECOMMENDATIONS

To the Medical Team:

1. The NDA is not approvable because of the absence of a valid mouse carcinogenicity study.

To the Sponsor:

1. The validity of the current mouse carcinogenicity may be established by demonstrating that the MD of 100 mg/kg is an acceptable challenge for tumorigenicity assessments. The males of this group must be evaluated histopathologically. Alternatively, a short-term mouse model could be considered.

2. Additional data should be provide to support the involvement of alpha$_2$ microglobulin in renal tumorigenesis. These data should address the discrepancies between the experimental findings and the established criteria for compounds that are thought to act via alpha$_2$ microglobulin deposition.

3. A more descriptive characterization of chronic progressive nephropathy in the one-year rat study should be submitted to determine if the findings should be included in labeling.

/S/

Thomas D. Steele, Ph.D.
Pharmacologist/Toxicologist

Original NDA 20796
cc.: /Division File, HFD-120
/G. Fitzgerald, Ph.D. /S/ 12/21/98 See T.L. memo
/R. Tresley, M.D.
/T. Wheelous, R.Ph.
/T. Steele, Ph.D.

Appendix 1

Agency Statistical Analysis

Steele

RECEIVED NOV 30 1998

Statistical Review and Evaluation

Review of Carcinogenicity Data

NOV 25 1998

NDA#: 20-796

APPLICANT: Orion Corporation

NAME OF DRUG: COMTAN (entacapone)

DOCUMENTS REVIEWED: Volumes 1.26 - 1.30 Containing the Mouse and Rat Studies and One Volume from Target Research Associates Containing the Diskettes, Dated Dec. 5, 1997.

PHARMACOLOGY REVIEWER: Tom Steele, Ph.D. (HFD-120)

I. Background

Dr. Steele requested from the Division of Biometrics I a statistical review of the mouse and rat studies data as well as an evaluation of the sponsor's reports.

II. The Mouse Study

II.1 Sponsor's Findings

In this study, 50 CD-1 mice per treatment group per sex received entacapone via gavage at dose levels of 0, 0, 20, 100, and 600 mg/kg/day for two years. The control animals received the vehicle only. Terminal sacrifice started at day 728 for all males and all females, except for the High Dose (HD) females which were terminated during week 95 due to high mortality. All animals dying prematurely and all terminally sacrificed (TS) animals of Control I and HD of both sexes were evaluated histologically. Due to the early termination of the HD females, the TS mid dose females were also histologically evaluated.

The sponsor made pair-wise comparisons using the Wilcoxon rank sum test modified for censored survival data to test for differences in survival of the treatment groups. The comparison with the combined controls showed statistically significantly ($p<0.001$) higher mortality for the HD groups of both sexes. The excess deaths were seen during the first year of the study.

The sponsor used Fisher's Exact Test to test histology and tumor data. The observed findings were considered typical of aging mice of this strain and none of the neoplastic findings were considered attributable to the administration of the drug in either sex.

II.2 Reviewer's Findings

As trend tests are usually more powerful than pair-wise comparisons, this reviewer performed Cox and the Kruskal-Wallis tests for survival data. The results for the male mice were highly statistically significant ($p=0.0000$) (Table 1). The Kaplan-Meier survival graph clearly shows the early and sustained increased mortality of the high dose group compared to any of the other groups (Figure 1). All pair-wise comparisons with the high dose group were also statistically significant ($0.0000 < p < 0.00258$), but none of the remaining pair-wise comparisons reached statistical significance. For the female mice, mortality was even more extreme in the high dose group (Table 1, Figure 2). By the end of the first year, 52 percent of the females had died and this arm was terminated at week 95 . All pair-wise comparisons with the high dose were also highly statistically significant ($p=0.0000$).

This reviewer's analyses produced occasionally different tumor incidences than the sponsor, but these discrepancies had no effect on the conclusions. As TS animals of the low and mid doses were not examined histopathologically, only pair-wise comparisons between the control and HD animals are appropriate. The sponsor's use of Fishers Exact test addresses this aspect of the study design, but it does not adjust for intercurrent mortality. However, the overall incidences were such that this reviewer agreed with the sponsor's conclusions after having re-analyzed some of the tumor incidences where statistical

aspect of the study design, but it does not adjust for intercurrent mortality. However, the overall incidences were such that this reviewer agreed with the sponsor's conclusions after having re-analyzed some of the tumor incidences where statistical significance might have been possible. These suspicions were not confirmed. Due to the extreme mortality in the high dose females, the TS mid dose animals were fully examined. The comparison of the control 1 and the mid dose animals did not yield statistically significant tumor findings.

II.3 Validity of the Mouse Study

As there were no statistically significant (positive) trends in tumors among either the male or female mice, the validity of the two study arms needs to be evaluated. Two questions need to be answered (Haseman, Statistical Issues in the Design, Analysis and Interpretation of Animal Carcinogenicity Studies, Environmental Health Perspectives, Vol 58, pp 385-392, 1984):

(i) Were enough animals exposed for a sufficient length of time to allow for late developing tumors?

(ii) Were the dose levels high enough to pose a reasonable tumor challenge in the animals?

The following rules of thumb are suggested by experts in the field: Haseman (Issues in Carcinogenicity Testing: Dose Selection, Fundamental and Applied Toxicology, Vol5, pp 66-78, 19985) had found that on the average, approximately 50 % of the animals in the high dose group survived a two-year study. In a personal communication with Dr. Karl Lin (HFD-720), he suggested that 50 % survival of the usual 50 initial animals in the high dose group between weeks 80-90 would be considered a sufficient number and adequate exposure. Chu, Cueto, and Ward (Factors in the Evaluation of 200 National Cancer Institute Carcinogen Bioassays, Journal of Toxicology and Environmental Health, Vol 8, pp 251-280, 1981) proposed that 'To be considered adequate, an experiment that has not shown a chemical to be carcinogenic should have groups of animals with greater than 50 % survival at one year'. From these sources, it appears that the proportions of survival at weeks 52, 80-90, and at two years are of interest in determining the adequacy of exposure and number of animals at risk.

In determining the adequacy of the chosen dose levels, it is generally accepted that the high dose should be close to the MTD. Chu, Cueto, and Ward (1981) suggest:

(i) 'A dose is considered adequate if there is a detectable weight loss of up to 10 % in a dosed group relative to the controls'.

ii) 'The administered dose is also considered an MTD if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical'.

(iii) 'In addition, doses are considered adequate if the dosed animals show a slightly increased mortality compared to the controls'.

In another paper, Bart, Chu and Tarone (Statistical Issues in Interpretation of Chronic Bioassay Tests for Carcinogenicity, Journal of the National Cancer Institute 62, pp 957-974, 1979), stated that the mean body weight curves over the entire study period should be taken into consideration with the survival curves, when adequacy of dose levels is to be examined. In particular, 'Usually, the comparison should be limited to the early weeks of a study when no or little mortality has yet occurred in any of the groups. Here a depression of the mean weight in the treated groups is an indication that the treatment has been tested on levels at or approaching the MTD.'

The mortality of the high dose females was so extreme that this arm had to be terminated early, but more importantly, over half of the animals (52 %) died during the first year of their life, leaving insufficient numbers to show any late developing tumors. The mid dose was substituted to determine whether it could pose as the new high dose. Half of the MD animals survived through week 96 and 36 % survived till terminal sacrifice, leaving probably a sufficient number to manifest late developing tumors. The female controls experienced the same overall mortality as this dose. For the HD males, the mortality experience was not as extreme (38 % in the first year) as for the HD females. However, it was still sufficiently high to doubt that any late developing tumors could have manifested themselves (mortality 58% at week 80 and 64% at week 90).

It is noted that the sponsor concluded that there were no notable intergroup differences of average body weights for either sex. This reviewer considered the observed differences helpful in interpreting whether the HD (males) or MD (females) was close to the MTD. During the early weeks of the study, there were several occasions where the mid dose females actually weighed more than the controls. Starting from week 11 till week 88, however, the average weights of the mid dose animals were generally lower (by less than 10 percent) than the controls. The reduction in average weight is somewhat delayed, but may be sufficient to indicate that this dose was close to the MTD. The body weight curves for the males show a generally higher verage body weight for the high dose animals compared to the controls, therefore, giving no indication that the high dose could e considered close to the MTD (Figures 3 and 4).

The final decision on whether the mid dose (females) or the high dose (males) was close to the MTD is referred to the pharmacologist using clinical signs or severe histopathologic toxic effects attributable to these doses. As mentioned above, the reduced body weight of the mid dose females may be a sufficient enough finding to declare this dose as being close to the MTD, but none of the criteria supported the high dose (male mice) as being close to the MTD.

III. The Rat Study

III.1 Sponsor's Findings

This study was also conducted for 104 weeks in 50 animals per sex per treatment group. The treatment was administered via gavage at doses of 20, 90, and 400 mg/kg/day. The two control groups per sex received the vehicle alone.

The administration of the drug did not affect the survival of either sex.

All early deaths and the terminal sacrifice animals of Control group 1 and HD of either sex were fully histopathologically examined. With this design only pair-wise comparisons of tumor findings between C1 and HD are meaningful. For the female rats, no comparisons were found statistically significant. For the male rats, the sponsor found an increase in kidney tumors and subsequently the kidneys of all control 2, low, and mid dose animals were histopathologically examined. The sponsor observed that adenomas were statistically significantly higher in the high dose than in the controls ($p<0.05$). No other findings reached statistical significance.

III.2 Reviewer's Findings

The mortality experience of the male rats was similar across the treatment groups and no trend or pair-wise comparisons were statistically significant. For the females, there was some separation in survival curves which reached statistical significance ($p=0.0430$) only with the Kruskal/Wallis test, which weighs early deaths more heavily. The pair-wise Kruskal/Wallis test for HD versus controls was also statistically significant ($p=0.0192$) (Table 2, Figures 5 and 6).

This reviewer had encountered difficulties in reproducing some tumor incidences. In order to remove any doubts, a separate diskette with only the kidney findings for the male rats was requested. Analyzing these data produced the same overall incidences but found no low and mid dose animals during TS, implying that the findings for these animals were not included. Therefore, pair-wise comparisons between the controls and the high dose animals were performed. These results are somewhat biased towards significance, IF the second control group was not fully examined, which this reviewer suspects, but which is contrary to the sponsor's comments. As both adenomas and carcinomas occurred as incidental and as fatal tumors, the asymptotic p-values are the appropriate ones. Using mortality adjusted pair-wise permutation tests, the p-value for a significant increase in adenomas of the kidney in the high dose males compared to the controls, is 0.0051. The same test for the carcinomas has an associated p-value of 0.0270. Combining the two tumors, resulted in a p-value of 0.0006. From a statistical point of view, these findings are rare (less than one percent among the concurrent controls), but whether considered rare or common, they pass the statistical criterion of significance ($\alpha \leq 0.05$)

The sponsor apparently used the two-sided probability of the Fishers Exact test, instead of the one-sided one, which tests only whether the high dose has an increased incidence. Also, when using the Fishers Exact test no adjustment for intercurrent mortality is done. Using an exact permutation test gives the one-sided probability of an increase in tumor incidence in the high dose as well as an adjustment for intercurrent mortality. However, as mentioned above, as it would have been difficult to separate the two control groups, this reviewer's p-values are somewhat biased towards significance, IF the sponsor did not fully examine the kidneys of ALL male control rats.

As there were no significant tumor findings for the female rats, the validity of this study arm needs to be evaluated. Following the criteria outlined above, the number of animals surviving till terminal sacrifice (30 %) may be insufficient to show late developing tumors. However, this slightly increased mortality (controls had 42 % survival at TS) may support this dose as being close to the MTD. The sponsor reports a small but persistently lower average body weight for the high dose females, starting at week 16 and persisting till the end of the study (Figure 7). The evaluation of clinical signs and severe histophathological toxic effects is left to the expertise of the pharmacologist. From a statistical point of view, the reduced average body weights and the reduced survival of the high dose females may be sufficient to indicate that this dose was close to the MTD.

IV. Summary

For both the mice and rat studies, this reviewer found it very difficult to reproduce the sponsor's tumor findings. The data were submitted in the STUDIES format, which is acceptable, but which is difficult to deal with or to locate the source of discrepancies. The mortality findings seem to be identical to the sponsor's. The sponsor was requested to send a subset of the rat data, namely, the male rat kidney findings, and this subset could be easily analyzed and the hard copy numbers could be confirmed. However, it appears that the kidney findings of the second control group and of the low and medium dose groups were not included in these data sets. Due to time constraints, this problem will be investigated later. None of this reviewer's findings suggested possible tumor trends other than kidney adenomas and carcinomas in the male rats.

For the mouse study the major problem was the high mortality among both sexes, but especially among the females where the high dose was terminated at week 95. All mid dose females were then fully examined histopathologically and served as the new comparison group with the controls. For the male mice, tumor comparisons were made between the controls and the high dose animals. Neither the females nor the males showed a statistically significant increase in tumor incidences. Investigating whether the study arms were valid, this reviewer doubts that the number of males surviving till terminal sacrifice was sufficient to manifest any late developing tumors. Using the mid dose of the female group as the relevant one, survival was not affected by the drug treatment, leaving sufficient numbers of animals to live long enough to manifest potential late developing tumors. In trying to establish whether the high dose (males) or mid dose (females) was close to the MTD, it was found that the average body weights of the high dose males was higher than the controls, not an indication that this dose was close to the MTD. The average body weights of the mid dose females was suppressed, starting at about week 11. The evaluation of clinical signs and severe histopathologic toxic effects is left to the expertise of the pharmacologist to render the final decision whether the mid dose for the females can qualify as the MTD. From a statistical point of view, the HD males had insufficient numbers at the end of the study and the dose was not close to the MTD.

The rat study was basically identical to the mouse study, except that the doses were reduced. The high dose of 400 mg/kg/day did not have a detrimental effect on the survival of the males. For the females, one statistical test which weighs the early deaths more heavily found a statistically significant trend and pair-wise comparisons between high dose and controls. This reviewer found that the tumor findings (adenomas and carcinomas) of the kidney of the males were of higher statistical significance than the sponsor reported, probably due to the sponsor using a two-tailed probability and a test which did not adjust for intercurrent mortality. There were no statistically significant tumor findings among the females and the evaluation of the validity of this study arm suggests that the high dose was close to the MTD (reduced mortality and reported reduced average body weights) but the reduction in survival may have been sufficient to hamper the manifestation of late developing tumors.

/S/

Roswitha Kelly, M.S.

Mathematical Statistician

/S/

Kun Jin, Ph.D.

Team Leader

/S/

George Chi, Ph.D.

Director, Division of Biometrics 1

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Table 1: Mortality for Mice.

Females

Interval/Dose	0	20 mg	100 mg	600 mg
0 - 52	11	5	6	26
53- 78	20	10	6	14
79- 92	21	5	10	1
93-104	12	9	10	9*
Term. Sac.	36	21	18	—
Total	100	50	50	50

* Terminally sacrificed in week 95

Males

Interval/Dose	0	20 mg	100 mg	600 mg
0 - 52	10	3	7	19
53- 78	11	7	6	10
79- 92	13	5	5	3
93-104	14	8	5	3
Term. Sac.	52	27	27	15
Total	100	50	50	50

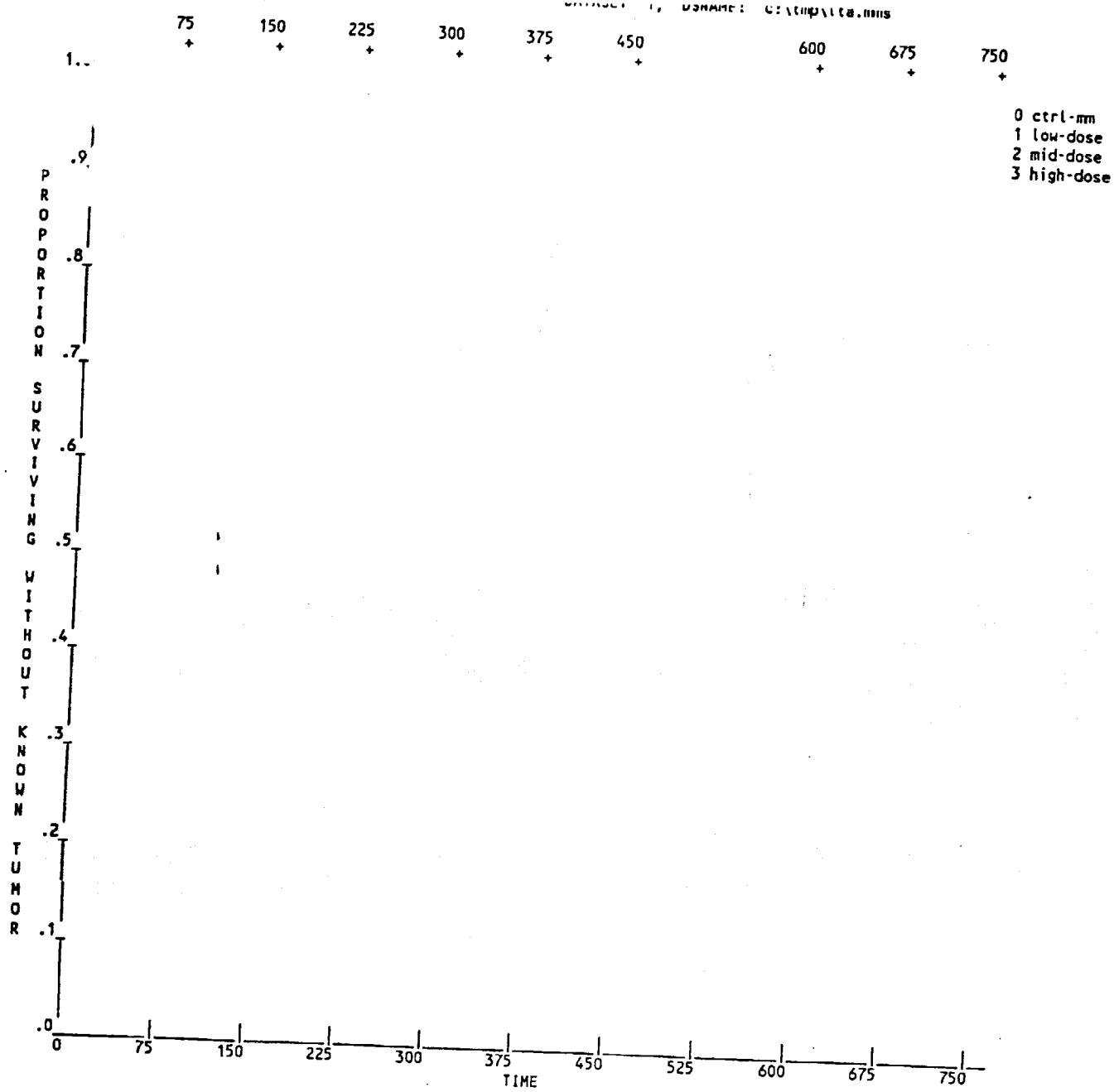


Figure 1: Male Mice

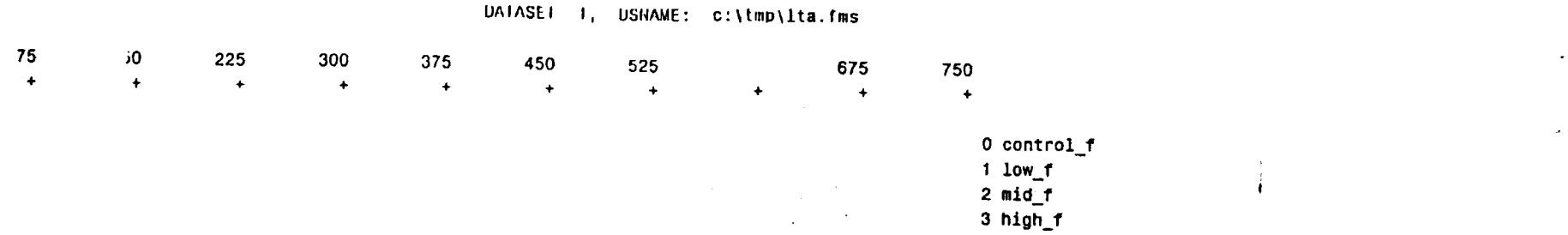
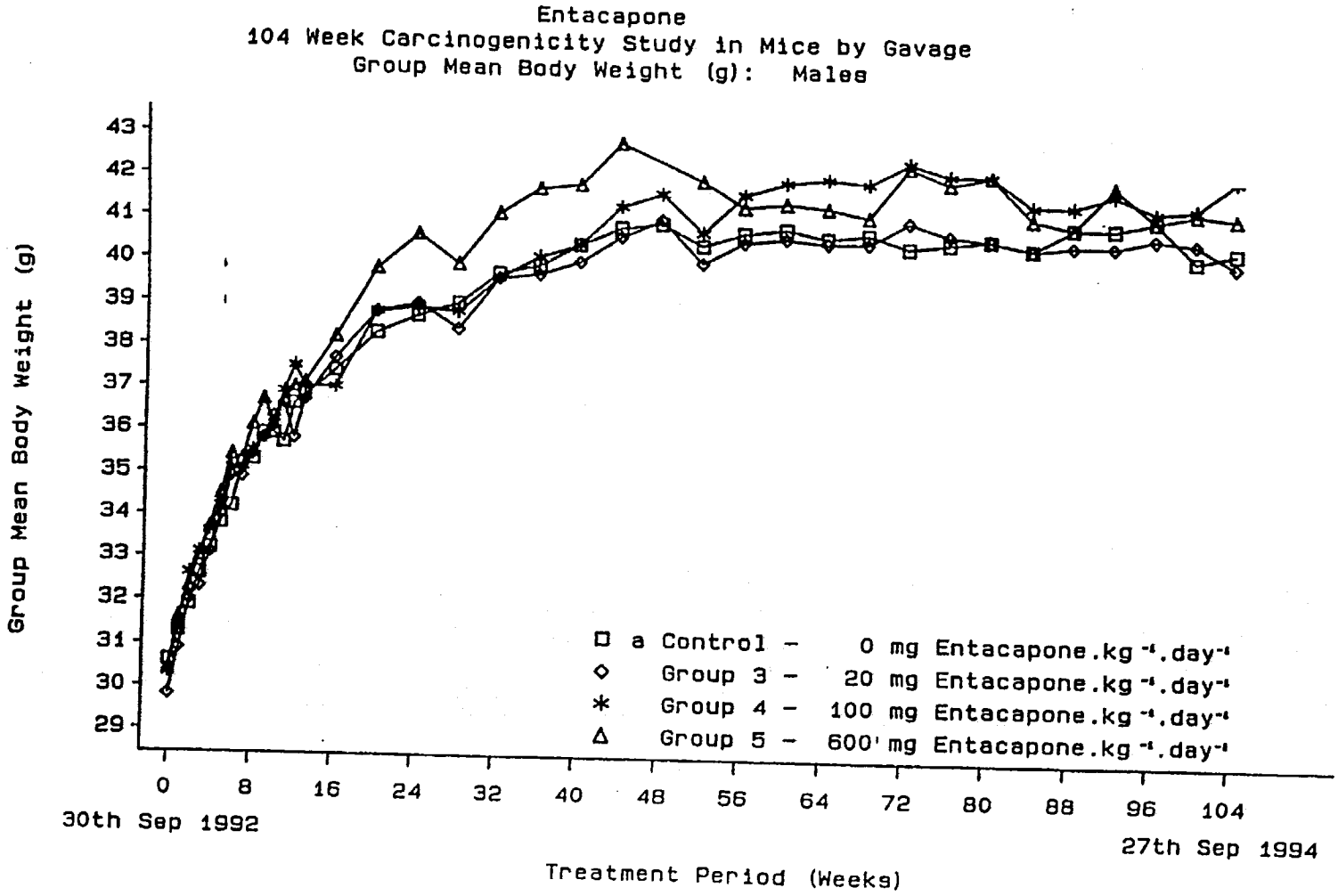


Figure 2: Female Mice

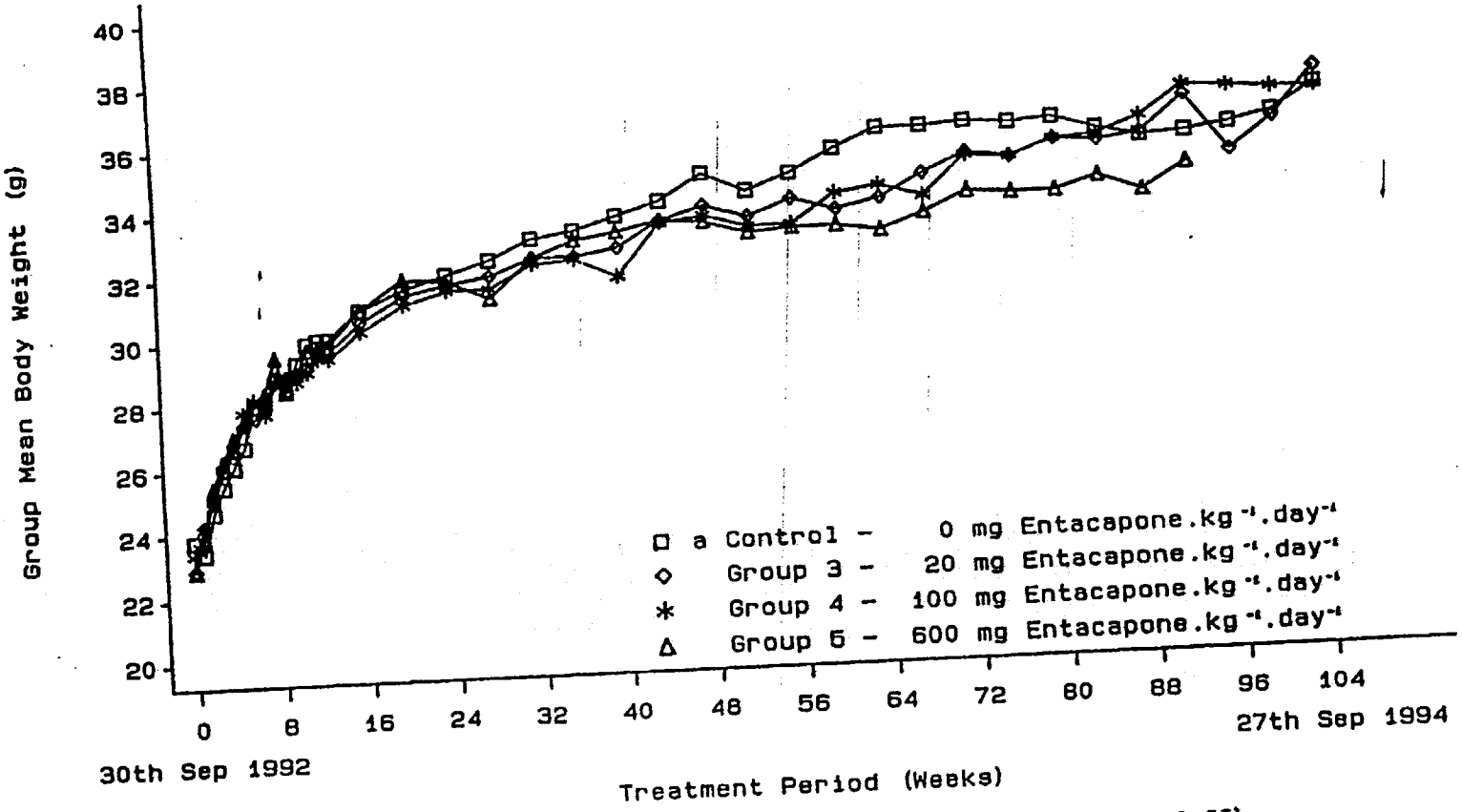
FIGURE 3



a = Values derived using the mean of group 1 (Control I) and Group 2 (Control II)

FIGURE 4

Entacapone
104 Week Carcinogenicity Study in Mice by Gavage
Group Mean Body Weight (g): Females



a = Values derived using the mean of group 1 (Control I) and Group 2 (Control II)

Table 2: Mortality for Rats

Females

Interval/Dose	0	20 mg	90 mg	400 mg
0 - 52	2	5	2	4
53- 78	20	12	11	15
79- 92	19	9	8	9
93-104	17	5	10	7
Term. Sac.	42	19	19	15
Total	100	50	50	50

Males

Interval/Dose	0	20 mg	90 mg	400 mg
0 - 52	10	5	10	4
53- 78	11	9	5	9
79- 92	20	8	9	13
93-104	19	10	8	7
Term. Sac.	40	18	18	17
Total	100	50	50	50

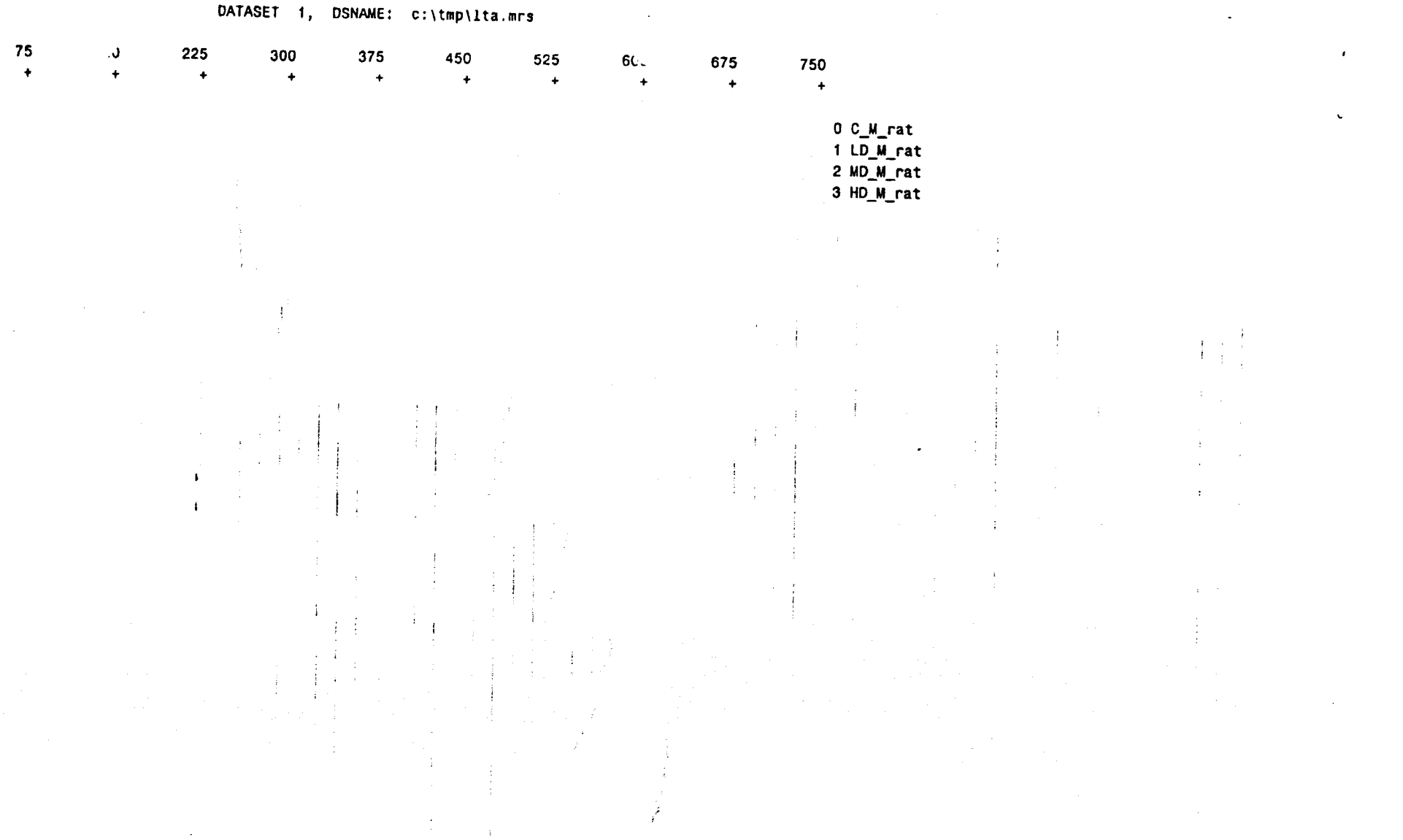


Figure 5: Male Rats

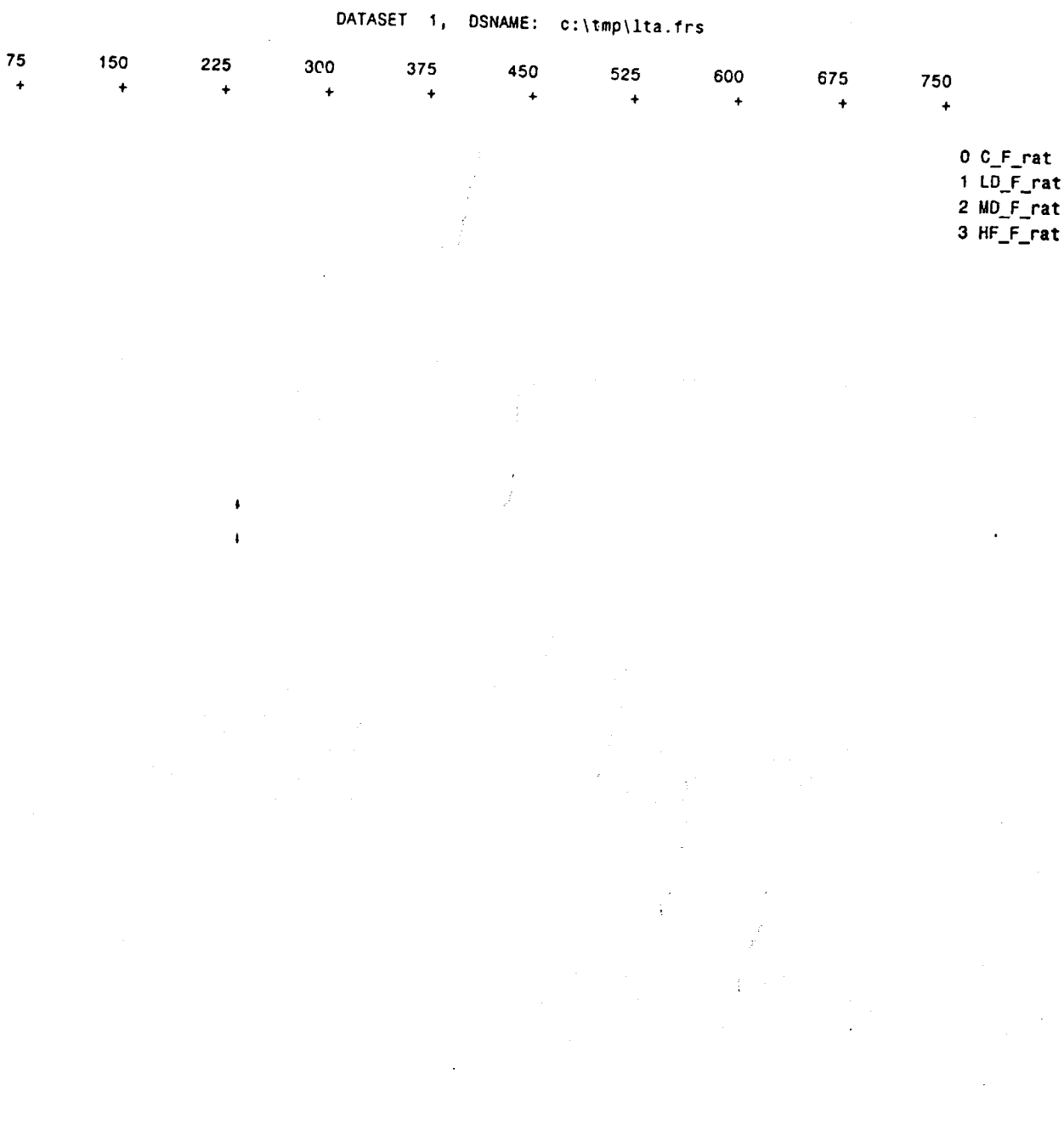
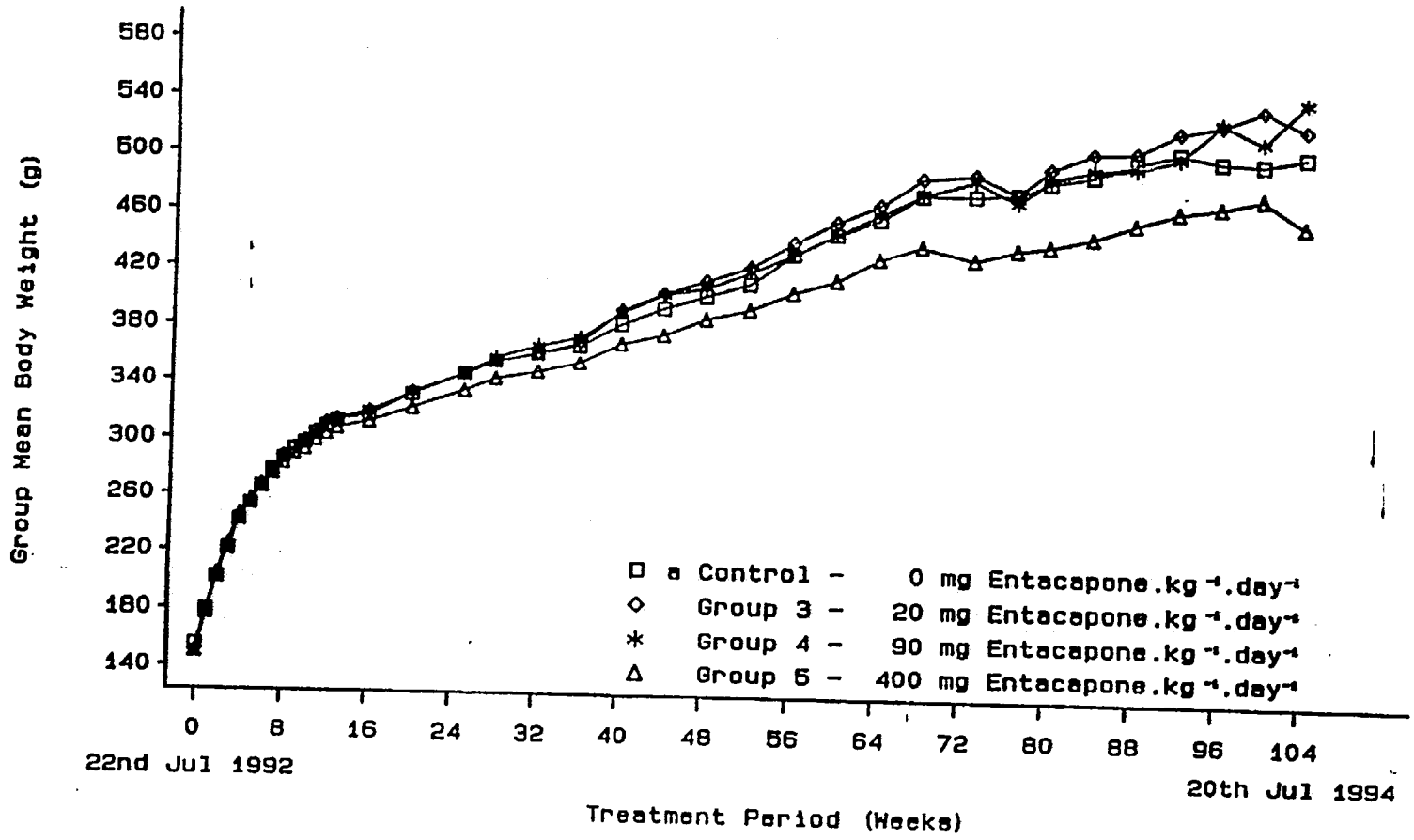


Figure 6 : Female rats

FIGURE 7

Entacapone
104 Week Carcinogenicity Study in Rats by Gavage
Group Mean Body Weight (g): Females



a - Values derived using the mean of Group 1 (Control I) and Group 2 (Control II)

Appendix 2

Tumor Historical Control Data

APPENDIX 22

Entacapone
104 Week Carcinogenicity Study in Rats by Gavage
Incidence of Tubular Epithelial Kidney Tumours in Control Rats from 104 Week Carcinogenicity Studies: Males and Females

Study No.	Sex	No. Examined[a]	Focal Hyperplasia	Benign Tumour [B]	Malignant Tumour [C]
1	♂	50	0	0	0
	♀	50	0	0	0
2	♂	47	0	0	0
	♀	47	1	0	0
3	♂	50	0	0	0
	♀	50	0	0	0
4	♂	50	0	0	0
	♀	50	0	0	0
5	♂	49	0	0	0
	♀	50	0	0	0
6	♂	50	0	0	0
	♀	50	0	0	0
7	♂	50	0	0	1
	♀	50	1	0	0
8	♂	49	0	1	0
	♀	50	0	0	0
9	♂	50	0	0	0
	♀	50	0	0	0
10	♂	49	0	1 (lipoma)	0
	♀	45	0	0	0

a = Severely autolysed tissues excluded

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TABLE 5b (Continued)
NEOPLASMS
24 MONTH STUDIES
FEMALE CD® RATS

LOCATION & TUMOR	# groups in which tissue examined	total # lesions	percent of total	# groups using this diagnosis	minimum % found	maximum % found
MUSCULOSKELETAL SYSTEM						
SKELETAL MUSCLE	19					
rhabdomyosarcoma		2	0.16	2	1.3	1.4
lipoma		1	0.08	1	--	1.0
BONE	18					
osteosarcoma		2	0.17	2	1.0	1.4
neurofibrosarcoma (M)		1	0.08	1	--	1.4
RESPIRATORY SYSTEM						
NASAL TURBINATES	8					
squamous cell carcinoma		1	0.22	1	--	2.0
basosquamous tumor, lateral sinuses		1	0.22	1	--	1.0
LUNG	19					
bronchiolar/alveolar carcinoma		1	0.08	1	--	2.0
adenocarcinoma		3	0.24	2	2.0	4.0
CIRCULATORY SYSTEM						
HEART	19					
endocardial sarcoma		1	0.08	1	--	2.0
DIGESTIVE SYSTEM						
STOMACH	19					
sarcoma		1	0.08	1	--	2.0
SMALL INTESTINE	19					
leiomyosarcoma		1	0.08	1	--	1.7
leiomyoma		1	0.08	1	--	1.5
LIVER	19					
nodular hepatocellular proliferation		9	0.71	2	8.0	10.0
hepatocellular adenoma		28	2.22	16	1.0	5.5
hepatocellular carcinoma		5	0.40	4	1.0	4.0
cholangioma		2	0.16	2	1.1	1.4
PANCREAS (EXOCRINE)	19					
acinar cell adenoma		1	0.08	1	--	1.0
URINARY SYSTEM						
KIDNEY	19					
renal cell adenoma		1	0.08	1	--	1.4
renal cell carcinoma		3	0.24	2	2.0	3.6
lipomatous tumor		2	0.16	2	1.0	1.4
liposarcoma		1	0.08	1	--	1.6
transitional cell carcinoma		1	0.08	1	--	1.4

TABLE 5a (Continued)
NEOPLASMS
24 MONTH STUDIES
MALE CD® RATS

LOCATION & TUMOR	# groups in which organ examined	total # lesions	percent of total	# groups using this diagnosis	minimum % found	maximum % found
LIVER	19					
nodular hepatocellular proliferation		9	0.72	2	8.0	10.2
hepatocellular adenoma		53	4.21	18	1.3	18.2
hepatocellular carcinoma		33	2.62	12	1.1	9.1
cholangioma		1	0.08	1	-	1.4
cholangiocellular carcinoma		2	0.16	2	1.0	2.0
carcinosarcoma		1	0.08	1	-	2.0
PANCREAS (EXOCRINE)	19					
acinar cell adenoma		7	0.56	7	1.3	2.0
sarcoma (NOS)		1	0.08	1	-	1.8
URINARY SYSTEM						
KIDNEY	19					
renal cell adenoma		3	0.24	3	1.4	2.1
renal adenocarcinoma		4	0.32	4	1.0	2.0
transitional cell carcinoma		2	0.16	2	1.4	2.0
hemangiosarcoma		1	0.08	1	-	2.1
lipoma		1	0.08	1	-	1.3
liposarcoma		1	0.08	1	-	2.1
lipomatous tumour (M)		1	0.08	1	-	1.0
mixed cell tumor (M)		3	0.24	2	2.0	3.0
mixed mesenchymal tumor (NOS)		1	0.08	1	-	1.4
URINARY BLADDER	19					
transitional cell papilloma		1	0.08	1	-	1.0
transitional cell carcinoma		3	0.24	3	1.4	1.5
mesothelioma		1	0.08	1	-	1.0
REPRODUCTIVE SYSTEM						
TESTIS	19					
interstitial (leydig) cell tumor (B)		59	4.68	18	1.4	10.0
interstitial cell tumor (M)		1	0.08	1	-	1.4
mesothelioma (M)		2	0.16	2	1.0	1.4
PROSTATE	19					
carcinoma (M)		3	0.24	3	1.0	1.8
lipoma		1	0.08	1	-	1.4
mesothelioma (M)		1	0.08	1	-	1.0
ENDOCRINE SYSTEM						
PANCREAS (ENDOCRINE)	19					
islet cell adenoma		103	8.29	17	2.9	24.0
islet cell carcinoma		25	2.01	10	1.6	8.2
mesothelioma		1	0.08	1	-	1.0
PITUITARY GLAND	19					
adenoma, pars intermedia		4	0.32	2	1.0	4.9
adenoma, pars distalis		750	60.68	19	37.1	81.3
carcinoma,						
pars distalis		79	6.39	10	1.0	33.3
craniopharyngioma		1	0.08	1	-	1.9
hemangioma		1	0.08	1	-	1.9

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 21, 1998

FROM: Glenna G. Fitzgerald, Ph.D.
Pharmacology Team Leader
Division of Neuropharmacological Drug Products, HFD-120

TO: NDA 20-796
Comtan® (entacapone)
Orion Corporation
200 mg tablets

SUBJECT: Pharmacology and Toxicology Overview

Comtan is a catechol-O-methyltransferase (COMT) inhibitor which is indicated as adjunctive therapy for Parkinsonian patients receiving Sinemet. By inhibiting COMT it not only increases plasma exposure to L-dopa, but also decreases levels of 3-O-methyl dopa, a dopa metabolite thought to be associated with undesirable side effects of L-dopa. The profile for activity closely resembles that of Tasmar, which was the first drug in this class (approved January 29, 1998). Tasmar, however, has recently been assigned a boxed warning for potentially fatal liver failure following reports of severe hepatocellular injury, including two deaths from acute fulminant liver failure, which have occurred since it was marketed. There was no indication of hepatotoxicity in preclinical studies for either of these drugs; target organ for both is the kidney in rats and dogs.

The pharmacology and toxicology studies submitted to this NDA have been reviewed by Dr. Thomas Steele. Dr. Steele has recommended that this NDA not be approved because of the lack of a valid mouse carcinogenicity study. The carcinogenicity studies were taken to the CAC, and that report is attached to this memo. It was faxed to the sponsor in early December. The CAC agreed that the mouse study, based on the data we have received, is inadequate. There was no evidence for tumor development in that study. However, there was an extrordinarily high incidence of mortality at the high dose of 600 mg/kg. The females were terminated at 95 weeks, and the males, though continued to 2 years, had a very low survival rate. Therefore, assessment of carcinogenicity rests on the middle dose of 100 mg/kg, which is problematic because of the wide spread between 600 and 100 mg/kg. First of all, 100 mg/kg has never been demonstrated to be anywhere near an MTD. Also, histopathology was not done on the

low and mid dose males or low dose females, so it is not known if there was an increase in tumors at lower doses. The recommendations from the CAC are that, for the middle dose to be deemed an acceptable high dose, the sponsor is requested to provide evidence that there is saturation of absorption for drug and major metabolites at 100 mg/kg. If this is not the case, they could also attempt to demonstrate, in a 3 month study, that 100 mg/kg is at least one half of the MTD. This recommendation, while not made by the CAC, would be an acceptable alternative approach, although is is doubtful that 100 mg/kg will meet the test. It will also be necessary to conduct histpathology on all dose groups. The information obtained by these approaches could potentially validate the mouse study. It would be my recommendation that the drug be made approvable with the understanding that the sponsor initiate these studies immediately. They could conceivably have the answers before final approval, but if not, they would have them early in Phase 4. If they cannot validate the study by any of these means, they will be required to commit to a Phase 4 mouse study, possibly an alternative assay. My reasons for not requiring the completed information prior to approval are based on demonstrated clinical efficacy and the fact that this will be the only drug acting by this mechanism of action which will be widely available, given the findings of liver failure for Tasmar.

Dr. Steele has also pointed out two other areas of concern with the preclinical studies for Comtan. These are not issues which would affect approvability. The first concerns the finding of an increased incidence of renal tubular adenomas and carcinomas in the rat carcinogenicity study. The sponsor proposes that these tumors are due to altered renal handling and deposition (i.e., excessive accumulation in hyaline droplets in kidney) of a male rat-specific protein, alpha 2-microglobulin (α2-μG), with subsequent development of nephrotoxicity and renal tubule neoplasia. This proposed mechanism is not considered (by most scientists in the field) to be relevant to humans, and the sponsor wishes to make this disclaimer in labeling. To support their case, they have provided histological and immunocytochemical evidence for the presence of hyaline protein droplets and α2-μG in male rat kidney sections from other toxicology studies (rat reprotox, 6- and 52-week rat). However, the sponsor's contract pathologist questioned the involvement of this mechanism because several other normally associated pathological changes were not present (necrosis, granular casts, linear mineralization of renal papilla) and hyaline droplet deposition was absent in the carcinogenicity study. We have consulted with Dr. Rick Hailey at NTP on this issue, and a memo of that telecon is attached. His conclusion is that Comptan is a subtle α2-μG inducer at most, and while some of the findings would support the mechanism, some of the findings, or lack thereof, are not in agreement with usual findings for this mechanism. Therefore, while there is a possibility that this mechanism may be involved, it is far from certain. The IARC monograph to which he refers was written by Dr. Ronald Melnick at NIEHS. Although this monograph was not available for review, Dr. Melnick is on record as concluding, with reference to the association between renal carcinogenesis and α2-μG nephropathy, that there are data inconsistent with the hypothesis linking these occurrences and that a greater understanding of the molecular changes occurring during renal carcinogenesis is needed before assuming that the

current hypothesis is correct (Melnick, R., Reg. Tox. Pharm. **16**, 111-125, 1992). Other factors which speak against this mechanism as the sole cause of tumorigenesis in Comtan treated rats are the following: renal carcinomas in two female rats represent a rare occurrence and one which could not be due to α2-μG which occurs only in males; Comtan was clastogenic in two in vitro assays; the related drug Tasmar caused renal tumors, probably by a different mechanism. We have therefore concluded that the mechanism for the renal tumorigenesis of Comtan is not known with any degree of certainty, and that the relevance to humans cannot therefore be determined. The sponsor's disclaimer has been removed from labeling.

The final issue involves the characterization and accurate description of the 'chronic progressive nephropathy' that occurred in the one-year rat study so that it can be described in labeling. The reason for this is that similar renal toxicities were well described for Tasmar, and are in labeling under Precautions. The sponsor should be asked to provide an accurate description of the findings with Comtan so that we can determine if they are serious enough to be included in labeling.

Recommendations:

This NDA is approvable for pharmacology and toxicology with concurrence from the sponsor to commit to the following:

I. The CDER Carcinogenicity Assessment Committee (CAC) has recommended that demonstration of an adequate study in the mouse is essential to appropriately assess the human carcinogenic risk of Comtan. The CAC report states that "The validity of the mouse carcinogenicity study was questionable because of inadequate survival at the high dose, the large spread in dose (based on nominal dose) between the high dose and middle dose, the absence of data to support the middle dose as the appropriate 'back-up' dose, and the absence of a full histopathological analysis, particularly in middle dose males." We request that you initiate studies as soon as possible, and prior to final approval, to attempt to validate the mouse study. These studies should include the following: 1) a study which 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 addition, 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.

II. Please provide specific details which characterize the "chronic progressive nephropathy" which occurred in the one-year rat study so that an accurate description may be included in labeling.

The Division's December 8, 1998 version of labeling contains final recommended labeling for the pharmacology and toxicology sections.

/S/

Glenna G. Fitzgerald, Ph.D.

2 Attachments

NDA 20-796
c.c. Div. File
Katz\Tresley\Wheelous\Fitzgerald

Executive CAC
11/24/98

Committee: Joseph DeGeorge, Ph.D., HFD-024, Chair
Joseph Contrera, Ph.D., HFD-900, Member
Laraine Meyers, Ph.D., HFD-160, Alternate Member
Glenna Fitzgerald, Ph.D., HFD-120, Team Leader
Thomas D. Steele, Ph.D., Presenting Reviewer

Author of Draft: Thomas D. Steele, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

NDA #: **20796**
Drug Name: **COMTAN (Entacapone) Tablets**
Sponsor: **Orion Corp.**

Mouse Carcinogenicity Study:

A 104-week carcinogenicity study of 20, 100, and 600 mg/kg/day entacapone (oral gavage, once daily) was conducted in CD-1 mice (n=50/sex; 2 control groups; 8/sex/group for TK). High dose selection was based on saturation of absorption (parent compound only) in a 13-week study. The CAC-EC was not consulted for protocol concurrence.

The main issue of concern was a high mortality rate in HD animals, most notably females. Less than 50% of HDF survived past one year, and the group was terminated at week 95 (only 9 remained). Only 14 HDM survived the entire 104 week study.

There was no evidence of a treatment-related effect on tumorigenesis.

Because of the inadequate survival at the HD and the apparent use of a dose that exceeded the MTD, the Committee asked for data on the relationship of the MD (100 mg/kg/day) to the MTD. No toxicities were associated with the MD, and the toxicokinetic data were not sufficient to determine if saturation of absorption occurred at this dose (no data on levels of major metabolites). It was noted in discussion that the mid dose was 1/6th the high dose, although the difference in exposure to drug and related metabolites between the mid and high dose may not have been so large. However, the MD males were not evaluated histopathologically.

Rat Carcinogenicity Study:

A 104-week carcinogenicity study of 20, 90, and 400 mg/kg/day entacapone (oral gavage, once daily) was conducted in SD rats (n=50/sex; 2 control groups; 5/sex/group for TK analysis). High dose selection was based on MTD determined in a 13-week range-finding study (13% reduction in body wt gain). The CAC-EC was not consulted for protocol concurrence.

The major study findings were renal tubular adenomas (6 HDM) and carcinomas (1 Con M, 1LDF, 1 MDF, 5 HDM). Tumor incidence was statistically significant for males ($p = 0.0006$ for combined tumors by pairwise comparison), but not females.

There was no evidence of any other treatment-related effects on tumorigenesis.

The sponsor presented evidence to support their hypothesis that the occurrence of tumors in males was through a male rat-specific mechanism (altered renal handling/deposition of α2-microglobulin [α2-μG], a male rat-specific protein). The committee considered the evidence as supportive but not convincing because of the occurrence of tumors in entacapone-treated females, positive clastogenicity findings, the

absence of the full spectrum of pathological changes normally associated with α2-μG nephropathy, and the occurrence of renal tumors after long-term administration of a closely related compound by a (putatively) different mechanism.

Executive CAC Recommendations and Conclusions:

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.

The committee recommended that the rat renal tumor findings should be included in the label. Because the supporting data were not convincing, it was recommended to the division that the labeling should not include the sponsor's description of the α2-μG mechanism and the statement that the findings are not relevant to humans, without further documentation of the applicability of this mechanism to this specific drug.

/S/ 12/3/98

Joseph DeGeorge, Ph.D.
Chair, Executive CAC

cc:\

/Division File, HFD -120
/GFitzgerald, HFD-120
/TSteele, HFD-120
/TWheelous, HFD-120
/ASeifried, HFD-024

APPEARS THIS WAY
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