CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-745

PHARMACOLOGY REVIEW

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	21-745
SERIAL NUMBER:	000
DATE RECEIVED BY CENTER:	Nov 28, 2005
PRODUCT:	Tramadol Contramid OAD
INTENDED CLINICAL POPULATION:	Moderate to severe pain
SPONSOR:	Labopharm
REVIEW DIVISION:	Division of Anesthesia, Analgesia and Rheumatology Products, HFD-170
PHARM/TOX REVIEWER:	Asoke Mukherjee, Ph.D
PHARM/TOX SUPERVISOR:	R. Daniel Mellon, Ph.D.
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PROJECT MANAGER:	Paul Balcer

Date of review submission to Division File System (DFS): August 2, 2006

TABLE OF CONTENTS

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability:

From the nonclinical pharmacology/toxicology perspective, NDA 21-745 for Tramadol Contramid OAD 100, 200 and 300 mg once a day may be approved.

B. Recommendation for nonclinical studies: None

C. Recommendations on labeling:

The recommended labeling below is derived from the FDA approved labeling for the referenced drug product, Ultram. The exposure ratios have been modified for the maximum recommended daily exposure to Tramadol Contramid® OAD.

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II. Summary of nonclinical findings

A. Brief overview of nonclinical findings:

The sponsor developed a once a day oral dosage regimen for tramadol. Except for the excipient Contramid, the inactive ingredients used in the formulation can be found in other FDA approved drug products at comparable exposure levels. The sponsor stated that Contramid is the proprietary product developed for the drug delivery system and it is a modified starch, i.e. hydroxypropyl distarch phosphate. A single dose toxicity study for

Contramid was conducted in rats at doses up to 2000 mg/kg/oral. No treatment-related mortality was observed in rats. The sponsor provided literature articles on the toxicity and reproductive effects of feeding several modified starches. In general, up to 30% of modified starch in the diet increased the weight of cecum and did not show any effect on the reproductive performance in a 3 generation study. A publication by Leegwater et al. suggested that the effect of the modified starch on cecum resulted from the physiological adaptation. Hydroxypropyl distarch phosphate is not mutagenic in the Ames assay.

The amount of Contramid in the formulation is abou[redacted] of the weight of the formulation and per day intake would be abou[redacted] The modified starch is considered to be generally safe and used in the food industry. The acceptability of the use of modified starch in food is published in the 21 CFR 172.892. Based on the safety and regulatory status, hydroxypropyl distarch phosphate is considered a modified starch. In consultation with the chemistry review team, Contramid falls under the classification of a modified starch. As the Agency has previously determined that modified starches are acceptable as food products, the use of Contramid as an inactive ingredient for an oral drug product is acceptable without additional toxicity studies

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The sponsor referenced previous correspondence with the Agency on November 2001. The Division agreed that the sponsor may request to reference nonclinical data for Pharm/Tox information from Ultram NDA file in support of 505(b)(2) application.

B. Pharmacologic activity:

Tramadol is a μ-opioid receptor agonist and inhibitor of monoamine uptake (serotonin and norepinephrine). It has an active metabolite (M1) that shares a similar pharmacological profile.

C. Nonclinical safety issues relevant to clinical use:

The major safety issues related to tramadol is seizure. However, no new nonclinical safety study has been submitted in the NDA.

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The FDA has approved the following tramadol NDAs:

NDA#	Drug Name	Div	Strength (route)	Marketing Status	AP Date	Indication	Company
20-281	Ultram	170	Oral	Approved	3/3/1995	Acute and chronic pain	Ortho McNeil Pharma.
21-123	Ultracet (Tramadol & APAP)	170	Oral	Approved	8/15/2001	Moderate to moderately severe pain	Ortho McNeil Pharma.
21-692	Ultram ER	170	100, 200, 300 mg Oral	Approved	9/8/2005	Moderate to moderately severe pain	Biovail Labs
21-693	Ultram ODT	170	50 mg Oral	Approved	5/5/2005	Moderate to moderately severe pain	Biovail Labs

Drug class: Centrally acting analgesic

Intended clinical population: For the treatment of moderate to moderately severe pain. Underlying disease condition has not been specified in the application.

Clinical formulation: The product will be formulated as 100, 200 and 300 mg tablets. The formulation is shown in the table below.

Component	Function	Mg/100 mg tablet	% of total	Mg/200 mg tablet	% of total	Mg/300 mg tablet	% total
Tramadol hydrochloride	Active drug	100		200		300	
Contramid,							
Xanthan gum							
Hydrogenated vegetable oil							
Magnesium stearate							
Colloidal silicone dioxide							
black ink							
Total							

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Most of the inactive ingredients were already used in pharmaceutical formulation of approved products. Contramid is hydroxypropyl distarch phosphate and considered to be a modified starch. Modified starch is considered by the FDA to be generally recognized as safe as a food additive. The maximum daily intake of Contramid would be about [redacted] of the formulation or [redacted] b(4)

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The DMF indicated that long term toxicity of [redacted] was studied up to 250 mg/kg/oral in rats and mice for 12 months. However, the study report was not provided. Considering previous history of the human use and rodent to human dose ratio over 10 (for equal body surface area), there is no safety concern related to the use of [redacted] in the formulation. b(4)

Route of administration: Oral

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

[For (b)(2) applications:

Data reliance: Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 21-745 are owned by Labopharm or are data for which Labopharm has obtained a written right of reference. Any information or data necessary for approval of NDA 21-745 that Labopharm does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Labopharm does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 21-745.

The sponsor of NDA 21-745 has referenced the Agency's previous findings of safety and efficacy for Ultram (tramadol; NDA 20-281).

Studies reviewed within this submission:

Acute oral toxicity of Contramid in albino rats, module 4, vol 1, page 9

A 2-year feeding and multigeneration study in rats on 5 chemically modified starches. Published by De Gout, Til and Feron, Food, Cosmetic and Toxicol, 651-663, 1974, from module 4, vol 2.

Bacterial reverse mutation assay, module 4, vol 1

Chronic (89-week) feeding study with hydroxypropyl distarch phosphate, starch acetate, lactose and sodium alginate in mice by Til, Feron, Immel and Vogel, module 4, vol 2

2-Year feeding and multigeneration studies in rats of five chemically modified starches by De Groot et al., module 4, vol 2.

The aetiology of caecal enlargement in the rat, Leegwater et al., Food Cosmet. Toxicol., 12, 687-697, 1974.

Hydroxypropyl distarch phosphate from tapioca reduces zinc and iron absorption, but not calcium and magnesium absorption, in rats, Kishida et al., Am. Soc. Nutrition 131, 294-300, 2000.

Studies not reviewed within this submission:

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1 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary:

Tramadol is an approved product and no new pharmacological studies were conducted in support of Tramadol Contramid OAD. The current application is made under 505(b) (2) of Food Drug and Cosmetic Acts. The sponsor referenced previous findings of safety and effectiveness for tramadol nonclinical information (Module 2, vol 1, nonclinical overview, page 3).

Tramadol exerts its analgesic effect by the activation of the mu-opioid receptor and inhibition of monoamine uptake. Both tramadol and its O-desmethyl metabolites (M_1) have pharmacological effects.

2.6.2.2 Primary pharmacodynamics

No primary pharmacodynamic study for tramadol was submitted in the NDA.

2.6.2.3 Secondary pharmacodynamics

No secondary pharmacodynamic study for tramadol was submitted in the NDA.

2.6.2.4 Safety pharmacology

No safety pharmacology study for tramadol was submitted in the NDA.

2.6.2.5 Pharmacodynamic drug interactions

No pharmacodynamic drug interaction study for tramadol was submitted in the NDA.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

[Pivotal studies pertinent to the primary indication and core pharmacology studies relevant to the primary pharmacodynamic effect, as available and as provided by the sponsor]

No pharmacology tabulated summary was submitted in the NDA

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary: No nonclinical pharmacokinetic data for tramadol were submitted in the NDA

2.6.4.2 Methods of Analysis: Nil
[See under individual study reviews]

2.6.4.3 Absorption

No nonclinical data for absorption of tramadol were submitted in the NDA.

2.6.4.4 Distribution

No nonclinical data for distribution of tramadol were submitted in the NDA.

2.6.4.5 Metabolism

No nonclinical data for metabolism of tramadol were submitted in the NDA.

2.6.4.6 Excretion

No nonclinical data for excretion of tramadol were submitted in the NDA.

2.6.4.7 Pharmacokinetic drug interactions

No nonclinical data for drug interaction of tramadol were submitted in the NDA.

2.6.4.8 Other Pharmacokinetic Studies: Nil

2.6.4.9 Discussion and Conclusions:

No new nonclinical pharmacokinetic data for tramadol were submitted in the NDA.

2.6.4.10 Tables and figures to include comparative TK summary

No comparative TK summary was submitted in the NDA.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

[Pivotal studies pertinent to the primary indication and core pharmacology studies relevant to the primary pharmacodynamic effect, as available and as provided by the sponsor]

No Pharmacokinetic tabulated summary was submitted in the NDA.

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology: No toxicology data for tramadol was submitted. The acute toxicity data for Contramid showed no mortality to rats up to 2000 mg/kg/oral.

Genetic toxicology: No genotoxicity data for tramadol were submitted. Contramid showed no genotoxicity in the Ames test.

Carcinogenicity: No carcinogenicity data for tramadol were submitted. A published data for several modified starch in rats showed no tumorigenic potential when fed in the diet for greater than one year when compared to the unmodified starch. However, the weight of cecum was increased. The published literature suggested that the increase weight to cecum in rats fed with modified starch was due to an adaptive change.

Reproductive toxicology: A published report showed no effect on the reproductive performance of male and female rats fed with several modified starch in a three generation study. Animals were fed with 10% modified starch in the diet.

Special toxicology: Modified starch reduced absorption of zinc and iron in the rat model at 59g/kg. The proposed clinical dose of hydroxypropyl distarch phosphate is 1.4 mg/kg. Based on the animal to human dose ratio, the clinical significance of the finding is insignificant.

2.6.6.2 Single-dose toxicity

Study Title: Acute oral toxicity study of Contramid in albino rats, module 4, vol 1, page 9

The study was conducted [redacted] according to GLP requirements of EPA and OECD on June 21, 2002. A quality assurance statement was attached in the report. The lot number for Contramid was HZ820. The certificate of analysis has been provided on page 43, module 4, vol 1. Albino rats were used for the experiment and the strain was not mentioned in the report. Rats weighed 226 to 258 g for male and 174 g to 204 g for female at the beginning of dosing. Animals were approximately 8-10 weeks old. Contramid was suspended in deionized water. The suspension was prepared overnight and stability of the suspension was not determined using any physicochemical or quantitative methods. However, the study could be accepted considering that no major changes are expected from the modified starch and if that happens, its controlled release property in the clinical trial would be limited. Two doses of the suspension were administered at 4 hour interval by oral gavage. Each dose was 1000 mg/kg and the total dose was 2000 mg/kg/day. The treatment was given at 30 ml/kg volume.

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The treatment was given to 5 male and 5 female overnight fasted rats.

Rats were observed for mortality up to 5 hours after the dose and twice daily for 14 days. Clinical signs were observed up to 5 hours after the dose and once daily for 14 days. Generally, appearance of skin, eyes, respiration, movements and any abnormal observations were recorded. The body weight was recorded on the day of dosing, day 7 and on day 14 after the treatment. Surviving animals were euthanized on day 14 and any macroscopic changes in the brain, thoracic and abdominal cavities were noted.

Results:

No mortality was reported. The average body weight was increased from 243 g on day 0 to 317 and 361 g on days 7 and 14, respectively in male rats. The average body weight for female rats was increased from 191 g on day 0 to 225 and 238 g on days 7 and 14, respectively. Both male and female rats appeared normal on the day of dosing and thereafter till necropsy. There was no control group for comparison and no histopathology data were provided in the study.

It is concluded that Contramid was tolerated up to 2000 mg/kg/oral as a single dose.

2.6.6.3 Repeat-dose toxicity

Study title: A 2-year feeding and multigeneration study in rats on 5 chemically modified starches. Published by Grout and Feron, Food, Cosmetic and Toxicol, 651-663, 1974.

Key study findings: Treatment related histopathological changes were not observed following chronic administration of modified starches up to 30% in the diet by oral route. However, the relative weight of cecum (empty) was increased in all modified starch treated rats at 30% in the diet with the exception of phosphated distarch phosphate (starch 6). The body weight of rats fed with 30% acetylated diamylopectin phosphate (starch 3) and hydroxypropyl distarch glycerol (starch 5) was reduced.

Starch 6 (phosphated distarch phosphate) had no effect in a feeding study for 2 years up to 30% in the diet.

Study no.: Published paper
Volume # 2, and page #: 651
Conducting laboratory and location: [redacted] b(4)

Date of study initiation: Not specified
GLP compliance: Not known
QA report: yes ( ) no (x)
Drug, lot #, and % purity: Not provided

Methods

Doses: 5, 10 and 30% in the diet
Species/strain: Weaning Wistar rats, male and female

Number/sex/group or time point (main study): 30 rats/sex
Route, formulation, volume, and infusion rate: Oral diet
Satellite groups used for toxicokinetics or recovery: Nil
Age: Weaning
Weight: Body weight ranged from 51-89 g for male and 50-79 g for female rats
Sampling times: Shown below
Unique study design or methodology (if any): Nil

The study design is shown below.

Group	Starch	Dose	Male	Female
1	Unmodified potato starch	Control	30	30
2	Acetylated distarch phosphate	5, 10, 30% in the diet	30/grx3=90	30/grx3=90
3	Acetylated diamylopectin phosphate	3, 10, 30% in the diet	30/grx3=90	30/grx3=90
4	Unmodified potato starch	Control	30	30
5	Starch acetate	5, 10, 30% in the diet	30/grx3=90	30/grx3=90
6	Hydroxypropyl distarch glycerol	5, 10, 30% in the diet	30/grx3=90	30/grx3=90
7	Unmodified maize starch	Control	30	30
8	Phosphated distarch phosphate	5, 10, 30%	30/grx3=90	30/grx3=90

Observations and times:
Mortality: Frequently
Clinical signs: Frequently
Body weights: Once every 2 weeks for 12 weeks and once every 4 weeks for rest of the study
Food consumption: Every two weeks
Ophthalmoscopy: Authors did not report that ophthalmic examinations were conducted.
EKG: Not recorded
Hematology: Hematology data were collected from 10 animals/sex on week 13, 26, 52, 80 and 102. Data for RBC, WBC, hemoglobin, differential counts and packed cell volume were recorded.

Clinical chemistry: Blood sugar and BUN levers were determined on weeks 13, 26, 52, 81 and 103. Serum SGOT, SGPT and alkaline phosphatase activities, serum albumin and total serum protein were determined at terminal sacrifice. However, authors did not mention how blood samples were collected.
Urinalysis: Urine samples from 10 rats/group were examined. The authors did not specify when the urine samples were collected.
Gross pathology: Surviving animals were sacrifice on week 104. Macroscopic changes were recorded.
Organ weights (specify organs weighed if not in histopath table): The authors stated major organs were weighed.
Histopathology: Adequate Battery: yes (x), no ( )—explain
Peer review: yes ( ), no (x)

Tissues were preserved in 10% formalin and processed for microscopic examinations after staining with hematoxylin and eosin.

Histopathology of the control groups (3 controls) and the high dose groups for each modified starch was examined on all protocol specified tissues indicated in the table below. In addition, histopathology for kidneys, urinary bladder, prostate and cecum was conducted on all treated rats. Histopathology of adrenals from acetylated distarch phosphate (starch 2), acetylated diamylopectin phosphate (starch 3), starch acetate (starch 4) and hydroxypropyl distarch glycerol (starch 5) from all treated rats were conducted. Histopathology of thyroid and liver from all treated rats for starch acetate (starch 4) and hydroxypropyl distarch glycerol (starch 5) was also conducted.

Results

Mortality:

Table 1 *Cumulative mortality in groups of 30 male and 30 female rats fed modified starches at dietary levels of 0–30% for 2 yr*

Starch in diet		Total no. of deaths in					
		Males at wk			Females at wk		
Type	Level (%)	72	96	104	72	96	104
1	(Control)	2	7	11	4	8	9
2	5	0	8	13	1	6	6
	10	4	12	18*	0	3	7
	30	3	10	15	2	5	7
3	5	1	5	11	1	4	6
	10	3	11	16	1	4	7
	30	1	8	10	1	8	10
1	(Control)	3	11	11	0	2	4
4	5	2	11	12	0	3	4
	10	1	8	12	1	5	8
	30	4	14	19	0	2	4
5	5	5	11	14	1	4	6
	10	3	8	11	0	6	8
	30	2	8	14	1	7	11
7	(Control)	4	7	11	3	6	7
6	5	2	7	12	0	0*	9
	10	3	8	11	2	2	5
	30	3	9	15	1	4	7

The value marked with an asterisk differs significantly (chi-square test) from that of the corresponding controls: *$P < 0.05$

Data taken from the published paper show that there was no treatment related mortality in the modified starch treated groups.

Clinical signs: Soft stool was observed at 30% dose in starch acetate (starch 4).

Body weights:

Male:

A 12% reduction in the mean body weight was noted ($p<0.05$) in male animals treated with acetylated diamylopectin phosphate starch (starch 3) at 10% and 30% in the diet at the end of week 104 when compared to the animals in the control group. Intermittent changes were noted in animals in the 30% hydroxypropyl distarch glycerol starch (starch 5) group.

Female:

Female rats treated with acetylated distarch phosphate (starch 2) and acetylated diamylopectin phosphate starch (starch 3) showed about 8-12% reduction in the body weight ($P<0.05$) at the end of week 104 at 30% in the diet compared to the corresponding control. Starch 5 (hydroxypropyl distarch glycerol) showed about 5-12% reduction in the body weight ($P<0.05$) at 30% in the diet between week 52 to 104.

It is concluded that oral feeding of acetylated diamylopectin phosphate starch (starch 3) and hydroxypropyl distarch glycerol starch (starch 5) at 30% in the diet had an effect on the body weight in male and female rats.

The body weight data are shown in the table below.

Table 2. *Mean body weights and food efficiency of rats fed modified starches at 0–30% of the diet for 2 yr*

Starch in diet		Body weight (g) at wk						Food efficiency† at wk 1–4
Type	Level (%)	0	4	28	52	76	104	
				Males				
1	(Control)	75	191	378	437	481	488	0·31
2	5	75	190	382	427	459	491	0·32
	10	75	189	368	423	457	445*	0·32
	30	75	187	367	426	456	450	0·31
3	5	75	189	379	437	472	463	0·32
	10	75	195	382	430	468	433*	0·32
	30	75	182	358*	409*	440**	431**	0·30
				Females				
1	(Control)	69	132	223	248	285	308	0·22
2	5	69	132	224	256	287	309	0·22
	10	69	132	230	244	274	293	0·23
	30	69	132	222	248	277	282*	0·21
3	5	69	131	228	246	278	306	0·22
	10	69	130	222	245	276	308	0·22
	30	69	130	219	241	262*	273**	0·22
				Males				
1	(Control)	89	200	386	431	493	484	0·30
4	5	89	193	384	439	481	484	0·29
	10	88	196	382	439	464	468	0·30
	30	88	194	382	430	456*	470	0·28
5	5	89	193	387	442	481	481	0·28
	10	89	187**	378	431	467	501	0·27
	30	89	180**	367*	419**	451**	465	0·24
				Females				
1	(Control)	79	136	230	250	295	322	0·19
4	5	79	135	222	250	285	297	0·20
	10	79	133	220	250	284	309	0·18
	30	79	134	222	251	280	298	0·19
5	5	79	132	225	252	292	318	0·18
	10	79	129*	221	252	281	319	0·17
	30	79	128**	220	243*	269**	285*	0·17
				Males				
7	(Control)	51	192	386	427	467	416	0·37
6	5	51	185	378	420	466	445	0·37
	10	51	187	388	421	449	449	0·37
	30	51	184	394	425	457	446	0·37
				Females				
7	(Control)	50	136	233	262	301	318	0·28
6	5	50	134	227	256	292	301	0·28
	10	50	133	225	252	286	312	0·28
	30	50	137	230	260	297	308	0·29

†Food efficiency = weight gain (g)/food intake (g)
Body weights are the means for groups initially comprising 30 rats. Those marked with asterisks differ significantly (Student's *t* test) from the corresponding controls: *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$

Food consumption:

The sponsor indicated that there was no treatment related change in the food consumption. The food efficiency (weight gain) table showed minor change in the food effiicency at 30% in the diet for starch 5 (hydroxypropyl distarch glycerol).

Hematology: No data table was included in the published paper. The authors stated that slight increase in the WBC in female rats was observed for starch 2 (acetylated distarch phosphate) and starch 4 (starch acetate) at 30% in the diet. Also, a slight reduction in the hemoglobin was noted in female rats treated with 30% starch 5 (hydroxypropyl distarch glycerol) in the diet.

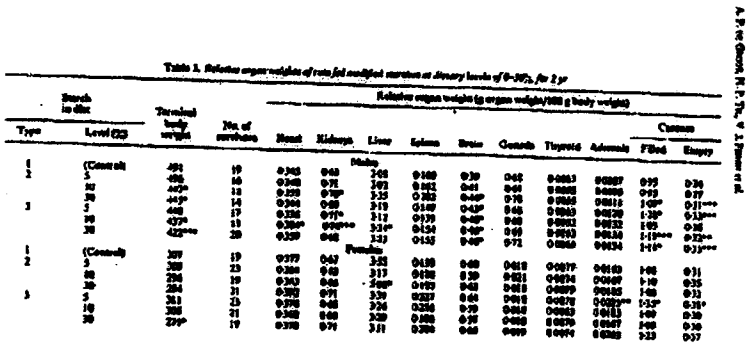
Clinical chemistry:

The sponsor indicated changes in the clinical chemistry were incidental.

Urinalysis: A urinalysis data table was not included in the report. However, the sponsor stated that there was no treatment related change in the rats treated with several modified starches.

Gross pathology: Enlarged cecum was noted at the highest dose for starch 2 (acetylated distarch phos), starch 3 (acetylated diamylopectin phosphate), starch 4 (starch acetate), and starch 5 (hydroxypropyl distarch glycerol).

Organ weights (specify organs weighed if not in histopath table):



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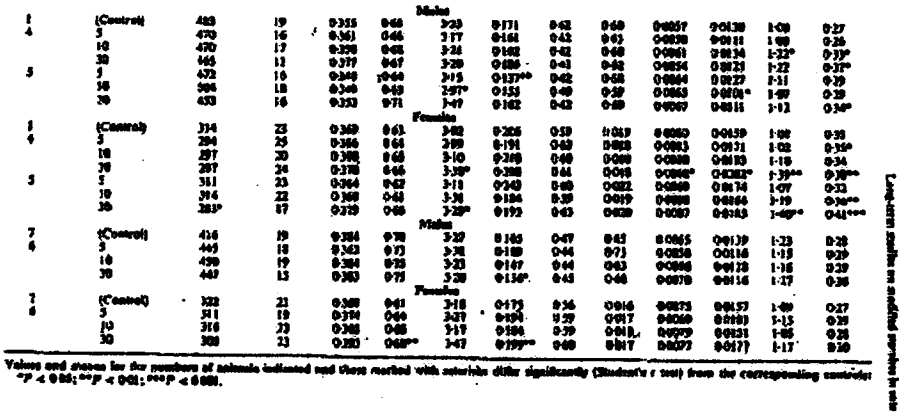


Organ weight data are shown above from the publication.

Male:

Acetylated distarch phosphate (starch 2), acetylated diamylopectin phosphate (starch 3) and starch acetate (starch 4) showed increase weight of cecum per 100 g body weight at 10 and 30% concentrations in the diet.

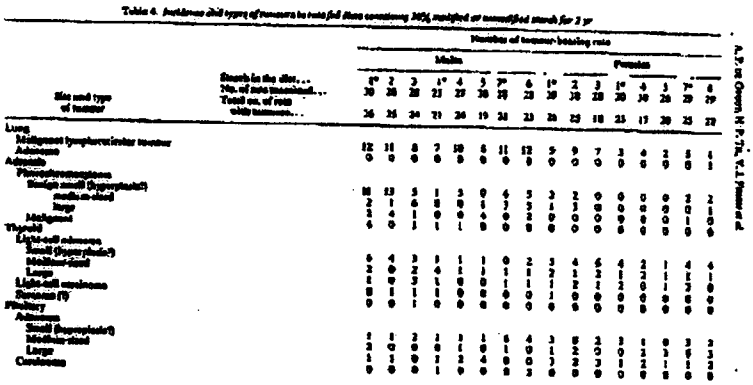
Female:

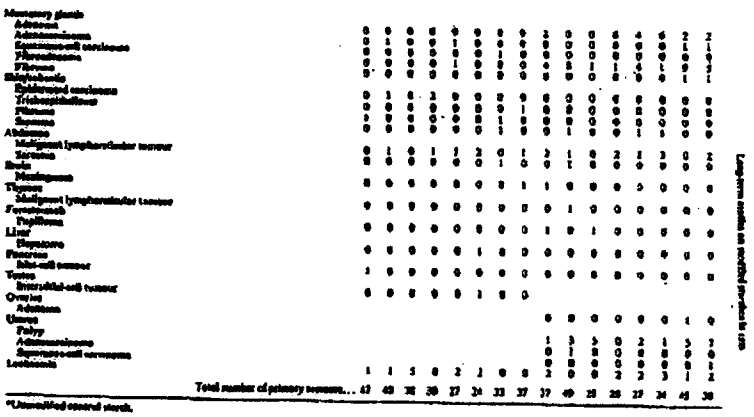
Acetylated distarch phosphate (starch#2), starch acetate (starch 4) and hydroxypropyl distarch glycerol (starch 5) showed an increase in the relative weight of cecum when fed with the starch at 30% in the diet. A decrease in the relative weight of thyroid and increase in the relative weight of adrenal was also observed in rats fed with 30% starch acetate (starch 4) in the diet.

Above data suggest that with the exception of phosphated distarch phosphate (starch 6), there was a tendency for an increase in the relative weight of cecum.

Histopathology: Adequate Battery: yes (x), no ( )—explain
Peer review: yes ( ), no (x)

Authors did not provide histopathology data for all organs. However, no histopathological relationships between the type of starch and doses in the diet were observed as shown in the table below. The sponsor also stated that no treatment related histopathological change was noted in the cecum. Based on the data provided in the published article, it was concluded that chronic feeding of modified starch listed in the publication did not show any treatment related histological changes at 5, 10 and 30% dose in the diet when compared with the corresponding control.





Toxicokinetics: Nil

Other:

Histopathology inventory (optional)

Study	2-year	89-week
Species	Wistar rat	SPF mice
Adrenals	X	X
Aorta	X	X
Bone Marrow smear		
Bone (femur)		
Brain*	X (three levels)	X
Cecum*	X	X
Cervix		
Colon*		X
Duodenum	X	X
Epididymis		X
Esophagus	X	X
Eye		X
Fallopian tube		
Gall bladder		
Gross lesions		
Harderian gland		
Heart*	X	X
Ileum	X	X

Study	2-year	89-week
Injection site		
Jejunum	x	x
Kidneys*	x	x
Lachrymal gland	x	x
Larynx		
Liver*	x	x
Lungs	x	x
Lymph nodes, axillary		x
Lymph nodes, cervical		
Lymph nodes mandibular		
Lymph nodes, mesenteric	x	x
Mammary Gland	x	x
Nasal cavity		
Optic nerves		
Ovaries	x	x
Pancreas	x	x
Parathyroid	x	
Preputial gland	x	x
Peripheral nerve	x	
Pharynx		
Pituitary	x	x
Prostate	x	x
Rectum		
Salivary gland	x	x
Sciatic nerve		x
Seminal vesicles	x	x
Skeletal muscle	x	x
Skin	x	x
Spinal cord	x	x
Spleen*	x	x
Sternum	x	x
Stomach	x	x
Testes*	x	X
Thymus	x	
Thyroid	x	x
Tongue		
Trachea	x	x
Urinary bladder	x	x
Uterus	x	x
Vagina		
Zymbal gland		

X, histopathology performed
*, organ weight obtained

2.6.6.4 Genetic toxicology

Study title: Bacterial reverse mutation assay

Key findings: Contramid was not genotoxic in the Ames test.

Study no.: AA65KB.503.BTL

Volume # 1, module 4, and page #: 1
Conducting laboratory and location: ——————— b(4)
Date of study initiation: Sept 16, 2006
GLP compliance: Yes
QA reports: yes (x) no ( )
Drug, lot # HZ3820, and % purity: not indicated, however, residue on ignition was 0.41%

Methods

Strains/species/cell line: *Salmonella typhimurium* strains TA 98, TA 100, TA 1535 and TA 1537 and *E. coli* strain WP2*uvr*A

Doses used in definitive study: 75, 200, 600, 1800, 5000 µg/plate

Basis of dose selection: Initial cytotoxicity assay, no cytotoxicity was observed up to 5000 µg/plate

Negative controls: Saline

Positive controls: In the absence of S-9 liver homogenates: 2-nitrofluorene, sodium azide, 9-aminoacridine, methyl methanesulfonate were used as positive controls. The positive control was 2-aminoanthracene in the presence of S-9 rat liver homogenates.

2. Incubation and sampling times: All dose levels, vehicle and the positive control were incubated in the culture medium in triplicate. 0.5 ml of S-9 mixture or sham mix, 100 µL of vehicle or test substance was added to 2 mL of molten agar medium. The mixture overlaid on the surface of 25 ml of minimal bottom agar. The plate was incubated for 48-72 hours at 3°C. Bacterial background lawn and precipitate was examined under a dissecting microscope. Cytotoxicity was determined from the thinning of the micro colony in comparison to the vehicle control.

Results

Study validity (comment on replicates, counting method, criteria for positive results, etc.):

A dose level considered to be toxic if one or both criteria are met as shown below.

1. More than 50% reduction of mean number of revertant colonies per plate compared to the mean of control plates.
2. Moderate reduction in the background lawn.

Criteria for a positive test:

1. Dose-related increase in the mean revertant colonies.

2. For *Salmonella typhimurium* strains TA 1535 and TA 1537, a three-fold increase in the revertant colonies compared to the control was considered a positive response.
3. For *Salmonella typhimurium* strains TA 98, TA 100 and *E. coli* WP2*uvr*A, a 2-fold increase in the mean revertant colony compared to the control at the peak of dose response was considered a positive response.

4. The mean number of spontaneous revertant colonies should be within the following range for a valid assay:

   TA 98 = 10-50, TA 100 = 80-240, TA 1535 = 5-45, TA 1537 = 3-21 and WP2*uvr*A = 10-60.

Study outcome:

The dose level tested in the initial cytotoxicity assay was 2.5, 7.5, 25, 75, 200, 600, 1800, and 5000 µg per plate. No precipitate and cytotoxicity were observed in the initial assay. Based on the data, the maximum dose for the confirmatory assay was set at 5000 µg/plate. At 75, 200, 600, 1800 and 5000 µg/plate, no cytotoxicity was observed. The vehicle control data were within the range provided by the sponsor.

It was concluded that Contramid was not mutagenic in Ames assay in the presence and absence of S-9 rat liver homogenates. The summary data in the absence of S-9 are shown below.

Dose, µg/plate	TA 98	TA 100	TA 1535	TA 1537	WP2 uvrA
Vehicle	12	175	11	9	13
75	13	180	11	8	12
200	12	168	12	8	14
600	13	162	12	9	12
1800	11	147	10	11	14
5000	11	151	10	11	13
Positive control	129	694	318	45	140

Summary of data in the presence of S-9 rat liver homogenates are shown below:

Dose, µg/plate	TA 98	TA 100	TA 1535	TA 1537	WP2 uvrA
Vehicle	12	163	9	8	13
75	12	136	12	10	13
200	13	173	10	11	12
600	11	139	9	11	12
1800	11	137	9	9	13
5000	10	143	6	9	12
Positive control	408	895	90	136	423

The study is acceptable and strains used in the study were as per recommendations of the ICH guidelines.

2.6.6.5 Carcinogenicity

Study title: Chronic (89-week) feeding study with hydroxypropyl distarch phosphate, starch acetate lactose and sodium alginate in mice.

Key study findings: Hydroxypropyl distarch phosphate (HP), starch acetate (AC), lactose and alginate did not show carcinogenic potential when compared to unmodified starch in mice.

Adequacy of the carcinogenicity study and appropriateness of the test model: The study was published in Food Chemistry and Toxicology, 34, 825, 1986 by Tu, Feron, Immel and Vogel at Netherlands. The study was not adequate by current standards for the assessment of carcinogenicity of the modified starch due to lack of adequate control group in the study.

Study no.: Not mentioned
Volume # 2, and page #: 825
Conducting laboratory and location: ——————— b(4)
Date of study initiation: Not indicated
GLP compliance: Not known
QA report: yes ( ) no (x)
Drug, lot #, and % purity: Not provided
CAC concurrence: Nil

Methods

Doses: Hydroxypropyl distarch phosphate (HP starch) at 55% in the diet, starch acetate (AC) at 55% in the diet, lactose at 55% in the diet, alginate at 25% in the diet Unmodified potato starch was used as control starch in the control group

Basis of dose selection (MTD, MFD, AUC etc.): Not mentioned

Species/strain: Albino SPF male and female mice
Number/sex/group (main study): 75/group/sex

The study design is shown below.

Group	Treatment	Dose	Male	Female
1	Control, unmodified starch	55% in the diet	75	75
2	Hydroxypropyl distarch phosphate (HP)	55% in the diet	75	75
3	Starch Acetate (AC)	55% in the diet	75	75
4	Lactose	55% in the diet	75	75
5	Alginate	25% in the diet	75	75

Route, formulation, volume: Oral diet
Frequency of dosing: ad lib
Satellite groups used for toxicokinetics or special groups: Nil
Age: 6 weeks, male weighed 21-32 g and female weighed 16-26 g
Animal housing: Males were housed individually and female mice were housed in a group of 5 at 22°C
Restriction paradigm for dietary restriction studies: Nil
Drug stability/homogeneity: Not mentioned
Dual controls employed: No
Interim sacrifices: Nil
Deviations from original study protocol: Not known

Observation times
Mortality: Daily
Clinical signs: Daily
Hematology: Hematology evaluations were conducted on weeks 40 and 78 from 10 mice/group/sex. Blood urea nitrogen and glucose levels were determined from 10 mice/sex/group on weeks 78 and 86. Blood samples were collected from the orbital plexus.

Body weights: Pre study, weeks 1, 2, 4 and once every 4 weeks thereafter
Food consumption: Not mentioned
Histopathology: Peer review: yes ( ), no (x)
Toxicokinetics: Nil

Results

Mortality:

The cumulative mortality data from the published paper is shown in the table below.

Table 1 Cumulative mortality of mice fed HP-starch, AC-starch, lactose or alginate for up to 89 wk

Treatment (% in diet)‡	No. of deaths† by end of wk:						
	26	39	52	65	78	83	89
Males							
Control	2	5	21	36	47	47	47
HP-starch (55)	0	2	7**	12***	23***	23***	28***
AC-starch (55)	2	3	10*	17**	25***	26***	32**
Lactose (55)	0	1	4***	11***	17***	23***	28***
Alginate (25)	2	3	7**	17**	33*	42	47
Females							
Control	6	10	13	14	18	25	27
HP-starch (55)	4	6	10	12	21	24	28
AC-starch (55)	2	2*	6	9	17	19	21
Lactose (55)	1	2*	2**	3**	5**	6***	9***
Alginate (25)	4	6	8	14	21	24	28

HP-starch = Hydroxypropyl distarch phosphate
AC-starch = Starch acetate

†The initial number of mice was 75/sex/group. In wk 80 ten mice/sex/group were killed. These are not included in this Table from wk 83 onwards.

‡Control mice were given diets containing 55% pregelatinized potato starch. The dietary levels of the test products were gradually increased to the percentages shown.

Values marked with asterisks differ significantly (chi-squared test) from those of the controls: *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$

Male mice showed significantly lower deaths in the HP starch, AC starch and lactose fed animals beginning 52 weeks of the treatment compared to unmodified starch. The authors stated that high mortality in the male control group contributed to the difference. Alginate fed male mice also showed high mortality like the control. Male mice showed hemorrhagic myocarditis that could contributed to higher mortality. Female mice fed with lactose in the diet showed lower mortality beginning 52 weeks of the treatment when compared to the control.

Data suggest that male mice had higher mortality and hemorrhagic myocarditis in the control and alginate fed groups. HP and AC starch fed male and female mice had a comparable mortality.

Clinical signs: Loose stool was noted in male and female mice fed with HP starch. Male mice treated with alginate diet showed swollen abdomen.

Body weights: The authors did not provide any data table. However, it was reported that male mice fed with HP starch showed a slight reduction in the body weight from weeks 10 to 48. Female mice fed with HP starch in the diet showed a slight reduction in the body weight after 40 weeks of the treatment. The body weight of mice fed with AC starch was comparable to the control.

Food consumption: The authors did not provide any food consumption data.

Organ weight: The authors stated that the relative weight of cecum and colon was increased in HP starch, AC starch, lactose and alginate fed male and female mice compared to the control fed with unmodified starch.

Gross pathology: Enlarged auricles were reported in male mice from unmodified starch fed control and alginate fed mice. Both groups showed higher mortality than control animals. Male mice fed with HP starch, AC starch and alginate also showed higher granular surface in the kidney. The authors stated that one male mouse in HP starch, one male mouse in the AC starch and 3 lactose fed male mice showed calculi in the urinary bladder. Enlarged seminal vesicles were reported in large number of male rats across the treatment groups.

Histopathology:

Non-neoplastic:

The authors provided a table for the histological changes in the kidney and urinary bladder. In the absence of an untreated control group, the effect of unmodified and modified starches could not be substantiated. However, increased incidences of distended tubules of the kidney were observed in alginate fed male and female mice. A summary table for lesions in the kidney and urinary bladder is shown in the table reproduced from the publication below.

Table 5. Type and incidence of histopathological changes found in the kidneys and urinary bladders of mice fed HP-starch, AC-starch, lactose or alginate for up to 80 wk

Type of lesion / Dietary group...	Incidence of lesion† Male: Control	HP-starch	AC-starch	Lactose	Alginate	Female: Control	HP-starch	AC-starch	Lactose	Alginate
Kidneys										
No. of mice examined‡	73	75	74	74	75	75	72	69	74	73
Chronic nephropathy*										
very slight	23	29	39**	35	35	28	27	33	38	23
slight	13	25*	13	28	16	5	16**	9	11	15*
moderate	5	9	6	3	7	7	8	4	3	11
severe	0	1	1	2	0	7	3	1*	1*	3
Round cell infiltrates:										
slight	48	51	47	56	53	52	40	45	52	50
moderate	7	10	12	7	5	13	18	10	9	11
severe	3	2	5	4	1	2	6	1	0	2
Focal peripyelitis:										
slight	24	23	29	24	32	32	34	33	40	36
moderate	9	13	10	8	3	7	4	7	7	1*
Intratubular calcareous deposits	29	40	39	29	37	13	23*	17	24*	24*
Cyst-like spaces in cortex:										
a few	20	42***	39**	36**	41***	17	27*	20	18	19
several	5	11	9	3	5	3	5	2	1	2
Distended pelvis:										
Unilateral—slight	8	2*	1*	1*	6	1	0	0	0	4
moderate	5	3	4	2	4	0	1	0	0	5*
severe	0	2	3	1	3	2	2	1	1	2
Bilateral—slight	1	2	0	1	4	0	1	0	1	2
moderate	4	0*	1	1	8	0	0	0	0	4*
severe	1	0	0	0	3	1	0	1	0	5
Distended distal tubules§	(28)	(47)	(43)	(47)	(29)	(48)	(45)	(52)	(63)	(48)
very slight	0	0	0	1	6*	2	0	5	4	6
slight	0	0	0	0	10***	0	0	0	0	19***
moderate	0	0	0	0	11***	0	0	0	0	16***
Concrements in pelvis:										
very slight	0	14**	6*	9*	2	2	3	3	5	3
slight	0	1	3	5	0	0	1	0	3	0
Submucosal hemorrhage	0	0	0	1	1	0	0	0	0	0
Lipofuscin-like pigment in cortical tubular epithelium cells	0	0	0	0	0	0	2	0	2	1
Abscess	0	0	1	0	0	0	0	0	0	0
Bladder										
No. of mice examined‡	73	75	74	72	74	69	67	61	70	66
Subepithelial round cell infiltrates:										
slight	16	17	16	19	32**	33	44*	27	40	40
moderate	1	3	3	2	5	6	3	6	4	13
severe	1	0	1	4	2	0	2	3	1	0
Thickened submucosa:										
slight	2	1	3	5	4	2	2	1	0	3
moderate	0	1	3	4*	0	0	0	0	0	0
Thickened epithelium:										
slight	6	8	3	3	7	2	1	2	1	5
moderate	1	0	3	5	4	0	1	0	0	0
severe	0	0	5*	3	3	0	0	0	0	0
Cystitis	3	4	5	9	5	0	1	1	0	2
Proteinaceous/granular material	17	20	21	12	14	0	1	2	0	1
Calcareous material	0	2	6*	7**	0	0	0	0	0	0
Subepithelial hemorrhage	2	3	7	3	5	0	0	0	0	0

HP-starch = Hydroxypropyl distarch phosphate AC-starch = Starch acetate

†Incidence in mice that died during the experiment or were killed at wk 80 or at the end of the experiment.

‡A number of mice could not be examined because of advanced autolysis or loss of tissue during the embedding procedure.

§Only the kidneys of mice that survived to the end of the experiment, and of those killed at wk 80 were examined for this lesion. The no of mice examined is given in brackets.

Values marked with asterisks differ significantly (chi-squared test) from the corresponding control values: *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$

Neoplastic:

Neoplastic lesions are listed in the table below.

Table 6. Site, type and incidence of primary tumours in mice fed HP-starch, AC-starch, lactose or alginate for up to 89 wk

Site and type of tumour — Dietary group...	Incidence of tumours†									
	Males					Females				
	Control	HP-starch	AC-starch	Lactose	Alginate	Control	HP-starch	AC-starch	Lactose	Alginate
No. of mice examined‡	74	75	75	75	74	75	72	69	74	73
No. of mice with tumours	19	22	19	15	14	22	31	26	23	32
Liver										
Firm nodule: type A (hyperplastic)	6	3	1	1	0	1	0	0	0	0
type B (neoplastic)	0	2	1	0	0	0	0	0	0	0
Cystic, haemorrhagic nodule	1	1	4	0	0	0	0	0	0	0
Hepatocellular carcinoma	0	1	0	0	0	0	0	0	0	0
Haemangiosarcoma	1	1	0	0	0	0	0	0	1	0
Reticulum cell sarcoma	1	1	0	1	0	0	0	0	0	0
Fibrosarcoma	0	0	0	0	0	1	0	0	0	0
Lungs										
Alveologenic tumour	4	7	4	3	5	5	4	4	5	3
Reticulum cell sarcoma	0	1	0	0	0	0	0	0	0	0
Blood										
Lymphocytic leukaemia	2	1	0	2	1	1	3	1	3	4
Myeloid leukaemia	1	0	1	1	0	1	2	0	1	0
Thymus										
Thymoma	0	1	0	0	0	1	0	0	2	1
Lymphosarcoma	1	1	0	0	1	0	1	1	2	0
Lymphoreticular malignancy§	0	0	0	0	0	0	1	1	1	1
Mesenteric lymph nodes										
Reticulum cell sarcoma	1	0	1	1	1	0	3	0	0	0
Lymphosarcoma	0	1	0	0	0	0	0	0	0	1
Axillary lymph nodes										
Lymphosarcoma	0	0	1	0	0	0	0	0	0	0
Subpaxotic lymph nodes										
Lymphosarcoma	1	0	0	0	0	0	0	0	0	0
Spleen										
Reticulum-cell sarcoma	0	0	0	0	0	2	0	0	0	1
Lymphosarcoma	0	0	0	0	0	0	1	0	0	0
Abdomen										
Reticulum-cell sarcoma	0	0	0	1	0	0	1	3	2	0
Lymphosarcoma	0	0	0	0	0	0	1	0	0	0
Lymphoreticular malignancy§	0	0	1	0	1	0	2	4	0	2
Fibrosarcoma	0	0	0	1	0	1	0	0	0	1
Sarcoma	0	1	0	0	0	0	0	0	0	1
Osteosarcoma	0	0	0	0	0	0	1	0	0	0
Mesenchymal type of tumour	0	1	0	0	0	1	0	0	1	0
Intestines										
Reticulum-cell sarcoma	1	1	0	0	1	1	3	1	1	4
Lymphosarcoma	0	0	1	1	1	1	0	1	0	0
Carcinoma	0	1	1	0	1	0	1	0	0	0
Lymphoreticular malignancy§	0	0	1	0	0	0	0	0	0	0
Pancreas										
Reticulum-cell sarcoma	1	0	0	0	0	0	0	0	0	0
Adrenals										
Phaeochromocytoma	0	0	1	0	0	0	0	0	0	0
Skin/subcutis										
Fibrosarcoma	0	1	0	2	1	0	3	0	0	2
Rhabdomyosarcoma	0	0	0	0	0	1	0	0	0	0
Myxofibrosarcoma	0	0	0	0	0	0	1	0	0	0
Angiosarcoma	0	0	0	0	0	0	0	1	0	0
Sarcoma	0	0	0	0	0	0	1	1	0	0
Adenocarcinoma	0	0	0	0	0	0	0	0	0	1
Squamous-cell carcinoma	0	1	0	0	0	0	0	0	0	0
Basal-cell carcinoma	0	0	0	0	0	0	0	0	0	1
Sebaceous-gland adenoma	0	0	0	0	0	1	0	0	0	0
Ear shell										
Sarcoma	0	0	0	0	1	0	0	0	0	0
Kidneys										
Lymphoreticular malignancy§	0	0	0	0	0	1	0	0	0	0
Adenoma	0	0	0	1	0	0	0	0	0	0
Thyroid										
Parafollicular-cell carcinoma	0	0	0	0	0	0	0	0	1	0
Parathyroid										
Adenoma	0	0	0	0	0	0	0	0	0	1
Brain										
Mesenchymal type of tumour	0	0	0	0	0	0	1	0	0	0
Pituitary										
Chromophobe adenoma	0	0	0	0	0	0	0	1	0	0
Ovaries										
Granulosa-cell tumour	—	—	—	—	—	1	0	0	1	0
Thecoma	—	—	—	—	—	0	1	1	0	0

[contd]

Table 6. *continued*

Site and type of tumour / Dietary group...	Incidence of tumours†									
	Males					Females				
	Control	HP-starch	AC-starch	Lactose	Alginate	Control	HP-starch	AC-starch	Lactose	Alginate
Uterus/cervix										
Leiomyosarcoma	—	—	—	—	—	0	1	2	0	2
Mesenchymal type of tumour	—	—	—	—	—	0	0	1	0	0
Polyp	—	—	—	—	—	0	0	1	0	0
Mammary glands										
Adenocarcinoma	—	—	—	—	—	3	0	2	2	6
Squamous-cell carcinoma	—	—	—	—	—	0	0	1	2	0
Adenoma	—	—	—	—	—	0	1	0	0	0
Seminal vesicles										
Malignant tumour (unclassified)	0	0	1	0	0	—	—	—	—	—
Total no. of mice with lymphoreticular neoplasms (including leukaemia)...	9	6	6	7	6	7	18*	12	10	13

HP-starch = Hydroxypropyl distarch phosphate AC-starch = Starch acetate
†Incidence in mice that died or were killed when moribund during the experiment or were killed at wk 80 or at the end of the experiment
‡A few mice were lost because of advanced autolysis
§Further classification was not possible.
The value marked with an asterisk differs significantly (chi-squared test) from the corresponding control value: *$P < 0.05$

There were incidental findings of neoplastic changes. However, in the absence of any statistical trend and an untreated control, it is concluded that the modified starches used in the study did not contributed to carcinogenic effect higher than those observed in the unmodified starch fed mice. The study was not conducted according to current standards.

Toxicokinetics: Nil

2.6.6.6 Reproductive and developmental toxicology

Fertility and early embryonic development

There were no fertility and embryonic development study for either tramadol or chemically modified starch submitted.

Embryofetal development

There were no embryofetal development studies for tramadol or chemically modified starch submitted.

Prenatal and postnatal development

Study title: 2-Year feeding and multigeneration studies in rats of five chemically modified starches

Key study findings: Five modified starches at 10% in the feed did not change reproductive performance, mortality, growth and sexual maturation in a three generation study when compared to unmodified starch.

Study no.: Nil (published in Food, Cosmetic, Toxicology, 12, 651-663, 1974
Volume # 2, and page #: 651
Conducting laboratory and location: ———————————————— b(4)

Date of study initiation: Not specified
GLP compliance: Not known
QA reports: yes ( ) no (x)
Drug, lot #, and % purity: Not provided

Methods

Doses: 10% in the diet
Species/strain: Weaning Wistar male and female rats
Number/sex/group: 10 male and 20 female per group
Route, formulation, volume, and infusion rate: Oral diet
Satellite groups used for toxicokinetics: Nil
Study design: The study design is shown below. The study procedures are discussed under parameters and endpoints below.

Group	Starch	Dose	Male (F0)	Female (F0)
1	Potato starch, control for starch in groups 2,3,4,5	10% in the diet	10	20
2	Acetylated distarch phosphate	10% in the diet	10	20
3	Acetylated diamylopectin phosphate	10% in the diet	10	20
4	Starch acetate	10% in the diet	10	20
5	Hydroxypropyl distarch glycerol	10% in the diet	10	20
6	Phosphated distarch phosphate	10% in the diet	10	20
7	Unmodified maize starch, control for starch in group 6	10% in the diet	10	20

Parameters and endpoints evaluated: The body weight was recorded biweekly until week 12. Rats in each group were mated on weeks 13 and 20. Five male and 10

female rats from same group were cohabited for each mating period. The offspring were designated as F1a and F1b for week of mating 13 and 20, respectively. Litter size was recorded. The total weight of the litter (F1 rats) was recoded on days 1, 10 and 20. All F1a litters were sacrificed after weaning. F1b litters were selected for further mating. Ten male and 20 female F1b rats were selected per diet group and fed with the same diet given to the F0 groups. F1b male and female rats were mated on weeks 12 and 20 to produce F2a and F2b pups. F2b offspring were further mated the same way as did for F1b to produce F3a and F3b generation of rats. F2b females were sacrificed after the weaning of all F3 pups. Uteri of F2b rats were treated with ammonium sulphide for counting implantations.

After weaning, 10 male and 20 female F3b rats per group were fed with the diet allotted to the corresponding group for a period of 3 weeks. Body weights of the rat were recorded. F3b rats were sacrificed on week 4, organ weight of selected organs, macroscopic and microscopic changes were examined.

Results

The authors presented the pregnancy rate (%), litter size, body weight of pups for F1a, F1b, F2a, F2b, F3a, F3b, mortality in F1a, F1b, F2a, F2b, F3a, F3b and resorption in the table below.

The pregnancy rate, litter size and average weight of the litter for three generations of rats were comparable between unmodified and modified starches. Mortality of weaning pups from F0 generation (F1a pups) was higher for starch 6 (phosphated distarch phosphate). However, a similar incidence of mortality in weaning rats (F3a generation) was also observed (pups from F2b rats fed with unmodified potato starch, starch 1). Therefore, it was concluded that pups nursed by dams fed with modified starches did not alter the survival of weaning rats. Resorption of fetuses in the multiple generation study was also not affected by feeding dams with modified starches.

Data suggest that modified starches used in the study had no effect on the reproduction of male and female rats in the three generation study.

Table 5 *Reproduction data for F_0–F_2 generation in rats fed modified starches at a dietary level of 10%*

Starch in diet†	Percentage of females with litter‡	Average no. of rats/litter at birth	Mean body weight (g) of young at day 1	Mean body weight (g) of young at day 10	Mean body weight (g) of young at day 20	Mortality (%) in young at day 10	Mortality (%) in young at day 20	Reception quotient§
			F_0, first mating					
1	100	9·9	6·4	20·8	42·0	0·7	1·4	
2	100	10·4	6·4	20·2	40·9	0	0·6	
3	95	10·7	6·1	20·8	41·4	1·4	1·4	
4	90	10·9	5·9	19·8	40·4	2·1	2·1	
5	100	10·5	6·2	21·3	41·3	0·7	0·7	
6	100	10·5	6·4	20·7	42·2	4·6	4·6	
7	100	11·7	6·0	19·8	40·2	0·7	0·7	
			F_0, second mating					
1	100	10·8	6·2	20·9	41·9	0	0	1·09
2	100	11·7	6·3	20·4	40·7	1·2	1·2	1·01
3	100	11·3	6·2	19·7	39·9	0·6	0·6	0·96
4	95	11·8	5·9	19·4	39·3	0	0	1·14
5	100	11·1	6·5	21·1	43·0	0	0	0·99
6	100	11·2	6·3	21·0	42·9	0·7	0·7	1·08
7	95	12·6	5·8	20·5	41·0	1·4	1·4	1·00
			F_{1a}, first mating					
1	100	10·7	6·5	19·8	38·3	2·0	2·0	
2	100	9·2	6·6	20·4	40·8*	0·7	0·7	
3	100	9·7	6·3	19·8	37·8	1·9	1·9	
4	100	9·6	6·5	19·8	38·2	0	0	
5	95	11·2	6·2	19·8	38·5	0	0	
6	100	10·1	6·5	20·1	39·5	0	0	
7	100	9·9	6·4	19·5	38·8	0	0·7	
			F_{1a}, second mating					
1	100	10·6	6·6	21·3	42·7	0	0	1·10
2	95	11·2	6·6	21·2	42·2	0	0	1·06
3	95	11·3	6·3	20·9	41·4	0·7	0·7	1·08
4	100	10·1	6·3	21·2	42·3	1·4	1·4	1·09
5	100	12·1	6·4	20·1	40·5	3·1	3·8	1·04
6	100	10·6	6·4	21·0	41·4	2·6	2·6	1·07
7	100	10·3	6·3	20·9	41·9	1·4	1·4	1·13
			F_{2a}, first mating					
1	100	11·2	6·6	21·6	40·6	5·3	5·3	
2	90	9·9	7·2	22·8	44·7**	0	0	
3	100	10·1	6·7	21·7	41·1	0	0	
4	100	10·7	6·8	21·0	41·2	0	0·6	
5	95	9·5	6·5	20·9	40·9	0	0	
6	100	11·1	6·6	22·5	39·4	1·3	1·3	
7	95	11·1	6·4	21·5	41·1	1·3	1·3	
			F_{2a}, second mating					
1	100	10·9	6·3	21·2	42·2	1·4	2·2	1·06
2	100	11·0	6·7	23·9*	45·3*	0·7	1·4	1·07
3	100	11·2	6·4	22·1	42·2	0	0	1·06
4	100	9·5	6·7	23·1	43·7	2·0	2·0	1·05
5	100	10·1	6·4	21·6	41·4	0	0	1·04
6	90	10·1	6·4	22·0	42·3	0	0	1·04
7	90	10·5	6·4	23·8	43·3	0	0·8	1·08

†Groups fed diets containing unmodified starches 1 and 7 were used as controls for groups given starches 2, 3, 4 and 5 and starch 6, respectively.
‡No. of females mated in each group was 19 or 20.
§No. of implantation sites/no. of young born.
Values marked with asterisks differ significantly (Student's *t* test) from the corresponding controls: *$P < 0·05$; **$P < 0·01$.

2.6.6.7 Local tolerance: No local tolerance studies were was submitted.

2.6.6.8 Special toxicology studies

Study title: Hydroxypropyl distarch phosphate from Tapioca starch reduces zinc and iron absorption, but not calcium and magnesium absorption in rats by Kishida et al., J. Nutr. 131, 294-300, 2000.

Key study findings: A reduction in the absorption of zinc and iron was noted in rats fed at 50 g/kg modified starch in rats.

Study no.: Nil
Volume # 2, module 4 and page #: 294
Conducting laboratory and location: [redacted] b(4)

Date of study initiation: Not mentioned
GLP compliance: Not mentioned
QA reports: yes ( ) no (x)

Results: The published article indicated that gelatinized hydroxypropyl distarch phosphate at 50 g/kg/oral for 21 days showed a reduction in the absorption of zinc and iron by 75 and 70% respectively, compared to the control in male Wistar rats.

2.6.6.9 Discussion and Conclusions

The sponsor provided acute toxicity, bacterial mutation and chronic toxicity data that show hydroxypropyl distarch acetate is not mutagenic and its potential for toxicity at about 85 mg daily dose is minimal. The modified starch is considered to be a food additive and considered to be safe. No new safety data were submitted for tramadol. Based on the nonclinical information Tramadol Contramid OAD is approvable.

2.6.6.10 Tables and Figures

Nil

2.6.7 TOXICOLOGY TABULATED SUMMARY

[Pivotal studies pertinent to the primary indication and core pharmacology studies relevant to the primary pharmacodynamic effect, as available and as provided by the sponsor]

Table 2.6.7 – 1 Toxicology Overview (continued)

Type of Study	Test article	Species and Strain	Administration/ Exposure	Dosing Duration	Doses	Testing Facility (GLP Compliance)	Study and reference	CTD Section/ Vol. / Pg.
Carcinogenicity	Unmodified potato starch (control)	Albino SPF mouse	Diet	88 weeks	50 %	Institute CIVO-Technology and Nutrition in cooperation with AVEBE BA and Koninklijke Scholten-Honig (NR)	Til et al. 1988	4.3 Lit. Ref. Vol. 2
	Hydroxypropyl distarch phosphate				50 %			
	Starch acetate				50 %			
	Lactose (control)				50 %			
	Sodium alginate (control)				25 %			
	Unmodified potato starch (control)	Wistar Rat	Diet	2 years	30 %	Central Institute for Nutrition and Food Research (CIVO) in cooperation with AVEBE GA, and Koninklijke Scholten-Honig(NR)	De Groot et al. 1974	4.3 Lit. Ref. Vol. 2
	Acetylated distarch phosphate				5, 10, 30 %			
	Acetylated distarch adipate				5, 10, 30 %			
	Starch acetate				5, 10, 30 %			
	Hydroxypropyl distarch glycerol				5, 10, 30 %			
	Unmodified maize starch (control)				30 %			
	Phosphated distarch phosphate				5, 10, 30 %			
	Unmodified maize starch (control)	OFA Rat	Diet	2 years	62 %	Centre de Recherches Toxicologiques (NR)	Toussaint et al. 1979	4.3 Lit. Ref. Vol. 2
	Acetylated distarch glycerol				62 %			
	Acetylated distarch adipate				62 %			
Reproduction, Multi-generation	Unmodified potato starch (control)	Wistar Rat	Diet	3 generations	10%	Central Institute for Nutrition and Food Research (CIVO) in cooperation with AVEBE GA, and Koninklijke Scholten-Honig(NR)	De Groot et al. 1974	4.3 Lit. Ref. Vol. 2
	Acetylated distarch phosphate							
	Acetylated distarch phosphate							
	Starch acetate							
	Hydroxypropyl distarch glycerol							
	Unmodified maize starch (control)							
	Phosphated distarch phosphate							

NR: Not Reported

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: The sponsor submitted toxicity studies for Contramid (hydroxypropyl distarch phosphate). A single dose study in rats showed no mortality to Contramid up to 2000 mg/kg. Based on the published literature, modified starch showed no carcinogenic potential when compared to the unmodified starch. However, an increase in the weight of cecum was noted at 30-50% in the diet. The clinical significance of the finding is unknown.

Contramid is considered to be a modified starch and does not require to be tested for its safety as an inactive excipient. Based on the available information, Contramid is relatively safe as an inactive ingredient. The sponsor did not submit any new data for tramadol.

Unresolved toxicology issues (if any): Nil

Recommendations: Tramadol Contramid OAD is recommended for approval from nonclinical safety point of view considering Contramid is a modified starch.

Suggested labeling:

Sponsor's proposed label was modified based on the maximum recommended human doe of Tramadol Contramid OAD. The proposed label is similar to Ultram label considering a 505(b)(2) application.

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✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

b(4)

Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____ Concurrence Yes ___ No ___

APPENDIX/ATTACHMENTS

C.C:

NDA 21-745 Div File/DAARP
Paul Balcer/Project Manager/DAARP
Asoke Mukherjee/Pharmacologist/DAARP
Daniel Mellon/Team Leader/DAARP
Ali Al Hakim/Chemist/DAARP
Jin Chen/Medical Officer/DAARP
Suresh Doddapaneni//Biopharm Team Leader/ DAARP

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

SUPERVISOR'S SECONDARY REVIEW
PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**21-745**
SERIAL NUMBER:	**000 AZ**
DATE RECEIVED BY CENTER:	**02-Jul-2008**
PRODUCT:	**Ryzolt (tramadol hydrochloride extended-release tablets)**
INTENDED CLINICAL POPULATION:	**Management of moderate to moderately severe pain**
SPONSOR:	**LaboPharma Canada**
REVIEW DIVISION:	**Division of Anesthesia, Analgesia, and Rheumatology Products (HFD-170)**
PHARM/TOX REVIEWER:	**Asoke Mukherjee, Ph.D.**
PHARM/TOX SUPERVISOR:	**R. Daniel Mellon, Ph.D.**
DIVISION DIRECTOR:	**Bob A. Rappaport, M.D.**
PROJECT MANAGER:	**Kathleen Davies**

Date of review submission to Division File System (DFS): December 5, 2008

Executive Summary

Recommendations

A. Recommendation on approvability

I concur with Dr. Mukherjee's original recommendation for this NDA. From a nonclinical pharmacology toxicology perspective, NDA 21-745 may be approved pending agreement on the product labeling.

B. Recommendation for nonclinical studies

None

C. Recommendations on labeling

b(4)

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_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

R. Daniel Mellon
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PHARMACOLOGIST

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