CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: NDA 20070/S-004, S-006

Trade Name: COGNEX

Generic Name: TACRINE HYDROCHLORIDE

Sponsor: PARKE-DAVIS PHARMACEUTICAL

Approval Date: OCTOBER 10, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: NDA 20070/S-004, S-006

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	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tentative Approval Letter			X	
Approvable Letter			X	
Final Printed Labeling		X		
Medical Review(s)	X			
Chemistry Review(s)				X
EA/FONSI				X
Pharmacology Review(s)				X
Statistical Review(s)				X
Microbiology Review(s)				X
Clinical Pharmacology Biopharmaceutics Review(s)				X
Bioequivalence Review(s)				X
Administrative Document(s)	X			
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20070/S-004, S-006

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-070/S-004, S-006

Parke-Davis Pharmaceutical Research
Division of Warner-Lambert Company
Attention: Byron Scott
2800 Plymouth Road, P.O. Box 1047
Ann Arbor, MI 48106-1047

OCT 10 1997

Dear Mr. Scott:

Please refer to your supplemental new drug applications dated July 19, 1995 (S-004) and March 27, 1996 (S-006) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cognex® (tacrine hydrochloride) Capsules 10, 20, 30 and 40 mg.

We also acknowledge receipt of the following submissions:

S-004:	S-006:
September 19, 1995	April 29, 1997 (received April 30, 1997) June 10, 1997 September 10, 1997 September 16, 1997

The User Fee goal date for supplement (S-006) is October 30, 1997.

Supplemental application S-004 provides for:

- Revision of the "WARNINGS:Gastrointestinal Disease and Dysfunction" section to clarify that patients are at risk for developing GI ulcers with or without a previous history of ulcer disease.
- The addition of "falling" as an ADVERSE REACTION.
- Changing "perforated duodenal ulcer" to "perforated peptic ulcer" in the "ADVERSE REACTION:Postintroductory Reports" section of labeling.

The *revised* supplemental application (S-006) provides for:

- Starting dose of 40 mg/day with dose escalation in 40 mg/day increments at 4-week intervals.

- Monitor serum transaminase levels every other week beginning 4 weeks after initiation of therapy to continue through week 16 after which monitoring may be decreased to every 3 months.

We have completed the review of these supplemental applications, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling in the submissions dated September 19, 1995 (S-004) and September 16, 1997(S-006) with the revision listed below. Accordingly, these supplemental applications are approved effective on the date of this letter.

The revision is as follows:

> We ask that you list the adverse reaction term "falling" under the "Postintroduction Reports" subsection of ADVERSE REACTIONS rather than under the "Other Adverse Events Observed During All Clinical Trials" subsection.

This revision is a term of the supplemental NDA approvals.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved supplemental NDAs 20-070/S-004/S-006. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

Should a letter communicating important information about this drug product (i.e., a "Dear Doctor" letter) be issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to these NDAs and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20852-9787

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Robbin Nighswander, R.Ph., Regulatory Management Officer, at (301) 594-2850.

Sincerely yours,

Paul Leber, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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cc:
Original NDA 20-070
HFD-120/Div. files
HFD-120/Leber
/Levin/Oliva
/Nighswander
HFD-002/ORM (with labeling)
HFD-101/Office Director
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-735/DPE (with labeling) - for all NDAs and supplements for adverse reaction changes.
HFD-560/OTC (with labeling - for OTC Drug Products Only)
HFI-20/Press Office (with labeling)

Drafted by:rmn/September 25, 1997
N20070s6.ap

APPROVAL (AP)

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20070/S-004, S-006

MEDICAL REVIEW(S)

Review and Evaluation of Clinical Data

NDA	**20-070**
Sponsor:	**Parke-Davis**
Drug:	**Cognex® (tacrine hydrochloride)**
Proposed Indication:	**Alzheimer's Disease**
Material Submitted:	**NDA Supplement**
Correspondence Date:	**3/27/96**
Date Received / Agency:	**3/28/96**
Date Received / Reviewer:	**8/27/96**
Date Review Completed	**10/9/96**

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Introduction:

This submission is a supplement to the approved NDA 20-070 for Cognex®. It includes changes to labeling, along with supporting documentation.

The sponsor requests the following changes:

1. Recommendation of a starting dose of 80 mg/day (vs. 40 mg/day currently)
2. Dose escalation every 4 weeks (vs. 6 weeks currently)
3. Monthly monitoring of ALT/SGPT (vs. every-other-week currently)
4. Revised statements on continued treatment and dose-escalation of patients with ALT elevations > 5x ULN (vs. current recommendations to stop treatment above this level)
5. Recommendation to stop treatment if ALT/SGPT > 20x ULN (vs. > 5x ULN currently), or in cases of jaundice, bilirubin > 3 mg/dL, or hypersensitivity (rash, fever) in association with ALT/SGPT elevations.
6. Add a statement that continued treatment, reexposure, and/or dose-escalation in patients with ALT/SGPT > 20 x ULN has not been studied, and the risks of treatment in these settings are unknown.

Chemistry:

Chemical Name: 1,2,3,4-tetrahydro-9-acridinamine monohydrochloride monohydrate, commonly referred to as THA
Chemical Formula: $C_{13}H_{14}N_2 \bullet HCl \bullet H_2O$
Molecular Weight: 252.74

Pharmacology:

Cognex® is a reversible inhibitor of cholinesterase.

Indication:

Cognex® is currently approved for the treatment of mild to moderate dementia of the Alzheimer's type.

Background Information Regarding Tacrine Safety

Tacrine was approved by the FDA in 1993 for the treatment of mild to moderate dementia of the Alzheimer's type. This approval was based on the demonstration of efficacy in two randomized, placebo-controlled trials of 12 and 30 weeks duration (970-26 and 61) respectively, at doses up to 160 mg/day. At the time of approval, 8,000 patients had received tacrine in clinical trials and treatment IND.

The primary side effects were and remain elevations in serum transaminases and dose related cholinergic effects on the gastrointestinal tract.

The major safety concern is the development of ALT/SGPT elevations and the potential for clinically significant hepatotoxicity. The first multi-center trial (970-1)

begun in 7/87 was halted temporarily in October after 48 patients had been treated. Forty percent had transaminases in the abnormal range, and 25% had elevations 3 times the upper limits of normal. None had symptoms of clinical hepatotoxicity and all transaminases returned to normal 4-6 weeks after discontinuation. ALT/SGPT appeared to be a more sensitive indicator of tacrine's hepatic effects, with AST/SGOT tending to follow with lower maximum values.

The effects on ALT/SGPT were evaluated in 2446 patients in clinical trials, the majority of whom underwent weekly testing. Weekly monitoring was effective in identifying patients with elevated levels but, in clinical practice, this added substantial cost and inconvenience for patients and caregivers.

A total of 276 patients underwent every-other-week monitoring of ALT/SGPT. The pattern of elevation seen was similar to those undergoing weekly testing. A panel of expert hepatologists concluded that every-other-week monitoring did not increase a patient's risk for hepatotoxicity. Based on this, the Agency in 1995 approved changes to labeling to allow every-other-week monitoring during the first 16 weeks of treatment.

The current product labeling recommends a starting dose of 40 mg/d and dose escalation every 6 weeks. The sponsor argues that in clinical practice, dose escalation every 6 weeks may result in treatment failure due to an extended period at lower tacrine doses, which may be below a patient's maximally effective dose. Approximately 1500 patients in clinical trials were titrated at intervals of 4 weeks or less. These patients showed no increase in the frequency of ALT elevations or clinically evident liver-related adverse events compared with every 6 weeks titration.

The current labeling also recommends reducing the tacrine dose by 40 mg/day for patients whose ALT/SGPT > 3x ULN, and stopping at > 5x ULN. Although most patients can be restarted on tacrine once their ALT/SGPT level returns to within normal limits, there are little data on the effects of continued treatment and dose-escalation in patients with ALT/SGPT elevations.

An open label study (970-77) in 625 patients with Alzheimer's Disease has been completed to evaluate ALT/SGPT monitoring at weeks 4, 6, 8, 12, and 16 (monthly plus week 6), dosage escalation every 4 weeks, a starting dose of 80 mg/day and continued treatment and dose-escalation in the setting of ALT/SGPT ≤ 20 x ULN. These results, plus supporting data from previous trials, form the basis for this supplemental NDA.

Data Sources

The following table contains the data source supporting the labeling changes.

Study	*N*	*Starting Dose (mg/d)*	*Escalation Frequency*	*Increment/ Max Dose (mg/d)*	*ALT/SGPT Monitoring*	*Patient Management*
970-6	144	placebo	NA	NA	weekly	No change if ALT≤3xULN
	146	40				stop if ALT>3xULN
	150	80				
970-26	387	20 or 40	q 6 wks	40/80	weekly	No change if ALT≤3xULN
						stop if ALT>3xULN
970-33	92	40	q 2 days & weekly	20/120	q 2 weeks	patients with "consistently raised LFT's" were withdrawn
970-48/52	85	40	q 2 days & weekly	20/120	q 2 weeks	patients with "consistently raised LFT's" were withdrawn
970-61	479	40	q 6 weeks	40/160	weekly	No change if ALT≤3xULN
						stop if ALT>3xULN
970-62	127	40	q 4 weeks	40/160	q 2 weeks	No change if ALT≤3xULN
						stop if ALT>3xULN
970-77	104	40	q 4 weeks	40/160	q 2 weeks	No change if ALT≤5xULN
	260	40	"		monthly	Weekly monitoring if ALT>5x &≤20x ULN
	261	80	"		monthly[1]	Stop if ALT>20xULN
Treatment IND	9861	40	q 6 weeks	40/160	weekly	No change if ALT≤3xULN
						Reduce dose by 50% if ALT>3x &≤5x ULN
						Stop if ALT>5xULN
US Post-Marketing	190K	40	q 6 weeks	40/160	weekly or q 2 weeks	Per current labeling

[1] according to the protocol, patients remained on 80 mg q.d. for 8 weeks prior to escalation.

Study 970-77 is included in this submission. 970-61 and 26 were the two pivotal studies. 970-62 was the open label extension of 970-61. 970-33/48/52 were done in the UK by Shire Pharmaceuticals. 970-6 used an enrichment design and only data from the first 2 weeks of treatment are used in this submission. The treatment IND and post-marketing experience provide additional information regarding the frequency of ALT/SGPT elevations >20x ULN and deaths due to hepatic dysfunction.

I provide a detailed review of the proposed changes to labeling (numbered 1-6) in the subsequent section.

1. Starting Dose of Tacrine 80 mg/day

Studies 970-6 and 77 provide data for comparison of tacrine 40 and 80 mg/d starting doses in over 900 patients. The issues determining the optimal starting dose are:

a. incidence and severity of cholinergic-mediated events
b. patient withdrawals due to adverse events
c. transaminase elevations:
   - incidence
   - severity
   - time to onset
   - time to recovery

Study 970-6

Patients were randomly assigned to one of three treatments: placebo, tacrine 40 mg/day, or tacrine 80 mg/day in 4 divided doses during the initial 2 weeks of treatment. Study medication was introduced gradually, over 3 days, such that patients took 2 capsules on day 1, 3 capsules on day 2, and began 4 times daily dosing on day 3. Adverse effects were the following:

Study 970-6: Adverse Events That Occurred During the First 2 Weeks in 2% of patients on Placebo, 40, or 80 mg/day Tacrine [Number (%) of Patients]

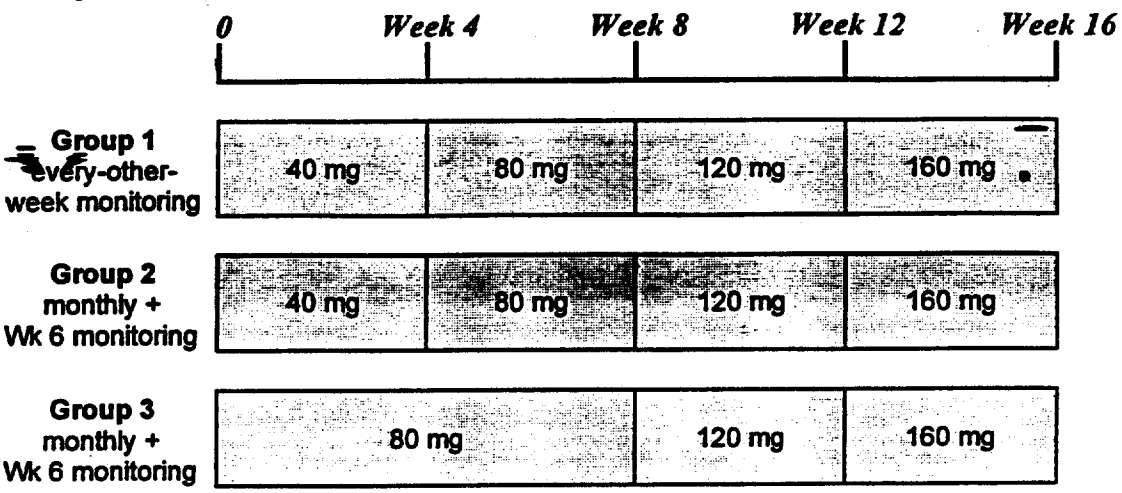
Adverse Event	Placebo N = 144	40 mg/day N = 146	80 mg/day N = 150
Nausea and/or Vomiting	5 (3)	4 (3)	34 (23)
Headache	7 (5)	6 (4)	8 (5)
Diarrhea	8 (6)	1 (1)	9 (6)
Dyspepsia	0 (0)	2 (1)	5 (3)
Abdominal Pain	1 (1)	3 (2)	3 (2)
Dizziness	2 (1)	1 (1)	5 (3)
Eructation	0 (0)	1 (1)	3 (2)
Anorexia	1 (1)	0 (0)	3 (2)
ANY	**33 (23)**	**33 (23)**	**59 (39)**

The 80 mg group experienced a remarkably increased incidence of nausea and vomiting. The incidence of other events were comparable. The following table summarizes the discontinuations. Those treated with 80 mg/day discontinued at roughly twice the rate of those at 40 mg (4% vs. 2%). Because of the short (2 week) observation period, the impact on transaminases could not be assessed.

Study 970-6:AEs That Led to Withdrawal of Patients During the First 2 Weeks

Adverse Event	Placebo N = 144	40 mg N = 146	80 mg N = 150
Elevated Transaminases	0	1	1
Nausea and/or Vomiting	0	0	1
Fracture	1	0	0
Atrial Fibrillation	0	1	0
Bradycardia	0	0	0
Dyspnea	0	1	0
Chest Pain	0	1	0
Pallor	0	0	1
Vasodilatation	0	0	1
Increased Sweating	0	0	1
Total Withdrawn	**1**	**3**	**6**

Study 970-77



Patients were assigned randomly to one of three treatment groups:

- Group 1 started at 40 mg/day tacrine with ALT/SGPT monitoring every other week;
- Group 2 started at 40 mg/day with ALT/SGPT monitoring monthly, and wk 6
- Group 3 started at 80 mg/day with ALT/SGPT monitoring monthly, and wk 6

Groups 1 and 2 were titrated in 40-mg/day increments every 4 weeks to 80, 120, and 160 mg/day. Group 3 stayed on 80 mg/day for 8 weeks[1], titrated to 120 mg/day for 4 weeks, and then 160 mg/day for 4 weeks.

All patients took tacrine in divided doses four times daily from Day 1 of treatment. Patients were required to stop tacrine treatment if their ALT/SGPT level was >20 x ULN. The following table summarizes the most common adverse events seen.

970-77: Adverse Effects during 1 4 weeks of Study
Number (%) of Patients

Adverse Event	40 mg/day N=364	80 mg/day N=261
Nausea and/or Vomiting	20 (5)	47 (18)
Diarrhea	7 (2)	16 (6)
Dyspepsia	11 (3)	10 (4)
Agitation	6 (2)	9 (3)
Headache	6 (2)	6 (2)
Myalgia	8 (2)	3 (1)
Dizziness	6 (2)	5 (2)
Anorexia	4 (1)	6 (2)
Rhinitis	8 (2)	2 (1)
Urinary Tract Infection	8 (2)	2 (1)
Insomnia	7 (2)	1 (<1)
Rash	3 (1)	5 (2)

[1] The proposed labeling allows escalation after only 4 weeks, which this study did not evaluate.

Gastrointestinal related side effects were higher in the 80 mg group vs. 40 mg (28% vs. 15%)[2]. The three most common GI effects (N/V, diarrhea, and dyspepsia) occurred in 28% vs. 10.4%. Similarly, severe side effects resulting in withdrawal, primarily consisting of severe nausea and vomiting, occurred with higher frequency in the 80 mg group (7% vs. 3%).

Over the next 4 weeks, Groups 1 and 2 were titrated to 80 mg/day while Group 3 remained on 80 mg/day. Overall during the first 8 weeks, 35 patients (9.6%) in Groups 1 and 2 stopped treatment because of adverse events, compared with 32 (12.2%) in Group 3. The sponsor states that starting treatment at 40 mg/day **did not make a significant difference** in the numbers of patients who eventually tolerated the 80 mg/day dose. The sponsor states that withdrawal rates due to adverse events were similar after 8 weeks when all patients had been exposed to 80 mg/day for at least 4 weeks[3] (see next table).

Study 970-77: Withdrawals due to Severe Side Effects
Number (%) of Patients

	40 mg N=364	80 mg N=261
Weeks 1-4	10 (2.7)	19 (7.3)
Weeks 5-8	25 (6.9)	13 (5)
Total Weeks 1-8	**35 (9.6)**	**32 (12.2)**

Hepatic Effects:

There was only a slightly greater (43% vs. 38%) incidence of ALT/SGPT elevation in the 80 mg group. There was no difference in the incidence of extreme elevations (>20 x ULN).

Study 970-77: Cumulative Incidence of Maximum ALT/SGPT Elevations
Number (%) of Patients

	Group 1 40 mg N=103	Group 2 40 mg N=249	Group 3 80 mg N=247
WNL	64 (62)	154 (62)	142 (57)
> ULN	39 (38)	95 (38)	106 (43)
>2 x ULN	31 (30)	59 (24)	70 (28)
>5 x ULN	16 (16)	31 (12)	34 (14)
>10 x ULN	8 (8)	15 (6)	21 (9)
>20 x ULN	3(3)	6(2)	7 (3)

[2] This comes from a complete list of adverse events located in Appendix 4 of the submission which includes questionable GI categories such as dental abnormalities and gum hemorrhage
[3] In fact, those at 80 mg for 8 wks had a 27% greater chance of discontinuing than those who started at 40 mg for 4 weeks ((12.2-9.6) / 9.6 x 100 = 27.1%)

There were no significant differences in time to onset, peak, onset to recovery, recovery, or in maximum ALT/SGPT elevations among the three treatment groups, as illustrated in the next table.

Study 970-77: Time to Onset, Peak, Recovery of first ALT/SGPT Elevation > 5xULN and Maximum ALT/SGPT

	Group 1 N = 103 40 mg	Group 2 N = 249 40 mg	Group 3 N = 247 80 mg
N (%) with ALT/ SGPT >5 x ULN[a]	16 (16)	31 (12)	34 (14)
Time (Days)			
To Onset			
Mean (SE)	47 (4)	48 (4)	47 (4)
95% CI	39,55	41,55	39,55
Median	43	43	43
Range			
Onset to Peak			
Mean (SE)	8 (2)	7 (2)	7 (2)
95% CI	3, 13	3, 10	3, 11
Median	8	0	0
Range			
Onset to Recovery			
Mean (SE)	36[b] (4)	42 (4)[c]	38 (3)[d]
95% CI	28,45	34,49	31,45
Median	36	42	33
Range			
Peak to Recovery			
Mean (SE)	29 b (3)	36 (3)[c]	32 (3)[d]
95% CI	23,35	29,43	26,38
Median	28	30	28
Range			
Maximum ALT/ SGPT (x ULN)			
Mean (SE)	12 (2)	12 (1)	13 (1)
95% CI	9, 15	9, 14	10, 16
Median	10	10	11
Range			

[a] p-value for group difference = 0.836 (CMH analysis)
[b] N = 14; 2 patients had not recovered by the last observation
[c] N = 30; 1 patient had not recovered by the last observation
[d] N = 28; 6 patients had not recovered by the last observation
[e] p-value for group difference = 0.903 (ANCOVA)

Summary

The sponsor states these data support a starting dose of 80 mg/day. They point out there is a higher (three fold or greater) increase in nausea/vomiting and diarrhea in the 80 mg/day group compared with 40 mg/day group (18% vs. 5% and 6% vs. 2% respectively). They further state that starting at 40 mg/day did not affect the number of patients who actually tolerated 80 mg/day. However, my calculations on the data show that withdrawals due to severe adverse events were 27% greater at 8 weeks in those patients who started on 80 mg/day compared with those who started on 40 mg/day and titrated to 80 mg/day after

four weeks (12.2% vs. 9.6% respectively).There were no significant differences among the three groups with respect to observed transaminase elevations.

2. Dose escalation every 4 weeks

The current labeling recommends a starting dose of 40 mg/day and dose escalation every 6 weeks in 40 mg/day increments to a maximum of 160 mg/day. The adverse event profile for patients treated in this fashion, along with 40 mg q 4 weeks and 20 mg q 2 weeks (last column) is summarized in the next table.

Studies 970-26/61, 970-77, 970-62, and 970-33/48/52 Adverse Events That Occurred in 2% of Patients Who Started Treatment With Tacrine 40 mg/day
[Number (%) of Patients]

	Titration Frequency			
	q 6 Weeks	q 4 weeks		<4 Week
Adverse Event[b]	970-26/61 N = 634	970-77 N = 364	970-62 N = 127	970-33/48/52 N = 166
Elevated Transaminases	184 (29)	57 (16)[c]	41 (32)	51 (31)
Nausea and/ or Vomiting	178 (28)	163 (45)	18 (14)	82 (49)
Diarrhea	99 (16)	59 (16)	10 (8)	29 (17)
Dizziness	73 (12)	29 (8)	4 (3)	21 (13)
Headache	67 (11)	22 (6)	3 (2)	15 (9)
Dyspepsia	57 (9)	31 (9)	5 (4)	13 (8)
Myalgia	54 (9)	23 (6)	0 (0)	4 (2)
Anorexia	54 (9)	54 (15)	12 (9)	32 (19)
Rhinitis	51 (8)	16 (4)	2 (2)	4 (2)
Abdominal Pain	48 (8)	41 (11)	5 (4)	18 (11)
Rash	46 (7)	14 (4)	4 (3)	9 (5)
Agitation	43 (7)	24 (7)	7 (6)	12 (7)
Confusion	42 (7)	18 (5)	4 (3)	16 (10)
Insomnia	37 (6)	21 (6)	5 (4)	6 (4)
Ataxia	36 (6)	14 (4)	8 (6)	5 (3)
Fatigue	26 (4)	14 (4)	1 (1)	7 (4)
Chest Pain	24 (4)	8 (2)	0 (0)	0 (0)
Constipation	24 (4)	18 (5)	2 (2)	1 (1)
Depression	22 (4)	17 (5)	5 (4)	21 (13)
Somnolence	22 (4)	12 (3)	4 (3)	7 (4)
Flatulence	22 (4)	9 (2)	0 (0)	8 (5)
Urination Frequency	21 (3)	2 (1)	1 (1)	6 (4)
Weight Decrease	21 (3)	30 (8)	6 (5)	1 (1)
Urinary Tract Infection	21 (3)	27 (7)	2 (2)	3 (2)
Upper Respiratory Infect.	18 (3)	10 (3)	3 (2)	6 (4)
Coughing	17 (3)	9 (2)	0 (0)	2 (1)
Thinking Abnormal	17 (3)	2 (1)	3 (2)	8 (5)
Vasodilatation	16 (3)	4 (1)	2 (2)	3 (2)
Anxiety	16 (3)	10 (3)	0 (0)	5 (3)
Urinary Incontinence	16 (3)	3 (1)	4 (3)	1 (1)
Hostility	15 (2)	4 (1)	2 (2)	17 (10)
Back Pain	15 (2)	6 (2)	2 (2)	0 (0)
Asthenia	15 (2)	9 (2)	6 (5)	2 (1)
Purpura	15 (2)	3 (1)	2 (2)	3 (2)
Hallucination	15 (2)	5 (1)	4 (3)	7 (4)
Tremor	14 (2)	10 (3)	1 (1)	9 (5)
Any Event	503 (79)	311 (85)	76)	152)

[a] All patients started treatment with tacrine 40 mg/day.
[b] A patient may have had more than one adverse event.

[c]Transaminase elevations were not consistently reported as adverse events in Study 970-77. Based on clinical laboratory data for patients in 970-77 who started on 40 mg/day and had pre- and post-treatment ALT/SGPT measurements, 20% of patients had an ALT elevation >3 x ULN.

Patients who were titrated every 4 weeks or less, had a higher incidence of nausea and/or vomiting than patients titrated every 6 weeks. The sponsor states it is unclear whether this is due to the rate of titration, or due to the fact that a higher proportion of patients in the later groups were exposed to higher tacrine doses in these studies. For example, in Study 970-77, patients were not required to stop treatment unless ALT/SGPT was >20 x ULN, and therefore a greater percentage of patients achieved doses of 120 and 160 mg/day than in earlier studies. Other than the incidence of nausea and/or vomiting, there are no clinically important differences in adverse event profile based on titration frequency. The sponsor states a shorter dose-escalation interval may allow more patients to achieve doses within the effective dose range more rapidly.

Hepatic Effects

There was no difference in incidence and severity of transaminase elevations in the patients titrated every 4 weeks in study 970-77 compared with those titrated every 6 weeks in study 970-61.

Studies 970-61 and 970-77: Cumulative Incidence of Maximum ALT/SGPT Elevations

Maximum ALT/ SGPT	970-61 N = 479[a]		970-77 N = 599[b]	
Within Normal Limits	221	(46)	360	(60)
> ULN	258	(54)	239	(40)
>2 x ULN	181	(38)	160	(27)
>3 x ULN	139	(29)	123	(21)
>10 x ULN	31	(6)	44	(7)
>20 x ULN	9	(2)	16	(3)

[a]Starting dose of 40 mg/day; dose escalation every 6 weeks.
[b]Starting dose of 40 or 80 mg/day; dose escalation every 4 weeks.

Summary

Patients titrated at 4 weeks had a higher incidence of nausea and vomiting compared with those titrated at 6 weeks (263/657 or 40% vs. 28%). This may be due, in part, to the fact that patients in 970-77 (and other studies as well) achieved higher total doses of tacrine since continued titration was allowed past ALT/SGPT>3x UNL. There were no other significant increases in adverse events with the 4 week titration interval, nor in the incidence and severity of ALT/SGPT elevations.

3. Monthly monitoring of SGPT (vs. every-other-week currently)

Data from study 970-77 are used to evaluate the safety of monthly ALT/SGPT monitoring. Group 1 underwent every-other-week monitoring. Groups 2 and 3 underwent monthly monitoring plus week 6. Since there was no difference in

ALT/SGPT elevation between Group 2 (40 mg onset) and Group 3 (80 mg onset), these two are combined for analysis.

Study 970-77: Time to Onset, Peak, and Recovery of first ALT/SGPT Elevations > 10x ULN and Maximum ALT/SGPT

	Group 1 q 2 wks N = 103	Groups 2 + 3 q month + wk 6 N = 496
N (%) with ALT/ SGFT >10 X ULN[a]	8 (8)	36 (7)
Time (Days)		
To Onset		
Mean (SE)	47 (5)	49 (4)
95% CI	36,58	40,58
Median	43	43
Range		
Onset to Peak		
Mean (SE)	4 (2)	4 (1)
95% CI	0, 8	1, 6
Median	3	0
Range		
Onset to Recovery		
Mean (SE)	30 (3)	40 (3)[b]
95% CI	23,36	34,45
Median	34	37
Range		
Peak to Recovery		
Mean (SE)	26 (2)	37 (3)[b]
95% CI	21,31	31,42
Median	28	33
Range		
Maximum ALT/ SGPT (x ULN)[c]		
Mean (SE)	17 (2)	17 (1)
95% CI	13,22	14, 19
Median	28	33
Range		

[a] p-value for group difference = 0.984 (CMH analysis)
[b] N = 32; 4 patients had not recovered by the last observation
[c] P-value for estimated treatment difference = 0.728 (ANCOVA)

There were no significant differences in the incidence, severity, or time to onset between the two groups (1 vs. 2+3). Time to recovery was prolonged by about 1 week for patients monitored monthly, and this difference was statistically significant for elevations >10x ULN (risk ratio = 0.4; 95% CI = 0.2, 0.9; p = 0.031; Cox regression). A panel of consultant hepatologists[4] did not consider this to be a clinically significant difference.

Week 6 was included in the monitoring schedule for Groups 2 and 3 because the majority of ALT/SGPT elevations seen during earlier clinical studies occurred at Week 6 of treatment, and the hepatologists were concerned about the

[4] The panel consisted of William C. Madrey, MD, Steven Schenker, MD, Paul B. Watkins, MD, and Hyman J. Zimmerman, MD

possible outcome for patients with high elevations continuing tacrine treatment. In order to address this concern, the sponsor points out that, in Study 970-77, three patients with ALT/SGPT elevations >20x ULN were identified at Week 6, and 13 were identified at Week 4, 8, or 12. Of the three patients who had an elevation >20x ULN at Week 6, one had an elevation >5 x ULN at Week 4 and was therefore being monitored weekly. The other two patients had ALT/SGPT elevations >20x ULN at Week 6, but their ALT/SGPT levels were within normal limits at Week 4. Thus, the two patients would have remained on treatment for an additional 2 weeks before their ALT/SGPT elevations were detected. Patients with ALT/SGPT elevations >3x, >5x, or >10x ULN who continued tacrine treatment showed no increase in the severity of elevations. Therefore, it is unlikely that patients with elevations >20x ULN who remain on treatment for 2 weeks would experience more severe elevations than they would have if treatment had been stopped sooner[5]. The advisory hepatologists discussed the need for a week 6 monitoring at their meeting on Jan 27, 1996 and concluded that *one is probably not necessary* (pg. 00654 of submission).

Summary

There were no significant differences in the incidence, severity, or time to onset between the two groups (every other week, vs. monthly + week 6 monitoring). Time to recovery was prolonged by about 1 week for patients monitored monthly, and this difference was statistically significant for elevations >10x ULN. A panel of consultant hepatologists did not consider this to be a clinically significant difference.

Monitoring at week 6 identified 3 patients with ALT > 20x ULN. One of these patients was undergoing weekly monitoring because of elevated ALT at week 4. The other two would go undiagnosed for additional 2 weeks if monthly monitoring is instituted. It is unknown how high their ALT levels would be at that point (with unknown consequences).

4. Continued Treatment with ALT/SGPT > 5x ULN

Currently, discontinuation of medication is advised if ALT/SGPT > 5x ULN. Patients in Study 970-77 remained on treatment as long as ALT/SGPT ≤ 20x ULN.

To examine the effect of continuing versus stopping treatment, the incidence and profile of ALT/SGPT elevations >10x ULN were compared for patients in Studies 970-77 and 970-62 (historical control). The patients in Study 970-62 had received placebo for up to 30 weeks in Study 970-61 and began tacrine treatment upon entry into Study 970-62, which was the open-label extension of

[5] This appears to contradict the previous statement, because one of the three patients described had >5xULN at week 4 and went to >20xULN at week 6-clearly not a stable elevation. At this rate of rise (4 fold in 2 weeks), a level >100xULN might be seen at 8 wks.

Study 970-61. They began tacrine treatment at 40 mg/day with dose titration every 4 weeks to a maximum dose of 160 mg/day. Their ALT/SGPT levels were monitored every 2 weeks during dose-titration, and treatment was stopped if ALT/SGPT was >3x ULN.

970- 62 (Historical Controls) and 970- 77: Time to Onset, Peak, and Recovery of First ALT/ SGPT Elevations >10 x ULN, and Maximum ALT/ SGPT

	All Patients With Elevations >10 x ULN	
	Historical Controls N = 127	970- 77 N = 599
N (%) with ALT/ SGPT >10 x ULN[a]	10 (8)	44 (7)
Time (Days)		
To Onset		
Mean (SE)	42 (3)	49 (4)
95% CI	35,50	41,56
Median	43	43
Range		
Onset to Peak		
Mean (SE)	1 (1)	4 (1)
95% CI	0, 2	2, 6
Median	0	0
Range		
Onset to Recovery		
Mean (SE)	29[c] (4)	38[d] (2)
95% CI	21,37	33,43
Median	28	35
Range		
Peak to Recovery		
Mean (SE)	28 C (4)	35[d] (2)
95% CI	20,37	30,39
Median	28	28
Range		
Maximum ALT/ SGPT (X ULN)		
Mean (SE)	16 (1)	17 (1)
95% CI	13, 18	15, 19
Median	16	14
Range		

[a] p- value for group difference = 0.837 (CMH analysis)
[b] p- value for group difference = 0.034 (Cox regression)
[c] N = 9; 1 patient had not recovered by the last observation
[d] N = 40; 4 patients had not recovered by the last observation
[e] p- value for estimated treatment difference = 0.380 (ANCOVA)

The incidence of ALT/SGPT elevations >10 x ULN was similar between the two studies. Median time to onset, time from onset to peak, and time from peak to recovery were similar between the studies, and the 95% confidence intervals overlapped. Median time from onset to recovery was longer for patients in Study 970-77. The Cox regression analysis showed a significant (p = 0.034) difference in time from onset to recovery favoring (i.e., shorter for) patients in 970-62. The Kaplan-Meier estimate of median days from onset to recovery was 35 for Study 970-77 and 28 for Study 970-62.

The distributions of time to first ALT/SGPT elevation >10 x ULN for the two studies were similar. For the majority of patients in both studies with ALT/SGPT >10 x ULN, the onset of the elevation occurred between Days 28 and 56. Elevations were apparent by Day 70 for all 10 patients with elevations >10x ULN in Study 970-62 and for 37 of the 44 patients in Study 970-77. In all cases, ALT levels returned to within normal limits. All elevations were asymptomatic and none were accompanied by increases in bilirubin.

Prior to Study 970-77, a total of 2446 patients, including the 127 in Study 970-62, had received tacrine in clinical trials and had both pre- and post-treatment ALT/SGPT measurements. Most of the 2446 patients began treatment with 40 mg/day tacrine with weekly ALT/SGPT monitoring; all discontinued treatment if ALT/SGPT was >3x ULN. The comparison of ALT/SGPT elevations >10x ULN in Study 970-77 with those in the 2446 patients again shows no difference in incidence or severity. A delay of approximately 1 week in time to recovery, as well and a delay of 1 week in time to onset, for patients in Study 970-77 are evident. The delay in time to onset can be attributed to the frequency of monitoring, and the delay in recovery time may reflect continued treatment. Longer time to first elevation was significantly associated ($p < 0.05$) with older age, males, and lower baseline ALT/SGPT (similar to previous studies).

Summary

A total of 599 patients in study 970-77 maintained treatment with Cognex® as long as ALT/SGPT ≤ 20xULN. The historical control group consisted of 127 patients (study 970-62) underwent the same treatment, but stopped medication if ALT/SGPT > 3xULN.

The incidence of ALT/SGPT elevations >10x ULN was similar between the two studies. Median time to onset, time from onset to peak, and time from peak to recovery were also similar between the two groups.

Time to onset of the elevation was delayed by about one week in 970-77. This may be due to decreased monitoring frequency (monthly vs. q 2 wks) which may have delayed detection. Median time from onset to recovery was longer for patients in Study 970-77. This again may be attributable to the differences in monitoring frequencies between the two groups.

All elevations were asymptomatic and none were accompanied by increases in bilirubin.

5. Stopping medication if ALT/SGPT > 20x ULN

In the integrated data base of 2446 patients from earlier clinical trials, 2% (n=40) experienced ALT/SGPT values greater than 20x ULN; the maximum elevation seen was 83x ULN. All of these patients recovered without sequelae. The vast

majority were asymptomatic. In those symptomatic case, symptoms included jaundice (n=1), rash (n=1), and abdominal pain.

In the treatment IND there were 53 patients with ALT/SGPT values greater than 20x ULN; the maximum elevation was 48 x ULN. None of these patients had clinical signs of liver dysfunction, and all values returned to normal without evidence of sequelae.

Throughout the clinical studies and treatment IND, there were no cases of death due to tacrine-related liver failure. Of 12 deaths temporally related to hepatic dysfunction during the first 2 years of post-marketing experience in the US, there have been four cases in which a role for tacrine could not be ruled out. The hepatology consultants considered an association with tacrine unlikely in three of the four cases. The fourth case was deemed possibly related based on the available information; no follow-up information could be obtained. In each of these four cases, monitoring frequency did not affect outcome. There have been no cases in which tacrine was unequivocally shown to have resulted in death due to hepatic failure.

The hepatologists agreed that tacrine should be stopped if ALT/SGPT > 20x ULN since there is no clinical experience continuing treatment at this level.

6. Continued treatment with ALT/SGPT > 20x ULN

As a corollary to #5 above, the sponsor points out that continued treatment, reexposure, and/or dose-escalation in patients with ALT/SGPT > 20 x ULN has not been studied, and the risks of treatment in these settings are unknown.

Draft Labeling:

I use the following convention in detailing the draft labeling:

-pre-existing text is in *italics*
-sponsor proposed deletions to pre-existing text is in ~~*[strikethrough italics]*~~
-sponsor proposed additions to pre-existing text is in *underlined italics*
-my suggested changes are in *[shaded italics in brackets]*
-any sponsor proposed additions which I believe should not be included in final labeling, I have *{enclosed in braces}*

The sponsor proposes the following 18 changes to labeling.

1. In the *Clinical Pharmacology* section, at the end of the *Clinical Trial Data* subsection, the sponsor adds the following information:

Dose Initiation, Titration, and Safety Monitoring Study

An open label study was conducted in 625 patients with clinical diagnosis of Alzheimer's disease to evaluate Cognex® starting dose, titration frequency, ALT/SGPT monitoring frequency, and continued Cognex® treatment and dose titration in patients

8 pages
PURGED

DRAFT Labeling

AOliva

Armando Oliva, M.D.
Medical Reviewer

cc:
HFD-120
original IND
HFD-120/Leber/Katz

Review and Evaluation of Clinical Data

NDA (Serial Number)	**20-070 (SE2-006(BM))**
Sponsor:	**Parke-Davis**
Drug:	**Cognex**
Proposed Indication:	**AD dementia**
Material Submitted:	**Response to Agency Letter**
Correspondence Date:	**4/29/97**
Date Received / Agency:	**4/30/97**
Date Review Completed	**5/5/97**

1. Introduction

This is the sponsor's response to the Division letter dated 3/17/97. The sponsor originally sought labeling changes to recommend:

- a starting dose of 80 mg/day rather than 40 mg/day,
- dose escalation every 4 weeks instead of 6 weeks,
- monthly monitoring of ALT/SGPT vs. every other week monitoring, and
- discontinuation of tacrine when ALT ≥ 20 xULN (vs. ≥5 xULN currently)

In the Division's non-approvable letter, we stated that sufficient evidence existed to permit:

- a 40 mg starting dose with titration by 40 mg every 4-6 weeks
- serum ALT monitoring every 2 weeks for 6 weeks following any increase in tacrine dose (except 120 → 160 mg), with subsequent q 3 month monitoring

This was based on the fact that the sponsor had not collected safety data on their proposed regimen, and the fact that they had not collected any efficacy data with the new regimen to allow any type of risk/benefit analysis. Furthermore, the numbers of patients with ALT ≥ 20xULN was sufficiently small to provide little reassurance regarding the safety of continuing tacrine in patients with ALT 5-20 xULN.

2. Sponsor's Response

In response to the Division letter, they now propose the following changes to labeling:

- starting dose of 40 mg/day with titration every 4 weeks
- monitor serum ALT monthly for the first 4 months, then q 3 months
- stop treatment if ALT ≥ 5xULN (same as current labeling)
- permit optional rechallenge following recovery to normal range (also consistent with current labeling)

In their current letter, they provide argument that, assuming a 2% incidence of ALT ≥ 20xULN seen in clinical trials, and assuming 200,000 patients treated to date with Cognex®, then 4,000 patients (200,000 x 0.02) can be assumed to have experienced elevations ≥20xULN. The fact that no serious events have occurred in that population makes the true probability of a serious event 0.00001.

They further argue that none of the 103 patients who developed ALT elevations in study 970-77 did so during the first two weeks of therapy.

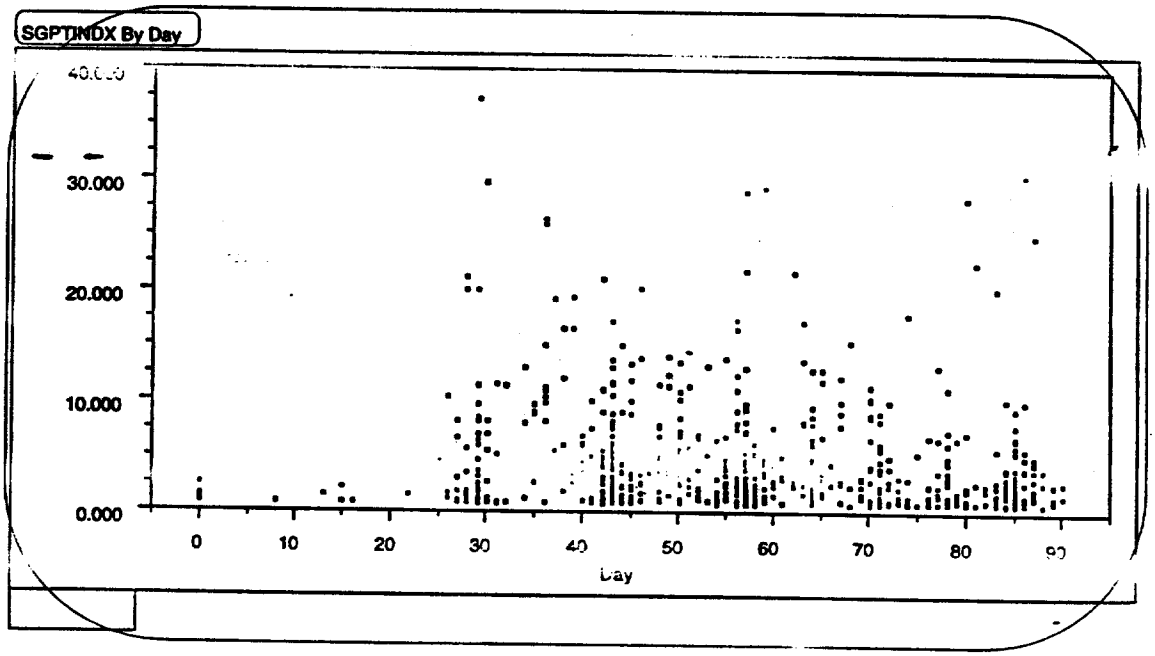
They also ask the Division to share with them our comfort level regarding the upper limit of ALT elevation that we could tolerate before stopping treatment, since it does not appear to be 20xULN.

3. Exploratory Analyses of Safety Data

In response to the sponsor's statement that no ALT abnormalities were seen in study 970-77 during the first two weeks of therapy, I have performed additional exploratory analyses of the ALT safety data in studies 970-61 (N=479, q 6 wk titration, stop if ALT≥3xULN, weekly monitoring), and 970-77 (N=665, q 4 or 6 wk titration, stop if ALT≥20xULN, q 2 wk or monthly monitoring).

Of the 1144 patients, 479 underwent weekly monitoring, 104 underwent biweekly monitoring, and 521 underwent monthly monitoring. A total of 278 patients (22%) experienced 790 ALT abnormalities within the first 90 days of treatment. These are plotted in Figure 1. The SGPT index is the normalized ratio (normal = 1.000).

Figure 1: SGPT Index Abnormalities vs. Time (Studies 970-61, 970-77)



Twenty-five (25) patients had ALT abnormalities at day 27 or lower. Twelve (12) of these were undergoing monthly monitoring and had their lab test performed a few days early. Of the remaining 13 patients, 5 patients had elevated ALT at baseline and are discarded from future discussion. The remaining 8 (<1%) represent patients who benefited from early ALT monitoring (at 1 or 2 wks).

In this group of 8 patients, the abnormalities were seen in days 8-27. The mean ALT elevation was modest (mean SGPT index = 2, median 1.1, range 1.03-7). Five (5) of the 8 actually had normal ALT levels on their next lab test. The remaining 3 patients experienced further rises in ALT (SGPT index = 1.1 to 6.3, 2.4 to 3.9, and 7 to 11). This represents a small fraction (0.5%) of all patients monitored at two weeks or less (of a total undergoing weekly or biweekly monitoring of 583).

4. Comments

1. The starting dose should remain 40 mg.
2. Titration by 40 mg every 4-6 weeks (depending on the presence or absence of cholinergic side effects) may be recommended.
3. Concerning the frequency of laboratory monitoring, there does appear to be little need for a 2 week lab test, since the numbers detected during this time are small. Therefore, I can recommend ALT monitoring at weeks 4, 6, 8 following a change in dose (except 120 → 160 mg for reasons previously outlined). I recommend a lab test at 8 weeks since Figure 1 indicates a significant number of abnormalities occur around this time.
4. The sponsor provides no new safety data in this submission to permit use of Cognex® beyond the currently recommended ALT level of 5xULN. Therefore, I recommend that the current labeling to stop treatment if ALT ≥ 5xULN should be maintained, with an optional rechallenge when ALT returns to normal.
5. In summary, my recommendations for labeling are:
   - starting dose of 40 mg/day
   - monitor serum ALT at weeks 4, 6 and 8 following each dose adjustment (except 120 → 160 mg), then q 3 months
   - stop treatment if ALT ≥ 5xULN (same as current labeling)
   - permit optional rechallenge following recovery to normal range (also consistent with current labeling)

Armando Oliva, M.D.
Medical Reviewer

R. Levin, M.D. R. L. 5/8/97

ao 5/5/97
cc:
HFD-120
NDA 20-070 (SE2-006(BM))
electronic copy-Levin

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20070/S-004,S-006

ADMINISTRATIVE DOCUMENTS

CSO ADMINISTRATIVE AND LABELING REVIEW
FOR
NDA FINAL PRINTED LABELING (FPL)

NDA #: 20-070

Dates of Submissions:
(S-004) July 19, & September 19, 1995
(S-006) March 27, 1996
April 29, June 10, September 10 & 16, 1997

Supplement #: S-004 & S-006 **Date Review Completed:** September 30, 1997

Applicant Name and Address: Parke-Davis Pharmaceutical Research
Division of Warner-Lambert Company
2800 Plymouth Road, P.O. Box 1047
Ann Arbor, MI 48106-1047

Trade Name: Cognex®
Generic Name: Tacrine hydrochloride
Dosage Form and Strengths: Capsules 10, 20, 30 and 40 mg
Pharmacological Category and/or Principal Indication: Alzheimer's Disease

Material Reviewed:

S-004: 7/25/95; Clinical Review; Dr. Levin
9/19/95; Draft package insert (0096G023FA, July 1995)

Annual Report: 12/19/96, Package insert (0096G023, July 1996)

S-006: 7/17/97; Supervisory Clinical Review; Dr. Levin
9/15/97; Draft package insert (0096G023:with proposed draft changes)

Evaluation:

S-004: provides for:

- Revision of the "WARNINGS:Gastrointestinal Disease and Dysfunction" section to clarify that patients are at risk for developing GI ulcers with or without a previous history of ulcer disease.
- The addition of "falling" as an ADVERSE REACTION.
- Changing "perforated duodenal ulcer" to "perforated peptic ulcer" in the "ADVERSE REACTION:Postintroductory Reports" section of labeling.

Annual Report:

The Annual Report included a change to the package insert to comply with the December 13, 1994 Pediatric Labeling Final Rule. Specifically, under "Precautions:pediatric use", the word "children" has been changed to "pediatric patients". This change was implemented on November 25, 1996.

S-006 provides for:

- Starting dose of 40 mg/day with dose escalation in 40 mg/day increments at 4-week intervals.
- Monitor serum transaminase levels every other week beginning 4 weeks after initiation of therapy to continue through week 16 after which monitoring may be decreased to every 3 months.

[NOTE: The labeling submitted on 9/16/97 to S-006 contains the change reported in the Annual Report dated December 19, 1996.]

The "draft" package inserts from both S-004 and S-006 were compared to the presently approved label (S-003) and no changes beyond those proposed by the firm in the supplemental applications or included in the Dec, 1996 annual report were identified. However, with regard to S-004, the firm has proposed to add the reaction "falling" to the "ADVERSE REACTIONS:Other Adverse Events Observed During All Clinical Trials" subsection of labeling due to the number of events being received as 15-day reports. This section of labeling refers to events observed during the clinical development of Cognex, not events reported post-marketing. Therefore, it would be more appropriate to list this reaction under the "Postintroduction Reports" subsection.

Recommendation:

An approval letter for both S-004 & S-006 can issue based on the submitted draft labeling which asks that "falling" be listed under the "Postintroduction Reports" rather than the "Other Adverse Events Observed During All Clinical Trials" subsection.

Robbin Nighswander, M.S.

attachments:
- S-004 package insert with highlighted changes
- S-006 package insert with proposed changes

9/25/97

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-070/S-006

MAR 17 1997

Parke-Davis Pharmaceutical Research
Division of Warner-Lambert Company
Attention: Byron Scott
2800 Plymouth Road, P.O. Box 1047
Ann Arbor, MI 48106-1047

Dear Mr. Scott:

We acknowledge receipt on March 28, 1996 of your March 27, 1996 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cognex® (tacrine hydrochloride) Capsules 10, 20, 30 and 40 mg.

We also acknowledge receipt of your submissions dated May 14 and June 5, 1996. The User Fee goal date for this application is March 28, 1997.

The supplemental application provides for:

> Recommendation of a starting dose of 80 mg rather than 40 mg/day with dose escalation every 4 weeks instead of 6 weeks, monthly monitoring of ALT/SGPT versus ever-other-week and revised statements on continued treatment of patients with ALT/SGPT elevations.

We have completed our review and find the information is inadequate, and the supplemental application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b).

We have determined, however, that some of the changes that you have proposed are potentially approvable, provided however, that they are incorporated into product labeling in the manner we suggest below. These changes could be submitted as a response to this action letter.

It may be helpful to explain the basis for our determination.

No drug is absolutely safe. Accordingly, the extent of risk tolerated with a drug is a function of its documented benefits and the risks of use reasonably likely to be associated with its use under the conditions of use recommended in its proposed and/or approved labeling. Whether or not a proposed labeling change will enhance the safe and effective use of an already approved drug product is ultimately a matter of informed judgment.

Redacted 1

page(s) of trade secret and/or confidential commercial information

These observations notwithstanding, some of the proposals made in the current submission can, based on the evidence provided, be deemed responsibly to have little, if any, potential to increase tacrine's risks of use. You have, for example, provided reports of experience gained with about 500 patients who began at a dose of 40 mg a day of tacrine and had it advanced on an every 4 week basis. We agree that, with the exception of a slight increase in the frequency of cholinergic side effects, experience reported for patients treated under that regimen reveals no findings that would signal a risk of use exceeding that posed by the regimen recommended in current labeling.

Accordingly, we would agree to a proposal that would recommend a starting dose of 40 mg a day, with escalation of that dose as either an every 4 or every 6 week interval.

We also find it reasonable to modify the frequency of required serum transaminase monitoring, but not precisely in the manner you propose. We would find it acceptable to have testing performed at every two week intervals for a period of at least 6 weeks following any dose escalation save the escalation from 120 to 160 mg a day. Our reasoning is based on our impression that most patients destined to develop transaminase elevations at a given dose of tacrine will do so within the first 4 to 6 weeks of being exposed to that dose. Experience also shows that the proportion of individuals who develop transaminase elevations falls with each successive 40 mg increment. Whether or not this represents a gradually decreasing hazard independent of dose, or the winnowing through the sequential titration regimen of patients vulnerable to tacrine is unknown. In any case, the risk of transaminase elevation following an increase from 120 mg to a 160 mg a day is relatively slight (circa 2% or so). Accordingly, once a dose of 160 mg is reached, the next required transaminase evaluation is 4 weeks later. [Please note that any patient being advanced to 160 mg. after only 4 weeks on 120 mg would still

require an evaluation 2 weeks after the start of the 160 mg dose because of the carryover of the every other week monitoring for 6 weeks required for the previous dose of 120 mg.] Thereafter, evaluations should occur at 3 month intervals.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application. Any amendments should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Should you have any questions, please contact Mr. Robbin Nighswander, Regulatory Management Officer, at (301) 594-2777.

Sincerely yours,

Paul Leber, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Memorandum

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: October 10, 1997

FROM: Paul Leber, M.D.
Director,
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: NDA 20-070
S-004 and S-006, revised
Explanation of action taken

TO: File NDA 20-070

This memorandum briefly explicates the basis for the issuance of an approval action letter that approves a series of changes to the labeling of Cognex concerning dosing regimen and the frequency of liver function test (LFT) monitoring .

My memorandum of 3/13/97 provides my views on a number of substantive matters affecting my decision to disapprove a series of modifications to the dosing and LFT monitoring recommendations provided in Cognex product labeling that were proposed for adoption in S-006 submitted by the sponsor on 3/27/96.

In response to the disapproval action letter (3/17/97) explaining the agency's decision and detailing the changes to labeling that the agency would be likely to accept, the firm acknowledged that it had sought to gain approval for recommendations for use under conditions that had yet to be systematically evaluated in patients. The sponsor asked the agency, however, to work with its representative to produce labeling that could be justified by the information and evidence available.

As noted by both Dr. Oliva (his review of 5/5/97) and Dr. Levin (Team leader overview of 7/16/97) the sponsor did not provide new evidence, but did present a number of analyses based on speculations concerning the likely risk of more aggressive dosing (i.e., a 80 mg rather than an 40 mg initial dose, dose increment at every 4 rather than every 6 weeks, and a

revised schedule for monitoring LFTs.

The review team has concluded that the new arguments presented by the sponsor are still insufficient to justify adoption of the changes the sponsor seeks. The review team has concluded, however, that Cognex can be recommended as safe for use under a regiment that provides for a starting dose of 40 mg/day with escalation in 40 mg/day increments at intervals of no less than 4 weeks. Under this regimen, it concludes, it will be acceptable to monitor ALT/AST at every other week intervals beginning 4 weeks after treatment initiation through week 16 of treatment. Thereafter, labeling may recommend monitoring at every 3 month intervals. Again, the monitoring sequence just described is to be undertaken de novo if there is a lapse of treatment of more than 4 weeks.

The firm is aware of the division's position, and acknowledged, by letter of 9/10/97, that it would adopt labeling as suggested by the division. Toward this end, there have been exchanges of draft labeling, the last version of which (submitted on 9/16/97) was reviewed by Mr. Nighswander and found to conform to the agreed upon changes.

Conclusion

I concur that Cognex will be safe for use under the conditions use recommended under the revised labeling.

Action

I am issuing on this date the approval action letter provided for my signature.

Paul Leber, M.D.
October 10, 1997

cc:
NDA 20-070
HFD-101
Temple
HFD-120
Katz
Levin
Oliva
Nighswander