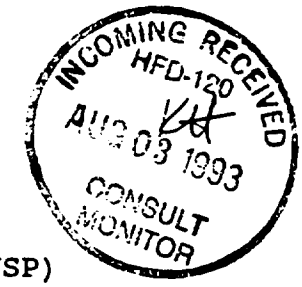
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20148

STATISTICAL REVIEW(S)

JUL 30 1993

Statistical Review and Evaluation



NDA#: 20-148/Drug Class 1S

Applicant: Sandoz Pharmaceuticals Corp.

Name of Drug: D.H.E. 45 (dihydroergotamine mesylate, USP) nasal spray

Indication: Common or Classic Migraine Headaches in Adults

Document Reviewed: Vols. 1, 39-55,
Submission dated April 30, 1991

Background:

In the submission, there are two U.S. controlled studies, No. 511 and No. 512, four foreign dose-finding controlled studies (0603-002, -003, -004, -005) and 4 foreign efficacy and safety controlled studies (0603-006, 007, 008, 111). The sponsor, Sandoz U.S., indicated that the foreign studies were not to provide pivotal evidence of effectiveness. The sponsor states it was not involved in the protocol design, monitoring, reporting or original data analysis of any of the foreign clinical studies.

I. US Studies (No. 511 and No. 512):

The two U.S. studies used identical protocols with multicenter double-blind, placebo-controlled parallel group design. Eight to ten participating centers were expected to complete a minimum of 10 patients each. Patients were assigned to one of the two treatment groups, 2.0 mg D.H.E. 45 Nasal Spray or placebo and were required to evaluate two separate migraine headache attacks. Patients were to complete a headache evaluation book for each migraine attack. Within 7 days of the migraine attack, the investigators were to rate the response to therapy based upon a review of the patient's headache evaluation books.

Entry criteria were 1. patients suffered from at least one migraine headache attack per month for the one year period prior to entering the study. 2. Patients had no analgesics, including aspirin for a period of eight hours prior to the study medication. 3. A two-week washout period for patients taking prophylaxis of migraine headache. 4. Two-week washout for antipsychotics, antidepressants, antiemetics and 5-day washout

period for minor tranquilizers, sedatives or hypnotics.

Each investigator received 16 sets of study medication. Each set consisted of two boxes identified by a single patient number and by a dispensing sequence (A and B). At screening visit, eligible patients were given Box A of the assigned study medication along with Headache Evaluation Book A. At the conclusion of the follow-up visit for the first migraine headache, Box B and Book B were dispensed. Patients received the same study medication for each migraine headache evaluation.

At the onset of the migraine headache attack, patients were to complete the "Before Taking Study Medication" column in the Patient Headache Evaluation Book. Then the patient administered one spray of study medication in each nostril followed 15 minutes later by a second spray of study medication in each nostril. Evaluation of Severity of headache pain, relief of pain, severity of nausea and whether or not vomiting took place at 1 hour, 2 hours, 3 hours and 4 hours after the first administration of study medication. For Headache Pain and Nausea the 5-point ordinal scale included 1. None, 2. Mild, 3. Moderate, 4. Severe, and 5. Incapacitating. For Relief of Pain the 5-point ordered scale was 1. Complete Relief, 2. A Lot or Good Relief, 3. Some or Moderate Relief, 4. A Little or Slight Relief, and 5. No Relief. The physician's evaluation of patient response to study medication included A. the effectiveness for the relief of migraine headache pain, B. relief of nausea and C. relief of vomiting. The rating scale was 1. No Effect, 2. Poor, 3. Fair, 4. Good, 5. Very Good, and 6. Not Applicable. For patients with headache 4 hours after the first dose, additional nonergot drugs could be taken to abort the attack.

Patients were expected to provide information on the duration of the headache, the times at which the study medication was taken, whether or not concomitant medication was used during the headache evaluation, and whether or not adverse reactions were experienced. Circumstances under which patients were to be terminated were protocol violation, intercurrent illness, inability to tolerate study medication, failure to take study medication, uncooperativeness, adverse reactions requiring discontinuation of study medication and/or necessitating breaking of the code, and lack of headache attacks.

The preliminary tests for interaction across centers and headaches, a two-way analysis of variance model was proposed to test for treatment, center and treatment by center interaction effects. A one-way analysis of variance with repeated measures on headache was proposed to test for homogeneity of results across headache attacks. For patient's self-rating scale and physician's global evaluation, analysis of covariance (pretreatment score) was to be used to compare treatments for the pain intensity difference scores (PIDS) at each evaluation and the sum of the PIDs over all evaluations (SPIDs), the pain relief scores (PARs) at each evaluation and the total relief over all evaluations (TOTPAR). Categorical analysis on proportion experiencing at least 50% pain relief or proportion improving at least one category from initial pain severity was used at each evaluation period "to provide a more clinically meaningful measure of response to therapy." Mantel-Haenszel procedures were to be used when appropriate.

The protocol stated that "an interim analysis might be performed after approximately 50% of the anticipated total sample has completed the study. This would provide variability estimates that allow for a determination as to the accuracy of the original sample size and power calculations." According to the sponsor, the interim analysis was not carried out.

Study No. 511:

Eight centers entered a total of 117 patients, of those 106 (91%) were included in the intent-to-treat analysis. Of the 11 (5, placebo, 6, DHE) patients excluded from the intent-to-treat analysis, none were administered any study medication. There were 11 additional patients (5, placebo, 6, DHE) who took only one study medication. Eight patients took unallowed concomitant medications during the four hour rating period. The last evaluation completed before the concomitant medication was taken was used for evaluations made after the concomitant medication was taken.

Study No. 512:

Ten centers enrolled a total of 112 patients; of those, 100 (89%) were in the intent-to-treat analysis. Six patients each in the DHE and the placebo group were excluded with reasons of no headaches (5), uncooperative (2), Did not use medication (2), discontinued (1), sprayer failed for headache A, no headache B (1), and headache A took concomitant medication prior to 1st hour; no headache B (1). Eight patients in each treatment group only treated one headache attack. Seventeen of the total of 184 headache failed to complete all four of the hourly evaluations. Two patients (DHE) fell asleep. The remaining 15 headache evaluations (3 DHE, 12 placebo) were not completed because the patient took a concomitant medication. The last evaluation before the concomitant medication was used for evaluations after the concomitant medication was taken.

Sponsor's Analysis:

For the repeated measures analysis of variance, in every case the p-value for the treatment by headache interaction was not significant. Therefore, the report presented the evaluation results for the average of headaches A and B. However, the appendices had analysis results for individual headaches. The unweighted means (average over center means) and p-values from analysis of variance on the intent-to-treat population with the LOCF for PID were in the following tables for studies 511 and 512.

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Table I. Analysis of Variance Results for Study 511

PID / Hour		Headache A			Headache B			Headache A&B		
		N	Mean	Std	N	Mean	Std	N	Mean	Std
1	DHE	53	0.25	0.80	48	0.18	0.82	54	0.23	0.69
	Pla	50	0.11	0.79	48	0.05	0.82	52	0.11	0.68
			p=0.3844			p=0.4365			p=0.3861	
2	DHE		0.52	1.16		0.40	1.17		0.43	0.99
	Pla		0.08	1.14		0.01	1.18		0.07	0.98
			p=0.0555			p=0.1028			p=0.0662	
3	DHE		0.67	1.23		0.76	1.42		0.65	1.16
	Pla		0.05	1.22		-0.07	1.42		0.02	1.15
			p=0.0117			p=0.0052			p=0.0066	
4	DHE		0.76	1.30		0.78	1.58		0.68	1.30
	Pla		-0.09	1.28		0.03	1.59		0.01	1.29
			p=0.0013			p=0.0221			p=0.0095	
SPID	DHE		0.55	1.03		0.53	1.15		0.50	0.96
	Pla		0.04	1.02		0.00	1.15		0.05	0.95
			p=0.0134			p=0.0273			p=0.0198	

Table II. Analysis of Variance Results for Study 512

PID Hour		Headache A			Headache B			Headache A&B		
		N	Mean	Std	N	Mean	Std	N	Mean	Std
1	DHE	48	0.39	0.84	40	0.25	0.85	48	0.34	0.74
	Pla	52	0.04	0.85	44	-0.11	0.82	52	-0.04	0.75
			p=0.0378			p=0.0503			p=0.0117	
2	DHE		0.57	1.15		0.62	1.21		0.57	1.01
	Pla		0.05	1.16		-0.13	1.16		-0.08	1.03
			p=0.0266			p=0.0052			p=0.0021	
3	DHE		0.86	1.32		1.00	1.53		1.17	1.63
	Pla		0.08	1.34		-0.20	1.47		-0.16	1.56
			p=0.0045			p=0.0005			p=0.0001	
4	DHE		0.95	1.49		1.17	1.63		1.06	1.36
	Pla		0.16	1.51		-0.16	1.56		0.01	1.38
			p=0.0094			p=0.0003			p=0.0003	
SPID	DHE		0.70	1.07		0.76	1.20		0.73	0.98
	Pla		0.08	1.09		-0.15	1.15		-0.05	1.00
			p=0.0057			p=0.0007			p=0.0002	

Reviewer's Analysis:

The baseline headache severity was comparable for both headaches A and B of the two studies as the following table for baseline and treatment shows:

Baseline severity

Study	Trt	1	2	3	4	5	N
511 A	DHE	1(2%)	3(6%)	27(51%)	18(34%)	4(8%)	53
	Placebo	0	2(4%)	30(60%)	15(30%)	3(6%)	50
511 B	DHE	1(2%)	4(8%)	19(40%)	18(38%)	6(13%)	48
	Placebo	0	9(19%)	18(38%)	18(38%)	3(6%)	48
512 A	DHE	0	1(2%)	20(42%)	22(46%)	5(10%)	48
	Placebo	0	2(4%)	21(40%)	24(46%)	5(10%)	52
512 B	DHE	0	5(13%)	12(30%)	16(40%)	7(18%)	40
	Placebo	0	4(9%)	16(36%)	15(34%)	9(20%)	44

Study 512, p-values are from Van Elteren test blocking on centers.

Headache Severity

Hr	Trt	1	2	3	4	5	p-value
1	DHE	5(10%)	6(13%)	17(35%)	14(29%)	6(13%)	
	Pla	1(2%)	7(13%)	17(33%)	18(35%)	9(17%)	.393
2	DHE	6(13%)	8(17%)	18(38%)	10(21%)	6(13%)	
	Pla	3(6%)	7(13%)	13(25%)	17(33%)	12(23%)	.028
3	DHE	13(27%)	6(13%)	13(27%)	13(27%)	3(6%)	
	Pla	4(8%)	8(15%)	14(27%)	11(21%)	15(29%)	.001
4	DHE	14(29%)	9(19%)	9(19%)	11(23%)	5(10%)	
	Pla	5(10%)	11(21%)	12(23%)	5(10%)	19(37%)	.007

SPID p=0.008

Pain intensity difference (PID) was compared between treatments at each time point using Van Elteren analysis adjusting for centers.

P-values are presented in Table II. for headache A and B.

Table II. P-values from Van Elteren test for PID

	1	2	3	4	SPID
511 A	0.266	0.039	0.012	0.001	0.002
511 B	0.393	0.028	0.001	0.007	0.008
512 A	0.046	0.019	0.007	0.010	0.008
512 B	0.130	0.001	0.000	0.000	0.001

When percent of patients with headache intensity None or Mild (1,2) was compared, the p-values from Cochran-Mantel-Haenzel test were as follow:

		1	2	3	4
511 A	DHE	9/53(17%)	17/53(32%)	23/53(43%)	25/53(47%)
	Pla	11/50(22%)	11/50(22%)	13/50(26%)	11/50(22%)
		p=0.647	p=0.151	p=0.022	p=0.002
511 B	DHE	11/48(23%)	17/48(35%)	23/48(48%)	20/48(42%)
	Pla	10/48(21%)	9/48(19%)	8/48(17%)	10/48(21%)
		p=0.847	p=0.092	p=0.002	p=0.032
512 A	DHE	11/48(23%)	14/48(29%)	19/48(40%)	23/48(48%)
	Pla	8/52(15%)	10/52(19%)	12/52(23%)	16/52(31%)
		p=0.333	p=0.199	p=0.056	p=0.075
512 B	DHE	9/40(23%)	13/40(33%)	20/40(50%)	24/40(60%)
	Pla	2/44(5%)	6/44(14%)	8/44(18%)	9/44(20%)
		p=0.032	p=0.055	p=0.004	p=0.001

The analysis of outcome variable PID showed a significant difference at the second hour after drug administration for study 511. Study 512 headache A had significant results starting at first hour; for headache B it started at the second hour.

From the analysis of proportions of patients with headache

severity of none or mild, the drug and placebo were statistically different at hours 3 and 4 except headache B of study 512 the statistical significance were achieved at the first hour.

For the most stringent analysis, which compared at each time point the proportion of patients with none or mild headache for both headache A and headache B the results are as follows:

		1	2	3	4
511	DHE	6/54(11%)	9/54(17%)	15/54(28%)	15/54(28%)
	Pla	4/52(8%)	5/52(10%)	4/52(8%)	3/52(6%)
		p=0.51	p=0.25	p=0.006	p=0.002
512	DHE	3/48(6%)	6/48(13%)	9/48(19%)	14/48(29%)
	Pla	0/52(0%)	4/52(8%)	5/52(10%)	7/52(13%)
		p=0.10	p=0.44	p=0.18	p=0.045

All analyses showed that DHE is efficacious in improvement of headache severity when compared to placebo. DHE in both studies had a significant difference from placebo at the second hour after dosing.

Foreign Studies:

Studies 603-002, 003, 004 and 005 were dose-finding studies comparing 1 mg DHE, 0.5 mg DHE with placebo. Studies 002, 003, and 004 had a 3 group parallel design with 30 patients. Each patient was treated for 4 migraine attacks if possible and the mean value over all headaches evaluated was used for analysis. Study 005 was a cross-over trial. Studies 603-006, 007 were cross-over trials of 1 mg DHE vs. placebo. But the actual doses can be increased to 1.5 mg and then 2 mg at 90 minutes after dosing. For the cross-over study 008, the protocol was titled as "2 x 1 mg DHE versus placebo." But the second dose of 1 mg (one puffs in each nostril) is optional within 15 minutes after the first dose of 1 mg. Patients treated 4 attacks, 2 consecutive attacks with the same trial drug then cross over to the other trial drug for 2 more consecutive attacks. Mean value of the two attacks with the same treatment was compared. Study 603-111 was a cross-over study comparing DHE with Cafergot and will not be discussed further. Note that all studies utilized a lower dose than that used in the U.S. studies.

For the foreign studies, there were U.S. statistical analyses in addition to the "European" statistical report. The series of U.S. supplemental statistical reports to the European Clinical Reports were intended to address the issue of treatment by investigator interactions on the analysis of four efficacy variables : (1) influence of the study medication on the migraine attack corresponding to the question of "Attack was controlled, strongly reduced, slightly reduced, unchanged", (2) duration of the migraine attack corresponding to the question "Total duration of attack (hrs)", (3) need for analgesic concomitant medication corresponding to the yes or no question for concomitant medication, and (4) the patient's overall rating of the efficacy of the study medication corresponding to the evaluation of "Overall rating: very good, good, moderate, no change, worse."

Study No. 603-002

A total of 140 patients entered this trial from 9 centers. Eight-three were considered "completely valid," 31 patients as "partially valid" and 26 patients "totally invalid."

The European reported results from Kruskal-Wallis test indicated that headache intensity before the treatment was not significantly different among treatment groups for valid patients ($p=0.289$) (for all patient, $p=0.096$). The influence of trial drugs on the attacks for valid + partially valid patients ($p=0.064$) and all patients together ($p=0.044$) were significantly different favoring DHE. For valid patient only analysis it failed to show significant differences ($p=0.808$).

Study No. 603-003

Of the 45 patients entered, only 13 patients were considered "completely valid" for efficacy analysis. Fifteen patients as "partially valid" and 17 patients as "totally invalid."

The report indicated there was no statistically significant difference between the three treatment regimens in any of the efficacy parameters.

Study No. 603-004

Fifty-two patients (20 male, 32 female) entered at two centers. Thirty-five patients were considered as completely valid, 12

patients as partially valid and 5 patients as invalid. No statistically significant differences between the three treatment groups were observed. There was qualitative center by treatment interaction (p=0.06, influence of trial drug on attacks) with one of the investigators having treatment results favoring the DHE and the other favoring the placebo.

Study No. 603-005

The objective of this cross-over study was to compare the initial dose of 1 mg (A) and 0.5 mg (B) DHE with placebo (C). No significant differences among study groups were claimed by the sponsor.

Study No. 603-006

Study DHE 603-006 was a cross-over study of DHE 1 mg vs placebo in the acute treatment of classical or common migraine attacks.

Each patient was treated for 4 attacks, two consecutive attacks with DHE and 2 consecutive attacks with placebo in a randomized order. The average of the two consecutive attacks of the same treatment was compared in the analysis.

At the onset of an attack, patient took two puffs, one in each nostril, corresponding to a dose of 1 mg. If relief is not satisfactory within 30 minutes a further puff in one nostril was taken, repeated if necessary half an hour later by a fourth spray. At 90 minutes after the first dosing, non-ergotic rescue medication can be taken if treatment was not effective.

The U.S. report listed six efficacy parameters: 1. intensity of attacks before treatment, 2. duration of attacks, 3. number of sprays, 4. influence of trial drug on attack, 5. concomitant medication, and 6. overall rating. The influence of trial drug on attack was treated as the primary parameter.

Thirty-nine patients (12 male, 27 female) entered the study from 2 investigational sites. Twenty-four (62%) (7 male, 17 female) were considered as completely valid for the efficacy analysis, 2 patients as partially valid and 13 (33%) patients as invalid.

The analysis of efficacy data is conducted for valid patients, and valid+partially valid patients. P-values for the carry-over

effect were 0.29, 9.98, and 0.22 for all, valid, and valid+partially valid patients, respectively. The period effect of influence on attack had p=0.1 for all 3 patient populations. The analysis on the first period data had a significant result favoring DHE with a p- value of 0.02.

Study No. 603-008:

This double-blind, placebo-controlled cross-over study evaluated the effect of DHE nasal 2 x 1 mg comparing to placebo in the acute treatment of migraine attacks.

At the first prodromal symptoms, patients should take 1 puff in each nostril, corresponding to a total dose of 1 mg. If relief is not satisfactory within 15 minutes, a further puff in each nostril should be taken corresponding to an additional 1 mg. If no beneficial effect was observed within 30 minutes after the first spray, a non-ergot medication can be taken.

From the randomization lists, the study under 008 was a combination of several studies.

All 18 patients at Investigator Rocchi (RA) had 2 sprays per attacks for all 4 attacks compared to most patients at other sites had 4 sprays for each headache attack.

This multicenter study included 13 sites from 5 countries. One hundred and seventeen patients were considered completely valid, 5 patients were partially valid and 24 patients were totally invalid for the efficacy analysis.

There was a significant difference on influence on attack ($p<0.001$) on both valid patients or valid and partially valid patients.

In the U.S. report on 130 patients, the influence of trial drugs on attacks had a significant treatment-by-investigator interaction (p=0.02). In investigator Ferkovic's site, placebo performed numerically better than DHE for the sequence group placebo/DHE.

Study No. 603-007

Eighty-seven patients were considered as completely valid, 8

patients were considered partially valid and 24 as totally invalid for the efficacy analysis.

The U.S. Statistical Analysis reported that of the 119 patients randomized, 87 had 2 or more migraine attacks with or without a protocol violation.

The only raw data available was the response of each headache as success or failure. No individual patient background data were available.

Instead of influence of the study medication on migraine attack, the binary variable of whether relief was obtained within 2 hours was used. The overall complete relief of attack within 2 hours for DHE was 33% compared to the 16% of placebo ($p<0.01$).

Reviewer's Comments:

1. For the foreign studies, the protocol was to compare 1mg DHE with placebo on migraine treatment. But the dosing of DHE varies among patients. All patients had the first dose of 1 mg DHE (2 puffs), which could be followed by the third and fourth puffs at 30 minute intervals each. The doses, therefore, can be 2, 3 or 4 sprays corresponding to 1 mg, 1.5 mg, or 2 mg, respectively. Most patients took 4 puffs (80/96, study 006) for each attack while a few took 3 (10/96) and even fewer for 2 puffs (5/96).

2. In the protocol there were no designated efficacy variables. The objective parameters included were duration of each single attack (Total duration of attack (hrs)), number of sprays necessary to give a relief (No. of sprays per attack) and general attitude of the patient before and after the treatment. The subjective parameters included severity of each single attack during the clinical trial period and degree of confidence in the efficacy of the medication.

In the patient evaluation form, the patient headache intensity before taking medication was recorded as severe (3), moderate (2), or mild (1) but severity rating was not recorded at any point after dosing. The question relevant to efficacy was to choose from the 4 boxes "Attack was controlled, strongly reduced, slightly reduced, or unchanged." There was also an overall rating of very good, good, moderate, no change, or worse.

The efficacy variable, influence on attack, in the study report was coded as 1. controlled, 2. strongly reduced, 3. slightly reduced, and 4. unchanged.

The intensity of the headache was not followed up after dosing at fixed time point. All ratings were taken retrospectively without a designated time point to record the response. The trial medication can be confounded with the rescue.

3. From the protocol, study 008 was not planned as a multicenter study. It was a combination of smaller studies.

4. The 'headache card' of study 007 had a record for severity of headache (4 point scale) before the first two sprays, before the third spray (30 min), before the fourth spray (60 min) and at 30 minutes after the fourth spray (90 min). This is the only foreign protocol with severity of headache being recorded during the attack. But the raw data of the study was either unavailable or changed to a binary outcome of success or failure. No individual patient background data were available. The influence on attack in study 007 was changed to the complete relief within 2 hours after medication intake without explaining how it was changed.

Conclusions from Foreign Studies:

The foreign trials utilized a lower dose than the 2 U.S. studies. The influence of the trial medication on migraine attacks was the main efficacy parameter. In trial 006 it showed positive effect for DHE compared to placebo. In study 007, data was not available for the influence of the trial medication. The main efficacy parameter was changed to relief before 2 hrs without explaining how the information was taken since it was not one of the items in the patient attack form. The 3-dose parallel group study of 004 found no evidence of difference from placebo. One of the investigators had a positive dose response effect while the other investigator had a reversed dose response effect.

The main efficacy variables taken retrospectively are confounded with other factors (e.g., rescue medication) in the trial. The results of these studies are considered unreliable by this reviewer.

Overall Conclusions:

The two U.S. studies provided evidence of DHE 2 mg nasal spray is effective in treatment of migraine when compared to placebo. The statistical significance occurred at 2 to 3 hours after dosing.

The foreign studies add little useful efficacy information. They do not appear, in general, to be adequate and well-controlled studies. In addition, the protocols called for lower doses than were utilized in the U.S. studies.

Lee-Ping Pian

Lee-Ping Pian, Ph.D.
Mathematical Statistician

Concur: Dr. Nevius SEN 7-30-93

for Dr. Dubey SEN 7-30-93

cc:
Orig. NDA 20-148
HFD-120
HFD-120/Dr. Leber
HFD-120/Dr. Collins
HFD-120/Dr. Katz
HFD-120/Ms. Higgins
HFD-713/Group 2 file
HFD-713/Dr. Pian
HFD-713/Dr. Dubey [File:DRU 1.3.2]
HFD-344/Dr. Lisook
Chron
This review contains 15 pages.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20148

ADMINISTRATIVE DOCUMENTS

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

DATE: November 24, 1997

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

SUBJECT: Migranal™[dihydroergotamine mesylate USP) Nasal Spray

TO: File NDA 20-148
&
Robert Temple, M.D.
Director, ODE-1

This memorandum conveys my recommendation that NDA 20-148 for Migranal® Nasal Spray, Novartis Pharmaceutical Corporation's brand of dihydroergotamine mesylate, USP) be approved. My views on the findings and arguments that support the conclusion that Migranal Nasal Spray is, within the meaning of the Act, safe for use and effective in use in the treatment of acute migraine under the conditions of use recommended in labeling developed by the Division's review team have been provided in earlier memoranda to the NDA file (5/9/95 and 4/8/97).

The Migranal Nasal Spray NDA was declared approvable in an agency action letter dated May 9, 1997. That letter advised that final approval of the application was contingent, in addition to the firm's satisfactory fulfillment of the usual set of post-approvable/pre-approval tasks, upon the sponsor's 1) agreement to market Migranal under a version of labeling developed by the Division, 2) submission of a draft report of an already completed rat CA study, and 3) commitment to provide results of a study after approval of the application.

Post approvable action review activities and findings.

Safety Update [SU]

Dr. Armando Oliva has reviewed ((7/3/97) the firm's safety update (for the interval 7/1/96 to 5/19/97). Two serious ADRs were identified;

neither, in my view, is important to the agency's determination to approve the NDA.

The SU also provided information on 15 deaths associated with the injectable formulation of dihydroergotamine, D.H.E. 45. that were recovered in a search of what is identified as a "International safety Database." The details provided are scanty, but in my view the timing of 3 deaths of, or presumably of, cardiac origin is consistent with a probable/possible causal link to the use of the injectable product (one affecting a 57 yo male that occurred some 20 min after a 2nd dose is on face most persuasive among the 3). These deaths are not unexpected in light of our knowledge of the pharmacology of the therapeutic class; they deserve mention primarily as further empirical support for our decision to insist that Migranal labeling carry Warnings and Precautionary statements concerning coronary heart disease and coronary spasm that are now regularly included in the labeling of all currently marketed anti-migraine drugs presumed to act through or bind to 5-HT1d like receptors.

Draft Final Report of the Rat life-time carcinogenicity Study on dihydroergotamine

Submission (as required in the approvable action letter) of the draft final report was made on 10/17/97, but has not yet been reviewed. In a memorandum to the file of October 16, 1997, Dr. Fitzgerald explains that because the preliminary report of the Rat CA study raises no substantive concerns about dihyrodroergotamine's neoplastic inducing potential, the lack of a completed review of a draft final report need not affect approval of the application. If it does prove necessary, the sponsor can submit a supplement to revise labeling to include any new information we conclude is required.

Labeling development

In the post-approvable action period, Dr. Levin, the team leader for this application, worked with the firm's representatives to develop a version of labeling under which Migranal could be responsibly deemed safe for use, effective in use, and accurately labeled.

Although a draft version of labeling developed as a result of those negotiations was largely acceptable to me, I concluded that the Clinical Trials, Dosage and Administration and Patient Information Sections required further revision. My concerns involved the following matters:

Clinical Trial Section

The data to be described and/or displayed

In the draft of labeling attached to the approvable action letter (hereinafter referred to as "approvable draft labeling"), 4 adequate and well controlled clinical trials (studies 301, 302, 511, and 512, identified respectively as studies 1,2 3 and 4) were cited as the sources[1] of the evidence relied upon to assess the efficacy of Migranal nasal spray in the management of acute migraine.

Table 1 of the approvable draft labeling provided a comparison among these 4 studies in regard to the proportion of patients in each study attaining a "response" at each hour over the course of their 4 hour duration.

In the new draft labeling (that developed via negotiations with the firm and provided to me for consideration in early October), only the results of Studies 301 and 302 were presented within a table. In his memorandum of September 15, 1997, Dr. Levin explained[2] that the sponsor did not want to include studies 511 and 512 in the same table as studies 301 and 302 because they are older studies that employed outcome measures that differ from those used in 301 and 302. Specifically, the outcome measure used to define a responder in studies 301 and 301 is pain relief while the definition of response in studies 511 and 512 is based on a composite measure that confounds pain relief and "functional" recovery.

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[1] It deserves note that of these four studies, only Studies 511 and 512 have actually been inspected by DSI.

[2] At my request, Dr. Levin subsequently issued a memorandum (10/16/97) explicating his reasons for revising the clinical trial section in the manner that he did

The Division was evidently unaware of the differences between the two definitions employed in these two pairs of studies; thus, at the time the approvable action letter was prepared, Table 1 in the Clinical Trial section of the approvable draft labeling was inaccurate[3].

The sponsor and Dr Levin proposed to repair Table 1 by using it to present only the outcome of studies 301 and 302. The description of Studies 511 and 512 was reduced to a statement that their results "were supportive to the conclusions of studies 1 and 2 [i.e., Studies 301 and 302]".

While I shared Dr. Levin's concern that a table comparing the results of several studies on what appear to be a single outcome measure (percent response) is at risk of misleading readers if that measure is actually defined by a different criterion for each study, I did not find the concern a basis to force a choice regarding which study results deserved citation in labeling and which did not.

Specifically, the fact that different outcome measures are used in different studies, does not, by itself, speak to the weight that should be accorded to the results of a study. To the contrary, the result of each adequate and well controlled study should be given equivalent weight unless there is a compelling reason to discount it. For example, if a study were found to have employed an invalid outcome measure, the trial could not be considered a probative source of evidence. However, that was certainly not the case in regard to Studies 511 and 512; their results provided valid support[4] for the Division Review Team's affirmative conclusions concerning Migranal. Accordingly, I concluded that the primary finding of each of these four studies should be presented in labeling in a manner that accorded each equal weight.

Toward that end, I asked that the new draft of labeling present two tables, one for each pair of clinical studies relying upon the same method

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[3] Table 1 in the agency approvable action letter incorrectly asserts that response in all 4 studies was based on a reduction in headache severity from moderate or severe to mild or no pain.

[4] A conclusion that Dr. Levin in no way disputed.

of outcome assessment and response definition.

I was mindful that response rates cited in product labeling are invariably at risk of being given far greater weight than they actually deserve[5]. Accordingly, I developed a statement[6] for placement in a location immediately following the two tables advising that comparisons among outcomes of studies conducted at different times, with different samples of patients, by different investigators, using different measures of assessment, could not be meaningfully compared.

I was mindful, too, that the enumeration of the results of studies 511 and 512 in a table did not fully compensate for the fact that only the combined results of studies 301 and 302 were provided in Figure 1 (a Kaplan Meier plot displaying the conditional probability of attaining a response as a function of time elapsed since treatment initiation with Migranal as compared to placebo). Moreover, I found it odd that the 2nd figure in the

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[5] The point estimates produced in a typical clinical drug effectiveness study have arguable external validity. Not only are the patients recruited for the study a "sample of convenience" (i.e., as distinguished from a "probability" sample), but the conditions (secular period, design, selection/exclusion criteria and assessment measures, investigators) under which a given study is conducted are variable. Since the extent to which these conditions confound each treatment effect estimate is unknown, the precision and accuracy of a particular realized estimate of a treatment effect size has limited external validity. Importantly, this limitation does not invalidate the RCT as a source of evidence to support a "proof of principle" determination. To the contrary, despite its limitations, the RCT remains the one and only reliable and valid experimental method to determine whether or not a drug actually works. Dr Levin, mindful of these issues suggests, in his memorandum of 10/16/97, dropping all citations of treatment effect size from labeling. This suggestion is not without merit but, I believe it goes too far. Although the estimates adduced in an RCT have limited external validity, they are the basis of the agency's regulatory determination that a drug is effective in use and that information, I believe, should be made available in product labeling.

[6] A variant of this statement was also placed in the draft labeling of two NCE anti-migraine drug products, Zomig (PDUFA date of 11/26/97) and , that were undergoing evaluation and review more or less contemporaneously with Migranal (PDUFA date of 12/10/97).

proposed draft of the Clinical Trials Section (a plot of the probability that a patient will use rescue medication over the first 24 hours following treatment with either placebo or Migranal) was based on data collected from patients who participated in all 4 of the adequate and well controlled clinical investigations.

Accordingly, I sought to have Figure 1 also provide the data for all patients in all 4 studies. I was informed, however, that agency staff were not in possession of the individual patient data necessary to construct a Kaplan Meier plot for studies 511 and 512. Accordingly, I decided to seek the required information from the sponsor, or, alternatively, to ask the firm to do the calculations so that a single Kaplan Meier plot could be presented for each of the 4 studies.

Describing the conditional probability of re-medication given an initial "response"

Another issue involving the clinical trial section, one that has subsequently proved to be of major and persisting interest to the sponsor, was a paragraph the sponsor sought to include that describes the proportion of patients attaining a full response who subsequently do not require further treatment over the ensuing 24 hours.

Dr. Levin believes the information provided promotes an inference not justified by the evidence. Accordingly, he prefers that product labeling not include this information (see his memorandum of 10/16/97 and his memorandum of 10/23/97 responding to the firm's letter of 10/22/97).

The argument is one that involves the different meanings that can be attached to the notion of conditional and joint probabilities.

A responder is defined for purposes of the analysis of recurrence that is of interest to the sponsor as an individual who starts with a moderate to severe headache and at the time of planned outcome assessment has no headache. The proportion of responders in a treatment group estimates

the probability of response under the treatment assigned to that group[7] (i.e, P [R|Rx], P[R|pbo]. An estimate of the probability of not requiring further treatment given a the initial treatment is actually a joint probability, representing the product of the probability of having a response (P[R|Rx], P[R|pbo]) with the probability of not requiring subsequent treatment, having had a response after drug, P[no Rx| R, Rx], or after placebo, P[no Rx| R, pbo.

Now, if P [R|Rx] is greater than P[R|pbo], as it is in all 4 trials, then, even if P[no Rx| R, Rx] equals the P[no Rx| R, pbo], the joint probability of P [R|Rx] x P[no Rx| R, Rx] will be greater than the joint probability of P[R|pbo] x P[no Rx| R, pbo). In other words, even if active treatment has no effect on the likelihood of headache recurrence (i.e, need for additional treatment), it will appear, based on a naive interpretation of the joint probability, to have had such an effect if P [R|Rx] > P[R|pbo].

A discussion in labeling that places emphasis on the joint probability is, in Dr. Levin's view, potentially misleading. I agree, but I am not entirely averse, if the firm would consider it, to allowing them to present the joint probability if they also make clear that it is due to the underlying difference in response and not the a difference in conditional probability of recurrence, given a response. Of course, if the sponsor were to obtain consistently, across several studies, clinical evidence of a statistically significant drug placebo difference in the conditional probability of re-medication, those findings could be presented in product labeling.

Dosage and Administration

Novartis initially objected to the statement, " The safety of doses greater than 3.0 mg in a 24 hour period and 4.0 mg in a 7 day period have not been established." that appeared in the agency's approvable draft labeling. The alternative they proposed asserted that the safety had not been established "in an adequate number of patients in clinical trials." In my

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[7] R = responder, Rx = active treatment , pbo = placebo, P[R | Rx] is read as the probability of response given active treatment and P[noRX | R,Rx] as the conditional probability of requiring no treatment given a response and treatment with drug. The other notions follow the same pattern

view, their statement could be understood to imply that the safety of such doses and durations had been established in some other way, however. Moreover, the agency's statement was, in my opinion at least, accurate and fair. Accordingly, I insisted that the version from the approvable draft labeling be used.

An account of the Division's effort to reach agreement with the sponsor about the content of product labeling prior to delivery of the approval action package to the Office

In mid October, I attempted to reach closure with Novartis about the Migranal NDA. This required that the Division take the application out of order in respect to its position in the "queue" of pending PDUFA projects. I concluded it would be appropriate to do so because the effort, which I thought would entail no more than a brief discussion of a few minor labeling details, would in no way compromise the timely completion of ongoing work on applications with earlier PDUFA dates.

Toward that goal, Dr. Levin and I called the sponsor on 10/17/97. I explained that the Division's goal was to expedite approval of the application by reaching agreement on the final wording of product labeling. It turned out, however, that the Division and Novartis were farther apart on the text than I expected. Accordingly, I explained that even if we could not reach agreement, it would be useful for them to explicate their arguments so that I could, in forwarding the Division's recommendations to the Office, make him fully aware of why the firm and the division disagreed in regard to the various issues in dispute. I emphasized that a rapid response was essential if we were to act on the application in advance of the PDUFA date as I had only a limited amount of time during the month of October available. At the conclusion of our conversation, a draft version of labeling that I intended to recommend be adopted for Migranal was provided (via fax) to the firm.

On 10/23/97, the Division received a fax of a letter dated 10/22/97.

Novartis announced[8] its agreement to adopt several of the changes I had requested, offered alternative text and/or layout for some other sections, but strenuously objected to two proposed sections. Because of the nature of their objections, I found it impossible to complete my review of the application in advance of its scheduled position in our PDUFA queue.

Final Divisional Draft Labeling

Attached to the approval action letter being forwarded for issuance is a version of product labeling for Migranal under which I and Dr. Levin can recommend the NDA be approved. This labeling incorporates some of the suggestions and alternative text proposed by the sponsor in its 10/22/97 letter to the Division as well as changes that parallel those made to the labeling of the other 5HT-1d/1b agonists that the Division has been evaluating pari passu.. There continue, however, to be the 2 areas of disagreement; these are of sufficient importance to deserve comment.

Celebration of the probability of headache recurrence among patients in product labeling remains a goal of the sponsor. The firm is adamant that they be allowed to present what they characterize as vital information; the Division is equally adamant that they not be allowed to do so. Dr. Kessler of Novartis informed Mr. Nighswander (telcon of 11/20/97) that he believes the inclusion of this information is so important that he "demands" the matter be discussed with Novartis officials prior to action on the NDA being taken by the Office. I attempted to call Dr. Kessler on the same day, but only reached a phone message system; I left a message.

As explained earlier, some discussion of this subject is acceptable, but only if it is makes clear that the difference in recurrence/remedication rate may be entirely explained by the difference in the initial treatment response rate.

The firm also takes very strong objection to the generic statement that I crafted warning of the limited external validity of effect size estimates adduced in randomized controlled clinical trials. In fact, they not only

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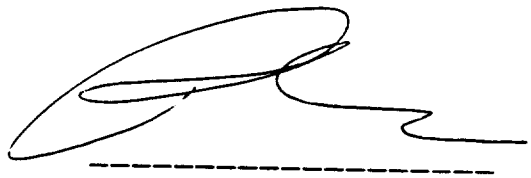
[8] Dr. Levin's review 10/23/97 provides a systematic review of their arguments.

objected to the statement, but offered a lengthy argument asserting that the Division lacks authority to request the introduction of such a statement in product labeling. Indeed, the sponsor goes so far as to specify steps that the Division should follow (e.g., gain concurrence from the MPCP) before requiring the introduction of such a statement. I clearly disagree with the sponsor and I have already made my own views clear on this point.[9] Nonetheless, the matter is now largely moot in light of the Office Director's decision in regard to the labeling of Zomig.

Although I have not discussed the issue with the sponsor, it seems likely that they will accept the revised statement as it is identical to that which will appear in the labeling of Zomig and

Conclusion and recommendation.

Provided that Migranal is marketed for use under the draft labeling being forwarded as an attachment to the approval action letter, I can conclude responsibly that Migranal will, within the meaning of the Act, be safe for use, effective in use, and marketed under labeling that is not false or misleading in any particular. Accordingly, under the condition specified, I can recommend that the application be approved.



Paul Leber, M.D.
November 24, 1997

[9] In my approvable action recommendations on Zomig and

cc:
NDA 20-148
HFD-101
TEmple
HFD-120
Katz
Levin
Fitzgerald
Oliva
Nighswander

SECTION XIII: PATENT INFORMATION

DHE-45® (dihydroergotamine mesylate) Nasal Spray is claimed in USP 4,462,983, which expires July 31, 2001; the DHE-45 Nasal Spray applicator is claimed in USP 4,758,423, which also expires July 31, 2001.

SECTION XIV: PATENT CERTIFICATION

There is no applicable or required patent certification for DHE-45® (dihydroergotamine mesylate) Nasal Spray.

Migranal™ (dihydroergotamine mesylate, USP) Nasal Spray

Section 13. Patent Information

There is no new patent information to include in the resubmission. This section is crossed referenced to the original Migranal™ Nasal Spray NDA No. 20-148 (submitted on December 28, 1990 and revised on April 30, 1991). The table of contents for this section includes a cross reference to the pagination from the original NDA for all previously submitted information, in addition to the pagination for the new information.

Migranal™ (dihydroergotamine mesylate, USP) Nasal Spray

Section 14. Patent Certification

The patent certification for this product has not changed since the original NDA submission. Section 14 is crossed referenced to the original Migranal™ Nasal Spray NDA No. 20-148 (submitted on December 28, 1990 and revised on April 30, 1991). The table of contents for this section includes a cross reference to the pagination from the original NDA for all previously submitted information, in addition to the pagination for the new information.

EXCLUSIVITY SUMMARY

for

NDA # 20-148 SUPPL # _____

Trade Name Migranal™ Nasal Spray **Generic Name** Dihydroergotamine Mesylate
Applicant Name Novartis Pharmaceutical Corp. HFD-120

Approval Date December 8, 1997

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA?

   YES /_X_/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /_X_/

   If yes, what type? (SE1, SE2, etc.) ____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /_X_/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   _____

   _____

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name_____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

5/31/95 Telecon with Don Hare:
The DESI upgrade for the inj. does not apply since clinicals were conducted specifically for the nasal spray. YES /__/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 5-929 D.H.E.™ Injection

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X_/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # 511

Investigation #2, Study # E301

Investigation #3, Study # E302

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /_X_/
Investigation #2	YES /___/	NO /_X_/
Investigation #3	YES /___/	NO /_X_/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #_____
NDA # _____ Study #_____
NDA # _____ Study #_____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /_X_/
Investigation #2	YES /___/	NO /_X_/
Investigation #3	YES /___/	NO /_X_/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #_____
NDA # _____ Study #_____
NDA # _____ Study #_____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1, Study # 511

Investigation #2, Study # E301

Investigation #3, Study # E302

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		
IND #_____	YES /_X_/	NO /___/ Explain: _____
		_____
Investigation #2		
IND #_____	YES /_X_/	NO /___/ Explain: _____
		_____
Investigation #3		
IND _____	YES /_X_/	NO /___/ Explain: _____
		_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

_____

_____

_____

Robbi W. Stubbs 2-26-97
Signature Date
Title: Regulatory Management Officer

[signature] 11/24/97
Signature of Division Director Date

cc: Original NDA
Division File
HFD-85 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

(NDA)/PLA # 20-148 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-120 Trade (generic) name/dosage form: Migranal Nasal Spray (dihydroergotamine mesylate) Action: AP (AE) NA

Applicant Novartis Pharm. Corp. Therapeutic Class Anti-Migraine

Indication(s) previously approved Migraine Pediatric labeling of approved indication(s) is adequate X inadequate __

Indication in this application Migraine (For supplements, answer the following questions in relation to the proposed indication.)

__ 1. **PEDIATRIC LABELING IS ADEQUATE.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.

__ 2. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

__ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

__ b. The applicant has committed to doing such studies as will be required.

__ (1) Studies are ongoing,

__ (2) Protocols were submitted and approved.

__ (3) Protocols were submitted and are under review.

__ (4) If no protocol has been submitted, explain the status of discussions on the back of this form.

__ c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

__ 3. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed.

__ 4. **EXPLAIN.** If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

R. [redacted] 4-8-97

Signature of Preparer and Title (PM, CSO, MO, other) Date

cc: Orig NDA [redacted] # 20-148
HFD-120 /Div File
NDA [redacted] Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

3/96

Migranal™ (dihydroergotamine mesylate, USP) Nasal Spray

Resubmission of a New Drug Application

SANDOZ CERTIFICATION
IN COMPLIANCE WITH THE
GENERIC DRUG ENFORCEMENT ACT OF 1992

SANDOZ PHARMACEUTICALS CORPORATION certifies that it did not and will not use in any capacity the services of any person debarred under section 306(a) or 306(b) of the Federal Food, Drug and Cosmetic Act in connection with this application.

May 17, 1996.
Date

Michael S. Perry, DVM, PhD
Vice President, North American
Drug Registration & Regulatory Affairs

M E M O R A N D U M

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

DATE: November 15, 1994

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

SUBJECT: Request for Assessment of a Trademark for a Proposed Drug Product

OUTGOING

NOV 16 1994

TO: Ms. Yana Mille,
Labeling and Nomenclature Committee
HFD-600, Metropark North II

Proposed Trademark: MIGRAMIST (Nasal Spray) NDA # 20-148

Established name, including dosage form: Dihydroergotamine Mesylate, USP

Other trademarks by the same firm for companion products:

None

Indications for Use (may be a summary if proposed statement is lengthy):
See draft labeling and container labeling attached

NOTE #1:Previously referred to a D.H.E.-45 Nasal Spray

cc: ORIG NDA 20-148, HFD-120, HFD-120/WBrannon,HFD-120/DGrilley

#408 OUTGOING

MEMORANDUM

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

DATE: November 15, 1994
(amended: January 31, 1995)

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

SUBJECT: Request for Assessment of a Trademark for a Proposed Drug Product

TO: Chair
Labeling and Nomenclature Committee
HFD-600, Metropark North II

Proposed Trademark: **MIGRAMIST®, MIGRANOL® NDA # 20-148**

Established name, including dosage form: **Dihydroergotamine Mesylate, USP, Nasal Spray**

Other trademarks by the same firm for companion products: **D.H.E. 45® Injection (NDA 5-929)**

Indications for Use (may be a summary if proposed statement is lengthy):

D.H.E. 45® (or MIGRAMIST®, or MIGRANOL®) Nasal Spray is indicated for the symptomatic treatment of common or classic migraine headaches in adults. For best results, treatment should commence at the first symptom or sign of migraine headache attack.

Initial comments from the submitter: (concerns, observations, etc.)

This application was originally submitted utilizing the "D.H.E. 45® Nasal Spray" tradename. The firm amended the application on 11-9-94 to provide for a change in tradename to MIGRAMIST®. The firm further amended the application on 1-25-95 to ask that the tradename MIGRANOL® be considered by the Labeling and Nomenclature Committee.

cc:
ORIG NDA
HFD-120
HFD-120/SBlum/Brannon
HFD-120/RNighswander

Consult #408 (HFD-120)

A) MIGRAMIST — Dihydroergotamine Mesylate Nasal Spray

B) MIGRANAL

A) MIGRAMIST

A review revealed one name which sounds or looks like the proposed name: Mucomyst. Due to differences in dosage forms, the Committee does not believe there is a significant potential for confusing involving the two names.

B) MIGRANAL

A review revealed one name which looks like or sounds like the proposed name: Migratine. Due to the difference in dosage forms (tablets vs. nasal spray), the Committee does not believe the two names are sufficiently similar to cause confusion.

Generally, the Committee opposes any reference to an indication (example: Migra = migraine) in a proprietary name, since a product could theoretically be approved for another indication in the future, thus making the name misleading at that point in time. However, in this case, the Committee believes that it is unlikely another indication will be approved for this product, and finds the use of the syllable "Migra" acceptable.

The Committee has no reason to oppose either of the proposed names.

CDER Labeling and Nomenclature Committee

Gloria Ruth Milli, Chair 3/1/95

COMPLETED