CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20148

MEDICAL REVIEW(S)

Review and evaluation of clinical safety data

NDA	20,148
Sponsor	Sandoz
Drug	D.H.E.45® Nasal Spray 4 mg/mL (dihydroergotamine mesylate, USP)
Drug class	Type 3 - new formulation Therapeutic potential - Standard
Proposed indications	Symptomatic treatment of common or classical migraine in adults
Material reviewed	Integrated Safety Summary (Vol 38/62)
Filing date	Jan 17, 1992

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I. Introduction.

A. The safety data base for this NDA consists of the populations of 28 studies (Clinical Pharmacology 10, Efficacy and Safety 12, Long-term Safety 6). A 29th study was carried out in Denmark in May, 1985. This was Study **603-016**: "An open trial on the topical safety of Dihydroergotamine as a nasal spray in healthy volunteers". This study was designed to compare the effects of single doses of D.H.E.45® nasal spray 1 mg and placebo on nasal airway resistance. N=12 male subjects participated. No clinical safety data were collected. Study protocol is at *Vol 12 / page 08-00666;* Study report begins at *page 08-00678.*

B. Study designs.

1. Nine of the 10 Clin Pharm studies were single-dose crossover designs, as follows:

303-002 - 1 mg nasal spray **vs** 1 mg intramuscular (N=10)
303-020 - 1 mg nasal spray **vs** 1 mg intramuscular (N=18)
303-021 - 2 mg nasal spray **with / without** caffeine (N=18)
303-022 - 1 **vs** 2 **vs** 4 mg nasal spray (N=15)
303-023 - 2 mg nasal spray **during / not during** an attack (N=19)
303-024 - 2 mg nasal spray **with / without** fenoxazoline chlorhydrate, a local vasoconstrictor (N=19)
303-025 - 1 mg nasal spray **vs** 2 mg intravenous (N=12)
303-026 - 1 **vs** 2 **vs** 4 mg nasal spray (N=9)
303-112 - 1 mg nasal spray at 0, +10, +70, and +80 min **with / without** propranolol (N=8)

Studies **-002** and **-112** were double-blind; **-024** was single-blind; the others were open-label.

The tenth study, **603-109**, was a long-term parallel-groups safety study in which drug was administered double-blind 6 days / week x 3 weeks to healthy males (active 12, placebo 6). Dose for all subjects was 1 mg nasal spray + 1 mg nasal spray 15 min later.

2. Five of the ten Efficacy and Safety trials in migraine were parallel-groups design and five were crossovers; 9/10 studies were placebo-controlled. All involved short-term treatment, as follows:

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511/512 - 2 consecutive headaches; parallel groups
603-002/-003/-004 - 4 consecutive headaches; parallel groups
603-005/-006/-007/-008 - 2 headaches per treatment; crossover
603-111 - 1 headache per treatment; crossover (vs Cafergot)

3. The two placebo-controlled studies in cluster headache (**603-009/-010**) required patients to use each treatment to treat all headaches occurring within one week, up to a maximum of 8 headaches per treatment. Dosing was limited to 1 mg / headache in **-009**; **-010** permitted additional 0.5 mg doses at 15 and 30 min.

4. Treatment schedules in the six open-label studies were as follows:

603-001 - 4 consecutive headaches
603-011 - at least 12 attacks in 12 months
603-012 - 24 attacks or 6 months
603-013 - at least 16 attacks (max 4/wk)
603-014 - at least 20 attacks (max 4/wk)
603-015 - 40 attacks or 12 months

II. Overview of clinical population.

A. Patients exposed to new drug.

1. A total of 1,311 subjects/patients were enrolled in the development program; of this number, 1,273 received study drug and 1,086 were exposed to D.H.E.45® in one or more of its formulations. The distribution of all patients by drug and type of study is shown in the following table.

Distribution of patients by treatment and type of study

	# of studies	DHE45	Cafergot	Pla	(X-O)	Total
Clin Pharm	10	140	-	23	(17)	146
Efficacy						
Migraine	10	766	191	490	(500)	947
Cluster	2	57	-	57	(57)	57
Open	6	123	-	-	-	123
TOTALS	28	1,086	191	570	(574)	1,273

Cafergot is ergotamine tartrate USP with caffeine. The tablet formulation was used in Study **603-011**.

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2. a) Demographic information in the US efficacy trials (Studies **511** and **512**) is summarized in the following table.

Baseline demographics

	DHE45	Pla	Total
N	102	104	206
Age			
mean ± S.D.	39±11	37+11	38+11
range	20-62	18-61	18-62
Sex			
male	15	19	34
female	87	85	172
Race			
white	97	99	196
black	4	3	7
other	1	2	3
Education			
≤12 yrs	24	33	57
13-16 yrs	52	52	104
>16 yrs	26	19	45

b) Demographic information reported in the non-US studies was limited to age ranges (18-62 years) and sex. Distribution of all patients by sex and type of study is shown below; the populations of the two US studies are included.

	Male	Female	n/a
Clin Pharm	96	50	-
Efficacy			
Migraine	203	773	9
Cluster	50	6	1
Open	45	78	-
Totals	394	907	10

B. Extent of exposure.

As indicated above, N=15 healthy volunteers (male 7, female 8) in **-022**, and N=9 males in **-026** received single doses of 4 mg nasal spray. N=8 male migraineurs in **-112**, a randomized cross-over study of the hemodynamic effects of D.H.E.45® with and without propranolol, received four 1 mg doses over 80 minutes for a total dose of 4 mg on each study day.

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All other subjects participating in the development program received doses within proposed labelling, ie, an initial dose of 0.5 to 1.0 mg, plus one or two optional 0.5 mg doses, for a maximum possible dosage of 2.0 mg.

III. Deaths and Discontinuations.

A. Deaths.

There were no deaths reported in association with the D.H.E.45® development program.

B. Discontinuations.

A total of 15/889 (1.7%) migraine patients exposed to D.H.E.45® discontinued study because of ≥1 AEs: 12/766 (1.6%) patients in DB efficacy trials, and 3/123 (2.4%) patients in long-term open-label safety trials. Three patients in short-term efficacy trials had symptoms possibly related to the CV system:

511/8010 - This was a 39 y/o obese (5'7", 265#) white female with an 18-year history of both common and classical migraine (avg 2/mo for the last year). Pre-treatment lab work was within normal limits except for sinus tachycardia (HR=110 bpm). Patient self-medicated a headache with two 1 mg doses of active at an interval of 15 min, as specified in the protocol, but reported no relief of symptoms. AEs included nausea (mild/moderate), dizziness (mild), and tightness in chest (moderate); Sx lasted approx 3 hrs. Attending physician could not be certain of the etiology of symptoms. Post-Rx ECG was within normal limits (HR=85 bpm). [*Vol 62 / page 12-00036*]

-007/112 - This was a 49-yr old French woman with a 20-yr history of common migraine. The patient initially experienced a mild fainting sensation which began after the first dose of study medication and lasted approx 24 hrs; BP was not recorded. Two to three hours after the onset of this symptom the patient also developed swollen eyelids and heavy-headedness; it was these latter symptoms which resulted in discontinuation. There were no sequelae. [*Vol 62 / page 12-00160*]

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-008/250016 - This was a 28-yr old German woman with a 15-yr history of common migraine. Immediately after the first dose of study medication the patient had the onset of paresthesias, nausea and vomiting, unstable gait, and hypotension (80/45). Symptoms were severe, lasting 90-180 min, but required no treatment and cleared without sequelae. The patient declined to take the second dose of medication (15 min after the first dose) as called for by the protocol but remained in study, completing the placebo arm of the study without incident. [*Vol 62 / page 12-00191*]

All other AEs associated with discontinuation by D.H.E.45®-treated patients were extensions of the pharmacologic actions of D.H.E.45® (chiefly nasal obstruction or numbness, increased nasal secretions, and vomiting), or of migraine itself (eyelid swelling), and were similar in character, intensity, and duration to AEs reported by subjects who did not discontinue.

There were no discontinuations in the two cluster headache studies.

There were no other serious or life-threatening events (as defined in 21CFR312.32 (a)).

IV. Routinely-collected primary safety data.

A. AE incidence tables.

1. Clin Pharm studies.

A total of 93 AEs (≤2 mg D.H.E.45® 54, ≤4 mg D.H.E.45® 37, placebo 2) were reported by the 146 subjects in the Clin Pharm studies. CNS symptoms related to D.H.E.45® were headache (6) and asthenia (3); GI symptoms: nausea 5, bitter taste 2. Musculoskeletal symptoms were pain, cramps, or heaviness of the limbs.

Distribution of all AEs in the Clin Pharm studies, by body system, is shown in the table below. Because of the crossover design, total N >146.

	DHE ≤2 mg	DHE 4 mg	Pla
N	156	32	23
Nasal symptoms	43 (27.6%)	28 (88%)	1
CNS symptoms	6 (3.8%)	3 (0.9%)	-
GI symptoms	3 (1.9%)	5 (1.6%)	1
Miscellaneous symptoms	2 (1.2%)	1 (<1%)	-

2. The distribution of AEs, by body system, among D.H.E.45® and placebo patients in all Efficacy and Safety studies is shown in the following table. A total of 104/227 (45.8%) complaints among D.H.E.45® patients and 23/40 (57.5%) complaints among placebo patients referred to the nose. (Sponsor's table of AEs, grouped by body system, is in the Appendix. Sponsor's dictionary of AEs is also in the Appendix.)

	DHE	Placebo
N	766	490
Nasal	104 (13.6%)	23 (4.7%)
Gastrointestinal	56 (7.3%)	8 (1.6%)
CNS	31 (4.0%)	7 (1.4%)
Cardiovascular	14 (1.8%)	0
Autonomic	10 (1.3%)	1 (<1%)
Musculoskeletal	8 (1.0%)	1 (<1%)
Miscellaneous	4 (<1%)	0

A total of 44 AEs were reported by the N=191 patients in Study 111 who received Cafergot® tablets (mean dose = 2.7 mg/headache), for an overall incidence of 23%. 25 AEs (13.1%) related to the GI tract (nausea, bitter taste, abdominal pain). Sponsor's table of AEs, grouped by body system, is in the Appendix.

3. Long-term open-label studies.

A total of 58 AEs were reported by the 123 subjects in the long-term safety studies. Commonest were nasal symptoms (33) and nausea / vomiting (12). Arrhythmia and pain near the heart were reported by Patient 006 participating in Study 001, an open-label study of migraineurs treating four attacks. Symptoms, judged mild in intensity, occurred after the first dose and cleared after 15 min without treatment; the investigator did not consider them to be drug-related. The patient remained in study for all four attacks.

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Distribution of all AEs, by body system, for the long-term studies is shown in the following table.

	DHE45
N	123
Nasal	33
Gastrointestinal	12
CNS	7
Cardiovascular	4
Other	2

B. Local tolerability.

1. A total of 232/418 (55.5%) AEs reported in all clinical studies referred to the nose. Individual symptoms included congestion, irritation, discomfort, tingling, burning, dryness, and itching; rhinitis and rhinorrhea; sneezing; and one report of epistaxis. None of the symptoms required treatment and none resulted in permament damage. The following table summarizes the frequency distribution of these symptoms.

	DHE	Placebo	Total
Clin Pharm	71/91 (78.0%)	1/2 (50%)	72/93 (77.4%)
Eff & Safety	104/227 (45.8%)	23/40 (57.5%)	127/267 (47.6%)
L-T safety	33/58 (56.9%)	-	33/58 (56.9%)

2. Glass particles.

a) In response to Agency concerns regarding delivery of glass particles expelled from the spray device used to administer D.H.E. 45®, with subsequent inspiration of these particles into the lungs, the Sponsor has submitted (7.23.92) a report by an outside consultant:

"Glass particles released from a Valois pump spray nasal nebulizer." July 9, 1992. Page 2 of 7.23.92 submission.

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The author reviews the anatomy of the nasal passages, and cites evidence to show that the configuration of the anterior nasal orifice and the position of the pump spray device leads to essentially complete deposition of sprayed aerosol onto the nasal mucosal surface. Evidence from aerosol deposition studies demonstrates that particles with aerodynamic diameters larger than 10 μm will be quantitatively removed at the orifice. Since the Sponsor's in-house studies of particle size (using 10 ampuls produced by each of four manufacturers) indicate a minimum aerodynamic particle diameter of 39.8 μm, the author concludes that: "... the possibility that glass particles produced from a Valois spray device containing D.H.E.45® can penetrate the nasal passage and deposit in the distal lung is essentially zero."

Sponsor's 7.23.92 submission also contained copies of reports of the two particle-size analyses carried out in-house, as follows:

- Gregory Argentieri. Staff scientist, Electron Microscopy Laboratory, Sandoz Research Institute. "DHE Nasal spray, Valois Apparatus (3 vendors: , Glass particulate study". Page 31 of 7.23.92 submission.

- G Argentieri. As above. Glass ampuls supplied by foreign vendor, Verretubex, to Sandoz Pharma Ltd, Basle, for use in non-US clinical studies. Page 50A of 7.23.92 submission.

b) As a further check on the possibility of glass particles being delivered to the nasal mucosa and thence inspired, the Sponsor reviewed all spontaneous reports of adverse effects from countries where the Nasal Spray is marketed. No reports of glass particles being found in the nasal mucosa, or of problems suggestive of inspiration of glass particles, have been received.

C. Clinical Laboratory Data.

Pre- and post-study laboratory evaluations were carried out in the two US Efficacy & Safety trials, **511/512**; and in six Clin Pharm studies: **020, 021, 022, 024, 112, and 109**. Review of mean change tables and individual patient listings showed no clinically significant changes or trends in laboratory parameters.

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D. Cardiovascular findings.

1. As noted above, cardiovascular symptoms were reported by 3 patients who dropped out of Efficacy and Safety trials. In addition, there were 14 AEs in E&S trials and 4 in long-term open-label studies that were grouped under the heading of Cardiovascular. The following symptoms were reported:

edema	palpitation
chest pressure/pain	leg cramps
hypotension	heart pounding
epistaxis	cold fingers

Epistaxis occurred in a 49-yr old female (Patient **#176**), participating in Study **111** (N=191), a randomized, double-blind crossover trial vs Cafergot®. Bleeding, judged severe, began 30 min after treatment with D.H.E.45® Nasal Spray and lasted approximately 1 hr. Relationship to study drug was considered probable; no other information is available. Other cardiovascular symptoms were transient, required no treatment, and cleared without residual impairment.

2. Pre- and post-study ECGs were done in four Clin Pharm studies (**022**, **024**, **109**, and **112**), and in the two US Studies **511/512**. There were no clinically significant changes observed in the Clin Pharm studies; 1/79 US patients (**512-#1012**) had a complete LBBB.

3. Pre- and post-treatment physical examinations were carried out in all studies; pre- and post-dose vital signs were recorded in five Clin Pharm studies (**020**, **021**, **026**, **109**, and **112**; total N =71) and in one long-term open-label study (**011**, N =78). No clinically or statistically significant changes were observed in vital signs or general health status.

V. Miscellaneous safety issues.

A. Drug-drug interactions.

Draft labelling, based on clinical experience with the parenteral product (available since 1947), states that because of its vasoconstrictor action D.H.E.45® should be used with caution in the presence of vasoconstrictors, beta blockers, and nicotine. Vasospastic reactions have also been reported with therapeutic doses of parenteral ergotamine mesylate when coadministered with macrolide antibiotics.

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Three drug interaction studies using the Nasal Spray are included in the Application:

- Study **021**, a three-period crossover in which N =18 healthy volunteers received D.H.E.45® by the intramuscular and nasal routes, the latter with and without **caffeine**. Bioavailability was unaffected by the presence of caffeine.

- Study **024**, in which N =19 healthy normals received D.H.E. 45® Nasal Spray either alone or 10 min after nasal application of 0.21 mg **fenoxazoline**, a local vasoconstrictor. Serial plasma and urine samples demonstrated a statistically significant ($p < 0.05$) decrease in C_{max} (25%), AUC (10%), and urinary DHE (9%), but the observed effect was not considered clinically meaningful.

- Study **112**, in which N =8 healthy normals were exposed to 1, 2, and 4 mg of D.H.E.45® Nasal Spray either alone or while receiving **propranolol**. No adverse effect on cardiovascular function was reported.

B. Other Drug Interactions.

The Sponsor conducted one crossover study, **023**, to assess whether the vascular changes associated with migraine might have an effect on DHE kinetics. N=11 patients participated; each received a 2 mg dose of the spray at the onset of a migraine and again three days later, migraine-free. Analysis of plasma samples showed no changed in t_{max}, C_{max}, or AUC, and no change in relative bioavailability.

No data are available on drug-demographic interactions of the Nasal Spray.

C. Withdrawal phenomena, abuse potential.

Cases of drug abuse and psychological dependence on various ergot alkaloids have been reported. The chronic recurrent pattern of migraine, with its major focus on pain, is considered the cause. No information on the abuse liability of D.H.E.45® Nasal Spray is included in the Application.

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D. Overdose experience.

The minimum lethal dose of ergotamine is thought to range from 15 to 20 mg, although fatalities have been reported following single injections of 0.5-1.0 mg of the tartrate. The dihydro- salt is thought to be somewhat better tolerated. There are no data in the Application on the effects of D.H.E.45® Nasal Spray in doses greater than 4 mg.

E. Effects in other indications.

The parenteral form of D.H.E.45® is indicated in cluster headache. As noted in the review of efficacy, two small studies of the nasal spray (**009** and **010**) have been conducted, but they failed to show efficacy.

F. Other pharmacologic effects.

As noted in draft labelling, dihydroergotamine mesylate possesses oxytocic properties and for this reason should not be administered during pregnancy. Labelling also notes that the drug passes into breast milk and should therefore not be given to women who are lactating. No new data bearing on these questions are included in the Application.

G. Foreign regulatory actions and post-marketing data.

1. At the time of submission of the NDA (12.28.90), D.H.E.45® Nasal Spray had been approved for use in five countries: Belgium, Brazil, France, Norway, and Switzerland; the product has been introduced in all of the above except Brazil. No adverse regulatory actions have been reported.

2. At the time of submission of the Application, 28 spontaneous reports of AEs had been received, all from France and almost all considered possibly / probably related to D.H.E.45®. A total of 51 individual AEs, none life-threatening, were identified; all cleared without residual impairment. The following AEs were reported more than once: paresthesia (4); nausea, vomiting, and angina pectoris / chest pain (3); nasal polyposis, vertigo, facial flushing, allergic reaction, and gait disorder (2).

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H. Published literature.

Computerized searches of the English and non-English literature were performed during 2Q90 for articles on the use of dihydroergotamine mesylate nasal spray in humans. No AEs were reported which had not been seen in sponsored studies.

Sponsor's bibliography is in the Appendix.

I. Safety Update.

A Safety Update, as required by 21 CFR 314.50(d)(5)(vi)(b), was submitted Mar 27, 1992. No studies were ongoing; no new safety data were submitted.

VI. Review of proposed labelling.

Section IV.C of the Application (Vol 3 / pages 04-00050 through 00062A) presents the text of Sponsor's draft labelling. It appears to be a melange of the data available from the Nasal Spray studies, esp AEs, and labelling for the parenteral formulation. Text of the clinical portion of labelling should be revised to show corrected Ns for the safety data base but is otherwise acceptable.

VII. Overall conclusions re: safety.

The AE profile associated with D.H.E.45® Nasal Spray is relatively benign, with about a third of all AEs arising from the local effects of drug on the nasal mucosa and all AEs being of short duration and without sequelae. There appears to be no impediment, from a clinical perspective, to approval.

VIII. Recommendations.

Approve.

David M Collins, MD

cc:NDA 20-148
HFD-120
HFD-120/Katz
/KHiggins
/Collins
ft/dmc/February 6, 1995

Review and evaluation of clinical efficacy data

NDA	20-148
Sponsor	Sandoz
Drug	D.H.E.45® Nasal Spray 4 mg/mL (dihydroergotamine mesylate, USP)
Drug class	Type 3 - new formulation Therapeutic potential - Standard
Proposed indications	Symptomatic treatment of common or classical migraine in adults
Material reviewed	Original NDA (62 vols)
Date of original submission	Dec 28, 1990
Filing date	Jan 17, 1992
Related INDs	
Related NDA	05-929 (Injection) - approved 7/12/46

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I. Introduction

This Application was submitted on Dec 28, 1990, in 44 volumes. The clinical portion consisted of full reports of two recently-completed controlled trials in migraine carried out in the United States, and summary information on 10 other controlled trials (migraine 8, cluster 2) conducted outside the US.

On initial review, the Application was judged adequate with regard to Chemistry, Manufacturing, and Controls, but deficient with respect to certain types of Pharmacology data. The reports of the non-US clinical trials were also considered deficient, in that they did not include:

- protocols
- case report tabulations required by 21 CFR 314.50(f)(1)
- CRFs for patients who discontinued because of AEs

The Sponsor responded April 30, 1991, with a package of material which it described as being "as complete as possible" for each non-US controlled trial in the NDA. The addition of this material required replacement of portions of the NDA, and had the effect of enlarging the submission from 44 to 62 volumes. The changes are summarized below:

NDA Sec	Content	Orig Volume(s)	Revised Volume(s)
1	Index	1.1	1.1
2	Overall Summary	1.1	1.1
8	Clinical Data	1.11-1.30	1.11-1.38
10	Statistical Data	1.31-1.42	1.39-1.60
11	Case report tab'ns	1.43	1.61
12	Case report forms	1.44	1.62

In submitting the additional material, the Sponsor noted (Ries:Leber 4/30/91) that it was not relying on any of the non-US studies to provide pivotal evidence of efficacy, inasmuch as it had not been involved in design of the protocols, monitoring of the studies, statistical analysis of the data, or preparation of the final reports.

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Citing the continuing lack of appropriate pharm/tox data, the Agency issued a refuse-to-file letter on June 28, 1991. After further negotiations, the Sponsor committed (Bitz:Leber 1/16/92) to nonclinical carcinogenicity studies (via the nasal route) and nonclinical reproductive studies (parenteral), and the Application was filed Jan 17, 1992.

II. Proposed indication, contraindications, dosage and administration; how supplied.

The following texts are taken from Draft Labelling submitted with the Application. [Vol 3 / pages 04-00051 et seq]

A. Proposed indication.

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

B. Contraindications.

- Dihydroergotamine mesylate is contraindicated in patients who have previously shown hypersensitivity to ergot alkaloids.

- The drug is also contraindicated in patients having conditions predisposing to vasospastic reactions, such as known peripheral arterial disease, coronary artery disease (in particular, unstable or vasospastic angina), sepsis, vascular surgery, uncontrolled hypertension, and severely impaired hepatic or renal function.

- Dihydroergotamine possesses oxytocic properties and, therefore, should not be administered during pregnancy.

- Dihydroergotamine should not be used in nursing mothers (see **PRECAUTIONS**).

- Dihydroergotamine should not be used with vasoconstrictors because the combination may result in extreme elevation of blood presssure.

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C. **Dosage and administration.**

At the first sign or symptom of a migraine headache, one spray (0.5 mg) of D.H.E.45® Nasal Spray should be administered to each nostril. Fifteen minutes later, an additional spray (0.5 mg) of D.H.E.45® Nasal Spray should be administered to each nostril, for a total dosage of four sprays (2.0 mg) of D.H.E.45® Nasal Spray.

No more than four sprays (2.0 mg) should be administered for any single migraine headache attack. No more than eight sprays (4.0 mg) should be administered during any 24-hour period. The maximum weekly dosage is 24 sprays (12.0 mg) of D.H.E.45® Nasal Spray.

Prior to administration, the pump must be primed (squeeze 4 times) before use. [**See Patient Information**]

[Sponsor's proposed labelling does not indicate the fact that the product is intended for self-administration.]

D. **How supplied.**

1. D.H.E.45® Nasal Spray is available as a clear, colorless to faintly yellow solution in 1 mL amber glass ampuls containing 4 mg of dihydroergotamine mesylate, USP. Each ampul also contains 10 mg of caffeine, anhydrous USP, as a solubilizing agent for the drug substance.

D.H.E.45® Nasal Spray is provided in individual kits, each containing one ampul, a nasal spray applicator and carrying case, and a patient information sheet. The dispensing carton contains 6 individual kits.

Once the nasal spray applicator has been prepared, it should be discarded (with any remaining drug) after 24 hrs.

2. D.H.E.45® Nasal Spray is claimed under US Patent 4,462,983; the Nasal Spray applicator, under US Patent 4,758,423; both patents expire July 31, 2001.

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III. Pharmacology.

Dihydroergotamine is an alpha-adrenergic blocking agent with a direct stimulating effect on the smooth muscle of peripheral and cranial blood vessels and a depressant effect on central vasomotor centers.

Dihydroergotamine also has the properties of a mixed agonist-antagonist of serotonin. Its mechanism of action is not known, but it is thought to compensate for insufficient plasma serotonin, possibly at the 5-HT_{1D} receptors, thus counteracting the loss of tone of extracranial vascular musculature.

IV. Pharmacokinetics and metabolism.

Absorption of intranasal dihydroergotamine is independent of dose (t_{max} = approx 45 min). Absolute bioavailability is 43%; plasma protein-binding is 93%. Primary route of excretion is biliary. Terminal half-life is 10 hrs; urinary recovery of unchanged drug is 2% of the administered dose. The -OH metabolite has vasoconstrictor effects and terminal half-life similar to those of the parent compound.

V. Adequate and well-controlled studies.

The efficacy data base for this Application consists of 12 controlled trials (N=1,004):

2	US studies in migraine	N =206
8	Non-US studies in migraine	N =741
2	Non-US studies in cluster headache	N = 57

Sponsor's list of all studies is in the Appendix. Reviews of the individual studies follow.

A. US studies in migraine.

Studies 511/512

Studies **511** and **512** were large multicenter trials carried out in the US according to a common protocol, described below. [See: Vol 16/page 08-02266 (**511**) and Vol 21/page 08-04411 (**512**)]

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I. Study plan.

A. Objective.

To assess the safety and efficacy of D.H.E.45® Nasal Spray in alleviating the pain, nausea and/or vomiting associated with migraine headache.

B. Design.

These were randomized, double-blind, multicenter, placebo-controlled parallel-groups studies in outpatients with a diagnosis of migraine headache. Eight to 10 investigators were to participate in each study, each investigator enrolling a minimum of 10 patients.

1. Eligibility. Patients of either sex, 18-65 yrs of age, who had a diagnosis of common or classical migraine headache with or without sensorimotor prodromata but were otherwise in good general health were eligible. Patients were required to have had at least one migraine per month for the one-year period prior to entering study. Diagnostic criteria for migraine used in these studies are shown in the Appendix.

Eligibility was confirmed by history and physical examination, standard 12-lead resting electrocardiogram, and clinical laboratory evaluations (urinalysis, hematology, and serum chemistries - see Appendix for list of tests). All evaluations were repeated at study exit.

2. Exclusions. Females who were pregnant, or reported >3 days unexplained amenorrhea beyond expected date of menses, or were lactating, were ineligible. The following were also exclusionary:

a) history of:

- organic or structural disease of head and neck
- psychiatric or neurological disorder other than migraine
- constant headache; cluster headache; complicated, hemiplegic, ophthalmoplegic, or "lower-half" migraine
- treatment during the preceding month with an hallucinogen, an investigational drug, or any drug with major organ toxicity or dependence liability

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b) current diagnosis of:

- hypersensitivity to ergot or its alkaloids, or to hydrogenated ergotamine
- disease of the nasal mucosa which might be expected to alter the rate of absorption of study medication
- peripheral occlusive vascular disease or coronary artery disease
- systolic BP >150 mm Hg or <90 mm Hg; diastolic BP >90 mm Hg or <50 mm Hg
- impaired hepatic or renal function
- sepsis

c) current treatment with:

- beta-blockers or calcium channel blockers for an indication other than migraine prophylaxis
- antipsychotics, antidepressants, antiemetics, or drugs with antiemetic activity
- any medication which could interfere with the quantitation of analgesia
- erythromycin or oleandomycin

3. Concomitant medications. Patients taking migraine prophylaxis were required to undergo tapered withdrawal followed by a two-week drug-free period prior to participation; washout was also required for any drug with antiemetic activity. So-called minor tranquillizers, sedatives, and hypnotics were forbidden for 5 days prior to study. Analgesics, including aspirin, were prohibited for 8 hrs prior to use of study medication.

4. Treatment groups. Patients were to be randomly assigned to treatment with 2 mg D.H.E.45® Nasal Spray (4 mg/mL) or identically-packaged placebo in the order in which they were empanelled.

a) Each treatment unit consisted of two boxes (A and B). Eligible patients were given Box A (1 mL ampul of study medication, ampul holder, and applicator nozzle), along with Headache Evaluation Book A, which contained detailed instructions on assembling the therapeutic unit, and a three-page self-rating scale for assessing headache pain, relief of pain, nausea, and vomiting (see Appendix).

b) A duplicate set of treatment units was issued to each investigator to be used to demonstrate assembly and use of the drug delivery system to each patient prior to study.

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5. Evaluation points. At the onset of the next migraine, each patient was required to assemble the treatment unit and complete the portion of the Headache Book titled "Before Taking Study Medication." Headache pain and nausea were to be rated on a five-point scale (see below); vomiting was scored present/absent.

The patient then administered one spray (0.5 mg of D.H.E.45® or placebo) of medication in each nostril, followed 15 min later by a second spray. Headache pain, nausea, and relief of pain were to be rated hourly x 4. Presence/absence of vomiting was to be noted at each time point. If needed, non-ergot rescue medication was permitted at 4 hrs.

a) The patient was required to return to the physician's office within 7 days of treatment. At this visit, patient's evaluations were discussed and possible AEs and the physician's global assessments were recorded. The second box of medication and Evaluation Book B were then dispensed.

b) Within 7 days of the second headache, the patient returned to the physician's office, where the possible occurrence of AEs was noted, physician's ratings were recorded, and an exit evaluation sheet was completed.

6. Case Report forms. A case report form, including pre-study evaluations, patient self-ratings, and physician's evaluations was completed for each patient. All reported AEs, with time of onsent, duration, and investigator's judgments of severity and causality were also to be included.

7. Dropouts. Patients discontinued from study for any reason except AEs were to be replaced.

8. Outcome measures. Efficacy assessments were made by both patients and physicians.

a) Patient's ratings. Pre- and post-treatment assessments of headache pain and nausea were made on a 5-point scale:

- none - symptom not present 1
- mild - symptom is present but it does not bother me 2
- moderate - symptom is bothersome 3
- severe - symptom interferes with my normal activities 4
- incapacitating - symptom does not allow me to continue with my normal activities 5

- cont'd -

The scale for relief of pain was as follows:

- Complete relief 1
- A lot of good relief 2
- Some or moderate relief 3
- A little or slight relief 4
- No relief 5

b) Physician's ratings. At followup, the investigator was required to rate patient's response to study medication for each headache with respect to: a) relief of migraine; b) relief of nausea; and c) relief of vomiting. Ratings were on a 6-point scale:

- no effect 1
- poor 2
- fair 3
- good 4
- very good 5
- not applicable 6

C. Statistics.

1. Sponsor's discussion of the statistical issues is contained in a "Statistical Statement" which appears as Appendix D to the protocol (for **511**, see: Vol 16 / page 08-02292; for **512**, Vol 21 / page 08-04436). The essential features are:

- all subjects who completed baseline evaluations, took one dose of study medication, and completed at least one post-treatment efficacy evaluation were included in the intent-to-treat analyses of all efficacy parameters

- in evaluating baseline homogeneity, one-way analyses of variance were to be used for interval scaled variables; chi-square tests were to be used for nominal variables

- one-way analysis of variance with repeated measures on headache was to be employed to test for homogeneity of results across headache attacks

- two-way analysis of variance was to be used to test for treatment, center, and treatment-by-center interaction effects

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- when the assumptions of the model were met, analysis of covariance appropriate for a multicenter design was to be used to compare treatments for the pain intensity difference scores (PIDs) at each evaluation and the sum of the PIDs (SPIDs) over all evaluations; if the assumptions were not met, analyses of variance were to be used

- similar analyses were to be employed for nausea scores; patients who did not report nausea at baseline were excluded

- contingency table analyses as well as one-way analyses of variance procedures followed by pairwise t-tests were to be used to examine physician's global evaluations of effectiveness

- one-tailed tests were to be used for all pairwise efficacy comparisons; statistical significance was set at $p \leq 0.05$.

2. Sponsor's power calculations indicated that with 40 valid patients in each treatment group, the study would have an 80% probability of detecting at least a 50% difference between a pair of treatments using a one-tailed t-test wih alpha = 0.05.

3. The statistical statement indicated that an interim analysis might be performed after 50% of the anticipated total sample had completed the study.

4. No parameter is identified as the primary efficacy parameter; no corrections were made for multiple end-points.

D. Safety monitoring.

Followup interview was arranged for each patient within 7 days of each treatment. Information regarding AEs was sought by interview, physical examination, and lab studies; results were recorded in the CRF.

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II. Study conduct.

Study 511

This study was carried out between August, 1987, and June, 1988 at 8 US treatment facilities, in conformance with the protocol. Two academic neurologists participated: John Byer, MD, University of Missouri at Columbia; and James Couch, MD, PhD, Southern Illinois University School of Medicine at Springfield. Six physicians in private practice also participated: J Roger Curran, MD, Nampa, ID; Jerome Goldstein, MD, San Francisco, CA; Thomas Henson, MD, Boise, ID; Herbert Markley, MD, Worcester, MA; Brian Mondell, MD, Baltimore, MD; and Alan Rapoport, MD, Cos Cob, CT. All but Dr Curran had clinical appointments in academic medicine.

Drug materials used in the study were D.H.E.45® Nasal Spray (Batch YO81E5) and placebo (Batch UO17L4). Study report begins at Vol 16 / page 08-02191.

A. Subject disposition.

1. Of the 117 subjects empanelled, 106 (91%) were included in the intent-to-treat analyses; 11 subjects (DHE 6, Pla 5) had no headaches or were uncooperative and were excluded from all evaluations. Contributions by individual study centers ranged from 13 (Rapoport, Markley) to 16 (Byer, Henson, Curran), empanelled (mean, 13.6/center); and 9 (Markely) to 16 (Henson), intent-to-treat.

2. Eleven subjects discontinued after treating only one headache: 10/11, for administrative reasons; 1/11, because of an AE. One additional subject (#8003, Pla) was excluded from analyses of Headache A; and one subject (#1005, DHE), from Headache B for protocol violations: both had taken prohibited medications prior to the first hour evaluation (Midrin and Phenergan, respectively).

3. Ten patients (DHE 6, Pla 4) took rescue medication prior to 4 hrs; the score at the last evaluation prior to taking the rescue medication was used for evaluations made after the medication was taken. An additional patient (#2010, DHE) fell asleep after completing the first hour evaluation for Headache B; the 1-hr score was used for all subsequent evaluation points for this patient.

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4. The following table summarizes these data:

Empanelled	117
Did not treat a headache (DHE 6, Pla 5)	11
Intent-to-treat population (DHE 54, Pla 52)	106 (91%)
Treated 2 headaches	95x2 = 190
Treated only one headache	11x1 = 11
Total number of headaches treated	201
Headaches excluded (prohibited concomitant Rx) (DHE 1, Pla 1)	2
Total number of headaches evaluated (DHE 101, Pla 98)	199
LOCF (rescue meds 10; fell asleep 1)	11

B. Demographics.

Treatment groups were comparable at baseline on demographic characteristics.

Baseline demographics

	DHE	Pla	Total
N	54	52	106
Age			
mean ± S.D.	38±	35	37
range	20-61	18-60	18-61
Sex			
male	7	6	13
female	47	46	93
Race			
white	51	48	99
black	2	2	4
other	1	2	3
Education			
≤12 yrs	12	18	30
13-16 yrs	28	25	53
>16 yrs	14	9	23

- cont'd -

C. Baseline comparability.

Treatment groups were comparable at baseline on all clinical details relating to their migraine history.

Migraine history at baseline

	DHE	Pla	Total
N	54	52	106
Migraine history			
common	41	42	43
classical	8	7	15
both	5	3	8
Age at onset			
mean ± S.D.	22	20	20
range	(1-40)	(8-48)	(1-48)
Usual severity			
moderate	3	1	4
severe	18	19	37
incapacitating	17	13	30
variable	16	19	35
Usual duration, with treatment (hours)			
mean ± S.D.	18	12	16
range			
Usual duration, without treatment (hours)			
mean ± S.D.	44	34	39
range			
Attacks/month - past year			
mean ± S.D.	4	4	4
range			

D. Outcome measures.

1. Statistical tests of the data found treatment-by-center interactions with respect to two parameters on physician's global: a) relief of Pain for Headache A ($p = 0.007$); and b) the average of Headaches A and B ($p = 0.049$). The interaction was shown to be caused by differences in the degree of superiority of DHE over Pla, as follows:

Physician's Global, Relief of pain, Headache A:

2 centers - DHE > Pla ($p < 0.05$)
6 centers - DHE > Pla ($p > 0.05$)

- cont'd -

Physician's Global, Relief of pain, Mean of A and B:

7 centers - DHE > Pla ($p > 0.05$)
1 center - DHE > Pla ($p < 0.05$)

These differences were not considered sufficient to require analysis by center; the pooled results from all centers were used for all statistical analyses.

2. Statistical tests of the data found no treatment-by-headache interactions for any efficacy variable. Based on this finding, the Sponsor elected to report the results in terms of the mean values for the two headaches. Mean intervals (days) between headaches were similar for the two treatment groups.

Inter-headache interval

	DHE	Pla[a]
N	46	49
Mean interval (days)	37.2	35.2
Median interval	27	28
Range		

[a] Data submitted Aug 19, 1992, in response to Agency request.

3. Patient-rated parameters.

a) At baseline, mean severity of pain reported by DHE patients was 3.43; by Pla patients, 3.36 ($p > 0.05$); on the 5-point scale described above, these values correspond to "moderate-to-severe". Differences in adjusted mean change from baseline (PIDs) in post-treatment pain evaluations were marginally significant at the second hour and statistically significant at the third hour.

PIDS and SPIDS

	DHE	Pla	p-values
N	54	51	-
Baseline	3.43	3.36	-
PID			
1st hour	0.21	0.12	.465
2nd hour	0.40	0.10	.060
3rd hour	0.61	0.05	0.004
4th hour	0.65	0.04	0.006
SPID	0.47	0.08	0.013

- cont'd -

b) Mean scores for relief of pain also showed statistically significant differences beginning at the third hour.

Relief of pain

	DHE	Pla	p-values
N	54	51	-
Relief of pain			
1st hour	1.87	1.83	.832
2nd hour	2.25	1.94	.126
3rd hour	2.62	1.93	.002
4th hour	2.75	2.01	.003
Mean over 4 hrs	2.37	1.94	.027

c) At baseline, mean severity of nausea reported by DHE patients was 1.91; by Pla patients, 2.12 ($p > 0.05$); on the 5-point scale, these values correspond to "mild". Post-treatment differences were nonsignificant. The data are summarized below; positive values indicate improvement.

Relief of nausea

	DHE	Pla
N	44	45
Baseline	1.91	2.12
Change from baseline		
1 hr	-0.25	-0.13
2 hrs	-0.29	-0.19
3 hrs	+0.06	-0.27
4 hrs	0.10	-0.18
Mean over 4 hrs	-0.07	-0.20

d) Not surprisingly, vomiting was reported by relatively few patients. The data are summarized below.

Relief of vomiting

	DHE	Pla
N	54	52
Headache A		
Vomiting at baseline	1	5
Vomiting post-treatment	4	10
Headache B		
Vomiting at baseline	6	8
Vomiting post-treatment	5	4

- cont'd -

4. Physicians' global evaluations of study drug's effects on headache pain, averaged over both headaches, showed a statistically significant difference in favor of DHE (p =0.001); comparisons with respect to nausea and vomiting were nonsignificant. The data are summarized below.

Physician's Global evaluations

	DHE	Pla	p-values
N	54	52	-
Relief of headache	2.8	2.0	0.001
Relief of nausea	2.3	1.2	0.522
Relief of vomiting	2.0	1.6	0.380

No effect (1); Poor (2); Fair (3); Good (4); Very Good (5).

5. Mean duration of headache, although not identified prestudy as an efficacy parameter, provides a useful index of therapeutic effect. (Recall that the last observation prior to use of rescue meds was used in calculating duration of headache.)

As shown in the table below, mean duration of headaches A and B (in hours) was approximately 1/3rd shorter in the DHE group compared with the Pla group (p =0.036).

Duration of headache

	DHE	Pla	p-values
N	50	51	-
Mean duration (hrs)	13.5	19.6	.036

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Study 512

This study was carried out at 10 US treatment facilities between July 1988 and February 1989, in conformance with the protocol. Four academic neurologists participated: John Hammerstad, MD, Oregon Health Sciences University; Jennifer Kriegler, MD, Case Western Reserve; Stephen Peroutka, MD, PhD, Stanford; and Dewey Ziegler, MD, Kansas University. Six physicians in private practice also participated: Robert Ford, MD, Birmingham, AL; R Michael Gallagher, DO, Moorestown, NJ; Marvin Hoffert, MD, Denver, CO; Noel Holtz, MD, Marietta, GA; Joel Saper, MD, Ann Arbor, MI; and Barry Vogel, MD, Glen Ridge, NJ. All except Dr Vogel had clinical appointments in teaching institutions.

*Drug materials used in this study were the same as in Study **511**, ie, D.H.E.45® Nasal Spray (Batch YO81E5) and placebo (Batch UO17L4). Study report begins at Vol 21 / page 08-04345.*

A. Subject disposition.

1. A total of 112 patients entered the study (11 / center). Contributions by individual study centers ranged from 7 (Gallagher) to 15 (Ford, Saper), empanelled; and 5 (Gallagher) to 15 (Ford), intent-to-treat.

2. Eleven patients did not treat a migraine headache; one patient (#3002, Pla) was excluded from analyses of Headache A because of prohibited concomitant medication (Tylenol) taken before the first hour evaluation, and did not have another headache. There were thus 100/112 (89%) patients in the intent-to-treat population.

3. A total of 16/100 patients treated only one headache. One patient discontinued after the first headache because of an AE (swelling of the eyelid); the remaining 15, for other reasons.

4. There were thus 184 headaches experienced by 100 patients in the intent-to-treat population. For 17/184 (9%) headaches, data are incomplete. Two DHE patients fell asleep; 15 patients (DHE 3, Pla 12) took early rescue meds. For these 17 headaches, the last observation prior to the event was carried forward.

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5. The following table summarizes these data.

Empanelled		112
Did not treat a headache		11
Headache excluded because of prohibited concom Rx (This patient had only one headache)		1
Intent-to-treat population (DHE 48, Pla 52)		100
Treated two headaches		84 x 2 = 168
Treated only one headache		16
D/C due to AE	1	
D/C for other reasons	15	
Total number of headaches in intent-to-treat population		184
Data incomplete; LOCF (early rescue meds 15; fell asleep 2)		17

B. Demographics.

As shown in the table below, treatment groups were comparable at baseline on demographic characteristics ($p > 0.05$).

Demographics

	DHE	Pla	Total
N	48	52	100
Age			
mean ± S.D.	39±11	37±11	38±11
range	(20-62)	(18-61)	(18-62)
Sex			
male	8	13	21
female	40	39	79
Race			
white	46	51	97
black	2	1	3
Education			
≤12 yrs	12	15	27
13-16 yrs	24	27	51
>16 yrs	12	10	22

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C. Baseline comparability.

Treatment groups were comparable at baseline on all clinical details relating to their migraine history.

Migraine history at baseline

	DHE	Pla	Total
N	48	52	100
Migraine history			
common	33	37	70
classical	8	9	17
both	7	6	13
Age at onset			
mean ± S.D.	20±9	21±10	21±10
range	(6-45)	(3-47)	(3-47)
Usual severity			
moderate	7	8	15
severe	22	21	43
incapacitating	11	8	19
variable	8	15	23
Usual duration, with treatment (hours)			
mean ± S.D.	8±11	13±20	11±17
range	(1-72)	(1-96)	(1-96)
Usual duration, without treatment			
mean ± S.D.	32±24	35±28	34±26
range			
Attacks/month - past year			
mean ± S.D.	5±13	3±2	4±9
range			

D. Outcome measures.

1. There were no treatment-by-center interactions. Data are presented as the pooled results from all centers.

2. As in Study **511**, statistical tests of the data found no treatment-by-headache interactions for any efficacy variable, and the Sponsor elected to report the results in terms of the mean values for the two headaches. As shown in the table below, mean intervals (in days) between headaches were similar for the two treatment groups.

Inter-headache interval

	DHE	Pla[a]
N	39	43
Mean interval (days)	23.8	28.2
Median interval	23	24
Range		

[a] Data submitted Aug 19, 1992, in response to Agency request.

3. Patient-rated parameters.

a) Differences in favor of active in adjusted mean change from baseline (PIDs) in post-treatment severity of pain were statistically significant at all four hours; SPIDs were also significantly different. The data are summarized below.

PIDs and SPIDs

	DHE	Pla	p-values
N	48	52	-
Baseline	3.66	3.62	-
PID			
1st hour	0.34	-0.04	.013
2nd hour	0.57	-0.08	.002
3rd hour	0.94	-0.08	<0.001
4th hour	1.06	0.01	<0.001
SPID	0.73	-0.05	<0.001

b) Mean scores for relief of pain also showed statistically significant differences beginning at the first post-treatment evaluation. The data are summarized below.

Relief of pain

	DHE	Pla	p-values
N	48	52	-
Relief of pain			
1st hour	2.12	1.50	.003
2nd hour	2.32	1.63	.004
3rd hour	2.77	1.79	<.001
4th hour	2.95	1.93	.001
Mean over 4 hrs	2.54	1.93	<.001

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c) At baseline, mean severity of nausea reported by DHE patients was 2.34; for Pla patients, 2.40 ($p > 0.05$); on the 5-point scale described above, these values correspond to "mild to moderate". Post-treatment differences were significant, beginning at the second hour. The data are summarized below. Positive values indicate improvement.

Relief of nausea

	DHE	Pla	p-values
N	41	41	-
Baseline	2.34	2.40	-
Change from baseline			
1 hr	0.08	-0.10	0.280
2 hrs	0.22	-0.25	0.025
3 hrs	0.41	-0.15	0.012
4 hrs	0.50	-0.08	0.019
Mean over 4 hrs	0.30	-0.15	0.016

d) As with Study **511**, vomiting was reported by few patients; between-groups differences, pre- and post-treatment, were nonsignificant. The data are summarized below.

Relief of vomiting

	DHE	Pla
N	48	52
Headache A		
Vomiting at baseline	3	5
Vomiting post-treatment	1	2
Headache B		
Vomiting at baseline	11	12
Vomiting post-treatment	3	6

4. Physicians' global evaluations of study drug's effects, averaged over both headaches, showed statistically significant differences in favor of DHE on headache pain and on nausea ($p < 0.01$). Results for vomiting were nonsignificant. The data are summarized on the next page.

- cont'd -

Physician's globals

	DHE	Pla	p-values
N	48	52	-
Relief of headache	3.08	2.04	<0.001
Relief of nausea	3.07	2.17	0.007
Relief of vomiting	3.00	2.22	0.299

No effect (1); Poor (2); Fair (3); Good (4); Very Good (5).

5. Mean duration of headache was 13.4 hrs in the DHE group and 15.2 hrs in the Pla group (p =0.533).

III. Discussion.

These are positive studies; results in both **511** and **512** demonstrate the efficacy of D.H.E.45® Nasal Spray in comparison with placebo in relieving the pain and nausea associated with migraine. Findings with regard to vomiting were nonsignificant, probably because relatively few patients had this complaint at baseline. The table below shows that study populations were comparable in size and baseline severity of treated headaches; those in Study **512** were slightly sicker (more severe pain, more disabling nausea), and showed somewhat greater benefit from D.H.E.®45. This, in turn, made for larger estimates of improvement by the investigators; in Study **511**, headache duration was significantly shortened.

Summary of 511/512

	Study **511**		Study **512**	
	DHE	Pla	DHE	Pla
Intent-to-treat N	54	52	48	52
Mean interval (days) between headaches	37	35	24	28
Patient-rated				
Pain severity				
Baseline	3.43	3.36	3.66	3.62
Earliest difference	3rd hour		1st hour	
Relief of pain	3rd hour		1st hour	
Nausea				
Baseline	1.19	2.12	2.34	2.40
Earliest difference	NS		2nd hour	
Vomiting	NS		NS	

- cont'd -

Summary of 511/512 - cont'd

	Study 511		Study 512	
	DHE	Pla	DHE	Pla
Intent-to-treat N	54	52	48	52
Physician-rated				
Relief of pain	2.78	2.02	3.08	2.04
Relief of nausea	NS		3.07	2.17
Relief of vomiting	NS		NS	
Duration of headache (hrs)	13.5	19.6	13.4	15.2

Patient ratings: none 1, mild 2, moderate 3, severe 4, incapacitating 5.
Physician ratings: no effect 1, poor 2, fair 3, good 4, very good 5.

IV. Conclusions.

In a cohort of 206 patients studied according to a common protocol, time to relief of pain and time to relief of nausea associated with 1 or 2 attacks of common or classical migraine were significantly shortened in patients treated with D.H.E.45® Nasal Spray compared with patients treated with placebo ($p < 0.05$).

These results require independent confirmation by Division of Biometrics (HFD-710).

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B. Non-US studies in migraine.

1. The Sponsor submitted results of 8 clinical trials of D.H.E.45® Nasal Spray carried out in Europe between 1982 and 1987 by Sandoz Ltd, of Basel, Switzerland, the corporate parent of Sandoz US. Types and numbers of studies were as follows:

- Parallel groups, placebo control - 3 studies
- Crossover, placebo control - 4 studies
- Crossover, active control - 1 study

2. The three parallel-groups studies were carried out according to a common protocol, details of which are given below. [Copies of the protocol are at: Vol 25 / Page 08-06071 (Study **0603-002**); Vol 27 / Page 08-06783 (Study **0603-003**); and Vol 28 / Page 08-06959 (Study **0603-004**).]

a) These were randomized, double-blind parallel-groups trials designed to evaluate the efficacy and safety of two doses of D.H.E. 45® Nasal Spray (4 mg/mL) compared with placebo in treating each of four consecutive migraine attacks in otherwise healthy subjects with common or classical migraine.

b) Outpatients, 18-65 yrs of age and of either sex, with a history of 1-2 severe or moderately severe migraine attacks per week, were eligible. All patients were required to discontinue migraine prophylaxis for 48 hrs prior to study.

c) Patients were instructed to self-medicate at the first warning of an attack. Two puffs (130 μL / puff), one in each nostril, were taken as the initial dose. For the high-dose group, each puff contained 0.5 mg active; for the low-dose group, one puff contained 0.5 mg active and one contained placebo.

d) If no relief was obtained, a third puff was permitted at 30 min; a fourth, at 60 min. For the active-treatment groups, both puffs contained active. Thus, a maximum of 4 puffs, corresponding to a total dose of active of 1.5 or 2.0 mg, were permitted during one attack. Non-ergot rescue medication (eg, aspirin or paracetamol) was permitted at 90 min; if used, study drug was to be considered a treatment failure. (Vol 25 / page 08-06078).

e) Each patient was expected to treat four migraine attacks and return for followup at the end of one month. At followup, clinical supplies were to be returned and the patient interviewed by the Investigator regarding AEs.

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f) Efficacy was rated on 3 parameters:

- post-treatment duration of each attack
- patient-rated effect of medication on headache (controlled 1, strongly reduced 2, slightly reduced 3, unchanged 4)
- Investigator's overall assessment of efficacy (none 0, slight 1, moderate 2, good 3, very good 4)

g) Patients were provided with a "Headache card" on which to record details of each headache. Investigators were given a case report form to record administrative details of each patient's participation.

h) The protocol called for a study population of 30; number of centers was not discussed, but pooling was anticipated (Vol 25 / page 08-06080). No other statistical issues were discussed.

Study 0603-002

This study was conducted at 9 centers in Austria, Germany, and Norway between April 1983 and August 1985. Eight of the nine principal investigators held faculty appointments in University medical centers. Report of the study begins at Vol 25 / page 08-06093.

A. A total of 140 subjects (32 male, 108 female) were empanelled; 114/140 completed treatment of one or more headaches and were included in the intent-to-treat analyses. Contributions to the efficacy population, by center, were: 2, 3, 3, 10, 12, 15, 20, 24, and 25 (avg = 12.7). (Vol 25 / page 08-06146)

A footnote to the protocol (page 08-06108) indicates that 21/114 (18.4%) efficacy patients (Hi 8/43, Lo 8/40, Pla 5/31) used a spray device that was modified from the one originally used, because of a defect (not described) in the earlier device.

Records of 26 patients were excluded, as follows:

	2.0	1.5	Pla
• prohibited concom med	5	5	6
• lost to followup	1	1	1
• cluster headache	-	1	2
• other	-	1	3
Totals	6	8	12

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B. Treatment groups were comparable at baseline. Frequency of migraines was not reported.

Demographics

	2.0	1.5	Pla
N	43	40	31
Sex			
Male	12	5	7
Female	31	35	24
Mean age (yrs)	37±10	38±10	36±11
Age at onset of migraine (yrs)	22	20	21
Type of migraine			
Common	17	13	11
Classical	26	27	20
Baseline severity of treated attacks (mild 1, moderate 2, severe 3)	2.3	2.5	2.4

C. Results.

Treatment group means were based on means of all headaches for each patient. The original Sponsor pooled results without testing for interactions. Collapsing the five investigators with the smallest populations (range: 2-12; mean =6) into one pseudo-investigator (Vol 25/page 06333), the US Sponsor found a statistically significant treatment-by-center interaction on baseline intensity of attack ($p = 0.0310$).

1. Statistically significant pairwise differences between high-dose and placebo were noted in the duration of attack after treatment and in patients' assessments of efficacy ($p \leq 0.05$). Hi-/low- differences were marginal ($p = 0.051$, duration; $p = 0.054$, effect); differences between low-dose and placebo were not significant ($p > 0.10$).

Duration of headache and effect of medication

	2.0	1.5	Pla	p-value
N	43	40	31	-
Duration of headache after Rx (hrs)	5.5	8.7	10.2	0.0028
Effect of medication (Controlled, 1; strongly reduced, 2; slightly reduced, 3; unchanged, 4)	2.6	3.0	3.1	0.0393

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2. Duration of study -- ie, the time required for patients to accumulate data on four headaches -- was similar in the three treatment groups, although longer than had been anticipated; only 26/83 (31.3%) patients (Hi 9/33; Low 11/30; Pla 6/20) who completed the trial -- ie, treated 4 headaches -- did so within the 30 days required by the protocol. Mean number of sprays (3.2-3.5) was also similar in the three treatment groups; the 20% mean difference between high and low dose groups in total dose/headache (1.5 mg vs 1.2 mg) may not have been sufficient to produce a clinical difference in effect.

The number of patients using rescue medication at 90 min (86/114, 75.4%) was similar among the three treatment groups, but was so large as to confound the principal quantitative efficacy parameter, namely, duration of headache after treatment.

Duration of study, sprays and dose per headache use of rescue medication

	2.0	1.5	Pla	p-value
N	43	40	31	-
Duration of study (days)				
Mean (±S.D.)	46±27	45±27	43±31	NS
Range	1-98	1-120	1-150	
Mean number of sprays per headache	3.2	3.5	3.3	NS
Total dose (mg)/headache	1.5	1.2	0	NS
Used rescue medication	28 (65%)	34 (85%)	24 (77%)	NS

3. Collapsing 5 scalar values into three categories, the Sponsor found no difference among treatments in Investigator's assessment of overall efficacy ($p > 0.05$).

Overall efficacy

	2.0	1.5	Pla
N	43	40	31
Overall efficacy			
very good (4)/good (3)	20 (47%)	16 (40%)	7 (22%)
moderate (2)/slight (1)	12 (28%)	8 (20%)	12 (39%)
none (0)	11 (25%)	16 (40%)	12 (39%)

- cont'd -

D. Discussion.

This study, ostensibly a positive one, has several deficiencies.

- Duration of attack after treatment, a design feature common to all the non-US studies and the only quantitative measure of efficacy used in those studies, was dose-related, ranging from 5.5 hrs for the high-dose group to 10.2 hrs for placebo. But 86/114 (75%) patients in the efficacy population are recorded as taking rescue medication at 90 min. Results beyond that point would appear to be confounded, therefore, and cannot be ascribed to the effects of study medication.

- Mid-way through the study, the spray device was changed, with 80% of the population using one device and 20% using another. Without a showing that total delivered dose of study medication was the same across all patients, and was the dose specified in the protocol, we don't know how much study drug (if any) each patient actually received.

- Variability in study population by center, and in study duration by patient, suggests that the study population was more heterogenous than permitted by the statistical assumptions used in analyzing the data.

E. It is concluded that study **0603-002** is weakly supportive of the Sponsor's claims for efficacy.

Study 0603-003

This study was conducted by Teresa Paiva, MD, at the Headache Clinic, Centro de Estudos Egas Moniz, Hospital de Santa Maria, Lisbon, Portugal, between July 1983 and October 1985. Report of the study begins at Vol 27 / page 08-06806.

A. A total of 45 subjects (6 male, 39 female) were empanelled; 28 completed treatment of one or more headaches and were included in the intent-to-treat analyses.

- cont'd -

Records of 17 patients were excluded, as follows:

	2.0	1.5	Pla
• prohibited concom med	4	5	1
• no attacks treated	3	1	1
• other	-	1	1
Totals	7	7	3

B. Treatment groups were comparable at baseline ($p > 0.05$). Frequency of migraines was not reported.

Demographics

	2.0	1.5	Pla
N	9	8	11
Sex			
Male	2	2	0
Female	7	6	11
Mean age (yrs)	43	35	37
Age at onset of migraine (yrs)	18	15	17
Type of migraine			
Common	9	7	11
Classical	0	1	0
Baseline severity of treated attacks (mild 1, moderate 2, severe 3)	2.1	2.2	2.2

C. Results.

1. Mean number of sprays was similar for the three treatment groups (high, 3.7; low, 3.7; pla, 3.6). Total dosages were also similar: high, 2.7 mg; low, 1.3 mg ($p > 0.05$).

2. No statistically significant differences were noted in duration of attack after treatment, patients' assessments of effect of medication, or Investigator's overall assessment of efficacy ($p > 0.05$).

- cont'd -

Duration of headache, effect of medication, and overall efficacy

	2.0	1.5	Pla	p-value
N	9	8	11	-
Duration of headache after Rx (hrs)	9.3	14.1	16.3	0.924
Effect of medication (Controlled, 1; strongly reduced, 2; slightly reduced, 3; unchanged, 4)	2.8	3.0	2.8	0.792
Overall efficacy				
very good (4)/good (3)	4	1	4	
moderate (2)/slight (1)	2	2	2	
none (0)	3	5	5	

3. Use of rescue medication was reported as a fraction of the number of attacks treated by all patients, including those excluded from the efficacy analysis: high-dose, 11/43 (26%); low-dose, 15/39 (38%); placebo, 25/41 (61%), p >0.05.

D. Discussion. Trends favoring high-dose over low-dose and active over placebo were noted on all parameters, but no statistically significant differences were found. As with **0603-002**, the use of rescue meds at 90 min confounds the data regarding duration of headache after treatment.

Study 0603-004

This study was conducted by A.D. Korczyn, MD, Dept of Neurology, Tel Aviv Medical Center; and Arieh Kuritzky, MD, Beilinson Medical Center, Petah Tiqva, Israel, between March 1984, and June, 1985. Report of the study begins at Vol 28 / page 08-06982.

A. A total of 52 subjects (26/center; 20 male, 32 female) were empanelled; 47 completed treatment of one or more headaches and were included in the intent-to-treat analyses. The remaining 5 patients failed to treat an attack.

B. Treatment groups were comparable at baseline (p >0.05). Frequency of migraines was not reported.

- cont'd -

Demographics

	2.0	1.5	Pla
N	17	16	14
Sex			
Male	3	9	4
Female	14	7	10
Mean age (yrs)	33	34	36
Age at onset of migraine (yrs)	22	22	20
Type of migraine			
Common	12	12	9
Classical	4	4	5
Baseline severity of treated attacks (mild 1, moderate 2, severe 3)	2.1	1.8	2.1

C. Results.

1. Mean number of sprays was similar for the three treatment groups (high, 3.3; low, 3.4; pla, 3.3) ($p > 0.05$).

2. No statistically significant differences were noted in duration of attack after treatment, patients' assessments of efficacy, or Investigator's overall assessment of efficacy ($p > 0.05$).

Duration of headache, effect of medication, and overall efficacy

	2.0	1.5	Pla	p-value
N	17	16	14	-
Duration of headache after Rx (hrs)	17.1	10.6	14.3	0.961
Effect of medication (Controlled, 1; strongly reduced, 2; slightly reduced, 3; unchanged, 4)	3.0	3.1	3.3	0.657
Overall efficacy				0.439
very good (4)/good (3)	4	0	3	
moderate (2)/slight (1)	6	3	3	
none (0)	5	7	4	

D. Study drug did not affect the outcome of treatment. This must be considered a negative study.

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3. Four placebo-controlled crossover studies were conducted. They are reviewed below.

Study 0603-005

This study was conducted by Peer Tfelt-Hansen, MD, of the Acute Headache Clinic, Dept of Neurology, University Hospital, Copenhagen, Denmark, between February 1985 and April 1986. The protocol begins at Vol 29 / page 08-07396.1; report of the study begins at Vol 29 / page 08-07396.53.

I. Study plan.

This study was similar in design to the three parallel-groups studies described above (page 25). The major difference was that this protocol called for patients to be randomized at the time of empanelment to treatment of two headaches with each of three agents (high- and low-dose active, and placebo) in a balanced three-way crossover, instead of treatment of four headaches with one agent. Other differences were:

a) that this study was confined to patients with common migraine, whereas the parallel-groups studies were open to patients with either common or classical migraine;

b) rescue meds were to be taken at 2 hrs instead of at 90 min (Vol 29 / page 08-07396.8);

c) overall rating of severity of migraine attack was made by the patient on a 3-point scale (1 =worse, 2 =as usual, 3 =milder)

A feature of the protocol not found in the parallel-groups studies was the inclusion of pre- and post- otoscopic examinations and safety interviews of each patient by a trained otopathologist, to assess local affects of nasal D.H.E. 45®.

In all other respects -- objectives, exclusion criteria, dosing plan for each headache, safety monitoring, and statistical analysis -- this is a replay of the parallel-groups studies.

- cont'd -

II. Study conduct.

A. A total of 47 patients were empanelled. Only 14/47 patients completed the trial as planned; records of an additional 21 patients, containing details of treatment of 101 headaches, were considered partially valid. Records of 12 patients, including two patients (Nos. 30 and 39) invalidated because of AEs, were excluded from all analyses. These data are summarized below.

Empanelled		47	
Excluded		12	
Lost to f/u	1		
Prohibited concom Rx	2		
D/c due to AEs	2		
Other	7		
Efficacy population		35	
Valid		14 x 6 =	84 headaches
Partially valid		21 =	101 headaches
Total			185 headaches

B. Treatment groups were comparable at baseline ($p > 0.05$). Frequency of migraines was not reported.

N	35
Sex	
Male	5 (14%)
Female	30 (86%)
Mean age (yrs)	40 ± 10 yrs
Age at onset of migraine (yrs)	18 ± 8 yrs
Baseline severity of treated attacks (mild 1, moderate 2, severe 3)	2.20

C. Results.

No statistically significant differences between active and placebo were observed on any of the efficacy parameters. Reanalysis by the US Sponsor found no statistically significant carryover or period effects.

- cont'd -

Study 0603-006

This study was conducted by two Swiss investigators, J J Dufresne, MD, Lausanne, and J Rohr, MD, Geneva, between July 1983 and March 1984. The protocol begins at Vol 30 / page 08-07397; report of the study begins at Vol 30 / page 08-07426.

I. Study plan.

This balanced cross-over study was also similar in design to the three parallel-groups studies, with patients treating four headaches (2 headaches / treatment), and maximum individual treatments consisting of 2.0 mg active (1.0 mg STAT + 0.5 mg at 30 and 60 min prn) or placebo. Patient eligibility and exclusions, efficacy parameters (duration of attack, patient's assessment of efficacy), and safety monitoring were the same as in the parallel-groups studies; both common and classical migraine were acceptable. Randomized patients returned to the investigator after the first two treatments, were interviewed for AEs, and then received their second packet of medication.

II. Study conduct.

A. A total of 39 patients (male 12, female 27) were empanelled (Dufresne 31, Rohr 9). Of the cohort, 24 completed the study; 2 additional patients were considered partially valid for efficacy; data for 13 patients were excluded.

Empanelled		39	
Excluded		13	
Lost to f/u	8		
Other	4		
Prohibited concom Rx	1		
Efficacy population		26	
Valid		24 x 4 =	96 headaches
Partially valid		2 x 3 =	6 headaches
Total			102 headaches

B. Treatment groups were comparable at baseline ($p > 0.05$). Frequency of migraines was not reported.

- cont'd -

Demographics

N	26
Sex	
Male	8 (14%)
Female	18 (86%)
Mean age (yrs)	38 ± 10 yrs
Age at onset of migraine (yrs)	25 ± 8 yrs
Median severity of treated attacks at baseline (mild 1, moderate 2, severe 3)	
DHE/Pla	2.0/2.5
Pla/DHE	2.0/2.5

C. Results.

1. The median number of sprays for all headaches in both sequences was 4, the maximum permitted.

2. Statistically significant differences between active and placebo were noted in mean values for all efficacy parameters (based on means of both headaches for each patient): duration of attack after treatment, patients' assessments of efficacy (median values), and Investigators' overall assessments ($p \leq 0.05$). Re-analysis by the US Sponsor found no treatment-by-center interactions and no carryover or period effects.

Duration of headache, effect of medication, and overall efficacy

	DHE/Pla	Pla/DHE	p-value
N	12	14	
Duration of headache after Rx (hrs)	3.6/13.1	15.0/8.5	0.029
Median rating, effect of medication (Controlled, 1; strongly reduced, 2; slightly reduced, 3; unchanged, 4)	1.75/3.75	3.75/2.5	0.018
Overall efficacy (very good 4, good 3, moderate 2, slight 1, none 0)	3.0/1.0	1.0/2.0	0.007

D. Assessment of the use of rescue medication was not possible, according to the Sponsor, because of misleading instructions on the case report form.

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E. This must be considered a supportive study. Even if the data on duration of headache after treatment are discarded because of the lack of information on use of rescue meds, results on patients' and physicians' ratings of efficacy both show an excellent clinical response, and good between-raters correlation. The absence of interaction or period effects strengthens this conclusion.

Study 0603-008

This study was conducted by 13 investigators in Argentina, Germany, Switzerland, Uruguay, and Yugoslavia, between February 1985 and January 1986. The protocol begins at Vol 31 / page 08-07819; report of the study begins at Vol 31 / page 08-07864.

I. Study plan.

This was a placebo-controlled, 4-headache balanced crossover study, with patients treating two consecutive headaches with active and two with placebo. Patients with either common or classical migraine were eligible. Initial dose of active was 1 mg for all patients; those needing additional medication self-administered a further 1 mg (2 puffs) at 15 min. Rescue medication was permitted 30 min after the first dose. Objectives, eligibility / exclusion criteria, efficacy parameters and rating scales were the same as in the other studies. The original Sponsor carried out tests of carryover and period effects.

II. Study conduct.

A total of 146 patients entered the study. Four Investigators contributed 4 patients each; the remaining nine Investigators contributed 10-18 patients. As in **-005**, patients who discontinued because of ≥1 AEs were excluded from analysis.

- cont'd -

Empanelled		146	
Excluded		24	
Ineligible	3		
Lost to f/u	3		
Prohibited concom Rx	3		
AE	5		
Other	11		
Efficacy population		122	
Valid		117 x 4	= 468 headaches
Partially valid		5	= 15 headaches
Total			483 headaches

B. Treatment groups were comparable at baseline ($p > 0.05$). Frequency of migraines was not reported.

Demographics

N	122
Sex	
Male	21
Female	101
Mean age (yrs)	38
Age at onset of migraine (yrs)	21
Median severity of treated attacks at baseline (mild 1, moderate 2, severe 3)	
DHE/Pla	2.5/2.5
Pla/DHE	2.0/2.5

C. Results.

1. The median number of sprays for all headaches in both sequences was 4, the maximum permitted.

2. Statistically significant differences between treatment group means (based on means for both headaches for each patient) were noted on all efficacy parameters ($p \leq 0.05$). There were no carryover or period effects.

- cont'd -

Duration of headache, effect of medication, and overall efficacy

	DHE/Pla	Pla/DHE	p-value
N	63	58	
Duration of headache after Rx (hrs)	7.6/11.0	7.3/7.3	0.007
Median rating, effect of medication (Controlled, 1; strongly reduced, 2; slightly reduced, 3; unchanged, 4)	2.5/3.5	3.5/2.8	<0.001
Overall efficacy (very good 4, good 3, moderate 2, slight 1, none 0)	3.0/1.0	1.0/2.0	0.007

3. The proportion of attacks treated with DHE that required additional antimigraine medication was lower (33%) than with placebo (52%) ($p < 0.001$).

D. Discounting between-treatments differences on duration of headache because of the confounding effect of rescue medication at 30 min, there remain statistically significant differences favoring active over placebo on effect of medication and overall efficacy. This study must therefore be considered supportive of the Sponsor's claim for efficacy.

Study 0603-007

This study was conducted by 13 French investigators (of whom only 10 appear to have contributed patients to the total) between June 1982 and December 1983. The protocol (translated from the French) begins at Vol 34 / page 08-08965; report of the study begins at Vol 34 / page 08-09009.

I. Study plan.

This was also a 4-headache study of active vs placebo in patients with common or classical migraine who were otherwise in good general health. The study differed from the others in that patients were re-randomized for each headache; patients were seen after the first two headaches to be examined and interviewed and then to receive drug for the remaining two headaches.

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Initial treatment was set at 2 puffs (130 μL, corresponding to 0.5 mg of active per puff), with additional single puffs permitted at 30 and 60 min and a maximum of 4 puffs (2 mg active) per headache. Rescue medication was permitted at 90 min, ie, 30 min after the last dose of study medication. Principal efficacy parameter was defined as complete relief within 2 hrs; other parameters were the same as in the studies described above.

Statistical analyses were performed by two methods. The Mantel-Haenzel test was used for all patients who received both test medications for at least one headache. Based on these results, a 2x2 contingency table, Success vs Failure, was prepared for each parameter for each patient for all headaches. In addition, McNemar's test was used to compare the results of the first DHE test with the first placebo test, again by means of 2x2 tables.

II. Study conduct.

A. A total of 119 patients (male 37, female 74, n/a 8) were enrolled, of whom 87 completed study. An additional eight patients treated one attack before discontinuing and were judged partially valid; the 95 patients in the efficacy population treated a total of 338 headaches. For 24 patients, no efficacy data were available and they were excluded from all efficacy analyses.

Enrolled	119
Valid	87
4 HA x 74 = 296	
3 HA x 8 = 24	
2 HA x 5 = 10	
D/C due to inefficacy or AE after 1 HA	8
No efficacy data	24

B. No individual patient background data were available to the US Sponsor. Original Sponsor's summary data are shown below; no statistically significant differences between sequences was observed in baseline severity or duration of headache before treatment.

N	119
Sex	
Male	37
Female	74
not reported	8
Diagnosis	
Common	92
Classical	18
not reported	9
Duration of disease	
mean	16±10 years
range	1-40 years
Baseline severity (0=absent, 1=mild, 2=moderate, 3=severe)	
Before active	2.00±0.75
Before placebo	1.91±0.74
Duration before treatment	
Active	43±71 min
Placebo	42±76 min

C. Results.

1. For the 330 headaches (DHE 185, placebo 165) treated by the 87 patients who completed study, statistically significant overall differences in favor of active were observed on the three principal efficacy parameters, as follows:

	Observed	Expected	p-value
Complete relief within 2 hrs	54	40	<0.001
Need for rescue med	91	77	<0.001
Patient's global	58	42	<0.001

2. Similar results were obtained on analysis of the first headache treated with each modality.

a) Complete relief within 2 hrs:

		DHE	
		Success	Failure
Placebo	Success	9	3
	Failure	25	50

p <0.001

b) Need for rescue medication:

		DHE	
		Success	Failure
Placebo	Success	27	7
	Failure	26	26

p <0.01

c) Patient's global:

		DHE	
		Success	Failure
Placebo	Success	10	4
	Failure	24	47

p <0.001

3. Sponsor's analyses showed no statistically significant carryover or period effect.

D. This study supports the Sponsor's claim for efficacy.

- cont'd -

4. One active-control crossover study was carried out. It is reviewed below.

Study 0603-011

This study was carried out by 13 Investigators in Austria, Germany, the Netherlands, Switzerland, and Yugoslavia between October 1986 and December 1987. No protocol was available; report of the study begins at Vol 34 / page 08-09129.

I. Study conduct.

A. A total of 191 patients (male 31, female 160) suffering from common or classical migraine participated in this randomized double-blind study of D.H.E.45® Nasal Spray vs Cafergot® tablets (ergotamine tartrate USP + caffeine) (one headache per treatment); 5/191 were inpatients. The double-dummy technique was used to preserve blinding. A total of 159/191 patients were included in the efficacy analyses; parameters were the same as in the earlier trials.

B. Method of administration of study drug was as follows:

• At first sign of migraine	1 puff (130 μL) in each nostril corresponding to 1 mg D.H.E.45® or placebo **and** 2 tablets (1.0 mg/tablet or placebo); total dose = 2.0 mg
• At 15 min, if relief was unsatisfactory	1 puff (0.5 mg) in each nostril corresponding to 1 mg D.H.E.45® or placebo
• At 30 min, if relief was still unsatisfactory	1 tablet (1.0 mg or placebo)

Maximum dosage, therefore, was either 4 puffs (2 mg ergotamine) or 3 tablets (3 mg ergotamine). In the event, mean dosages was 3.8 puffs/attack (1.9 mg ergotamine) and 2.7 tablets (2.7 mg) ($p > 0.05$).

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C. No statistically significant differences between treatments were seen on any efficacy parameter; proportions of patients requiring rescue meds were similar (DHE 44%, pla 43%).

D. Lacking a protocol and employing a highly unusual dosing plan which may have biased patients and investigators in favor of study drug, this study cannot be given much weight in the appraisal of D.H.E.45® Nasal Spray. It is of interest, however, that 2 mg of the dihydro spray was shown in this study to be equivalent to 3 mg of ergotamine by mouth. This result supports the Sponsor's claims for efficacy.

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C. Studies in cluster headache.

Two small studies in cluster headache carried out by Sandoz of Basel between July 1983 and March 1984 in non-US settings are reported. Each had one investigator and was of crossover design.

Study **0603-009** (N =21) was carried out in Denmark; the protocol begins at Vol 37 / page 09762; the report, at Vol 37 / page 09773. Study **0603-010** (N =16) was carried out in Italy; the protocol begins at Vol 37/ page 08-09881; the report, at Vol 37/ page 08-09892.

These were comparative, double-blind trials in which eligible patients were to treat one cluster period consisting of one week or a maximum of 8 headaches with active and one cluster period with placebo; order of treatment was randomized. Treatment consisted of two puffs, one in each nostril. If relief was unsatisfactory at 30 min, rescue medication was to be used. Efficacy parameters were duration of attack, influence of trial medication, and overall efficacy.

No statistically significant difference between active and placebo was observed in duration of attack or overall efficacy. Trial medication appeared to be active, but a period effect which was considered to be due to carryover was observed. When second period data were ignored, there were no statistically significant differences between treatments.

D. Discussion

Of the 12 randomized, double-blind, controlled studies described in this review (US 2, non-US 10), all those with N ≥100 were supportive of the Sponsor's Application; with one exception (**-006**), all those with N <100 were negative.

1. Outcome in the two US studies was unambiguous. These were multicenter studies of the effect of study medication (1 mg at the first sign of an attack, followed if necessary by a second 1 mg at 15 min) in comparison with placebo on two consecutive headaches. Baseline demographics, including severity of headache and inter-headache interval, were similar in the two treatment groups in each study ($p > 0.05$).

In each study, physicians' ratings of efficacy in relieving pain were roughly one interval (on a 4-interval scale) better in comparison with placebo ($p < 0.05$). Duration of headache was lessened by the administration of active in **511** but not **512**.

Summary of outcomes in studies 511/512

	Study **511**		Study **512**	
	DHE	Pla	DHE	Pla
Intent-to-treat N	54	52	48	52
Mean interval (days) between headaches	37	35	24	28
Baseline pain (none 1, mild 2, moderate 3, severe 4, incapacitating 5)	3.4	3.4	3.7	3.6
Physicians' ratings of efficacy: (no effect 1, poor 2, fair 3, good 4, very good 5)				
Relief of pain	2.8	2.0	3.1	2.0
Relief of nausea		NS	3.1	2.2
Relief of vomiting		NS		NS
Duration of headache (hrs)	13.5	19.6		NS

Note: NS = not significant; all other comparisons, $p < 0.05$.

2. Outcomes of five of the non-US studies (parallel-groups 1, crossover 4) were supportive. The following brief summaries outline the findings.

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-002 (page 26) This was a parallel-groups study conducted at 9 centers in Austria, Germany, and Norway. Efficacy was assessed in terms of patient-rated effect of medication, post-treatment duration of attack, and Investigators' overall assessments. All patients were to treat four headaches; 114/140 empanelled subjects were included in the efficacy population. Patient-rated efficacy was dose-related ($p = 0.0393$). Duration of headache after treatment was also dose-related ($p = 0.0028$), but was compromised by the use of rescue meds at 90 min by 75% of subjects. Investigators' assessments were nonsignificant.

-006 (page 36) This was was a crossover study (2 headaches per treatment) conducted by two Swiss investigators. A total of 26/39 enrolled patients had efficacy data; dosage was 1.5 or 2.0 mg active vs placebo. Statistically significant differences were seen on all efficacy parameters (duration after treatment, effect of medication, overall efficacy), but data on use of rescue meds were uninterpretable.

-008 (page 38) This 13-investigator study was similar to **-006**, with a cross-over design (2 headaches per treatment) and statistically significant between-treatments differences on the three efficacy parameters. DHE patients used fewer rescue meds (33% vs 52%, $p < 0.001$).

-007 (page 41) This French study also had 13 investigators and was of crossover design. Patients treated 2 headaches per treatment. Principal efficacy parameter was complete relief of symptoms in 2 hrs; others were similar to those in the other studies. A total of 119 patients were enrolled; 95 had efficacy data, but no individual patient data were available to the US Sponsor. Statistically significant differences between treatments were found on all parameters.

-011 (page 44) This was yet another 13-investigator crossover study (2 headaches per treatment) with 191 patients participating but no protocol available. Treatments were D.H.E.45® Nasal Spray and Cafergot tablets; double-dummy technique was used. The two treatments were shown to be equivalent on all parameters, ie, 2 mg of the spray were not different from 3 mg of the tablet.

3. There were no studies in which active or placebo was better than D.H.E.45®.

- cont'd -

4. It is a striking feature of all studies in this Application that the use of D.H.E.45® attenuated migraine attacks in both intensity of pain and duration of symptoms, but did not abort the attacks. Thus, duration of headache was 19.6 hrs when treated with placebo, but 13.5 hrs when treated with 2 mg active, in Study **511**; in Study **512**, the 2-hr difference was nonsignificant. In non-US studies, post-treatment duration was reported to be 3.6-8.5 hrs by patients receiving high-dose active (vs 7.3-15 hrs for placebo), even in the presence of rescue meds.

VI. Open studies.

A. Following is a list of open studies [with location of report, by Volume and page number].

603-001 (N=10) - [Vol 35/page 08-09238]
603-013 (N= 9) - ext of **-002** [Vol 35/page 08-09303]
603-014 (N=16) - ext of **-008** [Vol 36/page 08-09435]
603-015 (N=10) - ext of **-006** [Vol 36/page 08-09586]
603-011 (N=78) - ext of **-007** [Vol 36/page 08-09719]
603-012 (N=32) - ext of **-007** and subset of **-011** [Vol 36/page 08-09737]

No efficacy data were collected in these studies. Safety findings are discussed in a separate review.

VII. Foreign marketing history. [Vol 1 / page 02-00014]

At the time of submission of the NDA, D.H.E.45® Nasal Spray had been approved in five countries -- Belgium, Brazil, France, Norway, and Switzerland -- and had been introduced in all those countries except Brazil.

VIII. Recommendations

1. Data presented in this Application demonstrate that D.H.E.45® Nasal Spray is effective in reducing the pain and associated symptoms of acute attacks of common and classical migraine. Duration of headache is shortened by several hours. Sponsor's findings should be independently reviewed by Division of Biometrics. If that review confirms the Sponsor's conclusions, the Application may be considered approvable with respect to efficacy.

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2. Sponsor's analysis of data from studies in cluster headache fail to demonstrate an effect of D.H.E.45® Nasal Spray on the frequency, course, or intensity of cluster headache attacks. The use of D.H.E.45® for this indication should not be approved.

David M. Collins, MD

David M Collins, MD

cc: IND
HFD-120
HFD-120/Katz
/KHiggins
/Collins
ft/dmc/January 24, 1995

Review and Evaluation of Clinical Data

NDA	**20-148 N(BM & BZ)**
Sponsor:	**Sandoz**
Drug:	**DHE Nasal Spray**
Proposed Indication:	**migraine**
Material Submitted:	**Supplemental NDA, long-term safety**
Correspondence Date:	**11/4/96**
Date Received / Agency:	**11/5/96**
Date Review Completed	**11/18/96**

Introduction

This submission addresses the Agency's safety concerns regarding the long-term use (> 6 months) of Migranal™ Nasal Spray.

The active ingredient of Migranal ™ Nasal Spray is dihydroergotamine mesylate, an ergot derivative with partial agonist activity at 5HT and α-adrenergic receptors. It has been available in three different forms, oral, parenteral, and nasal. Oral and parenteral forms were introduced in 1946 and are now marketed in 27 countries. Dihydergot® Nasal Spray was first introduced in France in 1987 and is now available in a total of 11 countries. On Oct. 4, 1996, Migranal ™ Nasal Spray was approved in Canada.

The sponsor has filed this NDA in January 1992 to obtain approval for marketing of Migranal™ (Dihydroergotamine) Nasal Spray in the U.S. On July 17, 1996, the agency asked Sandoz to provide the number of patients in the NDA who have received Migranal™ for 6 months or longer. On July 24, the sponsor provided an answer but the Division again asked for clarification about long-term exposure safety.

Sandoz is aware of the final ICH guidelines (dated 10/26/94) regarding the length of exposure needed to demonstrate safety for drugs which are intended for long-term treatment of non-life-threatening conditions. Three hundred patients should be exposed for 6 months, and 100 patients should be exposed for one year. The frequency of exposure should be at least 2 per month.

The NDA was withdrawn in June 1995 because of pre-clinical issues. At that time, the Division concluded from the reviews that "from more than one adequate and well controlled clinical investigation Migranal ™ Nasal Spray is effective as a treatment for acute migraine headaches." The sponsor states that the Division also stated that Sandoz had "submitted evidence from a sufficiently large cohort of patients to conclude that there was no clinical signal of toxicity sufficient to preclude approval." In a meeting held 11/95, the Division agreed that the findings in the toxicology studies were the result of mild irritation and not

dysplasia. Sandoz resubmitted the NDA in May of 1996 with the understanding that all pending issues were addressed.

The sponsor now submits additional information that will hopefully clarify the long-term safety issues.

Toxicology

Cynomolgus monkeys were exposed to daily Migranal ™ nasal spray for 13 weeks. The study results indicated that the Migranal ™ treated animals experienced transient local effects on the nasal mucosa (previously submitted to the Division). The total exposure is the equivalent to a patient treating approximately 78 migraine episodes. According to the proposed labeling and usual clinical practice, this would extend over 6-12 months. No permanent ulceration was found. Early ulceration was self-limited so that at the completion of the 13 weeks study, the finding was similar in both the control and treated animals.

Rats have been treated intranasally for 51 weeks as part of a 24 month intranasal carcinogenicity study. Exposures were higher than in the monkey (details also submitted to the Division previously). Changes seen included mild goblet cell hyperplasia, mild focal epithelial hyperplasia, focal or multifocal submucosal inflammatory cell infiltration, and increased severity of eosinophilic inclusions in the respiratory or olfactory epithelium. No focal squamous metaplasia or other progressive lesions following 48 weeks of daily treatment. Clinically, this is equivalent to 336 migraines treated with doses higher than proposed human doses. According to proposed migraine labeling and usual clinical practice, the exposure would extend over 28 to 60 months (2.3 to 5 yrs).

In summary, the sponsor states that neither of these studies indicates a safety concern relative to the nasal mucosa after chronic Migranal ™ administration.

Formulation for Human Use

Migranal™ Nasal Spray comes in an ampoule containing 4 mg of DHE. Each puff contains DHE 0.5 mg after proper priming. The patient is instructed to prime the applicator 4 times. They then spray one puff in each nostril (1 mg total), wait 15 minutes and spray again one puff in each nostril. The total dose per attack is therefore 2 mg. One ampoule is used per attack. An interval of 8 hours is required before using another ampoule. No more than 2 ampoules should be used in a 24 hours period.

Previous Extended Human Experience

Human Volunteers

Twelve human volunteers self-administered Migranal ™ at a dose of 2 mg daily six days per week for three weeks. Three reported adverse events. Two reported

dry nose on Day 3 of the third week (15 doses) for a duration of 4 and 5 days respectively. The third patient "did not feel well" on Day 6 of the first week, lasting 2 days.

ENT examinations revealed hyperemia in one Migranal ™ treated volunteer and dryness and crusts in a second. One placebo volunteer was found to have dryness and hyperemia relative to baseline. These findings were considered normal.

Migraine Patients

Open Label Extensions of Clinical Trials

Four trials were conducted as open label safety and tolerability evaluations of the extended use of Migranal ™ nasal spray. These studies were extensions of double blind efficacy studies and involved 101 migraine patients. In addition, 10 cluster patients received long term treatment.

Within all four studies, 101 migraine patients used Migranal ™ for an average of 10.1 months and treated an average of 6.3 migraines per month per patient. Table 1 summarizes the number and duration of long-term exposures from these studies.

Table 1: Duration of Patient Open Label Exposure

STUDY	N	EXPOSURE (months)			
		<2	2-6	>6-12	>12
603-011	77[1]	8	19	16	34
603-013	9	0	3	0	6
603-014	14	1	12	1	0
603-015	10	0	0	1	9
TOTAL	**111**	**9**	**34**	**18**	**49**

[1]includes 10 cluster patients

Three patients prematurely discontinued participation due to nasal congestion, increased nasal secretions or nasal irritation.

A subset of 23 patients who used Migranal ™ for at least 6 months underwent ENT evaluations. 10 had baseline evaluations, 13 did not, and 10 were evaluated for mucociliary function. Polyposis was the only newly occurring abnormality noted. No nasal mucosa abnormalities were attributed to Migranal ™ use and neither mucociliary function nor ciliary beat frequency were found to be altered by Migranal ™ use. No serious or life-threatening adverse events were reported.

Open Label Clinical Experience

Open label Migranal ™ nasal spray has been available in Canada through the Emergency Drug Release Program (EDR) and through the Migranal ™ Access Program (Study DHE-CDN-01).

Since the initiation of the EDR Program in 1988, 263 patients have received 8,526 doses of Migranal™. Fifty (50) have received treatment for greater than one year, using an average of 4.2 doses per month. Thirty-six (36) patients received medication for 6-12 months, using an average of 5.5 doses per month. No serious adverse events were reported.

The Migranal™ Access Program began in 1996 in Canada and is ongoing. Thus far, 1,482 patients and 25,710 doses of Migranal ™ have been dispensed. Exposure data for 263 patients were available as of 10/3/96. Of these 263 patients, 69 have been using Migranal ™ for 3-6 months, with the majority treating between 1-8 headaches per month. No unexpected or serious adverse events have been reported. Since the study began this year, no safety data past 6 months are yet available.

U.S. Clinical Experience

A number of pharmacies in the U.S. will prepare a nasal spray of DHE 4 mg/mL in distilled water, on receipt of a valid prescription. Two physicians at the New England Headache Center, and one at the Palm Beach Neurological Group prescribe it in this fashion. Review of their treatment files reveals no reports of serious adverse events.

Foreign Open Marketing Experience

DHE Nasal Spray has been marketed in France since 9/87, Switzerland since 8/89, Belgium since 9/90, and Norway since 2/90. Between these dates and 12/95 there have been 29 spontaneous adverse event reports. All except 3 have come from France. The remaining are from Belgium (1) and Switzerland (2). These adverse events have fallen into nine broad categories. Each event occurred once, unless noted by parentheses. It is entirely unknown how long each patient was on medication:

1. Respiratory (rhinitis (2), pharyngitis, dyspnea, epistaxis),
2. Gastrointestinal (vomiting)
3. Nervous System (vertigo, convulsion, paresthesia (2), speech disorder)
4. Cardiovascular (peripheral edema, myocardial ischemia, angina pectoris (4)
5. Vascular-extracardiac (cerebrovascular disorder, flushing, vein disorder, allergic purpura, flushing)
6. Special Senses (parosmia)
7. Musculoskeletal (arthralgia)
8. Skin (erythematous rash)
9. Body as a whole (allergic reaction, face edema)

Conclusion

Table 2 summarizes the long-term exposure for Migranal ™ nasal spray. No serious adverse events have been reported in those patients who have documented long term (>6 months) exposures. Furthermore, the relatively

benign findings on ENT examinations, and the animal studies all are supportive, in the sponsor's opinion, of the long-term safety of Migranal ™.

Table 2: Long Term Exposure for Migranal Nasal Spray

Source	<6 mos	6-12 mos	>12 mos
New England Center for Headache	0	148	102
Palm Beach Neurological Group	0	11	14
Canadian Emergency Drug Release Program (EDR)	177	36	50
Canadian Migranal™ Access Program	263	0	0
Long Term Data in NDA (603-011/013/014/015)	34	18	49
Chronic Daily Use Study 603-109	0	12	0
Total	**474**	**225**	**215**

Spontaneous Adverse Events Reports

Approximately 2.5 million nasal spray devices have been sold worldwide up until 12/31/95. Assuming all devices are used to treat migraine, and assuming migraine patients treat an average of 12 headaches per year, this results in an estimate of 210,000 patient-years of treatment. Similar estimates for the injection result in 2.5 million patient-years worldwide since 1947.

As of 9/23/96, Sandoz has received 58 serious and non-serious reports for the nasal spray formulation and 164 serious and non-serious reports of injectable DHE. A total of 19 AE reports for the spray and 38 reports for the injection contains information about treatment duration. Three, and seven cases, respectively, were on treatment for greater than six months at the time of reporting. These are summarized in Table 3

Table 3: AE's in Patients Treated >6 months, DHE Nasal Spray and Injection

Route	Adverse Event	Duration of Therapy (until onset)
Nasal Spray	Angioedema	8 months
Nasal Spray	Sup Venous Thrombosis	10 years
Nasal Spray	Paresthesia	2 years
Injection	Hypoesthesia	2 years
Injection	Angina Pectoris	7 years
Injection	Pleural Fibrosis	4 years
Injection	Edema	10 years
Injection	Injection Site Pain	1 year
Injection	Injection Site Reaction	3 years
Injection	Chest Pain (? Angina)	21 months

Long-Term Exposure Safety Data Sources

The data for long term safety exposures come from the sources listed in Table 2. Below is a summary of each source.

Studies 603-011,013,014,015

These are long term, open label studies which were extensions of controlled clinical trials. These studies were submitted in the original NDA. Treatment schedules were as follows for each study:

- 603-011 at least 12 attacks in 12 months
- 603-013 at least 16 attacks (maximum 4 per week)
- 603-014 at least 20 attacks (maximum 4 per week)
- 603-015 at 40 attacks or 12 months

In total, 101 patients participated in these studies and used Migranal ™ for an average of 10.1 months during which time they experienced an overall average of 6.3 migraine episodes per month per patient. It is estimated that 60% of these episodes were treated with Migranal ™ Nasal Spray 2 mg. In 87 patients, the mean patient exposure approximated 1 year (10-13.1 months). These results are summarized in Table 4. In total, 3% of patients discontinued prematurely due to nasal congestion, increased nasal secretions, or nasal irritation. No serious adverse events were reported.

Table 4: Summary of Patient Open Label Exposure By Study

Study	N	Mean Exposure (months)	Mean Migraines (per month)	Total Migraines (Study)	Migraines Treated with Migranal™ N	%
603-011 (Range)	68	11.1	8 (1-23)	6038 [a]	3502	58%
603-013 (Range)	9	10 (2.7-16.4)	2.8 (0.6-11.4)	175	112	67%
603-014 (Range)	14	4.1 (1.4-10.2)	3.2 (1.3-6.3)	168	152	86%
603-015 (Range)	10	13.1 (7.7-17.5)	2.6 (2.0-3.3)	344	286	83%
TOTAL	**101**			**6725**	**4052**	**60%**
MEAN		**10.2**	**6.3**			

[a] estimated. Calculated from the summary exposure data and distribution of doses in study report

Study 603-109

This was a chronic daily use study, the results of which are not contained in this submission. However, the sponsor does state that 12 patients underwent exposures of 6-12 months which were the equivalent of 3-6 months of treatment. No serious adverse events were reported.

New England Center for Headache

Drs. Alan M. Rapoport and Fred Sheftell underwent an extensive file search of their records in order to identify patients who have used intranasal DHE for 6 or 12 months. The nasal spray is prepared for them and contains DHE diluted with water to make a concentration of 0.5 mg per puff. Patients take one puff in each nostril, to wait 10 minutes, and to repeat 1 puff in each nostril. They can repeat this series of 4 puffs in 4 hours if necessary.

They were able to identify 113 patients who used the DHE nasal spray at least once per month over 6 months, and 35 patients who used it at least 2 times per month for 6 months. There were 70 patients who used the spray at least once per month for 6 months, and 32 patients who used it at least 2 times per month for one year (see Table 7). No serious adverse events were reported.

Palm Beach Neurological Group

Dr. Reed Stone underwent an extensive file search of their records. The nasal spray is prepared for them and contains DHE diluted with water to make a concentration of 0.5 mg per puff. Patients take 1 puff in each nostril, wait 10 minutes, and repeat 1 puff in each nostril. These 4 puffs are repeated in one hour if necessary.

He identified 9 patients who have used the nasal spray at least once per month for six months, and 2 patients who have used it at least twice per month for six months. He also identified 7 patients who used it at least once per month for one year and 7 patients who used it at least twice per month for one year (see Table 7). No serious adverse events were reported.

Canadian Emergency Drug Release Program (EDR)

In Canada, Migranal™ was made available to patients through a compassionate use program in accordance with the requirements of the Health Protection Branch (HPB). Upon review and notification by the HPB that the patient may enter the program, Migranal ™ was provided to the physician to be dispensed to the patient.

There was no protocol for this program nor a patient case report form. Physician's records were not monitored. Treating physicians were required to notify either Sandoz Canada of the HPB of any serious or unexpected adverse events. The program was initiated in 1988 and continues up to the time of this submission.

For evaluation of Migranal ™ exposure, the duration of the patient's participation in the EDR program was calculated as the difference between the date of the patient's entry into the program and the date of the most recent shipment of drug to the physician for that patient. The total number of doses used was calculated as the total number of Migranal ™ doses shipped to the physician for the patient less the number of doses in the most recent shipment.

The assumptions are:

1. the patient had to be in the program at least up until the physician's last order of Migranal™ for the patient, and
2. the patient used all doses, one dose per migraine, prior to the last shipment
3. It was also assumed that if either condition were not satisfied, the physician would not have ordered additional supplies.

Two hundred sixty three (263) patients are included in the analyses. Six hundred seventy six (676) were excluded because the physician did not order additional medication for them, thus there maximum period of exposure could not be determined (based on assumption #1). An additional 2 patients were excluded because the duration of their participation could not be calculated.

Using these assumptions, 263 patients received Migranal ™ for a total of 2,344.4 months, or 195.4 patient-years during which time they treated 8,526 migraine episodes. The average patient was on Migranal ™ for 8.9 months and treated an average of 32.4 migraine episodes during this time, for a frequency of 3.6 headaches per month.

Table 5 identifies the distribution of patients in each treatment duration group by treatment frequency.

Table 5: Canadian EDR Program, Patient Mean Migraine Frequency/Month

Exposure Duration	<1	1-8	>8	TOTAL
Less than 6 months	38	106	33	177
Between 6-12 months	10	16	10	36
12 months & longer	14	32	4	50
TOTAL				263

Since the program was initiated in 1988, 11,006 Migranal ™ doses have been issued to 941 patients. Not one adverse event has been reported to Sandoz Canada nor to the HPB that was considered serious, unexpected, or alarming by the investigator.

Sandoz Canada Migranal Access Program

This is an open label study (DHE-CDN-01) to evaluate the effectiveness and tolerability of Migranal ™ treatment for migraine headache with or without aura in the Canada. A total of 300-400 neurologists and general practitioners were recruited to treat a total of 2,500 patients. The study was initiated in February 1996 and was scheduled to continue to September 1996, or until Sandoz Canada received marketing approval. The study has been allowed to continue following the receipt of approval on 10/4/96.

Since the study is not complete, the duration of patient exposure was derived from a subset of the total patient population whose data were available on 10/8/96. To be included in the analysis, patient data had to include at least 3 completed patient self reports by 10/8/96, or at least one self report received and at least one request for re-supply of Migranal ™ for the patient by the investigator. Three hundred fifty five (355) patients met these criteria.

The determination of Migranal ™ exposure was calculated as the difference between the date of the patient's self report for the first headache treated with

Migranal™ and the date of the most recent shipment of additional Migranal ™ doses for that patient. The number of doses used was calculated as the total number of Migranal™ doses shipped less the number of doses in the last shipment.

The assumptions for these calculations are:
1. the patient had to be in the program at least up until the physician's last order for more medication
2. the patient used all doses, one per migraine, prior to the last shipment, and
3. the patient's participation was seven days or longer, and
4. the patient had not used their most recent shipment of medication

It was also assumed that if 1 and 2 were not true, the physician would not have ordered additional medication.

Of the 355 patients, 83 were excluded because the duration of their participation could not be calculated due to either the absence of the date of their headaches or the dates of medication reorder preceded the date on the self report forms resulting in durations of negative days. Nine (9) additional patients were excluded due to participation of less than 7 days. Thus 263 patients are included in the analyses.

In total, the 263 patients received Migranal ™ for a total of 1412 months, or 117.7 patient-years, and treated 2,520 migraine episodes. Table 6 identifies the distribution of patients in each treatment duration group by treatment frequency.

Table 6: Canadian MA Program:

Exposure Duration	<1	1-8	>8	TOTAL
Less than 6 months	0	36	27	63
Between 1-3 months	0	117	14	131
Between 3-6 months	12	47	10	69
TOTAL				263

No patients have been treated for more than six months at the time of submission.

Summary of Long-Term Exposure

Table 7 is a table I generated from the safety data which subdivides patients according to treatment duration and headache frequency. One hundred four (104) patients have been exposed for greater than one year at a frequency of at least 2 doses per month. One hundred fifty nine (159) patients have been exposed for greater than 6 months at a frequency of at least 2 doses per month. No serious adverse events have been reported.

Table 7: Long-Term Safety Exposure by headache frequency, Migranal Nasal Spray

Source	N	>6 mos	>6 mos	>12 mos	>12 mos

		>1 ha/mo	>2 has/mo	>1 ha/mo	>2 has/mo
603-011[a]	77	48	45	32	30
603-013	9	6	2	3	0
603-014	14	1	1	0	0
603-015	10	10	10	4	4
603-109	12	12	12	0	0
NE Center for Headache	113	113	35	70	32
PB Neurological Group	16	9	2	7	7
Canadian EDR Program	263	59	52	49	31
Can. Access Program[b]	263	0	0	0	0
TOTAL	**777**	**258**	**159**	**165**	**104**

[a] Includes 9 or 10 patients with cluster headaches
[b] no patients have been treated for over 6 months

APPEARS THIS WAY
ON ORIGINAL

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ON ORIGINAL

Comments

1. It is clear from the data presented that patients exposed to long-term Migranal™ treated (> 6 months and > 12 months) suffer no serious adverse events.
2. ICH guidelines (dated 10/26/94) regarding the length of exposure needed to demonstrate safety for drugs which are intended for long-term treatment of non-life-threatening conditions state that three hundred patients should be exposed for 6 months, and 100 patients should be exposed for one year. The sponsor has met that guideline for exposures of 1 year (N=104), it has failed to meet the guidelines for 6 months (N=159).
3. On the other hand, it is also clear from the data presented that many patients use Migranal™ much more frequently than 2 per month. For example, in the Canadian EDR Program, the average frequency in patients treated over 6 months is 8 doses per month. In the open extensions of clinical trials, 101 migraine patients used Migranal ™ for an average of 10.1 months and treated an average of 6.3 migraines per month per patient. These data suggest but does not prove that chronic Migranal ™ use greater than six months of 2 doses/month is safe.
4. Given the presence of safe passage at 12 months, and lack of serious adverse events in patients taking many more than 2 doses/month over 6 months, and the large favorable worldwide experience (estimated at 210,000 patient years), I believe there is sufficient evidence to suggest chronic Migranal™ Nasal Spray therapy is safe and concerns about its long term safety should not preclude approval.

Armando Oliva, M.D.
Medical Reviewer

R. Levin, M.D. R.L.

ao 11/18/96
cc:
HFD-120
NDA 20-148 N(BM & BZ)
HFD-120/Leber/Katz
electronic copy-Levin

REVIEW AND EVALUATION OF CLINICAL DATA

NDA:	**20-148**
Sponsor:	**Sandoz**
Drug:	**Intranasal DHE 45**
Indication:	**Migraine**
Material Submitted:	**Safety data**

Background:

The safety data was evaluated by Dr. Katz and Dr. Collins when the NDA was resubmitted in 1995. At that time, they analyzed data from 500 patients who were treated with 2.0 mg intranasal. While they considered this database small for a migraine drug, they considered the size adequate based on the fact that the drug was already approved in a parenteral formulation and that data from a bioavailabilty study, 303-002, showed that the total amount of parent and metabolite was greater when the drug was given IM than when given intranasal.

The safety data base showed that the drug was relatively well tolerated with few patients discontinuing treatment. In three patients, there was a possibility of cardiac involvement though in all three cases, the symptoms of chest tightness resolved without intervention and were not associated with any sequelae. There were no other serious AEs noted. Most of the AEs were related to local nasal effects. They did not find any clinical events that would preclude approval.

The drug was not approved at that time because of findings on the preclinical studies that raised concerns for the potential for carcinogenicity.

The sponsor has provided additional information on the safety of the drug with the current submission. This information is from study 301, 302 and DHE-1, three controlled clinical trials. They have also provided additional information regarding the long term exposure to the drug. Dr. Oliva has reviewed the additional long term safety information. I will cover information provided for these studies.

Dosing:

The recommended dose is one spray (0.5 mg) in each nostril followed 15 minutes later by an additional single spray in each nostril for a total of 2 mg. The sponsor goes on to recommend that no more than eight sprays (4.0 mg) should be administered during any 24 hour period and that the maximum weekly dosage is

24 sprays (12.0 mg).

In the clinical studies, dosing was either fixed, in which patients received doses of 0.5 to 2.0 mg for each headache, or non fixed, where patients took doses as needed. In a nonfixed regimen, a patient assigned to a nonfixed dose of 2 mg could receive a dose anywhere from 1 to 2 mg. Studies 603-001 to 603-008, 603-010 to 603-015, and 603-111 used nonfixed doses. The sponsor has determined the exact dose used by each patient in the nonfixed studies.

As far as AEs are concerned, The sponsor has assigned AEs occurring in a patient on the non fixed dose of 2 mg to the 2 mg dose.

Exposure:

The sponsor notes that 1796 healthy subjects and patients have been exposed to the drug in 34 phase 1, 2 and 3 studies. The number of healthy subjects in phase 1 studies is summarized in the following table.

Number of subjects (+=crossover design)							
Study	1 mg	1.5 mg	2 mg	3 mg	4 mg	Plb	Total
Subjects							
303- 002+	10						
303- 020+	18						
303- 021+			18				
303- 022+	15		15		15		
303- 024 +			19				
303- 025 +	12						
303- 026 +	9		9		9	9	
303- 110 +			8				
603- 109			12			6	
603- 112+					8		
Total	64		81		32	15	192

The number of patients in double blind studies is summarized in the following table. Unless marked, the studies were parallel design. Patients in cross over

603- 001#		9	1	
603- 011 extension of study 007	14	19	45	
603- 012 subset of study 011			0	
603- 013 extension of study 002			9	
603- 014 extension of study 008			14	
603- 015 extension of study 006			10	
Total	14	28	79	121

The following table summarizes the enrollment in all studies. It is not clear if the patients in the open label studies were counted twice.

Total number of healthy subjects and patients receiving doses of DHE-45 nasal spray						
	Placebo	1 mg	1.5 mg	2 mg	3 mg	4 mg
Healthy Subjects	15	64		81		32
Patients in RCT	808	64	182	1,043	209	
Additional patients in open label trials		14	28	79		
All	823	142	210	1203	209	32

Duration of exposure:

In the controlled clinical trials, patients treated 1 to 4 attacks. The sponsor conducted 4 open label studies in Europe, 011, 013, 014 and 015, to evaluate the safety of long term exposure to the drug. In study 011, 14 patients used 1 mg, 19 used 1.5 mg and 45 used 2 mg. In the other studies, patients used 2 mg.

On 7/17/96, I requested information on the number of exposures over time for each of the long term studies. In these trials, there were 101 total patients enrolled excluding 10 patients with cluster headaches in study 011. The duration of exposure is summarized in the following table. I did not receive sufficient information to determine the number of duration of exposure for study 011.

Duration of exposure					
	603-013	603-015	603-011	603-014	Total
Double blind study	002	006	007	008	
Number of patients	9	10	68[a]	14	101
Duration of exposure					
< 2 months	0	0	13	1	14
2 to 6 months	3	0	20	12	35
6 to 12 months	0	1	11	1	13
> 12 months	6	9	24	0	39
Number of exposures					
1 to 6	1	0		7	
7 to 12	2	0		1	
13 to 18	1	0		2	
19 to 24	3	1		4	
> 24	2	9		0	

[a] there were 10 additional patients with cluster headaches treated in this study

Safety experience with long term exposure:

Discontinuations:

Three patients (3%) discontinued during the trial for adverse events. The reasons for discontinuation related to local effects of the drug including nasal congestion, increased nasal secretions or nasal irritation.

Serious AEs:

No serious AEs were reported with this exposure.

Adverse events:

The following table summarizes the most common AEs reported during the long

term treatment in patients taking 1 mg ± one additional mg

AEs reported during the long term exposure in patients taking 1 mg ± 1 mg (N=78)		
AE	Number of patients	%
Rhinitis	26	33
Nausea	12	15
dizziness	3	4
Local reaction	2	3
Respiratory disorder	2	3
Tinnitus	2	3

ENT evaluations:

23 patients from study 011 were evaluated with ENT evaluations in study 012. 13 had only post treatment evaluations while 9 had pre and post evaluations. Two of the nine had changes. One had inflammation of the mucosa and the other had congestive aspects of the cavum. Of the 13 with only post evaluations, 4 had essentially normal examinations, 2 had congestions, 2 had congestion and hypertrophy of the turbinates, 1 had discoloration and rhinorrhea, 1 had discoloration and hypertrophy, 1 had atrophic changes, 1 had respiratory allergy, and 1 had inflammation. The investigator concluded that these observations were comparable to observations noted with seasonal changes when viral or allergic changes are frequent.

10 additional patients had olfactory, tympanometry and ciliary function tested along with ENT evaluations. One patient had obstruction of the nasal fossa with tubal dysfunction and one patient had hypertrophic rhinitis with congestion with normal function. Ciliary function was absent in one patient though this was thought to be related to infectious rhinitis.

The sponsor subsequently provided additional information on the long term safety of the drug. This information has been reviewed by Dr. Oliva. See his review for details.

Comments:

The safety from systemic exposure to DHE has been derived from experience with parenteral DHE. The sponsor has provided additional safety information from over 1,200 patients exposed intranasal DHE with single doses of ≥ 2 mg. Long term safety has been added from around 100 patients treating on average 6 headaches per month. The safety data was found in various reviews not to reveal adverse events that would preclude approval.

I would recommend that the labeling carry the warnings and precautions described for other ergotamines and $5HT_1$ agonists. Dosing and administration sections should note that safety information is confined to use of a single 2 mg dose per headache or 24 hour period, treating no more than 1 to 2 headaches per week.

Randy Levin, M.D.
Medical Reviewer

cc:
Original IND
HFD-120
HFD-120/Nighswander
rl/December 20, 1996

REVIEW AND EVALUATION OF CLINICAL DATA

NDA:	**20-148**
Sponsor:	**Sandoz**
Drug:	**Intranasal DHE 45**
Indication:	**Migraine**
Material Submitted:	**NDA Application**
Correspondence Date:	**5/17/96**
Date Received:	**5/17/96**
Date Completed:	**12/20/96**

Introduction:

The following is a summary of the history of this NDA.

12/28/90: The sponsor originally submitted NDA 20-148 on 12/28/90. In the division's original review, both preclinical and clinical deficiencies were noted and the division refused to file the NDA. The deficiencies that led to the refuse to file were the lack of

, and the inadequate documentation of the clinical trials performed in Europe.

4/30/91: The sponsor resubmitted the NDA with additional information on the European trials. Because the preclinical deficiencies were not included in the re submission, the division again refused to file the application.

1/16/92: Following negotiations with the sponsor and internally, the division filed the NDA after the sponsor provided a written commitment to initiate

6/23/95: The sponsor withdrew the NDA.

6/27/95: The division sent a letter to the sponsor acknowledging the receipt of the request to withdrawal the NDA along with a list of comments and deficiencies from the review of the application. In this letter the division stated the following:

1. The submission provided sufficient information for the division to conclude that the drug is effective as a treatment for the acute management of migraine headaches and that there is evidence for safety as long as a rodent study is negative.

2. The safety data for the patients receiving a single dose of ≥ 2 mg should be provided to establish the safety at the effective dose.

3. The effect of oral contraceptives, race, sex and age on the PK of the drug by should be provided.

11/20/95: A meeting was held between the sponsor and the division to discuss the results of the CAR study and the plans on refiling the NDA. The sponsor noted that the division agreed that there was no dysplasia and that the lesions were the result of mild irritation.

5/17/96: Resubmission of the NDA. The sponsor stated that from the deficiencies in the letter dated 6/27/95 that they division had concluded that "Sandoz had submitted substantial evidence from more than one adequate and well controlled clinical investigation that Migranal™ Nasal Spray is effective as a treatment for acute migraine headaches, and that Sandoz had provided reports of sufficient clinical experience to permit approval of the application. It further stated that Sandoz had submitted evidence from a sufficiently large cohort of patients to conclude that there was no clinical signal of toxicity sufficient to preclude approval." In the resubmission, the sponsor has included reports on three additional efficacy studies completed since the original submission. They have presented an update of the safety information available since the original submission and they have included additional preclinical information addressing the concerns raised in the original submission.

Efficacy studies:

Studies 511 and 512:

This information comes from Dr. Katz's supervisory review. In the original NDA, Sandoz included 10 controlled clinical trials in patients with migraine. Two

studies performed in the US, studies 511 and 512, were identified as the pivotal studies and these studies were reviewed in detail by Dr. Collins, the reviewing medical officer, and Dr. Pian from the Division of Biometrics.

Study design:

Studies 511 and 512 used identical protocols. The studies were randomized, double blind, parallel and placebo controlled. Patients were randomized to either placebo or 2 mg of DHE to treat two migraine headache as an outpatient. Patients with common or classical migraines between the age of 18 to 65 with a headache frequency of 1 headache per month were enrolled. Patients treated a headache, severity not specified, with one spray (0.5 mg of DHE or placebo) in each nostril followed by a second spray in each nostril 15 minutes later. Headache and nausea severity, headache relief and the presence or absence of vomiting were noted on an hourly basis for 4 hours. Severity was rated on a 5 point scale from 1=none, 2=mild, 3=moderate, 4=severe and 5= incapacitating. Pain relief was rated on a 5 point scale with 1=complete relief, 2=a lot or good relief, 3=some or moderate relief, 4=a little or slight relief and 5=no relief. A primary outcome measure was not stated in the protocol.

Study 511 results:

Disposition and baseline demographics:

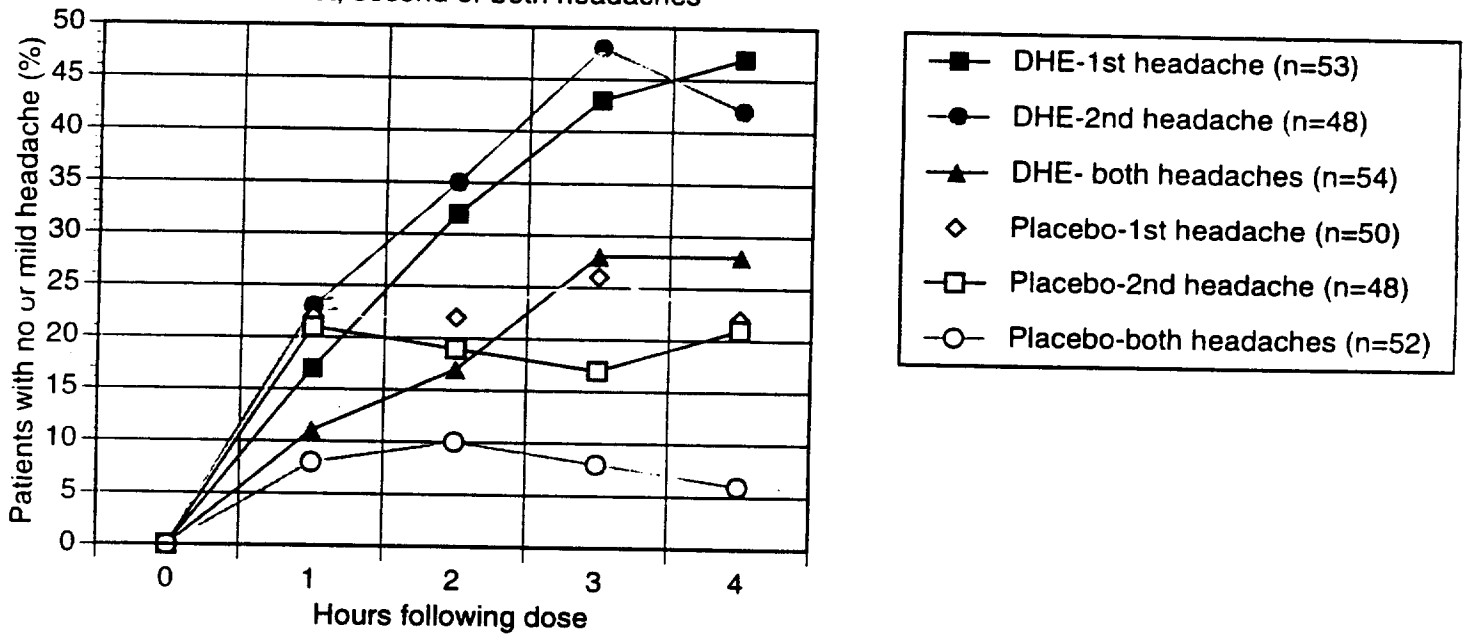
117 patients were enrolled at 8 centers with 11 patients not treating any headaches. 11 patients treated only one headache (only one because of an AE). One patient from each group was excluded from the analyses because they took prohibited medication prior to the one hour evaluation. Baseline demographics were similar between groups. For the first headache, 92% of the DHE patients and 96% of the placebo treated patients treated a headache of at least moderate severity. For the second headache, the percentages were 90% and 81% for the DHE and placebo groups, respectively.

Results:

The percentage of patients achieving no or mild pain of the first, second or both headaches is summarized in the following figure. The p values for the comparisons are in the following table:

Study 511: p values associated from the comparison of the placebo and DHE groups				
	1 hour	2 hour	3 hour	4 hour
First headache	0.65	0.15	0.02	0.002
Second headache	0.85	0.09	0.002	0.032
Both headaches	0.51	0.25	0.006	0.002

Study 511: Percentage of patients with no or mild headache following treatment of the first, second or both headaches



Study 512 results:

Disposition and baseline demographics:

112 patients were enrolled at 10 centers with 11 patients not treating any headaches. 11 patients treated only one headache and one was excluded for taking medication prior to one hour. Baseline demographics were similar between groups. For the first headache, 98% of the DHE patients and 96% of the placebo treated patients treated a headache of at least moderate severity. For the second

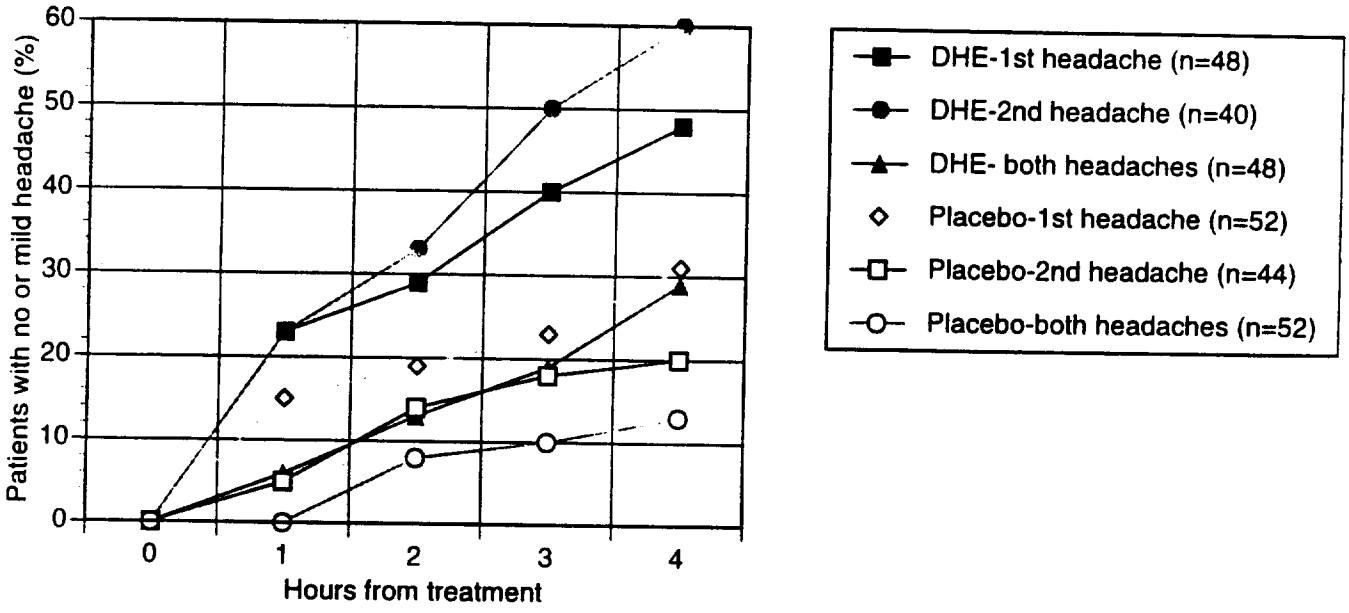
headache, the percentages were 88% and 91% for the DHE and placebo groups, respectively.

Results:

The percentage of patients achieving no or mild pain of the first, second or both headaches is summarized in the following figure. The p values are summarized in the following table:

Study 512: p values associated from the comparison of the placebo and DHE groups				
	1 hour	2 hour	3 hour	4 hour
First headache	0.33	0.2	0.56	0.075
Second headache	0.03	0.06	0.004	0.001
Both headaches	0.1	0.44	0.18	0.045

Study 512: Percentage of patients with no or mild headache following treatment of the first, second or both headaches



Study 301 and 302:

These studies were completed after the submission of the original NDA. Study 301 was conducted from 4/23/93 to 4/18/94 and study 302 was conducted from 5/6/93 to 6/8/94.

Design:

The studies were conducted using identical protocols as randomized, double blind, parallel, placebo controlled, outpatient studies. Patients age 18 to 65 with migraines with or without an aura occurring at a frequency of 1 to 6 per month were enrolled. Patients with prolonged or acute onset auras were excluded. Patients with familial hemiplegic, ophthalmoplegic, retinal, complicated or cluster headaches. Patients were taken off all preventative treatments during a 2 week washout prior to enrollment. Use of analgesics were prohibited 8 hours prior to use of study treatment. Patients were to treat 2 migraines of moderate to severe pain intensity, separated by at least 24 hours. Patients assessed headache pain, pain relief, symptoms associated with migraines (photophobia, phonophobia, nausea and vomiting) at .5, 1, 2, 3 and 4 hours following treatment. Headache recurrence and relapse was assessed by the patients for 24 hours post treatment. Patients were strongly discouraged against the use of rescue medication within the 4 hour following treatment. Aside from the rating of associated symptoms, a physician's global assessment and use of rescue medication, all measures were considered primary outcome measures.

Doses:

Patients were assigned to receive a total of 0, 2 or 3 mg. For patients taking 2 mg, the dose was a single spray of 0.5 mg in each nostril followed by a second round (0.5 mg in each nostril) after 15 minutes. For patients taking 3 mg, They will have a third round of treatment 15 minutes after the second. To maintain the blind, all patients received three rounds of treatment.

Analysis:

The primary outcome measure was the differences in pain intensity and the sum of pain intensity differences over the first four hours and the pain relief scores relative to the onset of pain and the total pain relief scores over the first four hours. Headache relapse was defined as a return of the headache pain after achieving complete disappearance of the headache after study treatment. While not in the original protocol, the sponsor defined a valid patient analyses as an

analysis performed on assessments for patients with moderate to severe headache pain prior to taking treatment who had not taken rescue treatment during the 4 hour treatment period.

Study 301 results:

Disposition and demographics:

There were no significant differences between groups with respect to sex, age, race, height and migraine history. Patients age 19 to 63 with a mean age of 39 were enrolled. 89% were female and 92% were white. 25% had migraines with aura. The mean number of headaches per month were 2.8. The disposition of patients in the following table:

Study 301: Disposition (number of patients)				
	Placebo	2 mg	3 mg	Total
Patients randomized	116	117	115	348
On treatment	102	107	101	310
Completers	90	94	79	263

Results:

The analysis of the first headache and all headaches yields similar results. At 2 through 4 hours, the percentage of patients receiving 2 or 3 mg of the DHE with headache relief is statistically greater than in patients on placebo. The 2 mg group differs from placebo at the first measurement of 30 minutes and continues through all measurements to 4 hours. The percentage of patients with no or mild headaches is summarized in the following table:

Study 301: Percentage of patients with headache relief (no or mild pain)					
First headache	0.5 hrs	1 hr	2 hrs	3 hrs	4 hrs
Placebo (n=102)	13	20	25	26	30
2 mg (n=107)	28*	45	61*	67*	70*
3 mg (n=100)	15	32	46	50	62
Second headache					
Placebo (n=102)	14	32	34	36	37
2 mg (n=107)	19	33	52*	65*	70*
3 mg (n=100)	13	29	47	50	59*
Both headaches					
Placebo (n=192)	14	26	30	31	33
2 mg (n=201)	24*	39*	57*	66*	70*
3 mg (n=180)	14	31	47*	53*	61*

*P<0.05 when compared to placebo

About 50% of patients treating the initial headache with 2 or 3 mg of DHE and 75% of patients on placebo used rescue medication. This difference was associated with a nominal p value of < 0.05. While the time to rescue was collected on the CRF, the data was not provided in the data sets.

At 4 hours, the presence of nausea, photophobia and phonophobia was less in the 2 and 3 mg groups compared to placebo. This difference was associated with a nominal p value < 0.05. At 2 hours, the direction was also in favor of patients on 2 or 3 mg but only the difference of phonophobia was associated with a nominal p value of < 0.05.

Study 302 results:

Disposition and demographics:

There were no significant differences between groups with respect to sex, age, race, height and migraine history. Patients age 18 to 65 with a mean age of 40 were enrolled. 87% were female and 97% were white. 22% had migraines with

aura. The mean number of headaches per month were 2.9. The disposition of patients in the following table:

Study 302: Disposition (number of patients)				
	Placebo	2 mg	3 mg	Total
Patients randomized	119	117	120	356
On treatment	104	104	108	316
Completers	89	88	96	273

Results:

The analysis of the first headache and all headaches yielded similar results. At 4 hours, the percentage of patients receiving 2 or 3 mg of the DHE with headache relief was statistically higher than in patients on placebo. The 3 mg group differed from placebo at 2 hours. There was a higher percentage of patients with pain relief at 2 hours for the 2 mg group when compared to placebo though the difference is associated with a p value of 0.064. The percentage of patients with no or mild headaches is summarized in the following table:

Study 302: Percentage of patients with headache relief (no or mild pain)					
First headache	0.5 hrs	1 hr	2 hrs	3 hrs	4 hrs
Placebo (n=104)	8	24	35	33	40
2 mg (n=104)	19	40	48	51*	58*
3 mg (n=108)	22	32	52*	60*	65*
Second headache					
Placebo (n=89)	12	25	26	27	29
2 mg (n=88)	9	33	57*	60*	65*
3 mg (n=97)	7	25	38	58*	62*
Both headaches					
Placebo (n=193)	10	24	31	30	35
2 mg (n=192)	15	37*	52*	55*	61*
3 mg (n=193)	15	29	45*	59*	63*

*P<0.05 when compared to placebo

About 56% and 47% of patients treating the initial headache with 2 and 3 mg and of DHE, respectively and 74% of patients on placebo used rescue medication. This differences were associated with a nominal p value of < 0.05. While the time to rescue was collected on the CRF, the data was not provided in the data sets. 20, 11 and 8% of patients had a return of their headache in the placebo, 2 and 3 mg groups, respectively.

At 4 hours, there presence of nausea, photophobia and phonophobia was less in the group of patients receiving 2 and 3 mg. Only photophobia was associated with a nominal p value of < 0.05. At 2 hours, the differences between groups was slightly in favor of the 2 and 3 mg groups. None of the differences were associated with a nominal p value of < 0.05.

Study DHE-1:

This study was performed on the request of Canadian authorities for comparison with sumatriptan and was conducted from 3/3/94 to 4/21/95.

Design:

This was an outpatient, double blind, randomized, double dummy, multicenter trial which contained both a placebo and active control group treated in parallel. The selection criteria was similar to other studies except that patients who had repeated failures on sumatriptan, ergotamine or DHE were excluded. Patients were randomly assigned to treat two headaches, separated by ≥ 72 hours with either a single dose of oral sumatriptan 100 mg , 2 mg of DHE nasal spray (same regimen as in study 301) or placebo. To maintain the blind, all patients taking DHE spray received a placebo oral medication and all patients receiving oral sumatriptan received placebo nasal spray. Patients assigned to placebo took an oral and nasal placebo. Doses were separated by ≥ 72 hours. Headache severity, associated symptoms were assessed at 1, 2, 4, 8 and 12 hours. The primary outcome measure was defined in an amendment to the protocol and was the percentage of patients with resolution of the headache within 4 hours with no rescue. The initial headache pain had to be rated as moderate to severe. The pain had to be reduced to mild or no pain within 4 hours, prior to any rescue treatment and the resolution of the pain sustained for 24 hours without any increase or return of pain after resolution. The primary analysis was on all patients randomized who received at least one dose of study medication. The secondary efficacy analysis excluded patients who did not meet the inclusion/exclusion criteria and did not take sumatriptan or ergotamine within 24 hours of taking the study medication.

Results:

Disposition and demographics:

There were no significant differences between groups with respect to sex, age, race, height and migraine history. Patients age 18 to 61 were enrolled. 80% were female and 96% were white. The mean number of headaches per month were 3.3. The disposition of patients in the following table:

Study DHE-1: Disposition (number of patients)				
	Placebo	Sumatriptan	DHE	Total
Patients randomized	75	77	79	231
On treatment	56	66	67	189
Completers	49	57	57	163

Results:

The percentage of patients with no or mild headaches by 4 hours without recurrence in 24 hours is summarized in the following table:

Study 301: Percentage of patients with no or mild pain (first headache) without recurrence in 24 hours

	Placebo	Sumatriptan	DHE
2 hours	6	30	24
P value		0.003	0.004
4 hours	11	41	33
p value		<0.001	0.003

Other studies:

As summarized by Dr. Katz in his memo, the sponsor had submitted the results of 7 other controlled clinical trials in the original NDA. 3 of the trials were parallel studies with designs similar to previously discussed studies. 4 of the trials used a cross over design. None of the trials were conducted in the US.

In the parallel studies, patients were randomized to a high dose, low dose or placebo. In the high dose group, patients received an initial dose of 1 mg (2 doses of 0.5 mg). If there was no relief, patients could take a second dose of 0.5 mg after 30 and 60 minutes for a total of 2 mg for each headache. In the low dose group, patients initially received a single dose of 0.5 mg. If there was no relief, patients could take a second dose of 0.5 mg after 30 and 60 minutes for a total of 1.5 mg. Patients were to treat 4 headaches in a 30 day period. Two studies enrolled 28 and 47 patients, respectively and no statistically significant differences were found. In the third study, 114 patients were enrolled. The sponsor reported that the duration of headache and a measure on how well the headache was controlled were associated with nominal p values of < 0.05. Dr. Katz notes that 65, 85 and 77% of the patients in the high, low and placebo groups used rescue medication within 90 minutes confounding the interpretation of the results.

In the three of the cross over studies, 39, 114 and 119 patients were enrolled, respectively. Patients treated a total of 4 headaches with two headaches treated in each period. These studies did not measure the severity of the headache and are difficult to compare with the other studies. The sponsor reported that the trials showed that the drug was superior to placebo on most of the effectiveness measures (duration of headache, effect of medication, overall efficacy, use of rescue). Most of the patients used a total of 2 mg to treat the headaches. The final cross over study was a single center study that the sponsor reported was a negative study.

Efficacy comments:

The sponsor has submitted 5 adequate and well controlled studies assessing the efficacy of Migranal in the acute treatment of migraine headaches.

Studies 511 and 512 used similar protocols. The 2 mg dose (0.5 mg in each nostril followed in 15 minutes by a second dose for a total of 2 mg) was compared to placebo. While a primary outcome measure was not defined, the results of the change in pain scores over the 4 hour period following treatment were statistically in favor of the drug when compared to those patients treated with placebo. These studies were reviewed by Dr. Collins and Dr. Katz and they concluded that the studies provided evidence for efficacy.

The sponsor has conducted three additional efficacy studies, 301, 302 and DHE-1. Studies 301 and 302 used similar protocols. In these two studies, 2 and 3 mg were compared to placebo. Patients did not receive a second dose of study treatment and were discouraged from receiving rescue prior to 4 hours following study treatment. The primary outcome measure was pain intensity over the first four hours. As in studies 511 and 512, statistically significant differences were found when active drug was compared to placebo thus providing evidence for efficacy. There was no statistically significant difference noted between the 2 and 3 mg dose and no evidence to suggest that the 3 mg dose was more effective than the 2 mg dose. When evaluating the percentage of patients with pain relief, all of the studies show a greater percentage of patients achieving pain relief starting 2 hours after initial dosing. In three of the four studies, the differences between placebo and 2 mg dose at 3 and 4 hours following treatment was associated with a p value of < 0.05.

In study DHE-1, a 2 mg dose was compared to placebo and 100 mg of oral sumatriptan. Non responders to sumatriptan were excluded. Pain relief without

need for further treatment was the primary outcome measure. Patients treated with either sumatriptan or Migranal did significantly better than patients on placebo.

The results of these studies provide definitive evidence for efficacy of 2 mg of DHE for the acute treatment of migraines. The question I have is how to present the evidence in labeling. Currently, for migraine drugs, the primary outcome is the percentage of patients with headache relief, defined as a headache going from moderate or severe pain to mild or no pain, 2 to 4 hours after treatment. This is consistent with the labeling for Imitrex injection and oral formulations. Supporting assessments of efficacy include percentage of patients requiring rescue or a second dose of study treatment, time to rescue or second dose, percentage of patients with recurrence, time to recurrence and percentage of patients with headache relief without the need for additional treatments.

I suggest that labeling for this and subsequent migraine drugs have similar labeling so as not to suggest that one treatment has a better profile than another without adequate evidence. As was done recently for the Imitrex labeling for the indication of cluster headaches, I would suggest trying to provide information on the entire course of the headache and how the drug benefitted the patients rather than just focusing on the initial 2 or 4 hours of treatment. This would take into account the use of rescue medication and the time course for recurrence of headaches.

While the presence of associated symptoms of migraines (photophobia, phonophobia, nausea, vomiting) has also be described in earlier labeling, the most recent labeling for cluster headaches did not include these results. The reason for not including these findings is that with secondary outcome measures there are multiple comparisons involved and the associated p values are of unclear statistical significance. Reporting that a secondary outcome measure is significant is misleading in that it does not take into account the multiple comparisons. In the Migranal studies, photophobia was associated with a nominal p value of < 0.05 in studies 301 and 302. The others were associated with a nominal p value of < 0.05 in study 301 but not 302. I would suggest not including these results in labeling.

I would recommend the following description in the clinical section of labeling:

> The efficacy of Migranal in the acute treatment of migraine headaches was demonstrated in three, randomized, double blind, parallel, placebo controlled studies. Patients age 18 to 65 were enrolled and instructed to treat a migraine headache and assess the pain severity over the 24 hours

following treatment. In one study, a total dose of 2 mg was compared to placebo while in two studies, doses of 2 and 3 mg were evaluated. Patients received 0.5 mg in each nostril at 15 minute intervals. Patients were encouraged not to take other medication until 4 hours following the initial dosing with the study treatment.

{Percent of patients in study 511, 301 and 302 who were female} percent of the {total number of patients enrolled in study 511, 301 and 302} patients enrolled were female. {percentage white of patients enrolled } percent were white with a mean age of {mean age}.

The proportion of patients gaining relief, defined as a reduction in headache severity from moderate or severe to mild or no pain, 3 or 4 hours after treatment for both headaches was significantly greater in patients receiving 2 mg doses of Migranal (See the following table). There was no evidence to suggest that the 3 mg dose provided any additional benefit when compared to the 2 mg dose.

Table: Efficacy Data from the Pivotal Studies

Patients with pain relief (no or mild)	Study 1		Study 2		Study 3	
	Placebo (n=50)	2 mg (n=53)	Placebo (n=102)	2 mg (n=107)	Placebo (n=104)	2 mg (n=104)
1 hour post dose	22	18	20	45	24	40
2 hours post dose	22	32	25	61*	35	48
3 hours post dose	26	45*	26	67*	33	51*
4 hours post dose	22	48*	30	70*	40	58*

$P < 0.05$

If possible, the sponsor should include some representation of the time course of the headache relief. In the cluster labeling a Kaplan Meier (product limit) Survivorship Plot below was constructed that provided an estimate of the cumulative probability of a patient with a migraine headache obtaining relief after being treated with either Migranal or placebo. The plot was constructed with data from patients who either experienced relief or did not require (request) rescue medication within a period of 4 hours following treatment. As a consequence, the data in the plot are derived from only a subset of the {total number of patients treated} patients treated (rescue medication was required in {number} of the {number} placebo treated headaches and {number} of the

{number} Migranal treated headaches).
Finally, I would include information about the recurrence of headaches and the need for rescue. This section would read as follows:

> In the three studies, {percent of patients treated with 2 mg with relief at 4 hours and no rescue treatment} of patients receiving 2 mg of Migranal experienced relief at 4 hours and continued to have headache relief without using additional treatments. This compares to {percent of patients treated with placebo} of patients receiving placebo. {Percentage} of the patients receiving 2 mg of Migranal had a return of their headache and/or used rescue treatment during the 24 hours following initial treatment. The mean time to recurrent headache and/or use of rescue treatment was {mean time} hours.
>
> The data from these studies did not suggest that Migranal treatment was associated with an increase in the severity of recurrent headaches.

Randy Levin, M.D.
Medical Reviewer

cc:
Original IND
HFD-120
HFD-120//Nighswander
rl/December 20, 1996

NDA #: 20-148 (resubmission)

Applicant: Sandoz JAN 28 1997

Name of drug: Migranal™ Nasal Spray (DHE 45® Nasal Spray)

Indication: Acute migraine

Volumes reviewed: 1.1, 1.48, 1.51, 1.59, 1.68, submission dated May 20, 1996

Medical reviewer: Randy Levin, M.D. (HFD-120)

RETURN
JAN 28 1997

This review evaluates the results of U.S. trials E-301 and E-302 (DHE 2mg, 3mg) and foreign Trial DHE-1 (DHE 2mg) in the resubmission of NDA 20-148. The original April 30, 1991, submission contained the results of two U.S. studies (511 and 512) which provided clear statistical evidence of the effectiveness of DHE 2mg in the treatment of migraine. Lee Pian, Ph.D., Division of Biometrics 2, reviewed the effectiveness data. (Her review is dated July 30, 1993.) The new U.S trials provide the first data in controlled trials on the effectiveness of the 3mg dose. The purpose of this review is to evaluate the consistency of the new results with previous results, and to determine if the new U.S. trials provide statistical evidence that DHE 3mg is more effective than 2mg.

Tables 1-7 are taken from the sponsor's current submission. Table 0 is taken from the sponsor's 1991 submission as abstracted by Dr. Pian in her review.

U.S. Trial E-301

Trial E-301 used a randomized, double-blind, placebo-controlled parallel group design at 25 centers. Outpatients were randomized in equal numbers to placebo, DHE 2mg or DHE 3mg. Study medication solutions were the same ones used in Trials 511 and 512. Patients used two nasal spray devices, in labelled sequence, applying three doses of test drug (one spray per nostril) at 15 minute intervals (six sprays total). (Patients in 511 and 512 used one spray device to administer two 1mg doses of test drug 15 minutes apart for a total of four sprays.) Patients in E-301 used the first device for the first two doses; it contained two 1mg doses of DHE or two doses of placebo. The second device was used for the third and final dose which contained 1mg of DHE or placebo.

As in Trials 511 and 512, patients treated two migraine headaches of moderate or severe pain at least 24 hours apart. For each headache, patients used a headache diary to report pain severity, pain relief, functional ability, incidence and severity of nausea, and incidences of vomiting, photophobia, phonophobia, and headache relapse during the 24-hour evaluation period. Evaluations were performed at baseline, and at ½, 1, 2, 3 and 4 hours after the first dose of study medication. Pain relief was assessed after baseline only. The patient also recorded times when: (1) additional medications were taken during post-treatment evaluation; (2) headache pain

started; (3) headache pain was fully relieved (return to mild/no pain); and (4) headache pain returned in the event of headache recurrence. Investigators used a 5-point scale to assess medication effectiveness in the context of the patient's usual migraine syndrome for pain relief, functional ability, nausea, vomiting, photophobia, and phonophobia.

Per the IHS headache guidelines, headache pain was rated on a 4-point scale: no pain, mild, moderate and severe. (Trials 511 and 512 used a 5-point scale: none, mild, moderate, severe, incapacitating.) Pain scores were assigned as: none=0, mild=1, moderate=2, severe=3. Pain relief was rated on a 5-point scale: no relief, a little, some, a lot and complete. Functional status was rated on a 4-point scale, nausea on a 5-point scale.

The protocol originally specified the following primary efficacy parameters:

- pain intensity differences (PIDS, relative to baseline)
- sum of pain intensity differences over the first four hours (SPIDS)
- pain relief scores (PARS, relative to onset of pain)
- total pain relief over the first four hours (TOTPARS)

SPIDS was calculated as the mean across all five time points, where hours ½ and 1 were weighted by 0.5 and hours 2-4 assigned a weight of 1. TOTPARS used the same weights. According to the sponsor, subsequent discussions with the FDA resulted in the addition of four additional primary variables, clinical correlates of the four original measures: (1) proportion of patients reporting no or mild headache pain, (2) incidence and severity of nausea, (3) functional ability and (4) proportion of patients reporting headache relapse.

The intent-to-treat (ITT) patient set consisted of randomized patients who completed a baseline efficacy evaluation, took at least one dose of study drug and completed at least one post-treatment efficacy evaluation. LOCF and OC analyses were performed on the ITT population. Per protocol, ANCOVA was performed for PIDS, SPIDS, PARS, TOTPARS, severity of nausea and functional ability at each time point, using pre-treatment values as covariate. ANOVA was to be used when assumptions of the ANCOVA (homogeneous slopes not equal to 0) were not met. For both ANCOVA and ANOVA, two-way models with interaction were used with factors for treatment and center. Fisher's exact test was used for pairwise comparisons of proportions (e.g., responders).

The sample size calculation in the protocol was based on data for SPIDS and TOTPARS from Trials 511 and 512. It was determined that 86 patients per group would be required to detect treatment-placebo differences (.45 for SPIDS, .43 for PARS) with 80% power at α=.05. The sample size was also deemed sufficient to detect a linear dose-response trend from placebo to 2mg to 3mg in the proportion of responders. This was intended as a demonstration of the expected 'clinical gain' from 2mg to 3mg. With the trial was underway, Sandoz and the Medical Division teleconferenced on May 10, 1993, to discuss a variety of issues concerning Trials E-301 and E-302, including the proposed method to show superiority of 3mg to 2mg. The Medical Division informed the sponsor that a dose-response analysis with an observed positive slope

from 0 to 2 to 3mg would be, by itself, inadequate for demonstrating superiority of 3mg to 2mg; a more direct method of analysis would be needed. Sandoz, in an August 24, 1993 memo to the Medical Division, proposed several additional calculations showing that, under the protocol specified sample size of 86/group and a range of estimated response rates, the confidence level was at least 74% that 3mg could be shown to be **no worse than** 2mg. Another calculation using a type 1 error rate of **20%**, 80% power, a 10% difference in response rates and a one-tailed test, was proposed to show that the combined sample for E-301 and E-302 (170/group) could be used to demonstrate the **superiority** of 3mg to 2mg.

Results

By way of comparison, results for Trials 511 and 512 on PIDS are shown in **Table 0**. The Table shows unadjusted unweighted means (average over center means) across time.

In Trial E-301, there were no significant differences between groups with respect to sex, race, age, or migraine history. Most patients were female (89%) and Caucasian (92%). The small number of non-Caucasian males, and the absence of patients >65 years old, precluded subgroup analyses of sex, age or race.

Three hundred forty-eight (348) patients were randomized to treatment: 116 placebo, 115 DHE 3mg and 117 DHE 2mg. Of these, 310 (89%) qualified for the ITT analyses. (This compares with 90% (206/229) for Trials 511 and 512 combined.) Two hundred sixty-three (263) patients completed (treated 2 headaches) the trial, although a lower relative percentage of patients assigned to the high dose group completed. Of the 310 patients who used study medication, 22 (22%) from the DHE 3mg group, 13 (12%) from the DHE 2mg group, and 12 (12%) from the placebo group withdrew prematurely due primarily to adverse events (n=14), failure to experience an 'evaluable' second migraine (n=14) and withdrawal of consent (n=8).

ITT/LOCF results for PIDS and SPIDS (averaged across headaches 1 and 2) are shown in **Table 1**. Both DHE 2mg and DHE 3mg were statistically superior to placebo in reducing pain intensity from baseline, 2mg beginning at the earliest measured time point (½ hour) and 3mg beginning at 2 hours. Greater reductions in pain intensity ensued linearly over time for both doses. The 2mg dose level was nominally **more effective** than 3mg (SPIDS, p=.023).

ITT/LOCF results for responder analysis (moderate or severe pain → mild or none), separately for headaches 1 and 2, are shown in **Table 2**. Seventeen headaches (10 first headaches, 7 second headaches) treated when rated as mild were not included in these data. Responder rates at 2 hours for headache 1 were 44%, 61% and 23% for 3mg, 2mg and placebo, respectively. For headache 2 the corresponding percentages were 45%, 51% and 33%. Both 3mg and 2mg produced significantly greater numbers of responders at 2 hours for headache 1 ($p \leq .002$), and 2mg at 2 hours for headache 2 (p=.023).

PARS and TOTPARS statistically favored 3mg and 2mg over placebo as did analyses of

functional ability.

U.S. Trial E-302

Trial E-302 used the same design as E-301 as well as the same outcome measures. It was conducted at 25 U.S. centers.

Results

There were no significant differences between groups with respect to sex, race, age, or migraine history. Most patients were female (87%) and Caucasian (97%). As in Trial E-301, the small number of non-Caucasian males and the absence of patients >65 years old precluded subgroup analyses of sex, age or race.

Three hundred fifty-six (356) patients were randomized to treatment: 119 placebo, 120 DHE 3mg and 117 DHE 2mg. Of these, 316 (89%) qualified for the ITT analyses. The numbers of ITT patients were: 104 placebo, 104 DHE 2mg, 108 DHE 3mg. Overall, 273 patients completed (treated 2 headaches) the trial, with roughly equal numbers completing in each treatment group. Of the 316 patients who used study medication, 12 (11%) from the DHE 3mg group, 16 (15%) from the DHE 2mg group, and 15 (14%) from the placebo group withdrew prematurely. Twenty patients dropped because they failed to experience an 'evaluable' second migraine.

ITT/LOCF results for PIDS and SPIDS (averaged across headaches 1 and 2) are shown in **Table 3.** Both DHE 2mg and DHE 3mg were nominally statistically superior to placebo in reducing pain intensity from baseline, 3mg at all time points (including ½ hour) except 1 hour and 2mg beginning at 2 hours. As in E-301, greater reductions in pain intensity ensued linearly over time for both doses.

Table 4 shows ITT/LOCF results for responder analysis, separately for headaches 1 and 2. Eleven (11) headaches (8 first headaches, 3 second headaches) treated when rated as mild were not included in these data. Responder rates at 2 hours for headache 1 were 49%, 47% and 33% for 3mg, 2mg and placebo, respectively. For headache 2 the corresponding percentages were 37%, 55% and 25%. Both doses produced significantly greater numbers of responders for both headaches starting at 3 hours. Results were mixed at 2 hours, depending on the headache number.

PARS, TOTPARS and functional ability statistically favored 3mg and 2mg over placebo.

Trial DHE-1

The trial used a randomized, double-blind, placebo-controlled parallel group design at 10

Canadian centers. Oral sumatriptan (100mg) was used as an active control[1]. Patients applied the nasal spray as a 1mg dose repeated at 15 minutes for the first headache attack. The same dose was administered at least 72 hours later for the second attack. Patients performed headache evaluations (4-point scale) at 0 (baseline), 1, 2, 4, 8 and 12 hours and again at 24 hours to evaluate headache return.

The primary efficacy parameter was the proportion of migraine headache attacks resolved (moderate/severe -> no/mild pain) within four hours that did not return at 24 hours ('treatment success')[2]. Per protocol, the Cochran-Mantel-Haenszel (CMH) test stratified by center was the primary statistical analysis. The sponsor also examined treatment response at 4 hours, PIDS, SPIDS and functional ability. PIDS and SPIDS were analyzed using ANCOVA with baseline as covariate, or the ANOVA if assumptions for the ANCOVA were not met.

There were no significant differences between groups with respect to sex, race, age, or migraine history. Most patients were female (80%) and Caucasian (96%). Again, the small number of non-Caucasian males and the absence of patients >61 years old precluded meaningful subgroup analyses of sex, age or race.

A total of 231 patients were randomized to one of three treatment groups: 79 DHE 2mg, 77 oral sumatriptan and 75 placebo. Of these, 188 (81%) qualified for the ITT analyses. (The ITT population was defined per Trials E-301 and E-302.) The numbers of ITT patients were 67 DHE (85%), 66 sumatriptan (86%) and 55 placebo (73%). One hundred sixty three (163) patients completed the trial. Of the 188 patients who used study medication, 25 (13%) prematurely discontinued from the trial, roughly equally divided between treatment groups. The most frequently cited reasons for discontinuation were failure to return (6) and study termination (6).

Results for the primary outcome variable are shown in the **Table 5**. DHE had a significantly greater percentage of treatment successes compared to placebo at 2 and 4 hours for both headaches. The responder analysis produced similarly strong results (**Table 6**, $p \leq .015$).

Results for PIDS and SPID are shown in **Table 7**. Averaged across both headaches, DHE patients experienced significantly higher reductions in pain intensity from baseline compared to placebo patients ($p<.009$) at each time point examined (1, 2 and 4 hours) and across time points.

DHE was superior to placebo on 'functional ability', but only for the second headache.

---

[1] No statistical comparisons between DHE and sumatriptan were performed by the sponsor.

[2] The original protocol originally specified three primary efficacy parameters: (1) proportion of treatment successes; (2) proportion of patients experiencing a return of headache pain within 24 hours of study drug administration for each of two migraine attacks separated by at least 72 hours; and (3) proportion of treatment failures for each of the two migraine attacks. The sponsor subsequently designated efficacy parameter (1) as the sole primary efficacy parameter, by protocol amendment. The amendment was finalized March 3, 1995, seven weeks prior to the enrollment of the last patient.

Discussion and Conclusions

DHE 2mg (3mg) was statistically superior to placebo in all three (two) trials for all primary and most secondary outcome measures. The statistical results for 2mg were stronger than those seen in 511 and 512. The larger sample sizes and, to a lesser extent, the use of a 4-point pain scale (vs the 5-point scale in 511 and 512) probably contributed to the slight statistical differences.

There was no statistical evidence that DHE 3mg was more effective than DHE 2mg. To the contrary, the 3mg dose was numerically inferior to 2mg overall in E-301, and statistically inferior to 2mg for SPIDS and TOTPARS, and for PIDS, PARS, responder rate and functional ability at some time points. The doses displayed roughly similar efficacy in E-302.

J. Todd Sahlroot, Ph.D.
Mathematical Statistician

concur: Dr. Chi 1/28/97

cc: Arch NDA 20-148
HFD-120/Dr. Leber
HFD-120/Dr. Katz
HFD-120/Dr. Levin
HFD-120/Mr. Purvis
HFD-120/Mr. Nighswander
HFD-710/Dr. Chi
HFD-710/Dr. Sahlroot
HFD-710/chron: T. Sahlroot/x45728/DB1/WordPerfect/migranal.mem

Table O.

Table I. Analysis of Variance Results for Study 511

PID Hour		Headache A N	Mean	Std	Headache B N	Mean	Std	Headache A&B 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 N	Mean	Std	Headache B N	Mean	Std	Headache A&B 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	

Table 1

Trial E-301

TEXT TABLE VI 2.4.2 Mean Change in Pain Intensity (PID) and Sum of Pain Intensity Differences Across Headaches (SPID)

Hour	Statistic	3 mg	2 mg	Plac	3 mg vs Plac	2 mg vs Plac	3 mg vs 2 mg
	N Baseline Mean	101 2.3	106 2.3	102 2.3			
HALF	Mean Change (adj)	0.2	0.4	0.2	0.361	0.005 **	0.061(*)
1	Mean Change (adj)	0.4	0.6	0.3	0.156	0.001***	0.061(*)
2	Mean Change	0.7	0.9	0.3	0.002 **	0.000***	0.128
3	Mean Change (adj)	0.9	1.1	0.3	0.000***	0.000***	0.017 *
4	Mean Change (adj)	1.0	1.3	0.4	0.000***	0.000***	0.053(*)
MEAN	Mean Change (adj)	0.7	1.0	0.3	0.000***	0.000***	0.023 *

(*)$p<0.10$, * $p<0.05$, **$p<0.01$, ***$p<0.001$
(adj) adjustments were made in cases where the assumptions of the analysis of covariance were met

Table 2

Trial E-301

TEXT TABLE VI 2.4.4 Percentage of Responders

HEADACHE	Hour	3 mg Total N	3 mg Present N Pct	2 mg Total N	2 mg Present N Pct	Placebo Total N	Placebo Present N Pct	Fisher's Exact 3 mg vs Placebo	Fisher's Exact 2 mg vs Placebo	Fisher's Exact 3 mg vs 2 mg
1	BASE	97	0 (0%)	105	0 (0%)	98	0 (0%)			
	HALF	97	12 (12%)	105	28 (27%)	98	10 (10%)	0.658	0.004 **	0.013 *
	1	97	28 (29%)	105	48 (46%)	98	18 (18%)	0.094 (*)	<0.001 ***	0.014 *
	2	97	43 (44%)	105	64 (61%)	98	23 (23%)	0.002 **	<0.001 ***	0.024 *
	3	97	51 (53%)	105	70 (67%)	98	23 (23%)	<0.001 ***	<0.001 ***	0.045 *
	4	97	58 (60%)	105	73 (70%)	98	27 (28%)	<0.001 ***	<0.001 ***	0.184
2	BASE	78	0 (0%)	91	0 (0%)	87	0 (0%)			
	HALF	78	9 (12%)	91	16 (18%)	87	11 (13%)	1.000	0.407	0.287
	1	78	22 (28%)	91	29 (32%)	87	27 (31%)	0.735	1.000	0.619
	2	78	35 (45%)	91	46 (51%)	87	29 (33%)	0.151	0.023 *	0.537
	3	78	39 (50%)	91	58 (64%)	87	29 (33%)	0.039 *	<0.001 ***	0.087 (*)
	4	78	46 (59%)	91	62 (68%)	87	31 (36%)	0.003 **	<0.001 ***	0.261

(*)p<0.10, * p<0.05, **p<0.01, ***p<0.001

Table 3

Trial E-302

TABLE VI 2.4.2 Mean Change in Pain Intensity (PID) and Sum of Pain Intensity Differences Across Headaches (SPID)

Hour	Statistic	3 mg	2 mg	Placebo	3 mg vs Placebo	2 mg vs Placebo	3 mg vs 2 mg
	N Baseline Mean	105 2.3	101 2.3	104 2.3			
HALF	Mean Change	0.2	0.2	0.1	0.020 *	0.161	0.365
1	Mean Change (adj)	0.4	0.5	0.3	0.181	0.082(*)	0.676
2	Mean Change (adj)	0.7	0.7	0.3	0.001***	0.001 **	0.888
3	Mean Change (adj)	1.0	0.9	0.3	0.000***	0.000***	0.180
4	Mean Change (adj)	1.2	1.1	0.3	0.000***	0.000***	0.292
MEAN	Mean Change (adj)	0.8	0.7	0.3	0.000***	0.000***	0.418

(*)p<0.10, * p<0.05, **p<0.01, ***p<0.001
(adj) adjustments were made in cases where the assumptions of the analysis were met

Table 4

Trial E-302

TEXT TABLE VI 2.4.4 Percentage of Responders

HEADACHE	Hour	3 mg Total N	3 mg Present N Pct	2 mg Total N	2 mg Present N Pct	Placebo Total N	Placebo Present N Pct	Fisher's Exact 3 mg vs Placebo	Fisher's Exact 2 mg vs Placebo	Fisher's Exact 3 mg vs 2 mg
1	BASE	102	0 (0%)	103	0 (0%)	102	0 (0%)			
	HALF	102	17 (17%)	103	19 (18%)	102	6 (6%)	0.025 *	0.009 **	0.855
	1	102	30 (29%)	103	39 (38%)	102	23 (23%)	0.338	0.022 *	0.238
	2	102	50 (49%)	103	48 (47%)	102	34 (33%)	0.033 *	0.064 (*)	0.780
	3	102	60 (59%)	103	52 (50%)	102	33 (32%)	<0.001 ***	0.011 *	0.263
	4	102	65 (64%)	103	58 (56%)	102	36 (35%)	<0.001 ***	0.003 **	0.319
2	BASE	94	0 (0%)	87	0 (0%)	88	0 (0%)			
	HALF	94	5 (5%)	87	7 (8%)	88	10 (11%)	0.180	0.611	0.556
	1	94	23 (24%)	87	27 (31%)	88	21 (24%)	1.000	0.313	0.406
	2	94	35 (37%)	87	48 (55%)	88	22 (25%)	0.081 (*)	<0.001 ***	0.017 *
	3	94	54 (57%)	87	52 (60%)	88	22 (25%)	<0.001 ***	<0.001 ***	0.765
	4	94	58 (62%)	87	56 (64%)	88	23 (26%)	<0.001 ***	<0.001 ***	0.759

(*)p<0.10, * p<0.05, **p<0.01, ***p<0.001

Table 5

Trial DHE-1

Table VI. 2.4.1 Percentages of Treatment Successes

[illegible]	Hour	Treatment						p values	
		DHE n.s.		Oral sumatriptan		Placebo			
		Total N	Success N (%)	Total N	Success N (%)	Total N	Success N (%)	DHE n.s. vs placebo	Sumatriptan vs placebo
1	2	67	16 (24%)	66	20 (30%)	54	3 (6%)	0.004**	0.003**
	4	67	22 (33%)	66	27 (41%)	54	6 (11%)	0.003**	<0.001***
2	2	57	14 (25%)	57	19 (33%)	50	2 (4%)	<0.001***	<0.001***
	4	57	23 (40%)	57	26 (46%)	50	5 (10%)	<0.001***	<0.001***

*p<0.05 **p<0.01 ***p<0.001

Table 6

Trial DHE - 1

Text Table VI. 2.4. 2 Percentage of Responders

Headache	Treatment						P value	
	DHE n.s.		Oral sumatriptan		Placebo			
	N Total	Responder N (%)	N Total	Responder N (%)	N Total	Responder N (%)	DHE n.s. vs placebo	Sumatriptan vs placebo
1	67	32 (48%)	66	39 (59%)	54	13 (24%)	0.005	<0.001
2	57	28 (49%)	57	37 (65%)	50	13 (26%)	0.015	<0.001

Tab! 7

Trial DHE-1

TEXT TABLE VI. 2.5.2 **Mean Change in Pain Intensity (PID) and Sum of Pain Intensity Differences Across Headaches (SPID)**

Hour	Statistic	Treatment			P value	
		DHE n.s. (N=67)	Oral Sumatriptan (N=66)	Placebo (N=55)	DHE vs Placebo	Sumatriptan vs Placebo
	Baseline Mean	2.4	2.4	2.3		
1	Mean change	-0.3	-0.4	-0.1	0.0089**	0.0032**
2	Mean change	-0.5	-0.7	-0.0	0.0001***	0.0001***
4	Mean change	-0.8	-1.0	-0.2	0.0001***	0.0001***
SPID	Mean change	-0.6	-0.8	-0.1	0.0001***	0.0001***

*p<0.05 **p<0.01 ***p<0.001

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration

Division of Neuropharmacological Drug Products (HFD-120)
Center for Drug Evaluation and Research

Date: 3/29/97

From: Randy Levin, M.D.
Neurology Team Leader
Division of Neuropharmacological Drug Products, HFD-120

Subject: NDA 20-148

To: File

Background:

The division filed the original NDA on 4/30/91. It was reviewed by Dr. Collins and Dr. Katz. They concluded that the drug was effective for the acute treatment of migraines. They also did not find clinical adverse events that would precluded approval of the drug. Because findings in the preclinical studies raised the question that the drug may be carcinogenic, Dr. Katz concluded, in his memo dated 5/25/95, that the drug not be approved.

Prior to issuing a letter of non approval, the sponsor withdrew the NDA. A letter was sent to the sponsor that noted that the NDA provided sufficient information for the division to conclude that the drug is effective as a treatment for the management of acute migraine headaches and that there is evidence for safety as long as a rodent carcinogenicity study is negative. It also stated that the safety data for the patients receiving a single dose of $\geq$ 2 mg should be provided to establish the safety at the effective dose and that the effect of oral contraceptives, race, sex and age on the PK of the drug by should be provided.

Subsequent discussions on the preclinical findings between the sponsor, expert pathologist and the division led to the conclusion that there was no evidence that the drug was carcinogenic because the lesions noted on the preclinical studies were a result of irritation not dysplasia.

Between the time the NDA was withdrawn and the time it was resubmitted, the division had addressed an issue regarding the need to document long term safety

for drugs used intermittently on a chronic basis. The ICH guidelines suggested that for drugs used intermittently on a chronic basis, a safety data base of at least three hundred patients exposed for 6 months and 100 exposed for one year be provided to adequately assess the long term safety of the drug. Following the submission of the NDA, we ask the sponsor to provide safety data for patients exposed to intranasal DHE on a long term basis. We asked that patients included in this long term data base have treated on average at least 2 headaches per month. These terms are the same provided to all sponsors evaluating drugs for migraines.

The sponsor resubmitted the NDA on 5/17/96. In this resubmission, the sponsor submitted additional preclinical studies that addressed the concerns regarding They also included reproductive toxicity studies. These preclinical studies were reviewed by Dr. Jessop, Dr, Atrakchi and Dr. Fisher under the supervision of Dr. Fitzgerald. Also included in the resubmission was additional safety data of 2 mg dose. A subsequent submission, prompted by our request long term safety data, included information on patients exposed to the intranasal formulation for period of up to one year. This data was evaluated by Dr. Oliva, the reviewing medical officer. Finally, the sponsor included reports on three additional efficacy studies. These studies were reviewed by myself and Dr. Salhroot, the consulting statistician.

Preclinical safety:

See Dr. Glenna Fitzgerald's supervisory memo dated 3/20/97 for details on the pharm/tox issues.

Initially, the pharm/tox reviewers had concerns that the drug may potentially be carcinogenic in animals. This was based on findings of nasal and respiratory changes in the 1 and 3 month toxicity studies and an abnormal in vitro chromosomal aberration study. Prior to the resubmission, these findings were reviewed by a Pathology Working Group, Dr. Ronald Moch, a Veterinary Pathologist from CFSAN and members of the division. The consensus was that the observed lesions were probably adaptive in nature and there was no evidence for dysplasia. To see if these lesions would progress over time, the sponsor was asked to perform a one year interim sacrifices of rats in the two year carcinogenicity study. The sponsor also conducted another chromosomal study.

The one year interim rat findings were reviewed by Dr. Moch. He concluded that no neoplastic lesions were seen and he did not anticipated that any of the lesions in the nasal/respiratory epithelium would become neoplastic in the second year of the carcinogenicity study. The rat carcinogenicity study has been completed but a report has not been submitted. A mouse carcinogenicity study is soon to begin or

has recently been initiated.

The genetic toxicity studies were reviewed by Dr. Atrakchi. The chromosomal aberration tests indicated that Migranal is a weak inducer of cytogenetic damage.

The reproductive toxicity studies were reviewed by Dr. Fisher. These studies showed evidence for intrauterine growth retardation which was thought to be related to a reduction in uteroplacental blood flow. There was also decreased ossification. The drug was shown to have oxytocic properties.

After review of all information available, Dr. Fitzgerald noted in her memo that approval of an NDA without systemic carcinogenicity studies and with evidence of weak cytogenetic damage would be a departure from the usual guidelines. She noted other factors to consider including: (1) that the drug has been marketed for years without carcinogenic effect noted though, she noted that this would be difficult to determine in a post marketing situation, (2) the lack of findings in the one year study would have likely revealed the potential for, at least a local carcinogenic effect, (3) the frequency of use expect for a migraine drug is marginal to be considered as chronic treatment and (4) the rat carcinogenicity study is completed and the report will be available soon.

Dr. Fitzgerald recommended that approval be contingent on: (1) submission of the completed rat carcinogenicity study report. She noted that a draft report would be acceptable with the final report following. (2) The mouse carcinogenicity study be submitted as a phase 4 commitment. (3) labeling include the following: (1) information about the local effects seen in animals in the Warning section, (2) a statement that the carcinogenicity studies are ongoing in the carcinogenicity study, (3) a description of the mutagenicity studies be included in the mutagenicity section and (4) the reproductive toxicity study be included in the Contraindication section and that the drug be labeled pregnancy category X.

Safety:

The safety data regarding intranasal DHE has been reviewed by Dr. Collins, Dr. Katz and Dr. Oliva. Safety information about systemic exposure to DHE is also provided by the experience with parenteral DHE.

The safety data base includes over 1,200 patients using single doses of $\geq$ 2 mg of intranasal DHE and about 100 patients using intranasal DHE to treat on average 6 headaches per month for a year. There is no indication, other than local effects of the intranasal dosing, of side effects to preclude approval of the drug. The local side effects have included nasal congestion, increased nasal secretions and nasal

irritation. Most of the information about local effects are from reported symptoms and simple examination. More extensive examinations were obtained in 23 patients who used the drug for 6 months. No mucosal changes were attributed to the drug in this study and mucociliary function was not altered in the 10 patients evaluated.

Other information on the long term exposure to DHE is derived from access programs in Canada (since 1988) and post marketing exposure in France (since 1987), Switzerland (1989), Belgium (1990) and Norway (1990). Local effects reported include rhinitis, pharyngitis, epistaxis and parosmia.

Efficacy:

In current trials evaluating acute treatments for migraines, the primary measure of efficacy is the rate of headache responders at 2 or 4 hours following treatment. A responder is a patients who has mild or no pain following treatment of a headache with moderate to severe pain at baseline. The sponsor conducted 4 efficacy studies comparing placebo and DHE in the acute treatment of patients with migraine headaches. These studies employed similar selection criteria and design features. I have based my assessment of efficacy on these studies.

Another efficacy study, DHE-1, was conducted to compare DHE and oral sumatriptan. This study excluded patients who were non responders to sumatriptan therapy. This exclusion criteria could lead to a different type of patient enrolled compared to other efficacy trials., The results may lead to some confusion when trials are described and data displayed in labeling. While I have not used the results of this study in my decision regarding the efficacy of the drug, the findings of this study supported the conclusion that the drug is an effective acute treatment for migraines.

When I evaluated the rate of responders for all of the studies, I found that in three of the four studies, patients dosed with 2 mg had a significantly higher rate of response at 3 and 4 hours compared to patients on placebo. While the percentage of responders was higher in patients on DHE at all time points (from 30 minutes to 4 hours), the differences prior to 3 hours were not associated with a nominal p value of < 0.05. In the forth study, 512, the differences were in favor of drug at all time points but the differences were not statistically significant ($p=0.075$ at 4 hours).

A 3 mg dose was studied in two studies, 301 and 302. There was no difference between the 2 and 3 mg groups, statistically. It should be noted that in study 302, the 3 mg dose group was not statistically different from placebo. This led the sponsor to recommend only the 2 mg dose.

For the associated symptoms of photophobia, phonophobia, nausea and vomiting, the findings were inconsistent. The differences in photophobia were associated with a nominal p value of < 0.05 in both study 301 and 302. Nausea and phonophobia were associated with a p value of < 0.05 in study 301 but not in study 302.

Conclusions:

Based on the current standards for the acute treatment of migraine headaches, intranasal DHE has been shown to be effective in more than one adequate and well controlled study. In regards to systemic safety, there is adequate information to conclude that the drug, which is already approved as in a parenteral formulation, can be used with reasonable safety. In regards to local effects of the intranasal formulation, intermittent use also appears not be associated with serious adverse effects though the experience is less than that for the systemic safety of the drug. The extent of exposure and what degree of assessment that is necessary to determine the local safety of an intranasal preparation that is already marketed in other formulations is not clear. In general, to determine safety for a drug to be used intermittently on a chronic basis, the ICH guidelines suggest exposure of 300 patients for 6 months and 100 patients for one year. The guidelines do not address the extent of exposure needed to assess local effects of the drug when systemic effects have already been determined. In my opinion, with labeling both defining the intermittent use of the drug and advising close follow up for local side effects, it is reasonable to conclude that the drug is safe for use.

Recommendations:

I recommend that the drug is approvable with approval based on agreement to labeling and, as recommended by Dr. Fitzgerald, submission of the rat carcinogenicity study report (in draft) and the sponsor's commitment to submit the mouse carcinogenicity study report.

Labeling:

Efficacy:

In regards to labeling, I recommend that there be some description of the headache course after the 4 hours time point. This would provide the prescriber with information on the duration of the effect of the drug.

In the Imitrex subcutaneous labeling for migraine, we included a description of

the headache relief over 2 hours. This outcome measure, while providing proof of efficacy of the drug, does not describe the total course of the headache. We found with sumatriptan, that while a high percentage of patients responded to treatment, many had a recurrence of pain and/or used rescue treatments. The same appears to be true for DHE. In study 301, about 50% of patients on DHE and 75% of patients on placebo used rescue treatment. In study 302, similar numbers were seen (56% on 2 mg and 74% on placebo). While the time to rescue was recorded in the CRF, it was not provided in the data sets.

To address this problem, I suggest that we use a Kaplan Meier plot of the time to rescue over the 24 hours following initial treatment. Patients who did not use rescue would be censored to 24 hours. This plot would provide an estimate of the probability of patients using rescue. It will provide information about the course of treatment after the initial 4 hours.

The clinical trials section of labeling would contain: (1) description of the studies, (2) the percentage of patients with headache relief at 1, 2, 3 and 4 hours following the initial dose of study treatment for each study and (3) the estimated probability of use of rescue over the 24 hours following the initial treatment displayed on a Kaplan Meier plot of the time to rescue over 24 hours, censoring patients not using rescue to 24 hours.

Safety:

In regards to safety, I would recommend that the labeling carry the warnings and precautions described for other ergotamines and 5HT agonists. Labeling for subcutaneous sumatriptan can be used as a model. Dosing and administration sections should note that safety information is confined to use of a single 2 mg dose per headache (24 hour period) and for treating no more than 6 headaches per month or 1 to 2 headaches per week. In the warning section, the prescriber should be advised to provide close follow up for potentially serious local side effect of the drug with long term use.

Preclinical:

The labeling should include all of the information recommended by Dr. Fitzgerald (see above).

Randy Levin, M.D.
Neurology Team Leader

Review and Evaluation of Clinical Data

NDA (Serial Number)	20-148
Sponsor:	Novartis
Drug:	Migranal
Proposed Indication:	migraine
Material Submitted:	Response to Approvable Letter
Correspondence Date:	6/9/97
Date Received / Agency:	6/10/97
Date Review Completed	7/3/97

1. Introduction

This submission contains the sponsor's response to the Division's approvable letter, dated 5/9/97 for Migranal Nasal Spray. The submission contains the following sections:

- Overview
- Revised Draft Labeling
- Revised Pump Specification
- Safety Update
- Deaths reported for DHE 45 Injection
- Interim Report for the Rat Carcinogenicity Study

This review focuses on the safety of Migranal™ Nasal Spray, therefore I review the safety update and deaths sections of the submission

2. Safety Update

The 120 day safety update was submitted on 9/18/96. The cutoff date for safety data contained in this update is 7/1/96. The safety update contained in this submission incorporates safety data gathered between 7/1/96 and 5/19/97.

The update is very brief and consists of two serious adverse events reported during this interval

The first SAE was in a 26 year old female who was taking both oral DHE and the nasal spray. She continued the medication during pregnancy, even though it is contraindicated in this setting. She had a threatened abortion at 28 weeks, which was successfully treated. At 37 weeks, she delivered by cesarean section. The baby was retarded and there was significant impairment of psychomotor development.

The second SAE was in a 24 year old female with anorexia nervosa. She took six puffs of Nasal Spray. The same day, she developed complete deafness of the left ear and progressive loss of hearing in the right ear, confirmed by audiometry. Five months later, she was still complaining of deafness but hearing

loss was minimal on the right side. She refused testing on the left. Testing was difficult due to underlying psychological problems. In the physician's opinion, the objective findings did not substantiate the subjective complaints. The French Pharmacovigilance Center assessed the event unrelated to therapy with DHE.

The safety update also contains a publication: Lipton, R. B., "Ergotamine Tartrate and Dihydroergotamine Mesylate: Safety Profiles, " Headache 1997;37 (suppl1): S33-S41.

This paper reviews the known safety profile of DHE, including intramuscular, intravenous, and intranasal administration. It provides no new safety information.

3. Deaths due to D.H.E. 45 (Injectable Form)

The sponsor searched the international safety database, SAVES, for all instances of death occurring in patients who took DHE. Fifteen cases (15) were found (Table 1).

Table: Deaths Associated with Injectable DHE Use

Case No.	Age/ Sex	Cause	Dose (mg)	Time to Onset
USA/80/00111	57/M	cardiac (MI)	2	20 min after 2nd dose
CDN/95/00191	45/M	cardiac (chest pain)	1	1.5 - 2 hours
USA/88/403	41/M	? (presumed cardiac)	1	2 hours
USA/96/00087	50/M	? (presumed cardiac)	1 mg x 6 over 48 hours	3 days
USA/89/00832	71/F	hemorrhagic stroke	1	7 days
USA/86/00386	65/F	intracerebral hematoma	1 x 2 over 24 hours	?
LIT/96/00173	20/F	Sag Sin Thromb - present 3 days prior to DHE	1	5 hours
USA/95/00403	38/F	Subdural Hematoma	1	1-3 minutes
LIT/96/159	67/F	head trauma	11 mg over 6 days	6 days
CH/86/00378	65/F	Pulmonary Embolus	2	?
F/89/00566	60/M	Pulmonary Embolus	?	?
USA/92/03061	50/F	PE, Ischemic Bowel	1	6 hours - PE 48 hours - bowel isch.
USA/68/00016	NEO	intrauterine death in mother taking DHE	?	?
D/90/02826	NEO	intrauterine death in mother taking DHE	1	6 hours
AUS/88/00437	44/M	dextropropoxyphene overdose	0.5-2	125 days

The cases can be broken down into the following categories:

- Cardiovascular (4)
- Cerebrovascular (5)
- Pulmonary Embolism (3)

- Neonatal (2)
- Overdose (1)

Of the cardiovascular deaths (4), one patient had a history of angina (USA/80/00111) and should not have been given DHE. The temporal association with DHE (20 minutes) makes causality more likely. Another case (DDN/95/00191) was of chest pain and sudden death 1.5-2 hours following DHE administration, again suggesting a causal relationship. The other two deaths lack sufficient clinical information to draw meaningful conclusions.

Of the cerebrovascular deaths (5), it is difficult to say whether the cerebrovascular event was pre-exisiting, coincidental, or actually was attributable to DHE.

In the three pulmonary embolism deaths, insufficient clinical information is present. In the last case listed (USA/92/030610) the P.E. was accompanied later with mesenteric ischemia, which may have been related to DHE.

The two neonatal deaths occurred in pregnant females taking DHE. DHE is contraindicated during pregnancy.

The last case was that of a dextropropoxyphene overdose. The autopsy findings confirmed large amounts of this drug in the liver. The contributory role of DHE in this setting is unlikely.

4. Comments

1. The safety data presented in this update fails to raise any new safety concerns regarding the use of Migranal™ Nasal Spray in humans. From a clinical safety standpoint, the drug remains approvable.

Armando Oliva, M.D.
Medical Reviewer

R. Levin, M.D. R. L.

ao 7/3/97
cc:
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NDA 20-148
electronic copy-Levin

Review and Evaluation of Clinical Data

NDA	**20-148**
Sponsor:	**Novartis**
Drug:	**Migranal Nasal Spray**
Proposed Indication:	**migraine**
Material Submitted:	**Response to Approvable Letter**
Correspondence Date:	**8/7/97**
Date Received / Agency:	**?**
Date Review Completed	**8/19/97**

1. Introduction

The approvable letter for Migranal Nasal Spray was sent 5/9/97. The sponsor responded 6/9/97 with their comments. Many of their proposed changes were unacceptable to the reviewing team. As a result of conversations between Randy Levin and the sponsor on 7/25, 7/29, and 7/30, the sponsor now submits its most recent proposed draft labeling for review.

Submitted is a 3.5 inch floppy disk containing the non-annotated draft labeling in WordPerfect format. In paper format, the sponsor has submitted annotated draft labeling, which contains the text of the labeling contained in the Division's approvable letter of 5/9/97, with annotated deletions and additions reflecting the sponsor's most recent changes.

2. Overview

This is a summary of the sponsor's changes to draft labeling, based on discussions with Dr. Levin.

2.1 Response to 2 Headaches

The Division has asked Novartis to include information about response to two headaches. Novartis believes this information should not be included in labeling. According to their argument, the response data from studies 301 and 302 support the fact that the probability of responding to Migranal is p=0.7. The estimated probability of treating repeated headaches decreases and approaches zero as the number of repeated headaches increases. According to the sponsor, no other product labeling presently approved in migraine therapy contains this information. It is not clear to Novartis how this information will be used, since patients treating a migraine will have no idea whether they will experience a second, or a third, or a fourth. Therefore, they believe this information should not be included in the package insert.

2.2 Clinical Trials Subsection

Novartis has removed all data pertinent to Studies 511 and 512. A statement has been included which mentions the results are supportive of the conclusions from studies 301 and 302. In order to be consistent, they have removed the data from

these studies from the Kaplan-Meier plot of the probability of the use of analgesics. Removing these data had no impact on the probability of analgesic used by the Migranal patients and very little impact on the probability among placebo patients.

The sponsor has included combined response data for only the first headache from Studies 301 and 302, as requested by Dr. Levin.

The sponsor incorporated the combined response data solely for the 0.5, 2 and 4 hour time points. The 2 and 4 hour time points are stressed by the IHS as critical times for efficacy. These time points are also referenced in other approved package inserts for other drugs indicated for migraine therapy.

The sponsor has incorporated recurrence data for Migranal Nasal Spray as defined by the Division. Therefore, the recurrence data in figure 2 of draft labeling is based upon all patients treated. In addition, the sponsor adds recurrence information on patients who experienced no pain at 4 hours and who did not take an analgesic up to 24 hours after treatment. In 301 and 302, Migranal Nasal Spray had a relatively low recurrence rate. The sponsor believes that the studies were designed to capture this information, that the information is an added benefit of the drug, and that the information should be contained in the package insert.

Novartis has incorporated new text regarding the response data for phonophobia, photophobia, and nausea observed with Migranal vs. placebo in both studies at the time points specified by Dr. Levin.

2.3 Contraindications and Adverse Reactions

The sponsor has incorporated all of the Division's comments in these sections.

2.4 Warning

Novartis has removed the reference to sumatriptan regarding cardiac events. They have identified cardiac events which have occurred with Migranal vs. DHE Injection. Novartis does not want to refer and focus on Migranal only as a 5HT agonist since the drug binds at so many other receptor sites and acts as an agonist and an antagonist.

2.5 Precautions

The sponsor retained the text regarding the symptoms observed when a 5HT agonist is co-administered with an SSRI. They have also included a statement regarding what has not been seen to date with Migranal and DHE Injection based upon lack of spontaneous reports.

2.6 Dosage and Administration

The daily and weekly dosing has been revised. Novartis has incorporated a recommendation that doses greater than 3 mg should not be used within a 24 hour period. This is based on data from 301 and 302. Novartis has also

incorporated the Division's recommendation that doses more than 4 mg in a 7 day period should not be used. The mention and focus on safety has been removed, and instead the issue is lack of adequate patient exposure to support additional doses of Migranal within 24 hours or a 7 day period.

3. Annotated Labeling

The changes to the clinical sections of labeling are detailed below.

3.1 Clinical Trials

This section is quite different from the original labeling contained in the Division approvable letter. The sponsor has dropped the data from trials 511 and 512, for reasons that are not stated. The implied reason is that these studies were not done using IHS guidelines. Instead, the sponsor includes a statement that these studies were conducted and are supportive of the conclusions of the 2 studies which are presented (301 and 302).

Table 1 has been modified to delete the data from 511 and 512. Table 1A shows the proportion of patients experiencing a response at 2 and 4 hours, as well as the proportion of patients experiencing complete pain relief at the same time points. It pools data from 301 and 302 and uses the response to the first headache only, as requested (each patient treated 2 headaches in each study).

Additional paragraphs describe the response to the associated migraine symptoms: nausea, photophobia, and phonophobia, at 2 and 4 hours.

3.2 Indications and Usage

This now states simply that Migranal Nasal Spray is indicated for the treatment of migraine headaches with or without aura. The sentence stating that it should not be used in patients with hemiplegic, or basilar migraine, has been moved to the *Contraindications* section.

3.3 Contraindications

The changes to this section incorporates the Division's comments.

3.4 Warnings

3.4.1 Cardiac Events and Fatalities

In the *Cardiac Events and Fatalities* section, the reference to other 5-HT_1 agonists and sumatriptan have been deleted. Instead, the actual occurrence of cardiac events with DHE are described.

In the *Drug-Associated Cerebrovascular Events and Fatalities* section, the reference to 5-HT_1 agonists is again removed and replaced with DHE injection.

3.4.2 Other Vasospasm Related Events

Minor changes in wording occur in this section, but the overall content remains unchanged, with the exception that "colonic ischemia" has been deleted and incorporated under "peripheral vascular" ischemia.

3.4.3 Increase In Blood Pressure

Reference to 5-HT_1 agonists has been removed. The risk of elevated BP with both Migranal Nasal spray and DHE are explicitly stated.

3.4.4 Local Irritation

The section on local nasal mucosa irritation has been completed, according to the Division's request.

3.5 Precautions

Grammatical point: the following statement should have a semicolon instead of a comma: Migranal Nasal Spray may cause coronary artery vasospasm; therefore, patients who experience....

The section on SSRI's describe the weakness, hyperreflexia, and incoordination reported with 5-HT_1 agonists and SSRI's, however states that there have been no reported cases from spontaneous reports of drug interaction between SSRI's and Migranal Nasal Spray.

3.6 Adverse Reactions

The reference to 5-HT_1 agonists have been replaced with DHE instead.

3.7 Dosage and Administration

The statement "Migranal Nasal Spray should be administered at the onset of a migraine attack" has been added. The reference to "safety" of doses greater than 3mg/d or 4mg/wk has been removed, and replaced by a statement that doses above these amounts have not been adequately studied.

4. Comments

1. In the clinical trials section, the sponsor has dropped data from studies 511 and 512. The reason is not stated, although it is implied that these were not conducted using IHS guidelines. Instead, a statement stating the conclusions of these studies support the conclusions of Study 1 and 2 (301 and 302). I find this reasonable, as the statement is true, and the net result is that it makes the tables in the clinical trials section much less cluttered and easier to read and understand.
2. The clinical trials section lacks information about consistency of response. Imitrex Nasal Spray labeling does include some information regarding response to multiple attacks. The sponsor has requested to leave this type of information out of labeling. I don't believe that it needs to be included for the safe and proper use of the drug.
3. As requested by the Division, The Kaplan-Meier plot for need for remedication (Figure 2 in draft labeling) now includes all patients who took

study medication, whether or not they achieved a response initially. In addition, the sponsor includes recurrence data on a sub-population of patients who took study medication and had complete headache relief at 4 hours. Using this sub-group, the recurrence rate for Migranal is very low—only 19%. This is not a standard definition of recurrence. Usually, we define recurrence as a headache which recurs with moderate to severe intensity within 24 hours of the initial dose after achieving a response at 4 hours. Since they define the sub-population on which recurrence rate was calculated, it is arguable whether this should be changed or deleted.

4. The Contraindications section incorporates the Division's comments.
5. The Warnings section removes references to 5-HT_1 agonists, and replaces them with DHE injection. This is acceptable. The sponsor has removed the explicit warning not to use Migranal Nasal spray if the migraine is atypical. This should remain in labeling.
6. The sponsor has, in several places, changed the wording from "Migranal Nasal Spray" to "any migraine medication causing vasoconstriction". Since the labeling is for Migranal Nasal spray, not for migraine therapies in general, the name of the drug should be retained in those instances.
7. The statement "Migranal Nasal Spray should be administered at the onset of a migraine attack" has been added to the beginning of the Dosage and Administration section. I believe this is unnecessary, since this is stated in the Indications section. In my judgment, it appears to be an indirect way to recommend treatment for any migraine attack, not just a moderate-to-severe migraine, as was studied in the clinical trials. Although it is logical to assume the drug would work for milder migraine headaches, this has not been studied in clinical trials.

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