CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

9-000/S-022/S-023

Trade Name: Cafergot Suppositories

Generic Name: ergotamine tartrate and caffeine

Sponsor: Novartis Pharmaceuticals Corporation

Approval Date: June 4, 2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

9-000/S-0222/S-023

CONTENTS

Reviews / Information Included in this ANDA Review.

Approval Letter(s)	X
Tentative Approval Letter(s)	
Final Printed Labeling	X
CSO Labeling Review(s)	
Medical Officer Review(s)	X
Chemistry Review(s)	
Microbiology Review(s)	
Bioequivalence Review(s)	
Administrative Document(s)	X
Correspondence	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

9-000/S-022/S-023

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 9-000/S-022/S-023

Novartis Pharmaceuticals Corp.
Drug Regulatory Affairs
Attention: Martina Struck, PhD
419/1164
59 Route 10
East Hanover, NJ 07936

Dear Ms. Struck:

Please refer to your supplemental new drug applications dated October 8, 1999, received October 15, 1999 and December 22, 1999, received December 27, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cafergot (ergotamine tartrate and caffeine) suppositories.

We acknowledge receipt of your submissions dated July 7, 2000, February 25, 2002 and April 16, 2002. Your submission of April 16, 2002 constituted a complete response to our June 29, 2001 approvable letter.

These supplemental application provide for proposed labeling describing the risk of drug-drug interactions with CYP3A4 inhibitors, as well as the risk of cardiac valvular fibrosis.

We have completed the review of these supplemental applications and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, these supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed to each application. Please mount individually ten of the copies on heavy-weight paper or similar material. Please also submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – NDAs* (January 1999). For administrative purposes, this/these submission(s) should be designated "FPL for approved supplement NDA 9-000/S-022/S-023 ." Approval of this/these submission(s) by FDA is not required before the labeling is used.

We acknowledge your commitment to issue a "Dear Health Care Practitioner" letter to physicians and others responsible for patient care. At the time that this letter issues to health care practitioners, we request that you submit a copy of the letter and label to this NDA, the electronic document room (EDR), and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

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

If you have any questions, call Ms. Lana Chen, R.Ph., Regulatory Project Manager, at (301) 594-5529.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

9-000/S-022/S-023

FINAL PRINTED LABELING

NOVARTIS

T2001-27
89000402

CAFERGOT®

(ergotamine tartrate and caffeine)
SUPPOSITORIES, USP

Rx only

WARNING

Serious and/or life-threatening peripheral ischemia has been associated with the coadministration of CAFERGOT® with potent CYP 3A4 inhibitors including protease inhibitors and macrolide antibiotics. Because CYP 3A4 inhibition elevates the serum levels of CAFERGOT®, the risk for vasospasm leading to cerebral ischemia and/or ischemia of the extremities is increased. Hence, concomitant use of these medications is contraindicated. ***(See also CONTRAINDICATIONS and WARNINGS section)***

DESCRIPTION

CAFERGOT® (ergotamine tartrate and caffeine) Suppository

ergotamine tartrate USP ..... 2 mg
caffeine USP ..... 100 mg

Inactive Ingredients: cocoa butter NF and tartaric acid NF.

CAFERGOT® (ergotamine tartrate and caffeine) suppositories are *sealed* in foil to afford protection from cocoa butter leakage.

If an unavoidable period of exposure to heat softens the suppository, it should be chilled in ice-cold water to solidify it before removing the foil.

CLINICAL PHARMACOLOGY

Ergotamine is an alpha adrenergic blocking agent with a direct stimulating effect on the smooth muscle of peripheral and cranial blood vessels and produces depression of central vasomotor centers. The compound also has the properties of serotonin antagonism. In comparison to hydrogenated ergotamine, the adrenergic blocking actions are less pronounced and vasoconstrictive actions are greater.

Caffeine, also a cranial vasoconstrictor, is added to further enhance the vasoconstrictive effect without the necessity of increasing ergotamine dosage.

Many migraine patients experience excessive nausea and vomiting during attacks, making it impossible for them to retain any oral medication. In such cases, therefore, the only practical means of medication is through the rectal route where medication may reach the cranial vessels directly, evading the splanchnic vasculature and the liver.

Pharmacokinetics: Interactions

Pharmacokinetic interactions (increased blood levels of ergotamine) have been reported in patients treated orally with ergotamine and macrolide antibiotics (e.g., troleandomycin, clarithromycin, erythromycin), and in patients treated orally with ergotamine and protease inhibitors (e.g. ritonavir) presumably due to inhibition of cytochrome P450 3A metabolism of ergotamine *(See CONTRAINDICATIONS)*. Ergotamine has also been shown to be an inhibitor of cytochrome P450 3A catalyzed reactions. No pharmacokinetic interactions involving other cytochrome P450 isoenzymes are known.

INDICATIONS AND USAGE

CAFERGOT® (ergotamine tartrate and caffeine)

Indicated as therapy to abort or prevent vascular headache, e.g., migraine, migraine variants or so-called "histaminic cephalalgia''.

CONTRAINDICATIONS

Coadministration of ergotamine with potent CYP 3A4 inhibitors (ritonavir, nelfinavir, indinavir, erythromycin, clarithromycin, and troleandomycin) has been associated with acute ergot toxicity (ergotism) characterized by vasospasm and ischemia of the extremities (see PRECAUTIONS: Drug Interactions), with some cases resulting in amputation. There have been rare reports of cerebral ischemia in patients on protease inhibitor therapy when CAFERGOT® (ergotamine tartrate and caffeine) was coadministered, at least one resulting in death. Because of the increased risk for ergotism and other serious vasospastic adverse events, ergotamine use is contraindicated with these drugs and other potent inhibitors of CYP 3A4 (e.g., ketoconazole, itraconazole) *(see WARNINGS: CYP 3A4 Inhibitors)*.

CAFERGOT® (ergotamine tartrate and caffeine) may cause fetal harm when administered to pregnant women. CAFERGOT® (ergotamine tartrate and caffeine) is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy or if the patient becomes pregnant while taking this product, the patient should be apprised of the potential hazard to the fetus.

Peripheral vascular disease, coronary heart disease, hypertension, impaired hepatic or renal function and sepsis.

Hypersensitivity to any of the components.

WARNINGS

CYP 3A4 Inhibitors (e.g. Macrolide Antibiotics and Protease Inhibitors)

Coadministration of ergotamine with potent CYP 3A4 inhibitors such as protease inhibitors or macrolide antibiotics has been associated with serious adverse events; for this reason, these drug should not be given concomitantly with ergotamine *(See CONTRAINDICATIONS)*. While these reactions have not been reported with less potent CYP 3A4 inhibitors, there is a potential risk for serious toxicity including vasospasm when these drugs are used with ergotamine. Examples of less potent CYP 3A4 inhibitors include: saquinavir, nefazodone, fluconazole, fluoxetine, grapefruit juice, fluvoxamine, zileuton, metronidazole, and clotrimazole. These lists are not exhaustive, and the prescriber should consider the effects on CYP3A4 of other agents being considered for concomitant use with ergotamine.

Fibrotic Complications

There have been a few reports of patients on CAFERGOT® (ergotamine tartrate and caffeine) therapy developing retroperitoneal and/or pleuropulmonary fibrosis. There have also been rare reports of fibrotic thickening of the aortic, mitral, tricuspid, and/or pulmonary valves with long-term continuous use of CAFERGOT® (ergotamine tartrate and caffeine). CAFERGOT® (ergotamine tartrate) suppositories should not be used for chronic daily administration (see DOSAGE AND ADMINISTRATION).

PRECAUTIONS

General

Although signs and symptoms of ergotism rarely develop even after long term intermittent use of the rectally administered drug, care should be exercised to remain within the limits of recommended dosage.

Ergotism is manifested by intense arterial vasoconstriction, producing signs and symptoms of peripheral vascular ischemia. Ergotamine induces vasoconstriction by a direct action on vascular smooth muscle. In chronic intoxication with ergot derivatives, headache, intermittent claudication, muscle pains, numbness, coldness and pallor of the digits may occur. If the condition is allowed to progress untreated, gangrene can result.

While most cases of ergotism associated with ergotamine treatment result from frank overdosage, some cases have involved apparent hypersensitivity. There are few reports of ergotism among patients taking doses within the recommended limits or for brief periods of time. In rare instances, patients, particularly those who have used the medication indiscriminately over long periods of time, may display withdrawal symptoms consisting of rebound headache upon discontinuation of the drug.

Rare cases of a solitary rectal or anal ulcer have occurred from abuse of ergotamine suppositories usually in higher than recommended doses or with continual use at the recommended dose for many years. Spontaneous healing occurs within usually 4-8 weeks after drug withdrawal.

Information for Patients

Patients should be advised that one suppository of CAFERGOT® (ergotamine tartrate and caffeine) should be taken at the first sign of a migraine headache. No more than 2 suppositories should be taken for any single migraine attack. No more than 5 suppositories should be taken during any 7-day period. Administration of CAFERGOT® (ergotamine tartrate and caffeine) suppositories should not exceed the dosing guidelines and should not be used for chronic daily administration (see DOSAGE AND ADMINISTRATION). CAFERGOT® (ergotamine tartrate and caffeine) should be used only for migraine headaches. It is not effective for other types of headaches and it lacks analgesic properties. Patients should be advised to report to the physician immediately any of the following: numbness or tingling in the fingers and toes, muscle pain in the arms and legs, weakness in the legs, pain in the chest or temporary speeding or slowing of the heart rate, swelling or itching.

Drug Interactions

CYP 3A4 Inhibitors (e.g. Macrolide Antibiotics and Protease Inhibitors)

See CONTRAINDICATIONS and WARNINGS.

CAFERGOT® (ergotamine tartrate and caffeine) should not be administered with other vasoconstrictors. Use with sympathomimetics (pressor agents) may cause extreme elevation of blood pressure. The beta-blocker Inderal (propranolol) has been reported to potentiate the vasoconstrictive action of CAFERGOT® (ergotamine tartrate and caffeine) by blocking the vasodilating property of epinephrine. Nicotine may provoke vasoconstriction in some patients, predisposing to a greater ischemic response to ergot therapy.

The blood levels of ergotamine-containing drugs are reported to be elevated by the concomitant administration of macrolide antibiotics and vasospastic reactions have been reported with therapeutic doses of the ergotamine-containing drugs when coadministered with these antibiotics.

Pregnancy

Teratogenic Effects

Pregnancy Category X: There are no studies on the placental transfer or teratogenicity of the combined products of CAFERGOT® (ergotamine tartrate and caffeine). Caffeine is known to cross the placenta and has been shown to be teratogenic in animals. Ergotamine crosses the placenta in small amounts, although it does not appear to be embryotoxic in this quantity. However, prolonged vasoconstriction of the uterine vessels and/or increased myometrial tone leading to reduced myometrial and placental blood flow may have contributed to fetal growth retardation observed in animals. *(See CONTRAINDICATIONS)*

Nonteratogenic Effects

CAFERGOT® (ergotamine tartrate and caffeine) is contraindicated in pregnancy due to the oxytocic effects of ergotamine. *(See CONTRAINDICATIONS)*

Labor and Delivery

CAFERGOT® (ergotamine tartrate and caffeine) is contraindicated in labor and delivery due to its oxytocic effect which is maximal in the third trimester. *(See CONTRAINDICATIONS)*

Nursing Mothers

Ergot drugs are known to inhibit prolactin but there are no reports of decreased lactation with CAFERGOT® (ergotamine tartrate and caffeine). Ergotamine is excreted in breast milk and may cause symptoms of vomiting, diarrhea, weak pulse and unstable blood pressure in nursing infants. Because of the potential for serious adverse reactions in nursing infants from CAFERGOT® (ergotamine tartrate and caffeine), a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Cardiovascular: Vasoconstrictive complications of a serious nature may occur at times. These include ischemia, cyanosis, absence of pulse, cold extremities, gangrene, precordial distress and pain, EKG changes and muscle pains. Although these effects occur most commonly with long-term therapy at

relatively high doses, they have also been reported with short-term or normal doses. Other cardiovascular adverse effects include transient tachycardia or bradycardia and hypertension.

Gastrointestinal: Nausea and vomiting; rectal or anal ulcer (from overuse of suppositories).

Neurological: paresthesias, numbness, weakness, and vertigo.

Allergic: Localized edema and itching.

Fibrotic Complications: (see WARNINGS).

DRUG ABUSE AND DEPENDENCE

There have been reports of drug abuse and psychological dependence in patients on CAFERGOT® (ergotamine tartrate and caffeine) therapy. Due to the chronicity of vascular headaches, it is imperative that patients be advised not to exceed recommended dosages with long-term use to avoid ergotism. *(See PRECAUTIONS)*

OVERDOSAGE

The toxic effects of an acute overdosage of CAFERGOT® (ergotamine tartrate and caffeine) are due primarily to the ergotamine component. The amount of caffeine is such that its toxic effects will be overshadowed by those of ergotamine. Symptoms include vomiting, numbness, tingling, pain and cyanosis of the extremities associated with diminished or absent peripheral pulses; hypertension or hypotension; drowsiness, stupor, coma, convulsions and shock. A case has been reported of reversible bilateral papillitis with ring scotomata in a patient who received five times the recommended daily adult dose over a period of 14 days.

Treatment consists of removal of the offending drug by enema. Maintenance of adequate pulmonary ventilation, correction of hypotension, and control of convulsions and blood pressure are important considerations. Treatment of peripheral vasospasm should consist of warmth, but not heat, and protection of the ischemic limbs. Vasodilators may be beneficial but caution must be exercised to avoid aggravating an already existent hypotension.

DOSAGE AND ADMINISTRATION

Procedure

For best results, dosage should start at the first sign of an attack.

RECTALLY	One suppository at start of attack; second suppository after 1 hour, if needed for full relief 1 hr 

Early Administration Gives Maximum Effectiveness

Maximum Adult Dosage

Rectally

Two suppositories is the maximum dose for an individual attack.

Total weekly dosage should not exceed 5 suppositories. CAFERGOT® (ergotamine tartrate and caffeine) suppositories should not be used for chronic daily administration.

In carefully selected patients, with due consideration of maximum dosage recommendations, administration of the drug at bedtime may be an appropriate short-term preventive measure.

HOW SUPPLIED

CAFERGOT® (ergotamine tartrate and caffeine) Suppositories, USP

Yellowish-white bullet-shaped, cocoa butter base suppositories wrapped in silver colored foil with NOVARTIS CAFERGOT® SUPPOSITORY 78-33 NOVARTIS'' printed in fuchsia.

Boxes of 12 (NDC 0078-0033-02).

Store and Dispense

Below 77°F (25°C); tight container (sealed foil). Protect from moisture.

NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz
6/4/02 09:16:17 AM

APPEARS THIS WAY
ON ORIGINAL

NOVARTIS

October 2002

IMPORTANT
DRUG
WARNING

Dear Health Care Provider

Novartis Pharmaceuticals Corporation would like to inform you of recent changes to the prescribing information (PI) for CAFERGOT® (ergotamine tartrate and caffeine) Suppositories and Tablets, which include a new BOXED WARNING section related to interactions with potent CYP 3A4 inhibitors as follows:

WARNING

Serious and/or life-threatening peripheral ischemia has been associated with the coadministration of CAFERGOT® with potent CYP 3A4 inhibitors including protease inhibitors and macrolide antibiotics. Because CYP 3A4 inhibition elevates the serum levels of CAFERGOT®, the risk for vasospasm leading to cerebral ischemia and/or ischemia of the extremities is increased. Hence, concomitant use of these medications is contraindicated.

Coadministration of ergotamine with potent CYP 3A4 inhibitors (ritonavir, nelfinavir, indinavir, erythromycin, clarithromycin, and troleandomycin) has been associated with acute ergot toxicity (ergotism) characterized by vasospasm and ischemia of the extremities, with some cases resulting in amputation. There have been rare reports of cerebral ischemia in patients on protease inhibitor therapy when Cafergot (ergotamine tartrate and caffeine) was coadministered, at least one resulting in death. Because of the increased risk for ergotism and other serious vasospastic adverse events, ergotamine use is contraindicated with these drugs and other potent inhibitors of CYP 3A4 (e.g., ketoconazole, itraconazole).

The sections CONTRAINDICATIONS, WARNINGS, PRECAUTIONS and CLINICAL PHARMCOLOGY: Pharmacokinetics: Interactions of the PI have been updated accordingly, see the enclosed revised PI of Cafergot (ergotamine tartrate and caffeine) Suppositories and Tablets for complete prescribing information.

Novartis is committed to providing you with the most current product information available for the management of patients receiving Cafergot (ergotamine tartrate and caffeine). You can further our understanding of adverse events by reporting them.

Health care professionals should report all serious adverse events suspected to be associated with use of Cafergot (ergotamine tartrate and caffeine) to Novartis Pharmaceuticals Corporation, One Health Plaza, East Hanover, New Jersey 07936, or phone at (888) 669 – 6682 or the internet at http://www.pharma.us.novartis.com.

Alternatively, this information may be reported to the FDA's MedWatch Reporting System by phone at 1-800-FDA-1088, by fax 1-800-FDA-0178, by mail using the Form 3500 at MedWatch, HF-2, 5600 Fishers Lane, Rockville, MD 20857; or the internet at http://www.accessdata.FDA.gov/scrips/medwatch.

Please see the enclosed revised PI Cafergot (ergotamine tartrate and caffeine) Suppositories and Tablets for complete prescribing information. Current and future patients being treated with Cafergot (ergotamine tartrate and caffeine) should be fully informed of the above information.

Alan L. Bess, M.D.
Vice President
Clinical Safety & Epidemiology

Stephen R. Cunningham, M.D., FRCP, FFPM
Vice President
Medical Affairs

CAFERGOT®

(ergotamine tartrate and caffeine)

SUPPOSITORIES, USP

Rx only

WARNING

Serious and/or life-threatening peripheral ischemia has been associated with the coadministration of CAFERGOT® (ergotamine tartrate and caffeine) with potent CYP 3A4 inhibitors including protease inhibitors and macrolide antibiotics. Because CYP 3A4 inhibition elevates the serum levels of CAFERGOT, the risk for vasospasm leading to cerebral ischemia and/or ischemia of the extremities is increased. Hence, concomitant use of these medications is contraindicated. *(See CONTRAINDICATIONS and WARNINGS.)*

DESCRIPTION

CAFERGOT® (ergotamine tartrate and caffeine) Suppository

ergotamine tartrate USP ..... 2 mg
caffeine USP ..... 100 mg

Inactive Ingredients: cocoa butter NF and tartaric acid NF.

CAFERGOT suppositories are *sealed* in foil to afford protection from cocoa butter leakage. If an unavoidable period of exposure to heat softens the suppository, it should be chilled in ice-cold water to solidify it before removing the foil.

CLINICAL PHARMACOLOGY

Ergotamine is an alpha adrenergic blocking agent with a direct stimulating effect on the smooth muscle of peripheral and cranial blood vessels and produces depression of central vasomotor centers. The compound also has the properties of serotonin antagonism. In comparison to hydrogenated ergotamine, the adrenergic blocking actions are less pronounced and vasoconstrictive actions are greater.

Caffeine, also a cranial vasoconstrictor, is added to further enhance the vasoconstrictive effect without the necessity of increasing ergotamine dosage.

Many migraine patients experience excessive nausea and vomiting during attacks, making it impossible for them to retain any oral medication. In such cases, therefore, the only practical means of medication is through the rectal route where medication may reach the cranial vessels directly, evading the splanchnic vasculature and the liver.

Pharmacokinetics

Interactions

Pharmacokinetic interactions (increased blood levels of ergotamine) have been reported in patients treated orally with ergotamine and macrolide antibiotics (e.g., troleandomycin, clarithromycin, erythromycin), and in patients treated orally with ergotamine and protease inhibitors (e.g., ritonavir) presumably due to inhibition of cytochrome P450 3A metabolism of ergotamine *(see CONTRAINDICATIONS).* Ergotamine has also been shown to be an inhibitor of cytochrome P450 3A catalyzed reactions. No pharmacokinetic interactions involving other cytochrome P450 isoenzymes are known.

INDICATIONS AND USAGE

CAFERGOT® (ergotamine tartrate and caffeine)

Indicated as therapy to abort or prevent vascular headache, e.g., migraine, migraine variants or so-called "histaminic cephalalgia."

CONTRAINDICATIONS

Coadministration of ergotamine with potent CYP 3A4 inhibitors (ritonavir, nelfinavir, indinavir, erythromycin, clarithromycin, and troleandomycin) has been associated with acute ergot toxicity (ergotism) characterized by sc[illegible]nd ischemia of the extremities *(see PRECAUTIONS: Drug Interactions)*, with some cases resulting an[illegible]on. There have been rare reports of cerebral ischemia in patients on protease inhibitor therapy when CAFERGOT® (ergotamine tartrate and caffeine) was coadministered, at least one resulting in death. Because of the increased risk for ergotism and other serious vasospastic adverse events, ergotamine use is contraindicated with these drugs and other potent inhibitors of CYP 3A4 (e.g., ketoconazole, itraconazole) *(see WARNINGS: CYP 3A4 Inhibitors).*

CAFERGOT may cause fetal harm when administered to pregnant women. CAFERGOT is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy or if the patient becomes pregnant while taking this product, the patient should be apprised of the potential hazard to the fetus.

Peripheral vascular disease, coronary heart disease, hypertension, impaired hepatic or renal function and sepsis.

Hypersensitivity to any of the components.

WARNINGS

CYP 3A4 Inhibitors (e.g., Macrolide Antibiotics and Protease Inhibitors)

Coadministration of ergotamine with potent CYP 3A4 inhibitors such as protease inhibitors or macrolide antibiotics has been associated with serious adverse events; for this reason, these drugs should not be given concomitantly with ergotamine *(see CONTRAINDICATIONS).* While these reactions have not been reported with less potent CYP 3A4 inhibitors, there is a potential risk for serious toxicity including vasospasm when these drugs are used with ergotamine. Examples of less potent CYP 3A4 inhibitors include: saquinavir, nefazodone, fluconazole, fluoxetine, grapefruit juice, fluvoxamine, zileuton, metronidazole, and clotrimazole. These lists are not exhaustive, and the prescriber should consider the effects on CYP 3A4 of other agents being considered for concomitant use with ergotamine.

Fibrotic Complications

There have been a few reports of patients on CAFERGOT® (ergotamine tartrate and caffeine) therapy developing retroperitoneal and/or pleuropulmonary fibrosis. There have also been rare reports of fibrotic thickening of the aortic, mitral, tricuspid, and/or pulmonary valves with long-term continuous use of CAFERGOT. CAFERGOT suppositories should not be used for chronic daily administration *(see DOSAGE AND ADMINISTRATION).*

PRECAUTIONS

General

Although signs and symptoms of ergotism rarely develop even after long term intermittent use of the rectally administered drug, care should be exercised to remain within the limits of recommended dosage.

Ergotism is manifested by intense arterial vasoconstriction, producing signs and symptoms of peripheral vascular ischemia. Ergotamine induces vasoconstriction by a direct action on vascular smooth muscle. In chronic intoxication with ergot derivatives, headache, intermittent claudication, muscle pains, numbness, coldness and pallor of the digits may occur. If the condition is allowed to progress untreated, gangrene can result.

While most cases of ergotism associated with ergotamine treatment result from frank overdosage, some cases have involved apparent hypersensitivity. There are few reports of ergotism among patients taking doses within the recommended limits or for brief periods of time. In rare instances, patients, particularly those who have used the medication indiscriminately over long periods of time, may display withdrawal symptoms consisting of rebound headache upon discontinuation of the drug.

There [illegible] of a solitary rectal or anal ulcer have occurred from abuse of ergotamine suppositories usually in higher than recommended doses or with continual use at the recommended dose for many years. Spontaneous healing [illegible]ion usually 4-8 weeks after drug withdrawal.

Information for Patients

Patients should be advised that one suppository of CAFERGOT® (ergotamine tartrate and caffeine) should be taken at the first sign of a migraine headache. No more than 2 suppositories should be taken for any single migraine attack. No more than 5 suppositories should be taken during any 7-day period. Administration of CAFERGOT suppositories should not exceed the dosing guidelines and should not be used for chronic daily administration *(see DOSAGE AND ADMINISTRATION).* CAFERGOT should be used only for migraine headaches. It is not effective for other types of headaches and it lacks analgesic properties. Patients should be advised to report to the physician immediately any of the following: numbness or tingling in the fingers and toes, muscle pain in the arms and legs, weakness in the legs, pain in the chest or temporary speeding or slowing of the heart rate, swelling or itching.

Drug Interactions

CYP 3A4 Inhibitors (e.g., Macrolide Antibiotics and Protease Inhibitors)
(See CONTRAINDICATIONS and WARNINGS.)

CAFERGOT should not be administered with other vasoconstrictors. Use with sympathomimetics (pressor agents) may cause extreme elevation of blood pressure. The beta-blocker Inderal (propranolol) has been reported to potentiate the vasoconstrictive action of CAFERGOT by blocking the vasodilating property of epinephrine. Nicotine may provoke vasoconstriction in some patients, predisposing to a greater ischemic response to ergot therapy.

The blood levels of ergotamine-containing drugs are reported to be elevated by the concomitant administration of macrolide antibiotics and vasospastic reactions have been reported with therapeutic doses of the ergotamine-containing drugs when coadministered with these antibiotics.

Pregnancy

Teratogenic Effects

Pregnancy Category X: There are no studies on the placental transfer or teratogenicity of the combined products of CAFERGOT. Caffeine is known to cross the placenta and has been shown to be teratogenic in animals. Ergotamine crosses the placenta in small amounts, although it does not appear to be embryotoxic in this quantity. However, prolonged vasoconstriction of the uterine vessels and/or increased myometrial tone leading to reduced myometrial and placental blood flow may have contributed to fetal growth retardation observed in animals. *(See CONTRAINDICATIONS.)*

Nonteratogenic Effects

CAFERGOT is contraindicated in pregnancy due to the oxytocic effects of ergotamine. *(See CONTRAINDICATIONS.)*

Labor and Delivery

CAFERGOT is contraindicated in labor and delivery due to its oxytocic effect which is maximal in the third trimester. *(See CONTRAINDICATIONS.)*

Nursing Mothers

Ergot drugs are known to inhibit prolactin but there are no reports of decreased lactation with CAFERGOT. Ergotamine is excreted in breast milk and may cause symptoms of vomiting, diarrhea, weak pulse and unstable blood pressure in nursing infants. Because of the potential for serious adverse reactions in nursing infants from CAFERGOT, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Cardiovascular: Vasoconstrictive complications of a serious nature may occur at times. These include ischemia, cyanosis, absence of pulse, cold extremities, gangrene, precordial distress and pain, EKG changes and muscle pains. Although these effects occur most commonly with long-term therapy at relatively high doses, they have also been reported with short-term or normal doses. Other cardiovascular adverse effects include transient tachycardia or bradycardia and hypertension.

Gastrointestinal: Nausea and vomiting; rectal or anal ulcer (from overuse of suppositories).

Neurological: Paresthesias, numbness, weakness, and vertigo.

Allergic: Localized edema and itching.

Fibrotic Complications: (See WARNINGS.)

DRUG ABUSE AND DEPENDENCE

There have been reports of drug abuse and psychological dependence in patients on CAFERGOT® (ergotamine tartrate and caffeine) therapy. Due to the chronicity of vascular headaches, it is imperative that patients be advised not to exceed recommended dosages with long-term use to avoid ergotism. *(See PRECAUTIONS.)*

OVERDOSAGE

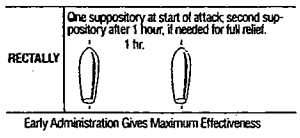
The toxic effects of an acute overdosage of CAFERGOT® (ergotamine tartrate and caffeine) are due primarily to the ergotamine component. The amount of caffeine is such that its toxic effects will be overshadowed by those of ergotamine. Symptoms include vomiting, numbness, tingling, pain and cyanosis of the extremities associated with diminished or absent peripheral pulses; hypertension or hypotension; drowsiness, stupor, coma, convulsions and shock. A case has been reported of reversible bilateral papillitis with ring scotomata in a patient who received five times the recommended daily adult dose over a period of 14 days.

Treatment consists of removal of the offending drug by enema. Maintenance of adequate pulmonary ventilation, correction of hypotension, and control of convulsions and blood pressure are important considerations. Treatment of peripheral vasospasm should consist of warmth, but not heat, and protection of the ischemic limbs. Vasodilators may be beneficial but caution must be exercised to avoid aggravating an already existent hypotension.

DOSAGE AND ADMINISTRATION

Procedure

For the best results, dosage should start at the first sign of an attack.



Early Administration Gives Maximum Effectiveness

Maximum Adult Dosage

Rectally

Two suppositories is the maximum dose for an individual attack.

Total weekly dosage should not exceed 5 suppositories. CAFERGOT® (ergotamine tartrate and caffeine) suppositories should not be used for chronic daily administration.

In carefully selected patients, with due consideration of maximum dosage recommendations, administration of the drug at bedtime may be an appropriate short-term preventive measure.

HOW SUPPLIED

CAFERGOT® (ergotamine tartrate and caffeine) Suppositories, USP

Yellowish-white bullet-shaped, cocoa butter base suppositories wrapped in silver colored foil with "NOVARTIS CAFERGOT® SUPPOSITORY 78-33 NOVARTIS" printed in fuchsia.

Boxes of 12 (NDC 0078-0033-02).

Store and Dispense

Below 77°F (25°C); tight container (sealed foil). Protect from moisture.

REV.: JULY 2002 PRINTED IN USA T2002-68 89000404

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

NOVARTIS

CAFERGOT®

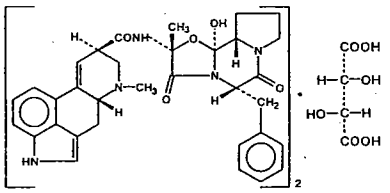
(ergotamine tartrate and caffeine tablets, USP)

℞ only

WARNING: Serious and/or life-threatening peripheral ischemia has been associated with the coadministration of CAFERGOT® with potent CYP 3A4 inhibitors including protease inhibitors and macrolide antibiotics. Because CYP 3A4 inhibition elevates the serum levels of CAFERGOT®, the risk for vasospasm leading to cerebral ischemia and/or ischemia of the extremities is increased. Hence, concomitant use of these medications is contraindicated (see also CONTRAINDICATIONS and WARNINGS section).

DESCRIPTION: Each tablet for oral administration contains 1 mg ergotamine tartrate, USP, and 100 mg caffeine, USP.

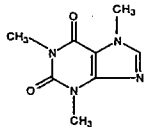
ERGOTAMINE TARTRATE:



$(C_{33}H_{35}N_5O_5)_2 \cdot C_4H_6O_6$ M.W. 1313.43

Ergotaman-3',6',18-trione, 12'-hydroxy-2'-methyl-5'-(phenyl-methyl)-,(5' α)-, [R-(R*,R*)]-2,3-dihydroxy-butanedioate (2:1) (salt).

CAFFEINE:



$C_8H_{10}N_4O_2$ (anhydrous) M.W. 194.19

1*H*-Purine-2,6-dione, 3,7-dihydro-1,3,7-trimethyl-.

Inactive ingredients include acacia, calcium carbonate, compressible sugar, confectioner's sugar (sucrose and corn starch), magnesium stearate, methylparaben, microcrystalline cellulose, povidone, propylparaben, sodium benzoate, sodium starch glycolate, starch (potato), sucrose, synthetic iron oxide, titanium dioxide and other ingredients.

CLINICAL PHARMACOLOGY: Ergotamine is an alpha adrenergic blocking agent with a direct stimulating effect on the smooth muscle of peripheral and cranial blood vessels and produces depression of central vasomotor centers. The compound also has the properties of serotonin antagonism. In comparison to hydrogenated ergotamine, the adrenergic blocking actions are less pronounced and vasoconstrictive actions are greater.

Caffeine, also a cranial vasoconstrictor, is added to further enhance the vasoconstrictive effect without the necessity of increasing ergotamine dosage.

Many migraine patients experience excessive nausea and vomiting during attacks, making it impossible for them to retain any oral medication. In such cases, therefore, the only practical means of medication is through the rectal route where medication may reach the cranial vessels directly, evading the splanchnic vasculature and the liver.

Pharmacokinetics:

Interactions: Pharmacokinetic interactions (increased blood levels of ergotamine) have been reported in patients treated orally with ergotamine and macrolide antibiotics (e.g., troleandomycin, clarithromycin, erythromycin), and in patients treated orally with ergotamine and protease inhibitors (e.g. ritonavir) presumably due to inhibition of cytochrome P450 3A metabolism of ergotamine (see CONTRAINDICATIONS). Ergotamine has also been shown to be an inhibitor of cytochrome P450 3A catalyzed reactions. No pharmacokinetic interactions involving other cytochrome P450 isoenzymes are known.

INDICATIONS AND USAGE: CAFERGOT® (ergotamine tartrate and caffeine tablets, USP) are indicated as therapy to abort or prevent vascular headache, e.g., migraine, migraine variants, or so-called "histaminic cephalalgia".

CONTRAINDICATIONS: Coadministration of ergotamine with potent CYP 3A4 inhibitors (ritonavir, nelfinavir, indinavir, erthromycin, clarithromycin, and troleandomycin) has been associated with acute ergot toxicity (ergotism) characterized by vasospasm and ischemia of the extremities (see PRECAUTIONS: Drug Interactions), with some cases resulting in amputation. There have been rare reports of cerebral ischemia in patients on protease inhibitor therapy when CAFERGOT® (ergotamine tartrate and caffeine tablets, USP) was coadministered, at least one resulting in death. Because of the increased risk for ergotism and other serious vasospastic adverse events, ergotamine use is contraindicated with these drugs and other potent inhibitors of CYP 3A4 (e.g., ketoconazole, itraconazole) (see WARNINGS: CYP 3A4 Inhibitors).

CAFERGOT® (ergotamine tartrate and caffeine tablets, USP) may cause fetal harm when administered to pregnant women. CAFERGOT® (ergotamine tartrate and caffeine tablets, USP) is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy or if the patient becomes pregnant while taking this product, the patient should be apprised of the potential hazard to the fetus.

Peripheral vascular disease, coronary heart disease, hypertension, impaired hepatic or renal function and sepsis.

Hypersensitivity to any of the components.

WARNINGS:

CYP 3A4 Inhibitors (e.g. Macrolide Antibiotics and Protease Inhibitors): Coadministration of ergotamine with potent CYP 3A4 inhibitors such as protease inhibitors or macrolide antibiotics has been associated with serious adverse events; for this reason, these drugs should not be given concomitantly with ergotamine (see CONTRAINDICATIONS). While these reactions have not been reported with less potent CYP 3A4 inhibitors, there is a potential risk for serious toxicity including vasospasm when these drugs are used with ergotamine. Examples of less potent CYP 3A4 inhibitors include: saquinavir, nefazodone, fluconazole, fluoxetine, grapefruit juice, fluvoxamine, zileuton, metronidazole, and clotrimazole. These lists are not exhaustive, and the prescriber should consider the effects on CYP 3A4 of other agents being considered for concomitant use with ergotamine.

PRECAUTIONS:

General: Although signs and symptoms of ergotism rarely develop even after long-term intermittent use of the orally administered drug, care should be exercised to remain within the limits of recommended dosage.

Ergotism is manifested by intense arterial vasoconstriction, producing signs and symptoms of peripheral vascular ischemia. Ergotamine induces vasoconstriction by a direct action on vascular smooth muscle. In chronic intoxication with ergot derivatives, headache, intermittent claudication, muscle pains, numbness, coldness and pallor of the digits may occur. If the condition is allowed to progress untreated, gangrene can result.

While most cases of ergotism associated with ergotamine treatment result from frank overdosage, some cases have involved apparent hypersensitivity. There are few reports of ergotism among patients taking doses within the recommended limits or for brief periods of time. In rare instances, patients, particularly those who have used the medication indiscriminately over long periods of time, may display withdrawal symptoms consisting of rebound headache upon discontinuation of the drug.

Information for Patients: Patients should be advised that two tablets of CAFERGOT® (ergotamine tartrate and caffeine tablets, USP) should be taken at the first sign of a migraine headache. No more than 6 tablets should be taken for any single migraine attack. No more than 10 tablets should be taken during any 7-day period. CAFERGOT® (ergotamine tartrate and caffeine tablets, USP) should be used only for migraine headaches. It is not effective for other types of headaches and it lacks analgesic properties. Patients should be advised to report to the physician immediately any of the following: numbness or tingling in the fingers and toes, muscle pain in the arms and legs, weakness in the legs, pain in the chest or temporary speeding or slowing of the heart rate, swelling or itching.

Drug Interactions:

CYP 3A4 Inhibitors (e.g. Macrolide Antibiotics and Protease Inhibitors): See CONTRAINDICATIONS and WARNINGS.

CAFERGOT® (ergotamine tartrate and caffeine tablets, USP) should not be administered with other vasoconstrictors. Use with sympathomimetics (pressor agents) may cause extreme elevation of blood pressure. The beta-blocker Inderal (propranolol) has been reported to potentiate the vasoconstrictive action of CAFERGOT® (ergotamine tartrate and caffeine tablets, USP) by blocking the vasodilating property of epinephrine. Nicotine may provoke vasoconstriction in some patients, predisposing to a greater ischemic response to ergot therapy.

The blood levels of ergotamine-containing drugs are reported to be elevated by the concomitant administration of macrolide antibiotics and vasospastic reactions have been reported with therapeutic doses of the ergotamine-containing drugs when coadministered with these antibiotics.

Pregnancy:

Teratogenic Effects:

Pregnancy Category X: There are no studies on the placental transfer or teratogenicity of the combined products of CAFERGOT® (ergotamine tartrate and caffeine tablets, USP). Caffeine is known to cross the placenta and has been shown to be teratogenic in animals. Ergotamine crosses the placenta in small amounts, although it does not appear to be embryotoxic in this quantity. However, prolonged vasoconstriction of the uterine vessels and/or increased myometrial tone leading to reduced myometrial and placental blood flow may have contributed to fetal growth retardation observed in animals (see CONTRAINDICATIONS).

Nonteratogenic Effects: CAFERGOT® (ergotamine tartrate and caffeine tablets, USP) is contraindicated in pregnancy due to the oxytocic effects of ergotamine (see CONTRAINDICATIONS).

Labor and Delivery: CAFERGOT® (ergotamine tartrate and caffeine tablets, USP) is contraindicated in labor and delivery due to its oxytocic effect which is maximal in the third trimester (see CONTRAINDICATIONS).

Nursing Mothers: Ergot drugs are known to inhibit prolactin but there are no reports of decreased lactation with CAFERGOT® (ergotamine tartrate and caffeine tablets, USP). Ergotamine is excreted in breast milk and may cause symptoms of vomiting, diarrhea, weak pulse and unstable blood pressure in nursing infants. Because of the potential for serious adverse reactions in nursing infants from CAFERGOT® (ergotamine tartrate and caffeine tablets, USP), a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS:

Cardiovascular: Vasoconstrictive complications of a serious nature may occur at times. These include ischemia, cyanosis, absence of pulse, cold extremities, gangrene, precordial distress and pain, EKG changes and muscle pains. Although these effects occur most commonly with long-term therapy at relatively high doses, they have also been reported with short-term or normal doses. Other cardiovascular adverse effects include transient tachycardia or bradycardia and hypertension.

Gastrointestinal: Nausea and vomiting.

Neurological: paresthesias, numbness, weakness, and vertigo.

Allergic: Localized edema and itching.

DRUG ABUSE AND DEPENDENCE: There have been reports of drug abuse and psychological dependence in patients on CAFERGOT® (ergotamine tartrate and caffeine tablets, USP) therapy. Due to the chronicity of vascular headaches, it is imperative that patients be advised not to exceed recommended dosages with long-term use to avoid ergotism (see PRECAUTIONS).

OVERDOSAGE: The toxic effects of an acute overdosage of CAFERGOT® (ergotamine tartrate and caffeine tablets, USP) are due primarily to the ergotamine component. The amount of caffeine is such that its toxic effects will be overshadowed by those of ergotamine. Symptoms include vomiting, numbness, tingling, pain and cyanosis of the extremities associated with diminished or absent peripheral pulses; hypertension or hypotension; drowsiness, stupor, coma, convulsions and shock. A case has been reported of reversible bilateral papillitis with ring scotomata in a patient who received five times the recommended daily adult dose over a period of 14 days.

Treatment consists of removal of the offending drug by induction of emesis, gastric lavage, and catharsis. Maintenance of adequate pulmonary ventilation, correction of hypotension and control of convulsions and blood pressure are important considerations. Treatment of peripheral vasospasm should consist of warmth, but not heat, and protection of the ischemic limbs. Vasodilators may be beneficial but caution must be exercised to avoid aggravating an already existent hypotension.

DOSAGE AND ADMINISTRATION:

Procedure: For the best results, dosage should start at the first sign of an attack. Adults: Take 2 tablets at the start of attack; 1 additional tablet every 1/2 hour, if needed for full relief (maximum 6 tablets per attack, 10 per week).

Maximum Adult Dosage: Total dose for any one attack should not exceed 6 tablets. In carefully selected patients, with due consideration of maximum dosage recommendations, administration of the drug at bedtime may be an appropriate short-term preventive measure.

HOW SUPPLIED: CAFERGOT® (ergotamine tartrate and caffeine tablets, USP) for oral administration are available as:

1 mg/100 mg: round tablets, sugar coated beige and imprinted CAFERGOT in black ink.

Bottles of 100 . . . . . NDC 0078-0349-05

Store at controlled room temperature 15°-30°C (59°-86°F).

Dispense in a tight, light-resistant container.

Rev. 11-2002M

7229

Manufactured By
Geneva Pharmaceuticals, Inc.
Broomfield, CO 80020

Distributed By
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

9-000/S-022/S-023

MEDICAL OFFICER REVIEW(S)

Review and Evaluation of Clinical Data

NDA (Serial Number)	09-000: SLR-022, SLR-023
Sponsor	Novartis
Drug	Cafergot Suppositories
Material	Proposed Labeling
Correspondence Date	February 20, 2002
Date Received by Agency	February 20, 2002
Date Review Completed	March 7, 2002
Reviewer	Gerald Tremblay, MD

Introduction

Copies of pertinent parts of correspondence that address Cafergot labeling are attached.

Unmarked text is the current labeling. Underlined text is proposed by the Sponsor.

Undisputed Issue: CYP 3A4 Inhibition

The Sponsor agreed to a box warning about CYP 3A4 inhibiting drugs that interact with Cafergot. The new Contraindications and "CYP 3A4 Inhibitors" language in the labeling is essentially the same as that which the Division proposed to the Sponsor last year. The language in the box warning is the Sponsor's; we did not make any proposals as to its content when we told them (in a December 2001 teleconference) that such a warning would be required.

Disputed Issues: Fibrotic Complications and Dose

The Adverse Reactions section of the Cafergot label already mentions "rare reports of fibrotic thickening" of the heart valves "with long-term, continuous use" of Cafergot. In 1999 the Sponsor proposed moving this language to a new Warnings: Fibrotic Complications section. The Adverse Reactions section would cross-reference the latter. The Division agreed, but also wanted to add

[redacted]

With respect to dosage, the current label recommends **two** suppositories is the maximum dose for an individual attack, and the total weekly dosage should not exceed **five** suppositories. There is a Drug Abuse and Dependence section that states that there "have been reports of drug abuse and psychological dependence in patients" on Cafergot, and that "it is imperative that patients be advised not to exceed recommended dosages with long-term use to avoid ergotism. (See PRECAUTIONS)"

CAFERGOT®

(ergotamine tartrate and caffeine)
SUPPOSITORIES, USP

Rx only

(See also CONTRAINDICATIONS and WARNINGS section)

DESCRIPTION

CAFERGOT® (ergotamine tartrate and caffeine) Suppository

ergotamine tartrate USP.....2 mg
caffeine USP.....100 mg

Inactive Ingredients: cocoa butter NF and tartaric acid NF.

CAFERGOT® (ergotamine tartrate and caffeine) suppositories are *sealed* in foil to afford protection from cocoa butter leakage.

If an unavoidable period of exposure to heat softens the suppository, it should be chilled in ice-cold water to solidify it before removing the foil.

CLINICAL PHARMACOLOGY

Ergotamine is an alpha adrenergic blocking agent with a direct stimulating effect on the smooth muscle of peripheral and cranial blood vessels and produces depression of central vasomotor centers. The compound also has the properties of serotonin antagonism. In comparison to hydrogenated ergotamine, the adrenergic blocking actions are less pronounced and vasoconstrictive actions are greater.

Caffeine, also a cranial vasoconstrictor, is added to further enhance the vasoconstrictive effect without the necessity of increasing ergotamine dosage.

Many migraine patients experience excessive nausea and vomiting during attacks, making it impossible for them to retain any oral medication. In such cases, therefore, the only practical means of medication is through the rectal route where medication may reach the cranial vessels directly, evading the splanchnic vasculature and the liver.

Pharmacokinetics: Interactions

Pharmacokinetic interactions (increased blood levels of ergotamine) have been reported in patients treated orally with ergotamine and macrolide antibiotics (e.g., troleandomycin, clarithromycin, erythromycin), and in patients treated orally with ergotamine and protease inhibitors (e.g. ritonavir) presumably due to inhibition of cytochrome P450 3A metabolism of ergotamine *(See CONTRAINDICATIONS)*. Ergotamine has also been shown to be an inhibitor of cytochrome P450 3A catalyzed reactions. No pharmacokinetic interactions involving other cytochrome P450 isoenzymes are known.

INDICATIONS AND USAGE

CAFERGOT® (ergotamine tartrate and caffeine)

Indicated as therapy to abort or prevent vascular headache, e.g., migraine, migraine variants or so-called "histaminic cephalalgia".

CONTRAINDICATIONS

Coadministration of ergotamine with potent CYP 3A4 inhibitors (ritonavir, nelfinavir, indinavir, erythromycin, clarithromycin, and troleandomycin) has been associated with acute ergot toxicity (ergotism) characterized by vasospasm and ischemia of the extremities (see PRECAUTIONS: Drug Interactions), with some cases resulting in amputation. There have been rare reports of cerebral ischemia in patients on protease inhibitor therapy when CAFERGOT® (ergotamine tartrate and caffeine) was coadministered, at least one resulting in death. Because of the increased risk for ergotism and other serious vasospastic adverse events, ergotamine use is contraindicated with these drugs and other potent inhibitors of CYP 3A4 (e.g., ketoconazole, itraconazole) *(see WARNINGS: CYP 3A4 Inhibitors)*.

CAFERGOT® (ergotamine tartrate and caffeine) may cause fetal harm when administered to pregnant women. CAFERGOT® (ergotamine tartrate and caffeine) is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy or if the patient becomes pregnant while taking this product, the patient should be apprised of the potential hazard to the fetus.

Peripheral vascular disease, coronary heart disease, hypertension, impaired hepatic or renal function and sepsis.

Hypersensitivity to any of the components.

WARNINGS

CYP 3A4 Inhibitors (e.g. Macrolide Antibiotics and Protease Inhibitors)

Coadministration of ergotamine with potent CYP 3A4 inhibitors such as protease inhibitors or macrolide antibiotics has been associated with serious adverse events; for this reason, these drug should not be given concomitantly with ergotamine *(See CONTRAINDICATIONS)*. While these reactions have not been reported with less potent CYP 3A4 inhibitors, there is a potential risk for serious toxicity including vasospasm when these drugs are used with ergotamine. Examples of less potent CYP 3A4 inhibitors include: saquinavir, nefazodone, fluconazole, fluoxetine, grapefruit juice, fluvoxamine, zileuton, metronidazole, and clotrimazole. These lists are not exhaustive, and the prescriber should consider the effects on CYP3A4 of other agents being considered for concomitant use with

PRECAUTIONS

General

Although signs and symptoms of ergotism rarely develop even after long term intermittent use of the rectally administered drug, care should be exercised to remain within the limits of recommended dosage.

Ergotism is manifested by intense arterial vasoconstriction, producing signs and symptoms of peripheral vascular ischemia. Ergotamine induces vasoconstriction by a direct action on vascular smooth muscle. In chronic intoxication with ergot derivatives, headache, intermittent claudication, muscle pains, numbness, coldness and pallor of the digits may occur. If the condition is allowed to progress untreated, gangrene can result.

While most cases of ergotism associated with ergotamine treatment result from frank overdosage, some cases have involved apparent hypersensitivity. There are few reports of ergotism among patients taking doses within the recommended limits or for brief periods of time. In rare instances, patients, particularly those who have used the medication indiscriminately over long periods of time, may display withdrawal symptoms consisting of rebound headache upon discontinuation of the drug.

Rare cases of a solitary rectal or anal ulcer have occurred from abuse of ergotamine suppositories usually in higher than recommended doses or with continual use at the recommended dose for many years. Spontaneous healing occurs within usually 4-8 weeks after drug withdrawal.

Information for Patients

Drug Interactions

CYP 3A4 Inhibitors (e.g. Macrolide Antibiotics and Protease Inhibitors)

See CONTRAINDICATIONS and WARNINGS.

CAFERGOT® (ergotamine tartrate and caffeine) should not be administered with other vasoconstrictors. Use with sympathomimetics (pressor agents) may cause extreme elevation of blood pressure. The beta-blocker Inderal (propranolol) has been reported to potentiate the vasoconstrictive action of CAFERGOT® (ergotamine tartrate and caffeine) by blocking the vasodilating property of epinephrine. Nicotine may provoke vasoconstriction in some patients, predisposing to a greater ischemic response to ergot therapy.

The blood levels of ergotamine-containing drugs are reported to be elevated by the concomitant administration of macrolide antibiotics and vasospastic reactions have been reported with therapeutic doses of the ergotamine-containing drugs when coadministered with these antibiotics.

Pregnancy

Teratogenic Effects

Pregnancy Category X: There are no studies on the placental transfer or teratogenicity of the combined products of CAFERGOT® (ergotamine tartrate and caffeine). Caffeine is known to cross the placenta and has been shown to be teratogenic in animals. Ergotamine crosses the placenta in small amounts, although it does not appear to be embryotoxic in this quantity. However, prolonged vasoconstriction of the uterine vessels and/or increased myometrial tone leading to reduced myometrial and placental blood flow may have contributed to fetal growth retardation observed in animals. *(See CONTRAINDICATIONS)*

Nonteratogenic Effects

CAFERGOT® (ergotamine tartrate and caffeine) is contraindicated in pregnancy due to the oxytocic effects of ergotamine. *(See CONTRAINDICATIONS)*

Labor and Delivery

CAFERGOT® (ergotamine tartrate and caffeine) is contraindicated in labor and delivery due to its oxytocic effect which is maximal in the third trimester. *(See CONTRAINDICATIONS)*

Nursing Mothers

Ergot drugs are known to inhibit prolactin but there are no reports of decreased lactation with CAFERGOT® (ergotamine tartrate and caffeine). Ergotamine is excreted in breast milk and may cause symptoms of vomiting, diarrhea, weak pulse and unstable blood pressure in nursing infants. Because of the potential for serious adverse reactions in nursing infants from CAFERGOT® (ergotamine tartrate and caffeine), a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Cardiovascular: Vasoconstrictive complications of a serious nature may occur at times. These include ischemia, cyanosis, absence of pulse, cold extremities, gangrene, precordial distress and pain, EKG changes and muscle pains. Although these effects occur most commonly with long-term therapy at relatively high doses, they have also been reported with short-term or normal doses. Other cardiovascular adverse effects include transient tachycardia or bradycardia and hypertension.

Gastrointestinal: Nausea and vomiting; rectal or anal ulcer (from overuse of suppositories).

Neurological: paresthesias, numbness, weakness, and vertigo.

Allergic: Localized edema and itching.

DRUG ABUSE AND DEPENDENCE

There have been reports of drug abuse and psychological dependence in patients on CAFERGOT® (ergotamine tartrate and caffeine) therapy. Due to the chronicity of vascular headaches, it is imperative that patients be advised not to exceed recommended dosages with long-term use to avoid ergotism. *(See PRECAUTIONS)*

OVERDOSAGE

The toxic effects of an acute overdosage of CAFERGOT® (ergotamine tartrate and caffeine) are due primarily to the ergotamine component. The amount of caffeine is such that its toxic effects will be overshadowed by those of ergotamine. Symptoms include vomiting, numbness, tingling, pain and cyanosis of the extremities associated with diminished or absent peripheral pulses; hypertension or hypotension; drowsiness, stupor, coma, convulsions and shock. A case has been reported of reversible bilateral papillitis with ring scotomata in a patient who received five times the recommended daily adult dose over a period of 14 days.

Treatment consists of removal of the offending drug by enema. Maintenance of adequate pulmonary ventilation, correction of hypotension, and control of convulsions and blood pressure are important considerations. Treatment of peripheral vasospasm should consist of warmth, but not heat, and protection of the ischemic limbs. Vasodilators may be beneficial but caution must be exercised to avoid aggravating an already existent hypotension.

DOSAGE AND ADMINISTRATION

Procedure

For best results, dosage should start at the first sign of an attack.

RECTALLY	One suppository at start of attack; second suppository after 1 hour, if needed for full relief 1 hr 

Early Aministration Gives Maximum Effectiveness

Maximum Adult Dosage

Rectally

HOW SUPPLIED

CAFERGOT® (ergotamine tartrate and caffeine) Suppositories, USP

Yellowish-white bullet-shaped, cocoa butter base suppositories wrapped in silver colored foil with NOVARTIS CAFERGOT® SUPPOSITORY 78-33 NOVARTIS'' printed in fuchsia.

Boxes of 12 (NDC 0078-0033-02).

Store and Dispense

Below 77°F (25°C); tight container (sealed foil). Protect from moisture.

Comment & Recommendation

Given the critical importance of the CYP 3A4 inhibitor-interaction warning to public health, and the large number of generic manufacturers affected, I recommend that the remaining areas of

disagreement be resolved in Sponsor's favor, and that their version of Cafergot labeling be approved. The remaining areas of dispute are too minor to warrant further delay.

Gerald Tremblay, MD

Medical Officer, HFD-120

Armando Oliva, MD

Team Leader, HFD-120

cc: HFD-120

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Gerald Tremblay
3/11/02 02:24:18 PM
MEDICAL OFFICER

Armando Oliva
3/13/02 10:16:37 AM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

Review and Evaluation of Clinical Data

NDA (Serial Number)	09-000: SLR-022, SLR-023
Sponsor	Novartis
Drug	Cafergot Suppositories
Material	Proposed Labeling
Correspondence Date	April 16, 2002
Date Received by Agency	April 16, 2002
Date Review Completed	April 29, 2002
Reviewer	Gerald Tremblay, MD

Introduction and Summary of Labeling Changes

The purpose of the recommended labeling changes for Cafergot Suppositories is to warn of the risks of coadministration of Cafergot with CYP 3A4 inhibitors, the risk of fibrotic complications (e.g., of the heart valves), and to warn against chronic daily administration. On March 25, 2002, the Division sent Sponsor a facsimile that stated that their previously proposed labeling changes were generally acceptable, but that additional changes were recommended. These recommended additional changes included:

1. Changing the black box warning so that it describes what is known to have occurred with the use of Cafergot rather than what might occur. Specific language was recommended. Sponsor adopted the recommended language verbatim.
2. A Fibrotic Complications paragraph with specific wording was recommended to be added to the Warnings section. Sponsor adopted the recommendation verbatim.
3. In the Information for Patients section the Division recommended a sentence stating that the use of Cafergot should not exceed the dosing guidelines and should not be used for chronic daily administration. Sponsor incorporated this recommendation verbatim in the Information for Patients section.
4. It was recommended that the Adverse Reactions: Fibrotic Complications section be amended to refer the reader to the Warning section (which now has a Fibrotic Complications heading and paragraph). Sponsor has incorporated this recommendation.
5. The Sponsor corrected a typographical error (i.e., the spelling of "Administration" in the Dosage and Administration section, under the illustration of the suppositories).
6. The latter section has also been changed, as the Division recommended, to include another statement that the drug should not be used for chronic daily administration. The Sponsor adopted the recommended sentence verbatim.
7. The Sponsor corrected a mistaken use of the word '[redacted]' instead of the correct word, "ergotamine," in the Division's recommended CYP 3A4 paragraph of the Warnings section.

Below is the final proposed labeling submitted by the Sponsor on April 16, 2002. It incorporates the changes listed above. The new text that is not present in the current labeling is underlined. Text that has been deleted from the current labeling is marked with a ~~strikethough~~.

NOVARTIS

T2001-27
89000402

CAFERGOT®

(ergotamine tartrate and caffeine)
SUPPOSITORIES, USP

Rx only

WARNING

Serious and/or life-threatening peripheral ischemia has been associated with the coadministration of CAFERGOT® with potent CYP 3A4 inhibitors including protease inhibitors and macrolide antibiotics. Because CYP 3A4 inhibition elevates the serum levels of CAFERGOT®, the risk for vasospasm leading to cerebral ischemia and/or ischemia of the extremities is increased. Hence, concomitant use of these medications is contraindicated.

(See also CONTRAINDICATIONS and WARNINGS section)

DESCRIPTION

CAFERGOT® (ergotamine tartrate and caffeine) Suppository

ergotamine tartrate USP.....2 mg
caffeine USP .....100 mg

Inactive Ingredients: cocoa butter NF and tartaric acid NF.

CAFERGOT® (ergotamine tartrate and caffeine) suppositories are *sealed* in foil to afford protection from cocoa butter leakage.

If an unavoidable period of exposure to heat softens the suppository, it should be chilled in ice-cold water to solidify it before removing the foil.

CLINICAL PHARMACOLOGY

Ergotamine is an alpha adrenergic blocking agent with a direct stimulating effect on the smooth muscle of peripheral and cranial blood vessels and produces depression of central

vasomotor centers. The compound also has the properties of serotonin antagonism. In comparison to hydrogenated ergotamine, the adrenergic blocking actions are less pronounced and vasoconstrictive actions are greater.

Caffeine, also a cranial vasoconstrictor, is added to further enhance the vasoconstrictive effect without the necessity of increasing ergotamine dosage.

Many migraine patients experience excessive nausea and vomiting during attacks, making it impossible for them to retain any oral medication. In such cases, therefore, the only practical means of medication is through the rectal route where medication may reach the cranial vessels directly, evading the splanchnic vasculature and the liver.

Pharmacokinetics: Interactions

Pharmacokinetic interactions (increased blood levels of ergotamine) have been reported in patients treated orally with ergotamine and macrolide antibiotics (e.g., troleandomycin, clarithromycin, erythromycin), and in patients treated orally with ergotamine and protease inhibitors (e.g. ritonavir) presumably due to inhibition of cytochrome P450 3A metabolism of ergotamine *(See CONTRAINDICATIONS).* Ergotamine has also been shown to be an inhibitor of cytochrome P450 3A catalyzed reactions. No pharmacokinetic interactions involving other cytochrome P450 isoenzymes are known.

INDICATIONS AND USAGE

CAFERGOT® (ergotamine tartrate and caffeine)

Indicated as therapy to abort or prevent vascular headache, e.g., migraine, migraine variants or so-called "histaminic cephalalgia''.

CONTRAINDICATIONS

Coadministration of ergotamine with potent CYP 3A4 inhibitors (ritonavir, nelfinavir, indinavir, erythromycin, clarithromycin, and troleandomycin) has been associated with acute ergot toxicity (ergotism) characterized by vasospasm and ischemia of the extremities (see PRECAUTIONS: Drug Interactions), with some cases resulting in amputation. There have been rare reports of cerebral ischemia in patients on protease inhibitor therapy when CAFERGOT® (ergotamine tartrate and caffeine) was coadministered, at least one resulting in death. Because of the increased risk for ergotism and other serious vasospastic adverse events, ergotamine use is contraindicated with these drugs and other potent inhibitors of CYP 3A4 (e.g., ketoconazole, itraconazole) *(see WARNINGS: CYP 3A4 Inhibitors).*

CAFERGOT® (ergotamine tartrate and caffeine) may cause fetal harm when administered to pregnant women. CAFERGOT® (ergotamine tartrate and caffeine) is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy or if the patient becomes pregnant while taking this product, the patient should be apprised of the potential hazard to the fetus.

Peripheral vascular disease, coronary heart disease, hypertension, impaired hepatic or renal function and sepsis.

Hypersensitivity to any of the components.

WARNINGS

CYP 3A4 Inhibitors (e.g. Macrolide Antibiotics and Protease Inhibitors)

Coadministration of ergotamine with potent CYP 3A4 inhibitors such as protease inhibitors or macrolide antibiotics has been associated with serious adverse events; for this reason, these drugs should not be given concomitantly with ergotamine *(See CONTRAINDICATIONS).* While these reactions have not been reported with less potent CYP 3A4 inhibitors, there is a potential risk for serious toxicity including vasospasm when these drugs are used with ergotamine. Examples of less potent CYP 3A4 inhibitors include: saquinavir, nefazodone, fluconazole, fluoxetine, grapefruit juice, fluvoxamine, zileuton, metronidazole, and clotrimazole. These lists are not exhaustive, and the prescriber should consider the effects on CYP3A4 of other agents being considered for concomitant use with ergotamine.

Fibrotic Complications:

There have been a few reports of patients on CAFERGOT® (ergotamine tartrate and caffeine) therapy developing retroperitoneal and/or pleuropulmonary fibrosis. There have also been rare reports of fibrotic thickening of the aortic, mitral, tricuspid, and/or pulmonary valves with long-term continuous use of CAFERGOT® (ergotamine tartrate and caffeine). CAFERGOT® (ergotamine tartrate and caffeine) suppositories should not be used for chronic daily administration (see DOSAGE AND ADMINISTRATION).

PRECAUTIONS

General

Although signs and symptoms of ergotism rarely develop even after long term intermittent use of the rectally administered drug, care should be exercised to remain within the limits of recommended dosage.

Ergotism is manifested by intense arterial vasoconstriction, producing signs and symptoms of peripheral vascular ischemia. Ergotamine induces vasoconstriction by a direct action on vascular smooth muscle. In chronic intoxication with ergot derivatives, headache, intermittent claudication, muscle pains, numbness, coldness and pallor of the digits may occur. If the condition is allowed to progress untreated, gangrene can result.

While most cases of ergotism associated with ergotamine treatment result from frank overdosage, some cases have involved apparent hypersensitivity. There are few reports of ergotism among patients taking doses within the recommended limits or for brief periods of time. In rare instances, patients, particularly those who have used the medication indiscriminately over long periods of time, may display withdrawal symptoms consisting of rebound headache upon discontinuation of the drug.

Rare cases of a solitary rectal or anal ulcer have occurred from abuse of ergotamine suppositories usually in higher than recommended doses or with continual use at the recommended dose for many years. Spontaneous healing occurs within usually 4-8 weeks after drug withdrawal.

Information for Patients

Patients should be advised that one suppository of CAFERGOT® (ergotamine tartrate and caffeine) should be taken at the first sign of a migraine headache. No more than 2 suppositories should be taken for any single migraine attack. No more than 5 suppositories should be taken during any 7-day period. Administration of CAFERGOT® (ergotamine tartrate and caffeine) suppositories should not exceed the dosing guidelines and should not be used for chronic daily administration (see DOSAGE AND ADMINISTRATION). CAFERGOT® (ergotamine tartrate and caffeine) should be used only for migraine headaches. It is not effective for other types of headaches and it lacks analgesic properties. Patients should be advised to report to the physician immediately any of the following: numbness or tingling in the fingers and toes, muscle pain in the arms and legs, weakness in the legs, pain in the chest or temporary speeding or slowing of the heart rate, swelling or itching.

Drug Interactions

CYP 3A4 Inhibitors (e.g. Macrolide Antibiotics and Protease Inhibitors)

See CONTRAINDICATIONS and WARNINGS.

CAFERGOT® (ergotamine tartrate and caffeine) should not be administered with other vasoconstrictors. Use with sympathomimetics (pressor agents) may cause extreme elevation of blood pressure. The beta-blocker Inderal (propranolol) has been reported to potentiate the vasoconstrictive action of CAFERGOT® (ergotamine tartrate and caffeine) by blocking the vasodilating property of epinephrine. Nicotine may provoke vasoconstriction in some patients, predisposing to a greater ischemic response to ergot therapy.

The blood levels of ergotamine-containing drugs are reported to be elevated by the concomitant administration of macrolide antibiotics and vasospastic reactions have been reported with therapeutic doses of the ergotamine-containing drugs when coadministered with these antibiotics.

Pregnancy

Teratogenic Effects

Pregnancy Category X: There are no studies on the placental transfer or teratogenicity of the combined products of CAFERGOT® (ergotamine tartrate and caffeine). Caffeine is known to cross the placenta and has been shown to be teratogenic in animals. Ergotamine crosses the placenta in small amounts, although it does not appear to be embryotoxic in this quantity. However, prolonged vasoconstriction of the uterine vessels and/or increased myometrial tone leading to reduced myometrial and placental blood flow may have contributed to fetal growth retardation observed in animals. *(See CONTRAINDICATIONS)*

Nonteratogenic Effects

CAFERGOT® (ergotamine tartrate and caffeine) is contraindicated in pregnancy due to the oxytocic effects of ergotamine. *(See CONTRAINDICATIONS)*

Labor and Delivery

CAFERGOT® (ergotamine tartrate and caffeine) is contraindicated in labor and delivery due to its oxytocic effect which is maximal in the third trimester. *(See CONTRAINDICATIONS)*

Nursing Mothers

Ergot drugs are known to inhibit prolactin but there are no reports of decreased lactation with CAFERGOT® (ergotamine tartrate and caffeine). Ergotamine is excreted in breast milk and may cause symptoms of vomiting, diarrhea, weak pulse and unstable blood pressure in nursing infants. Because of the potential for serious adverse reactions in nursing infants from CAFERGOT® (ergotamine tartrate and caffeine), a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Cardiovascular: Vasoconstrictive complications of a serious nature may occur at times. These include ischemia, cyanosis, absence of pulse, cold extremities, gangrene, precordial distress and pain, EKG changes and muscle pains. Although these effects occur most commonly with long-term therapy at relatively high doses, they have also been reported with short-term or normal doses. Other cardiovascular adverse effects include transient tachycardia or bradycardia and hypertension.

Gastrointestinal: Nausea and vomiting; rectal or anal ulcer (from overuse of suppositories).

Neurological: paresthesias, numbness, weakness, and vertigo.

Allergic: Localized edema and itching.
Fibrotic Complications: see WARNINGS.

DRUG ABUSE AND DEPENDENCE

There have been reports of drug abuse and psychological dependence in patients on CAFERGOT® (ergotamine tartrate and caffeine) therapy. Due to the chronicity of vascular

headaches, it is imperative that patients be advised not to exceed recommended dosages with long-term use to avoid ergotism. *(See PRECAUTIONS)*

OVERDOSAGE

The toxic effects of an acute overdosage of CAFERGOT® (ergotamine tartrate and caffeine) are due primarily to the ergotamine component. The amount of caffeine is such that its toxic effects will be overshadowed by those of ergotamine. Symptoms include vomiting, numbness, tingling, pain and cyanosis of the extremities associated with diminished or absent peripheral pulses; hypertension or hypotension; drowsiness, stupor, coma, convulsions and shock. A case has been reported of reversible bilateral papillitis with ring scotomata in a patient who received five times the recommended daily adult dose over a period of 14 days.

Treatment consists of removal of the offending drug by enema. Maintenance of adequate pulmonary ventilation, correction of hypotension, and control of convulsions and blood pressure are important considerations. Treatment of peripheral vasospasm should consist of warmth, but not heat, and protection of the ischemic limbs. Vasodilators may be beneficial but caution must be exercised to avoid aggravating an already existent hypotension.

DOSAGE AND ADMINISTRATION

Procedure

For best results, dosage should start at the first sign of an attack.

RECTALLY	One suppository at start of attack; second suppository after 1 hour, if needed for full relief 1 hr 

Early ~~Aministration~~ ⟵ Gives Maximum Effectiveness

Maximum Adult Dosage

Rectally

Two suppositories is the maximum dose for an individual attack.
Total weekly dosage should not exceed 5 suppositories. CAFERGOT® (ergotamine tartrate and caffeine) suppositories should not be used for chronic daily administration.

In carefully selected patients, with due consideration of maximum dosage recommendations, administration of the drug at bedtime may be an appropriate short-term preventive measure.

HOW SUPPLIED

CAFERGOT® (ergotamine tartrate and caffeine) Suppositories, USP

Yellowish-white bullet-shaped, cocoa butter base suppositories wrapped in silver colored foil with NOVARTIS CAFERGOT® SUPPOSITORY 78-33 NOVARTIS'' printed in fuchsia.

Boxes of 12 (NDC 0078-0033-02).

Store and Dispense

Below 77°F (25°C); tight container (sealed foil). Protect from moisture.

NOVARTIS
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

T2001-27
REV: APRIL 2001 PRINTED IN USA 89000402

Comment

The Sponsor has adopted the recommended changes to the Cafergot labeling essentially verbatim. Minor editorial corrections have been made that are not substantive. A "Dear Doctor Letter" is currently being written by the Sponsor. It will alert prescribers to these labeling changes.

Recommendation

I recommend the Sponsor's final proposed labeling (above) be approved. There are no comments to convey to the Sponsor.

Gerald Tremblay, MD

Medical Officer, DNDP, HFD-120

Armando Oliva, MD

Team Leader, DNDP, HFD-120

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Gerald Tremblay
4/30/02 12:16:27 PM
MEDICAL OFFICER

Armando Oliva
5/7/02 11:17:29 AM
MEDICAL OFFICER

Review and Evaluation of Clinical Data

NDA	**05-929, 09-000, 20-148**
Sponsor:	**Novartis**
Drug:	**Ergotamine & dihydroergotamine**
Proposed Indication:	**Migraine**
Material Submitted:	**Adverse Event Reports**
Correspondence Date:	**10/17/01**
Date Received / Agency:	**10/17/01**
Date Review Completed	**12/14/01**
Reviewer:	**Gerald Tremblay, MD**

1. Introduction

"Because the ergot peptide alkaloids have such a low oral bioavailability (Fpo <5%), blockade of even one of their major metabolic pathways would be likely to produce a several fold increase in the ergot parent substance in biological fluids, tantamount to a quite sizeable ergotamine or dihydroergotamine overdose."[1] Both drugs are metabolized via the CYP 3A4 pathway.[2]

The Division is currently aware of at least 30 serious cases of ergotism caused by CYP 3A4 inhibition. In each case the patient was taking either a protease inhibitor or a macrolide antibiotic (CYP 3A4 inhibitors) and then took either ergotamine tartrate or dihydroergotamine. Five cases resulted in amputations, two patients had strokes, one had a myocardial infarction, and one died from global cerebral ischemia. These cases are detailed in a consultation by Lauren Lee, Pharm.D, dated 11/12/01 and available in DFS on 12/10/01.

The Division wrote to Novartis on 6/29/01 and proposed changes to labeling for Cafergot Suppositories, DHE 45, and Migranal Nasal Spray. The labeling changes were intended to inform users of the risk of cardiac valvular fibrosis and of the risk of CYP 3A4 inhibitor interactions. Novartis has not responded to the 6/29/01 proposal yet.

With respect to the CYP 3A4 inhibitor interactions, the proposed language in the 6/29/01 letter cited a potential risk of ergotism in the Precautions section of the dihydroergotamine (DHE 45 and Migranal) labels, but added "no reports of serious adverse events in connection with the coadministration of dihydroergotamine and potent CYP 3A4 inhibitors" had been seen. This language does not reflect our current knowledge, however. Four of the 30 cases cited above involved dihydroergotamine, and one of them had a stroke.

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[1] MJ Eadie, Clinically Significant Drug Interactions with Agents Specific for Migraine Attacks, *CNS Drugs* 15(2)105-118, 2001.

[2] Id. at 108; See also, AS Moubarak and CF Rosenkrans, Jr., Hepatic metabolism of ergot alkaloids in beef cattle by cytochrome P450, *Biochem Biophys Res Commun* 274(3):746-749, 2000 (providing evidence that, like dihydroergotamine, ergotamine is likely also to be metabolized by the CYP 3A4 system.)

The proposed language for ergotamine tartrate (Cafergot Suppositories) was stronger than that proposed for dihydroergotamine. At the time, there were known cases of gangrene and amputations in patients from coadministration of Cafergot and either macrolides or protease inhibitors. The labeling that the Division suggested to Novartis in June, 2001, would have contraindicated Cafergot in patients taking CYP 3A4 inhibitors and the proposed Warning section emphasized the hazardous interaction. Since the time of these initial labeling suggestions, cases involving stroke and death from ergotism have come to the Division's attention.

Besides the growing awareness of serious AEs caused by ergots taken with CYP 3A4 inhibitors, there is an inconsistency among the labels for the relevant groups of drugs. Protease inhibitor and macrolide labeling, for example, state that coadministration of either ergotamine or dihydroergotamine is contraindicated. Ritonivir has a "black box" warning to this effect. Ergot labeling, in contrast, contains no such warning.

2. Comments

The OPDRA consultation by Lauren Lee, Pharm.D., provides more detail on the cases cited here. OPDRA recommended the labeling for ergotamine and dihydroergotamine "be revised to reflect the potential for this interaction [with CYP 3A4 inhibitors] and the possibility of serious adverse events..."

The Division agrees with OPDRA. We believe that the labeling for all ergotamine and dihydroergotamine preparations should warn that the coadministration of these drugs with CYP 3A4 inhibitors is contraindicated. The need for a "black box" warning is supported by: the gravity of harm; the number of reported events; the widespread, chronic use of protease inhibitors; the existence of effective alternatives to ergots; and the high probability of causation. We told Novartis by telephone on 12/6/01 that a boxed warning is required, and that they should provide us with draft labeling within a week.

Although not the subject of this review or the telephone conference, we reminded Novartis also that the revised labels must address the risk of cardiac valvular fibrosis. (See Armando Oliva's review of this subject dated 3/22/01).

Because there are many generic versions of the ergots, especially ergotamine, the Office of Generic Drugs should notify all manufacturers of the need for the same labeling changes that Novartis is making.

Gerald Tremblay, M.D.
Medical Reviewer

Armando Oliva, M.D.
Team Leader _____

12/14/01
cc:
HFD-120
NDA 05-929, 09-000, 20-148

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Gerald Tremblay
12/14/01 03:24:26 PM
MEDICAL OFFICER

The agreement with OPDRA is added; This document linked to 3 different NDAs, each of which has several labeling supps. --jt

Armando Oliva
12/17/01 10:56:39 AM
MEDICAL OFFICER

Review and Evaluation of Clinical Data

NDA (Serial Number)	**5-929, 9-000, 20-148** **[5-929: SLR-032, SLR-033]** **[9-000: SLR-022, SLR-023]** **[20-148: SLR-007, SLR-008]**
Sponsor:	**Novartis**
Drug:	**DHE 45, Cafergot suppos., Migranal**
Proposed Indication:	**migraine**
Material Submitted:	**Labeling Supplement**
Correspondence Date:	**7/7/00**
Date Received / Agency:	**7/10/00**
Date Review Completed	**3/22/01**
Reviewer:	**Armando Oliva, MD**

1. Introduction

This submission contains the sponsor's proposed changes to product labeling for DHE 45, Cafergot suppositories, and Migranal nasal spray. This submission is the most recent in a series of lengthy negotiations between the Agency and the sponsor. Our goal is to strengthen the labeling for these products with regard to drug interactions with CYP 3A4 inhibitors and the potential risk of cardiac valvular fibrosis associated with prolonged chronic daily use.

On 10/8/99, the sponsor submitted draft labeling. These only included mention of the CYP3A4 interaction.

1.1 Cardiac Valvulopathy

On 10/20/99, we met with the sponsor to discuss labeling changes to these products. I have reviewed the FDA meeting minutes. We requested that the sponsor incorporate, for all ergotamine products, appropriate warnings for cardiac valvular changes based on the potential of these events with drugs of this class (ergot alkaloids). During the meeting, I recall that we discussed the 4 known cases of cardiac valvular fibrosis associated with dihydroergotamine (the fifth was merely and inquiry). These are listed below (taken from sponsor's slides of their presentation):

- USA/76/00531/DHE Heart Valve Disorder
  Long-term Sansert use. Heart valve disorder began while on Sansert
- USA/87/000338/DHE Mitral Valve Insufficiency
  Not a case, but rather a physician inquiry regarding any effect of DHE on heart valves or contractility
- USA/97/00265/DHE Endocardial Fibrosis
  Previous treatment with other ergot containing products
- USA/99/00843/DHE Mitral Valve Regurgitation[1]
  Treated with Redux, pending litigation

[1] This is the case made known to me by an independent source prior to the meeting.

- European Case
  Oral DHE with 30 years of daily use.

The sponsor asserts that Dr. Temple did not feel that any of the cases reported thus far were compelling enough to implicate DHE is a potential cause of this complication in labeling.[2] However, because DHE is a member of the class of ergot alkaloids, other members of which are associated with this complication, we felt it was necessary to include this information in labeling.

1.2 CYP3A4 Inhibition

Although the exact metabolic pathways of ergotamine are not known, isolated post-marketing reports strongly suggest that CYP3A4 is a prominent metabolic pathway. We also requested that potential interactions with CYP3A4 inhibitors should be prominently displayed in labeling, specifically in the contraindications section. We stated that pharmacokinetic studies may be needed to determine which drugs are potent inhibitors.

We agreed to provide a formal response to their 10/8/99 submission. We conveyed our response via fax on 2/9/00 (see Appendix A - page 16). The sponsor agreed to provide data to support the statement that ergotamine and dihydroergotamine are themselves CYP3A4 inhibitors.

This submission contains the sponsor's response to the 2/9/00 fax and to the comments made at the 10/8/99 meeting. In the response, the sponsor states that the proposed FDA labeling changes do not properly reflect the comments exchanged during the 10/20/99 meeting.

2. Sponsor's Comments to FDA Labeling Proposal

2.1 DHE 45 and Migranal Nasal Spray

2.1.1 Fibrotic Complications

The current labeling for these two products contains a statement in the adverse events section, postmarketing reports that retroperitoneal and pleural fibrosis have been reported following long-term use of DHE.

The sponsor proposed a statement in the Precautions/General section that reports of pleural and retroperitoneal fibrosis have been reported following prolonged daily use of injectable DHE.

The FDA proposed (in the 2/9/00 fax), new language in Warnings (under a new subsection "Fibrotic Complications") which included mention of pleural and retroperitoneal fibrosis, and the possibility of cardiac valvular fibrosis because reports of this event with other ergot alkaloids. We proposed a "fibrotic complications" section in Adverse Events, and adding a cross-reference to Warnings in the Dosage and Administration section.

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[2] This is also my recollection of the meeting.

The sponsor reminds us that, in the 10/20/99 meeting, they reported that their review of the world-wide safety database and over 50 years of marketing experience revealed only 4 cases of cardiac valvular changes in patients receiving DHE and that three of the four cases involved co-medications labeled for valvular changes. All of these lacked sufficient information regarding the patient's medical histories. There was one case of valvular changes in a patient who had taken DHE 45 oral tablets (available only in Europe) on a daily basis for 30 years. There were no reported cases of cardiac valve changes for Migranal Nasal Spray, which has been marketed in some European countries since 1987.

The sponsor believes there is insufficient evidence to conclude that DHE may cause cardiac valvular fibrosis. Therefore, they respectfully submit that any reference to this complication be removed from DHE and Migranal be removed and that their proposal be accepted instead, "as agreed upon at the October 20 meeting."[3]

2.1.2 Dosage

In the dosage and administration section, the sponsor points out the dosing limits that are already in place in both labels. In addition, the recommendation not to exceed recommended limits are already described in Drug Abuse and Dependence and Overdosage sections of labeling. In their 10/20/99 proposal, the sponsor recommended changes to Precautions/General, Information For Patients, and Dosage and Administration. They added the statement in each section that DHE 45/Migranal should not be used for chronic daily administration.

In our 2/9/00 fax, we recommended adding a statement in Warnings/Fibrotic Complications section that DHE/Migranal are not for prolonged daily use (with a reference to the dosage and administration section). We also added statements in

The sponsor still prefers their wording over ours. They believe there is no justification, based on clinical and post-dosing experience, to limit dosing to two headaches per week. In their view, the relevant criterion is not the weekly number of headaches treated, but the weekly total dosage, as reflected in current label.[4]

2.1.3 CYP3A4 Interaction

The DHE/Migranal labeling already includes an interaction with macrolide antibiotics (troleandomycin) in the clinical pharmacology/pharmacokinetics section and in the Precautions/Drug Interactions section.

In the 10/8/99 proposal, the sponsor suggested adding additional macrolide antibiotics to the list (clarithromycin, erythromycin), and adding protease inhibitors (ritonavir and indinavir).

---

[3] I don't recall making this agreement at that meeting, but our minutes are silent on this particular issue.
[4] This is an arguable point, as there is, to my knowledge, no data to support either argument. Upon reconsideration of this issue, I believe the sponsor's proposed text for dosage instructions is acceptable.

In our 2/9/00 fax, we proposed expanding the list to include other CYP3A4 inhibitors. In the clinical pharmacology section, we added, in parenthesis "increased blood levels of ergotamine." The sponsor generally agrees with our changes, although points out that this latter sentence is incorrect and should be deleted. Also, they point out that the reported interactions involve other ergot alkaloids and macrolide antibiotics.[5] Finally, they believe the proposed list of CYP3A4 inhibitors be modified to include just the potent ones. Therefore, they propose the following new labeling to DHE/Migranal labeling:

Clinical Pharmacology
Pharmacokinetics: Interactions

[

]

Precautions

[

]

2.2 Cafergot Suppositories

2.2.1 Fibrotic Complications

The current label includes a statement in the Adverse Reactions section of a few reports of retroperitoneal, pleuropulmonary fibrosis, and rare reports of fibrotic thickening of the cardiac valves with long-term continuous use of Cafergot.

On 12/22/99, the sponsor recommended moving this section to a new Warnings/Fibrotic Complications section, and maintaining a reference in adverse reactions to this new Warnings section.

[

]

[5] I believe this last statement is correct. Charlene Flowers, in OPDRA, was unable to find any cases directly involving DHE and macrolide antibiotics.

[ ]

2.2.2 Dosage

The current text limits treatment to two suppositories for one attack and a maximum of 5 suppositories in one week. The overdosage and drug abuse and dependence section already warn against exceeding the recommended dosage

On 12/22/99, the sponsor recommended adding a statement in Warnings and in the Precautions/Patient Information sections that Cafergot should not be used for chronic daily administration, and has a reference to the dosage and administration section. The dosage and administration section also contains the statement that "Cafergot suppositories should not be used for chronic daily administration."

[ ]

2.2.3 CYP3A4 Interactions

The current label contains text in the Precautions/Drug Interactions section to indicate that blood levels of ergotamine have been elevated by the concomitant administration of macrolide antibiotics and vasospastic reactions have been reported.

On 10/8/99, the sponsor recommended revising the clinical pharmacology/pharmacokinetics: Interactions section to identify specific macrolide antibiotics and add language to Precautions/Drug Interactions concerning protease inhibitors.

In our 2/9/00 fax, we adopted the sponsor's revisions to the clinical pharmacology/pharmacokinetics: Interactions section, and added new Contraindications and Warnings sections that discuss the "alleged" interaction of CYP 3A4 inhibitors with ergotamine and provided a detailed list of more potent and less potent inhibitors, and added a cross reference in the Precautions/Drug Interactions section.

The sponsor accepts our modifications with certain modifications of their own. The proposed reference in Contraindications section to " ——— should be replaced with "ergotism" which they argue is more descriptive and complete. They propose adding a cross reference in the Contraindications section to the Precautions section. Finally, they propose modifying the list of CYP 3A4 inhibitors, as described in the DHE/Migranal

proposed labeling (including moving troleandomycin from the list of less potent inhibitors to more potent inhibitors).

3. Additional Cases of DHE Associated Valvulopathy

Before I comment on the sponsor's proposed labeling changes, I would like to describe additional cases of DHE associated valvulopathy that would help determine the appropriate changes to labeling.

In early 1999 (date unknown), I received an unsolicited call from an attorney in [redacted], informing me of a known case of DHE associated valvulopathy [redacted]. He verbally gave me as many details about the case as he knew. This is the case that led to my internal investigation of this issue. This is the same case that the sponsor reported in one of the four cases they uncovered. We discussed this case at the 10/20/99 meeting with the sponsor and concluded that it could not be used to implicate DHE as a potential cause of valvulopathy because of the concomitant use of Redux in this case.

[redacted] subsequently contacted me again and gave me the name of another attorney, [redacted] who knew of additional cases. I successfully contacted [redacted]. I was interested in the clinical details of any additional cases he might have, but I explained to him that I really needed to contact the physicians involved with those cases. He wrote a letter (dated 9/19/00, see Appendix B - page 19) and provided important contact information for five cases known to him. One of the cases is the same case of which we are already aware (USA/99/00843/DHE) and I don't include it here. I wrote, called, and faxed these contacts (one on numerous occasions) and received responses from three of them. All three were new cases, to the best of my knowledge. I summarize the three new cases below. In all instances, the information I obtained came directly from the contact that [redacted] provided me and did not come from him or his law firm.

3.1 Case #1 – [redacted]

I received information about this case from [redacted] an attorney in [redacted]. She provided a cover letter dated 11/21/00, as well as copies of consultations from a [redacted], and an operative report from [redacted], as well as the pathology report of the diseased valve. The details are in Appendix C - page 22.

This is a 29 y/o female who presented to [redacted] on 9/2/98 complaining of a two-month history of shortness of breath and mild ankle swelling. She had a past medical history of hypothyroidism, and almost daily migraine headaches, treated with DHE 0.75 cc every three hours as needed for one year, usually taking " about 6 injections a day at the minimum." [redacted] writes in her cover letter that the patient took DHE 0.75mg every 4-6 hours each day from 2/97 until 1/99.). Concomitant medications included Synthroid, propranolol 80mg tid, Norontin (sic) 200mg tid (?Neurontin), and Naproxyn prn. Her exam revealed evidence of congestive heart failure with a heart murmur suggestive of mitral regurgitation. She was found to have severe mitral regurgitation (presumably on transesophageal echo and cardiac catheterization, which were done but the results were

not reported). She underwent mitral valve replacement surgery on 11/3/98. The final pathological diagnosis was fibromyxoid changes of the mitral valve consistent but not diagnostic of valve disease secondary to "amine-type dietary supplements."

[redacted] cover letter also adds that the patient took the diet pill, Redux (dexfenfluramine), in the summer of 1998, which she later corrected in a separate letter dated 11/27/00, in which she identified the correct period of Redux use from 7/25/97 until 9/17/98, whereupon the patient stopped taking it when she learned that "it was being withdrawn from the market."

The concomitant use of Redux in this case makes it impossible to discern DHE's potential role in her disease. I chose not to pursue this case any further.

3.2 Case # 2 - [redacted]

I received information about the second case from [redacted] a neurologist in [redacted] who states he specializes in the management of headache. The details of the case are in Appendix D - page 35.

He describes the case of RSD, a 46 y/o female whom he first saw in December, 1990 for chronic migraine headaches since age 16. The patient tried various treatment regimens, including ergotamine in various formulations, eventually settling on DHE around 1994. She quickly became DHE dependent. Between 1995 and 1999 she needed a dose of DHE five to seven days out of each week. In the early spring of 1999, she had been complaining of mild dyspnea on exertion, which was initially thought to be related to beta blocker therapy which she was taking concurrently for migraine prophylaxis. Withdrawal of the beta blocker did not improve her symptoms.

A cardiac consultation revealed severe mitral stenosis and moderate mitral regurgitation. The transesophageal echo also noted mild aortic valve thickening and mild aortic regurgitation, as well as mild tricuspid regurgitation. She subsequently underwent a mitral valve replacement. At the time of surgery, the cardiac surgeon indicated that the valve was calcific and seemed to be compatible with old rheumatic heart disease. The pathology description was very sparse and mentioned only that there was valvular tissue with specks of calcium.

I contacted [redacted] again on 12/28/00 and specifically asked whether the patient had a history of rheumatic fever as a child, or a history of Fen-Phen use. In his fax to me 1/3/2001 at 9:42am, he responded no to both questions (also in Appendix D - page 35).

3.3 Case #3 – [redacted]

I received information about the third case from [redacted] a cardiologist who works in the [redacted] The details of the case are located in Appendix E - page 43.

He describes the case of JLM ([redacted]. She is a 49 y/o white female who presented to the cardiology department with a two year history of progressive dyspnea on exertion. She also has a history of severe migraines, asthma, and depression.

She had been on chronic intermittent intravenous DHE treatment for approximately five years. Concomitant medications included Allegra 60mg bid, Zoloft 15 mg qd, thyroid hormone replacement, desipramine 100mg qd, azmacort, and vicodin prn.

Echocardiogram revealed "rheumatic" appearing valvular structures with severe mitral stenosis and regurgitation. There was also severe tricuspid regurgitation. She underwent mitral valve replacement surgery (the pathology report has a date listed of 5/10/00).

At the time of surgery, significant valvular disease with severe scarring and fusion of the tricuspid and mitral valve apparatus was noted. There was moderate shortening of the subvalvular chordae. The surgeon noted that this was an unusual presentation for rheumatic disease.

I contacted [redacted] to request additional information. Specifically:

1. did she have a history of rheumatic fever or any other condition that would predispose her to valvular heart disease,
2. I requested more detailed exposure history to DHE,
3. did she have a history of fen-phen use, and
4. was there a pathology report available

He faxed me a copy of the pathology report. On gross inspection, marked thickening of the valve and chordae tendinae were noted. Unfortunately, no microscopic examination was performed.

He could not answer the other questions, and referred me to the patient's primary care provider, [redacted]. Due to persistent difficulties in contacting [redacted], and the need to have better documentation and interpretation of this (and any additional) cases, we formally consulted OPDRA. I describe the results of their consult below.

4. OPDRA Consult

We asked OPDRA to review known cases of cardiac valvular disease associated with dihydroergotamine use (either injectable or nasal spray formulations, Appendix F -). We also asked them to use sumatriptan (injectable and nasal spray) as a comparator (Appendix G -).

They identified and reviewed seven cases of valvular disorders associated with DHE use. These were obtained from AERS, PUBMED, as well as the information I had provided from the three cases described above.

From their cases series, they report that the patients were predominantly female, ranging 29-66 years. The average dose of DHE was 1mg, generally administered via the intramuscular route. Three patients used both injectable and intranasal DHE. The duration of DHE use prior to the development of symptoms ranged from 2 to 30 years. The most common presenting symptom was dyspnea on exertion. The reported diagnoses included cardiac valve regurgitation, insufficiency, fibrosis, prolapse, and/or stenosis,

involving one or more valves (e.g. mitral/tricuspid/aortic) in various stages of abnormal function. Six patients required valve replacements. The mitral valve was the most commonly replaced valve. There was one death reported after the valve replacement due to the post-op complications.

The pathology findings were suggestive of possible drug-induced cardiac valvulopathy, but OPDRA could not conclude a causal relationship between DHE use and cardiac valvulopathy because there are many confounding factors that could challenge this association in at least 6 cases. In 5 cases, there was concomitant treatment with other drugs that are well associated with valvulopathy (ergotamine, Redux, Sansert). In two cases, the concomitant use of other suspect drugs was not mentioned with DHE use, but one case lacked details to confirm the sole use of DHE.

OPDRA cannot conclude that there is a direct association between DHE and cardiac valvulopathy, but they cannot also exclude the possibility that an association exists between DHE and cardiac valvular fibrosis. They recommend continued monitoring of cardiac valvulopathy and DHE use.

In a separate review of cases with sumatriptan, OPDRA reviewed 6708 reports in AERS of all adverse drug events reported in associated with sumatriptan use. This resulted in 3 possible cases of cardiac valvulopathy. One was mitral valve prolapse detected on routine exam in an otherwise asymptomatic patient, one was mitral regurgitation diagnosed via echocardiogram in a patient who presented with chest pressure and increased PVC's and an abnormal ECG. The third case involved mitral regurgitation in a patient who presented with exacerbation of "breathing problems" after one year of Imitrex use.

As a result of this second review involving sumatriptan, OPDRA cannot be certain of any associations between Imitrex and cardiac valvulopathy. Therefore, they could not make a meaningful comparison between the DHE and sumatriptan case series.

5. Comments

The sponsor's counter-proposal to our suggested labeling changes (as detailed in the 2/9/2000 fax) are generally acceptable, with one main exception and some minor exceptions. I detail the changes here with my comment.

5.1 DHE/Migranal

CLINICAL PHARMACOLOGY
The sponsor suggests alternate text to emphasize that pharmacokinetic interactions with of other ergot alkaloids have been reported. I concur with the change.

WARNINGS
The sponsor proposes moving the proposed warning regarding fibrotic complications to the Precautions section, and deleting the reference to cardiac valvular fibrosis being a class effect.

I still believe that these problems are serious enough that inclusion as a warning is appropriate. Although OPDRA did not find substantial evidence to implicate DHE as

causative for cardiac valvular fibrosis, it does not take a tremendous leap of faith to believe that this can occur with DHE. The reasons are that DHE is already associated with fibrotic complications elsewhere in the body, and DHE is a member of a class of compounds (ergot alkaloids) that are known to lead to fibrotic complications **including cardiac valvular fibrosis**. Furthermore, we have cases that suggest DHE may have had at least a contributing role in the development of this pathology in some patients.

Therefore, I believe it is appropriate to include a statement that DHE is a member of a class of drugs that is associated with this condition. This is analogous to triptan class labeling. For newly approved triptans, we include class labeling for myocardial infarction, even though no document cases of myocardial infarction for that particular drug may exist at the time of approval. As post-marketing reports of MI have surfaced, we have strengthened the labeling of these products to implicate the drug directly.

The sponsor may argue that DHE is different from newly approved triptans in that it has a very long post-marketing history and the lack of substantial evidence of this association compels us to conclude that such an association probably doesn't exist. I would take issue with this argument. For most of its post-marketing history, DHE has been available only as a parenteral formulation, which effectively limits the potential for chronic daily use. It is possible we haven't seen more cases simply because it hasn't been used chronically very much as an injectable medication. With the recent approval of Migranal Nasal Spray, the potential for chronic abuse is substantially increased; therefore I believe it is necessary to alert prescribers and users of this possibility.

PRECAUTIONS
The propose inserting the Fibrotic Complications paragraph in the section. I prefer to keep it in Warnings (as described above) and refer the reader to the Warnings section.

They propose inserting a section "Information for Patients." I concur with this change.

They propose modifying the proposed section on CYP3A4 inhibition. Their version emphasizes that no reports of serious adverse events in connection with coadministration with CYP3A4 inhibitors and DHE has been reported. This is a true statement and thus is acceptable. They modify slightly the list of inhibitors, which is also acceptable.

ADVERSE EVENTS
There is a statement that fibrotic complications have been associated with long-term [redacted] use. I have changed [redacted] to " [redacted] and refer the reader to the Warnings section {this is a new change that was not present in the original fax).

As a result of my review, and the OPDRA consults, I make the following recommendations to labeling.

DOSAGE AND ADMINISTRATION
The sponsor has deleted the section that [redacted] and instead includes a statement that DHE is not for chronic daily administration. I

concur with the change, particularly since the section already includes limits on how much drug should be taken in a week (6ml (mg)/ wk for DHE 45, and 4mg/week for Migranal).

5.2 Cafergot Suppositories

CONTRAINDICATIONS
The sponsor has added troleandomycin to the list of CYP3A4 inhibitors that are contraindicated. I agree with the change. They have deleted the phrase that some cases of

WARNINGS
Fibrotic Complications
They have reworded this paragraph that describes the risk of fibrotic complications (including retroperitoneal, pulmonary, and cardiac valvular fibrosis). The essence of the message is unchanged and I concur with the change.

CYP3A4 Inhibitors
They have modified the list of less potent CYP3A4 inhibitors. I concur with the change.

PRECAUTIONS
They have deleted the section on CYP3A4 inhibitors and refer the reader to the Contraindications and Warnings sections instead. I concur with this change.

Information for patients.
They have included a section instructing patients not to exceed the dosing guidelines and that Cafergot should not be used for chronic daily administration. I concur with this statement.

DOSAGE AND ADMINISTRATION
As in the DHE/Migranal labeling, they have deleted
and instead include a statement that the drug is not for chronic daily administration. I agree with the change, since the labeling already includes a statement not to use more than 5 suppositories per week.

6. Labeling

The following labeling [in black] represents the text we faxed to the sponsor on 2/9/00. The marked up changes in blue represent the sponsor's response in their 7/7/00 submission. The marked up changes in red represent my recommended changes to the sponsor's changes. Clean running version of the recommended changes to labeling is available in Appendix H - page 48.

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pages of

trade secret and/or

confidential

commercial

information

Review and Evaluation of Clinical Data

OCT 21 1999

NDA (Serial Number)	**05-929, [redacted], 20-148**
Sponsor:	**Novartis**
Drug:	**DHE 45, Cafergot (supp), Migranal**
Proposed Indication:	**migraine**
Material Submitted:	**labeling supplements**
Correspondence Date:	**10/8/99**
Date Received / Agency:	**10/15/99**
Date Review Completed	**10/21/99**
Reviewer:	**Armando Oliva, MD**

1. Introduction

These three submissions contain the sponsor's official response to our request conveyed in a teleconference last month during which we asked the sponsor to update their labeling for ergotamine and dihydroergotamine products with regard to ergotism associated with concomitant use of ergotamine and CYP3A4 inhibitors and with regard to cardiac valvulopathy with prolonged daily use. These issues have been reviewed by me previously and I don't describe them here (valvulopathy: NDA 05929, 10/15/99; ergotism: reviews submitted to NDA 06620 on 4/2/99 and 7/16/99, and to NDA's 06620, 05929, 20148 on 9/15/99).

Before I describe the sponsor's proposed changes to these products, I'd like to make two points:

1. The proposed labeling changes are submitted to the NDA's for the two marketed products for DHE (DHE 45 injectable-05929, and Migranal Nasal Spray-20148) and to the Cafergot suppository NDA (0900). They have not submitted proposed changes to the Cafergot tablet NDA (06620), to which these changes should also apply. I note that in the proposed changes to the suppository, the text also mentions that these changes apply to the tablet, although the submission to the NDA is not made. In this review, I also address needed changes to Cafergot tablet labeling.

[redacted]

I have already seen the sponsor's proposal for changes to labeling of these products via a fax sent to me on 9/13/99 and reviewed by me on 9/15/99. I verified that their proposed labeling changes in that fax were the same as those contained in the formal submissions. I noted minor wording changes in the formal submission compared to those contained in the fax. I outline those proposed changes below.

2 pages redacted from this section of the approval package consisted of draft labeling

1. [redacted] Since there are no cases reported for DHE/Migranal, I don't recommend changes to their Warnings section).
2. The drugs known to be associated with the severe effects are not contraindicated (*i.e.*, no modifications to the contraindications sections are proposed).
3. The labeling does not warn prescribers about potential interactions with other CYP 3A4 inhibitors.
4. The wording "(DHE45/Migranal) ... should not be used when protease inhibitor ... treatment is initiated in patients" suggests that they can be used once initiation of therapy is complete and patients are on therapy chronically.
5. As mentioned before, we should also include changes to labeling to describe the [redacted]. The sponsor is planning to address this in a separate submission, but I prefer to include our draft changes here.

As a final comment, the sponsor does describe PK information that ergotamine and dihydroergotamine are CYP 3A4 inhibitors. I do not know where that information comes from. In the meeting with the sponsor yesterday, we requested they share that information with us.

I include my recommended labeling text below. There are some minor changes compared with the text in my memo dated yesterday (10/20/99). These differences are outlined below:

1. I've included Dr. Levin's comments to my memo.
2. I've included recommended changes to the Cafergot suppository labeling, which I had inadvertently excluded in my memo.
3. I've recommended modifications to the Clinical Pharmacology: Pharmacokinetic interactions sections to agree with the new sections in Contraindications, Warnings, and Precautions.
4. I've reworded the Precautions section for DHE/Migranal to recommend that potent CYP3A4 inhibitors not be used with DHE/Migranal. This is more in line with the sponsor's recommendation and is stronger than my initial proposal. It seems a prudent change.

Proposed labeling changes:

5.1 DHE 45 (NDA 05929) and Migranal Nasal Spray (NDA 20148)

The current labeling reads:

[
]

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Review and Evaluation of Clinical Data

JAN - 5 2000

NDA (Serial Number)	**05929, [redacted] 20148**
Sponsor:	**Novartis**
Drug:	**DHE 45, Cafergot Suppositories, Migranal Nasal Spray**
Proposed Indication:	**migraine**
Material Submitted:	**Labeling Supplement**
Correspondence Date:	**12/22/99**
Date Received / Agency:	**12/27/99**
Date Review Completed	**1/5/00**
Reviewer:	**Armando Oliva, MD**

1. Introduction

These submissions contain proposed labeling changes to injectable DHE45, Cafergot suppositories, and Migranal Nasal Spray. The changes are intended to strengthen each product labeling with respect to the risk of fibrotic complications.

These submissions come at the heel of labeling supplements for these three products, submitted to the Division on 10/8/99. These earlier supplements propose changes to labeling in with respect to the risk of concomitant use with CYP 3A4 inhibitors. We have just finished review of the 10/99 supplements and we were about to fax the sponsor our response to their proposal. In this response, we note that they had not recommended changes with respect to the risk of fibrotic complications, and we have already included our proposed changes.

As a result, my review of these submissions focus on what changes, if any, are needed to the fax to the sponsor.

2. FAX to Sponsor

Prior to my knowledge of these new submissions, we were ready to send the following fax to the sponsor. It contains our proposed changes to labeling of four products: DHE 45 (NDA 05-929), Migranal Nasal Spray (NDA 20-148), Cafergot Tablets (NDA 06-620), and Cafergot Suppositories (NDA 09-000).

DHE 45 (NDA 05-929) and Migranal Nasal Spray (NDA 20-148)

The current labeling reads:

CLINICAL PHARMACOLOGY

[ ]

9 pages redacted from this section of the approval package consisted of draft labeling

Armando Oliva, M.D.
Medical Reviewer

R. Levin, M.D. R. L

Agree

ao 1/5/00
cc:
HFD-120
NDA 05929, 9000, 20148
electronic copy-Levin

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

9-000/S-022/S-023

ADMINISTRATIVE DOCUMENT(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM

Date: April 30, 2002
From: Armando Oliva, MD
To: Russell Katz, MD
Subject: NDA 09-000 SLR-22/23 Cafergot Suppositories

We have been trying for quite some time now to update the labeling for Cafergot in order to adequately describe the risk to patients of dangerous drug-drug interactions with CYP 3A4 inhibitors, as well as the risk of cardiac valvular fibrosis with prolonged daily use.

Most recently, we issued an approvable letter on 06/29/01 in which we outlined the specific labeling changes that we proposed for three products: DHE-45 injection, Migranal Nasal Spray, and Cafergot suppositories.[1] This action affects only the Cafergot product, as the labeling for the DHE products are being negotiated and adopted separately.

Subsequent to that letter, and prior to a response from the sponsor, we continued to receive reports of serious drug-drug interactions with CYP 3A4 inhibitors, including one patient who suffered a fatal stroke. We called the sponsor on 12/06/01 to express our increased concern over this issue. We informed them that the suggested wording for Cafergot in the 06/29/01 letter we felt was no longer sufficient (basically, we had, at that time, suggested adding statements in the Contraindications, Warnings, and Precautions: Drug Interactions section). We now believed that a black box warning was appropriate to describe this potentially serious and fatal drug interaction. This is consistent with the black box warning present in the ritonavir labeling which describes the same interaction.

The sponsor responded to the 6/29/01 letter and to the 12/06/01 teleconference in a submission dated 02/25/02. This February submission only addresses the Cafergot labeling issues. DHE and Migranal labeling will be addressed in a separate submission.

Dr. Tremblay has reviewed this submission. The proposed labeling does now contain a black box warning, as we had suggested. It also adopts most, but not all, of the additional language that we had included in the approvable letter of 06/29. Dr. Tremblay recommended approval of their proposed version, even though it doesn't contain everything that we had previously proposed. He presents a good argument that the outstanding differences are minor and that the critical importance of the CYP 3A4 issue to the public health warrants a timely resolution of this issue and therefore recommends that we resolve the minor remaining differences in the sponsor's favor.

[1] I point out that Novartis no longer markets Cafergot tablets, so the labeling of that product is not affected; however any changes to the Cafergot suppository labeling would and should impact the labeling of the many generic ergotamine products currently marketed for migraine.

He and I both agree that this important issue requires quick action. However, on my review of the sponsor's February 2002 proposed labeling, I felt that additional changes were necessary. Specifically:

1. The sponsor February 2002 version of the black box warning describes what might occur with future use of Cafergot and CYP 3A4 inhibitors. I believe stronger language should be incorporated to describe what has been known to have occurred with concomitant use. This is similar to language used in other black boxes for drugs in this Division, to include Depakote, and the recently approved black box warning for intrathecal baclofen.
2. We had originally suggested describing the risk of fibrotic complications (currently listed in the Adverse Events section) in the *Warnings* section. The February 2002 version recommended maintaining the section where it currently exists, since no new cases have been reported to warrant its placement in *Warnings*. I argued that our position on this issue has changed and that we believe these adverse events are serious enough to include in *Warnings*. This is consistent with the agreement we achieved with the sponsor on the new *Warnings:Fibrotic Complications* section for DHE/Migranal labeling.
3. We had originally proposed new text in the *Precautions: Information for Patients* section and in *Dosage and Administration* that emphasizes the need to avoid chronic daily administration. The sponsor felt that this was already adequately addressed in the *Drug Abuse* section. I disagree and felt the proposed text in these two additional sections is appropriate.

We faxed our response on 3/25/02. They have since responded and have essentially agreed to all of our proposals, with only some minor additional editorial changes. At this point, we have resolved all outstanding differences at the team level and I can recommend approval of the sponsor's most recently proposed labeling. Dr. Tremblay concurs.

The only outstanding issue is that we had requested, in the 3/25/02 fax, they commit to send a Dear Health Care Provider (DHCP) letter to disseminate the new labeling information. We asked to see a draft of the letter. At this point, they are still in the process of writing the letter and we have not yet seen a copy. I don't believe this should hold up the approval action, as they have committed to issue a DHCP letter and will send us a draft beforehand.

Finally, I recommend that a copy of this action go to the Office of Generic Drugs, as there are many generic ergotamine products that are affected by this change. The labeling for those products will also need to be changed accordingly.

Armando Oliva, M.D.
Neurology Team Leader, DNDP

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Armando Oliva
4/30/02 12:03:46 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

FOOD AND DRUG ADMINISTRATION
DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
(HFD-120)
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857
FAX (301) 594-2858

Telecopier Cover Sheet

DATE: March 25, 2002

DELIVER TO: Ms. Martina Struck
Fax Number: 973.781.6325

FROM: Lana Chen, R.Ph.
Regulatory Management Officer.
Ph 301.594.5529

Total number of pages, including cover page:
If you do not receive all pages or have any problems with receiving, call (301) 594-2850.

MESSAGE:

Martina,

Re: Cafergot Suppositories (NDA 09-000)

We have reviewed your latest proposal for Cafergot Suppository labeling and find your changes generally acceptable. However, we would like to propose the additional changes described below, and contained in the attached version of the labeling.

1. Black Box Warning - We believe that the black box warning should describe what is **known** to have occurred with the use of Cafergot, rather than what **might** occur with future use. As examples, please see the approved black box warning for Depakote or the recently approved black box warning for intrathecal baclofen. Our proposal for the text in the black box is in keeping with this strategy.

2. Warnings: Fibrotic Complications - Regardless of whether there are or are not any new cases, our thinking in the Division has evolved to our current position. We currently believe that these adverse events are serious enough such that they should be included in the Warnings section. This is consistent with the recently agreed upon wording for DHE/Migranal and Fibrotic Complications, achieved at the meeting between Novartis and the Division on 03/06/02.
3. Precautions: Information for Patients - new text that emphasizes the need to avoid chronic daily administration (we believe that the text in Drug Abuse section is insufficient regarding this matter).
4. Adverse Reactions: Fibrotic Complications - now references the new section in Warnings.
5. Dosage and Administration - corrected misspelling of "Administration"
6. Dosage and Administration - new text that emphasizes the need to avoid chronic daily administration (same reasoning as #3 above).

We seek your concurrence with these changes in a timely manner so that we may proceed expeditiously to a final action on this important supplement.

Also, we believe that the new black box warning warrants issuance of a Dear Doctor letter to alert prescribers of this important labeling change. Please respond with your commitment to issue such a letter, and provide a copy of the proposed text of the letter.

NOVARTIS

T2001-27
89000402

CAFERGOT®

(ergotamine tartrate and caffeine)
SUPPOSITORIES, USP

Rx only

WARNING

Serious and/or life-threatening peripheral ischemia has been associated with the coadministration of CAFERGOT® with potent CYP 3A4 inhibitors including protease inhibitors and macrolide antibiotics

Because CYP 3A4 inhibition elevates the serum levels of CAFERGOT®, the risk for vasospasm leading to cerebral ischemia and/or ischemia of the extremities is increased. Hence, concomitant use of these medications is contraindicated.

(See also CONTRAINDICATIONS and WARNINGS section)

DESCRIPTION

CAFERGOT® (ergotamine tartrate and caffeine) Suppository

ergotamine tartrate USP.....2 mg
caffeine USP.....100 mg

Inactive Ingredients: cocoa butter NF and tartaric acid NF.

CAFERGOT® (ergotamine tartrate and caffeine) suppositories are *sealed* in foil to afford protection from cocoa butter leakage.

If an unavoidable period of exposure to heat softens the suppository, it should be chilled in ice-cold water to solidify it before removing the foil.

CLINICAL PHARMACOLOGY

Ergotamine is an alpha adrenergic blocking agent with a direct stimulating effect on the smooth muscle of peripheral and cranial blood vessels and produces depression of central vasomotor centers. The compound also has the properties of serotonin antagonism. In comparison to hydrogenated ergotamine, the adrenergic blocking actions are less pronounced and vasoconstrictive actions are greater.

Caffeine, also a cranial vasoconstrictor, is added to further enhance the vasoconstrictive effect without the necessity of increasing ergotamine dosage.

Many migraine patients experience excessive nausea and vomiting during attacks, making it impossible for them to retain any oral medication. In such cases, therefore, the only practical means of medication is through the rectal route where medication may reach the cranial vessels directly, evading the splanchnic vasculature and the liver.

Pharmacokinetics: Interactions

Pharmacokinetic interactions (increased blood levels of ergotamine) have been reported in patients treated orally with ergotamine and macrolide antibiotics (e.g., troleandomycin, clarithromycin, erythromycin), and in patients treated orally with ergotamine and protease inhibitors (e.g. ritonavir) presumably due to inhibition of cytochrome P450 3A metabolism of ergotamine *(See CONTRAINDICATIONS)*. Ergotamine has also been shown to be an inhibitor of cytochrome P450 3A catalyzed reactions. No pharmacokinetic interactions involving other cytochrome P450 isoenzymes are known.

INDICATIONS AND USAGE

CAFERGOT® (ergotamine tartrate and caffeine)

Indicated as therapy to abort or prevent vascular headache, e.g., migraine, migraine variants or so-called "histaminic cephalalgia".

CONTRAINDICATIONS

Coadministration of ergotamine with potent CYP 3A4 inhibitors (ritonavir, nelfinavir, indinavir, erythromycin, clarithromycin, and troleandomycin) has been associated with acute ergot toxicity (ergotism) characterized by vasospasm and ischemia of the extremities (see PRECAUTIONS: Drug Interactions), with some cases resulting in amputation. There have been rare reports of cerebral ischemia in patients on protease inhibitor therapy when CAFERGOT® (ergotamine tartrate and caffeine) was coadministered, at least one resulting in death. Because of the increased risk for ergotism and other serious vasospastic adverse events, ergotamine use is contraindicated with these drugs and other potent inhibitors of CYP 3A4 (e.g., ketoconazole, itraconazole) *(see WARNINGS: CYP 3A4 Inhibitors)*.

CAFERGOT® (ergotamine tartrate and caffeine) may cause fetal harm when administered to pregnant women. CAFERGOT® (ergotamine tartrate and caffeine) is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy or if the patient becomes pregnant while taking this product, the patient should be apprised of the potential hazard to the fetus.

Peripheral vascular disease, coronary heart disease, hypertension, impaired hepatic or renal function and sepsis.

Hypersensitivity to any of the components.

WARNINGS

PRECAUTIONS

General

Although signs and symptoms of ergotism rarely develop even after long term intermittent use of the rectally administered drug, care should be exercised to remain within the limits of recommended dosage.

Ergotism is manifested by intense arterial vasoconstriction, producing signs and symptoms of peripheral vascular ischemia. Ergotamine induces vasoconstriction by a direct action on vascular smooth muscle. In chronic intoxication with ergot derivatives, headache, intermittent claudication, muscle pains, numbness, coldness and pallor of the digits may occur. If the condition is allowed to progress untreated, gangrene can result.

While most cases of ergotism associated with ergotamine treatment result from frank overdosage, some cases have involved apparent hypersensitivity. There are few reports of ergotism among patients taking doses within the recommended limits or for brief periods of time. In rare instances, patients, particularly those who have used the medication indiscriminately over long periods of time, may display withdrawal symptoms consisting of rebound headache upon discontinuation of the drug.

Rare cases of a solitary rectal or anal ulcer have occurred from abuse of ergotamine suppositories usually in higher than recommended doses or with continual use at the recommended dose for many years. Spontaneous healing occurs within usually 4-8 weeks after drug withdrawal.

Information for Patients

CYP 3A4 Inhibitors (e.g. Macrolide Antibiotics and Protease Inhibitors)

See CONTRAINDICATIONS and WARNINGS.

CAFERGOT® (ergotamine tartrate and caffeine) should not be administered with other vasoconstrictors. Use with sympathomimetics (pressor agents) may cause extreme elevation of blood pressure. The beta-blocker Inderal (propranolol) has been reported to potentiate the vasoconstrictive action of CAFERGOT® (ergotamine tartrate and caffeine) by blocking the vasodilating property of epinephrine. Nicotine may provoke vasoconstriction in some patients, predisposing to a greater ischemic response to ergot therapy.

The blood levels of ergotamine-containing drugs are reported to be elevated by the concomitant administration of macrolide antibiotics and vasospastic reactions have been reported with therapeutic doses of the ergotamine-containing drugs when coadministered with these antibiotics.

Pregnancy

Teratogenic Effects

Pregnancy Category X: There are no studies on the placental transfer or teratogenicity of the combined products of CAFERGOT® (ergotamine tartrate and caffeine). Caffeine is known to cross the placenta and has been shown to be teratogenic in animals. Ergotamine crosses the placenta in small amounts, although it does not appear to be embryotoxic in this quantity. However, prolonged vasoconstriction of the uterine vessels and/or increased myometrial tone leading to reduced myometrial and placental blood flow may have contributed to fetal growth retardation observed in animals. *(See CONTRAINDICATIONS)*

Nonteratogenic Effects

CAFERGOT® (ergotamine tartrate and caffeine) is contraindicated in pregnancy due to the oxytocic effects of ergotamine. *(See CONTRAINDICATIONS)*

Labor and Delivery

CAFERGOT® (ergotamine tartrate and caffeine) is contraindicated in labor and delivery due to its oxytocic effect which is maximal in the third trimester. *(See CONTRAINDICATIONS)*

Nursing Mothers

Ergot drugs are known to inhibit prolactin but there are no reports of decreased lactation with CAFERGOT® (ergotamine tartrate and caffeine). Ergotamine is excreted in breast milk and may cause symptoms of vomiting, diarrhea, weak pulse and unstable blood pressure in nursing infants. Because of the potential for serious adverse reactions in nursing infants from CAFERGOT® (ergotamine tartrate and caffeine), a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Cardiovascular: Vasoconstrictive complications of a serious nature may occur at times. These include ischemia, cyanosis, absence of pulse, cold extremities, gangrene, precordial distress and pain, EKG changes and muscle pains. Although these effects occur most commonly with long-term therapy at relatively high doses, they have also been reported with short-term or normal doses. Other cardiovascular adverse effects include transient tachycardia or bradycardia and hypertension.

Gastrointestinal: Nausea and vomiting; rectal or anal ulcer (from overuse of suppositories).

Neurological: paresthesias, numbness, weakness, and vertigo.

Allergic: Localized edema and itching.

Fibrotic Complications: (see WARNINGS).

DRUG ABUSE AND DEPENDENCE

There have been reports of drug abuse and psychological dependence in patients on CAFERGOT® (ergotamine tartrate and caffeine) therapy. Due to the chronicity of vascular headaches, it is

imperative that patients be advised not to exceed recommended dosages with long-term use to avoid ergotism. *(See PRECAUTIONS)*

OVERDOSAGE

The toxic effects of an acute overdosage of CAFERGOT® (ergotamine tartrate and caffeine) are due primarily to the ergotamine component. The amount of caffeine is such that its toxic effects will be overshadowed by those of ergotamine. Symptoms include vomiting, numbness, tingling, pain and cyanosis of the extremities associated with diminished or absent peripheral pulses; hypertension or hypotension; drowsiness, stupor, coma, convulsions and shock. A case has been reported of reversible bilateral papillitis with ring scotomata in a patient who received five times the recommended daily adult dose over a period of 14 days.

Treatment consists of removal of the offending drug by enema. Maintenance of adequate pulmonary ventilation, correction of hypotension, and control of convulsions and blood pressure are important considerations. Treatment of peripheral vasospasm should consist of warmth, but not heat, and protection of the ischemic limbs. Vasodilators may be beneficial but caution must be exercised to avoid aggravating an already existent hypotension.

DOSAGE AND ADMINISTRATION

Procedure

For best results, dosage should start at the first sign of an attack.

RECTALLY	One suppository at start of attack; second suppository after 1 hour, if needed for full relief 1 hr 

Early ——————Administration Gives Maximum Effectiveness

Maximum Adult Dosage

Rectally

Two suppositories is the maximum dose for an individual attack.

Total weekly dosage should not exceed 5 suppositories. CAFERGOT (ergotamine tartrate) suppositories should not be used for chronic daily administration.

In carefully selected patients, with due consideration of maximum dosage recommendations, administration of the drug at bedtime may be an appropriate short-term preventive measure.

HOW SUPPLIED

CAFERGOT® (ergotamine tartrate and caffeine) Suppositories, USP

Yellowish-white bullet-shaped, cocoa butter base suppositories wrapped in silver colored foil with NOVARTIS CAFERGOT® SUPPOSITORY 78-33 NOVARTIS'' printed in fuchsia.

Boxes of 12 (NDC 0078-0033-02).

Store and Dispense

Below 77°F (25°C); tight container (sealed foil). Protect from moisture.

NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

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/s/

Lana Chen
3/26/02 02:07:40 PM
CSO
Ok'd by Dr. Oliva 3/26/02

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

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

DATE: February 22, 2001

FROM: Lauren Lee, Pharm.D.
Post-marketing Safety Evaluator
Division of Drug Risk Evaluation I, HFD-430

THROUGH: Julie Beitz, M.D., Director *Signed 02-27-01*
Division of Drug Risk Evaluation I, HFD-430

TO: Russell Katz, M.D., Director
Division of Neuropharmacological Drug Products, HFD-120

SUBJECT: OPDRA Post-marketing Safety Review (PID# D010004)

- **Drugs:** **NDA 5-929 / Applicant: NOVARTIS**
  D.H.E.45 (dihydroergotamine mesylate injection)
  NDA 20-148 / Applicant: NOVARTIS
  Migranal (dihydroergotamine mesylate nasal spray)
- **Reaction:** **Cardiac valvular disorder**

CONFIDENTIAL: CONTAINS IMS DATA; NOT TO BE USED OUTSIDE OF THE FDA WITHOUT CLEARANCE FROM IMS.

I. EXECUTIVE SUMMARY:

We reviewed 7 cases of valvular disorders associated with DHE use from AERS and the Medline *(Pubmed)* internet site. All cases were received in recent years, ranging from 1997-2000. It is unknown if the publicity of cardiac valvulopathy with Redux use has contributed to the awareness of drug-induced valve diseases and the reporting of such cases. The patients were predominantly female with ages ranging from 29 to 66 years. The average dose of DHE was approximately 1 mg, and the most frequent route of administration was intramuscular injection. In three patients, both the injectable, D.H.E. 45, and the nasal spray, Migranal, were used (e.g. IM (2), Nasal/IV, Nasal/IM/IV, SC, PO, IM/IV/SC/Nasal). The duration of DHE use prior to the development of symptoms ranged from 2 to 30 years. The most common symptom was dyspnea on exertion. The reported diagnoses included cardiac valve regurgitation, insufficiency, fibrosis, prolapse, and/or stenosis, involving one or more valves (e.g. mitral/tricuspid/aortic) in various stages of abnormal function. Six patients required valve replacements. The mitral valve was the most commonly replaced valve. There was one death reported after the valve replacement due to the post-op complications.

The pathology findings were suggestive of possible drug-induced cardiac valvulopathy, but we could not conclude a causal relationship between DHE use and cardiac valvulopathy because there are many confounding factors that could challenge this association in at least 6 cases. For example, in five cases, the concomitant use of other drugs that are well associated with cardiac valvulopathy, such as Redux, Sansert, and/or ergotamine, precludes a direct association between cardiac valvulopathy and DHE use.

Also, a prior history of rheumatic fever could not be ruled out in three cases. Moreover, in two cases, the concomitant use of other suspect drugs was not mentioned with DHE use, but one case lacked details to confirm the sole use of DHE.

Although we cannot conclude from our seven cases that there is a direct association between DHE and cardiac valvulopathy, we also cannot exclude the possibility that DHE could be associated with this adverse reaction especially since other ergot-alkaloids have shown an association with cardiac valvulopathy. Therefore, at this time, we recommend continued monitoring of cardiac valvulopathy with DHE use.

II. INTRODUCTION:

This consult is in response to a January 8, 2001 request, by the Division of Neuropharmacological Drug Products, to review the case reports submitted to FDA describing the possible association between *dihydroergotamine (DHE)* and *cardiac valvular fibrosis.* Furthermore, an additional request was made on January 11, 2001 to review the events of interest associated with the *subcutaneous* and *intranasal* forms of DHE separately.

A. RELEVANT HISTORY

In March 1998, the Office of Epidemiology and Biostatistics (HFD-700) conducted a comparative review of valvulopathy, pulmonary hypertension, and associated cardiac conditions with thirteen drugs that modulate serotonin, including ergot-alkaloids such as *dihydroergotamine, ergotamine*, and *methysergide.* The review of post-marketing reports for ergotamine (9) and methysergide (25) concluded an association with cardiac valvulopathy, which is a labeled adverse event for these drugs. However, the review did not *specifically* address any association between dihydroergotamine and valvulopathy because the adverse event reports involving dihydroergotamine were grouped together with ergotamine reports, and were not separately assessed. The review concluded that a *"consideration should be given to describe cardiac valvulopathy in the labeling of all ergotamine products."*

B. PERTINENT BACKROUND INFORMATION

DHE and Cardiac Valvulopathy

Dihydroergotamine (DHE) is a derivative of ergotamine and binds to the serotonin, noradrenaline and dopamine receptors. The therapeutic activity of dihydroergotamine in migraine is attributed to its agonist effect at the 5-HT $_{1D}$ receptors. Two current theories have been proposed to explain the efficacy of 5-HT $_{1D}$ receptor agonists in migraine. One theory suggests that the activation of 5-HT $_{1D}$ receptors located on intracranial blood vessels leads to vasoconstriction, resulting in the relief of migraine headache. The alternative hypothesis suggests that the activation of 5-HT $_{1D}$ receptors on sensory nerve endings of the trigeminal system results in the inhibition of pro-inflammatory neuropeptide release.[1]

According to Soler-Soler et al., "drugs that act via the serotonin pathways are potentially dangerous as seen with ergot alkaloids (e.g. methysergide) and appetite suppressants in causing cardiac valve diseases." Although the pathophysiologic underlying mechanism that explains the development of cardiac lesions is unknown, ergot alkaloids share a common chemical structure as serotonin, the agent potentially responsible for endocardial fibrosis in the carcinoid syndrome. While carcinoid-associated valve disease is restricted to the right-sided valves, ergot alkaloid-associated valve disease can

potentially involve all four valves. [2] According to Rothman et al., ergotamine, methysergide, and fenfluramine affect primarily the valves of the left side of the heart.[3]

III. DRUG INFORMATION AND LABELING:

A. PRODUCT INFORMATION

Drug Product	NDA	Applicant	FDA Approval	Approved Strength	Supplied
D.H.E. 45 (dihydroergotamine mesylate injection)	5-929	Novartis	**4/12/1946**	1mg/ mL	1 mL sterile ampuls
Migranal (dihydroergotamine mesylate nasal spray)	20-148	Novartis	**12/8/1997**	4 mg/ mL or 0.5 mg/ spray	1 mL amber glass ampuls

B. RECOMMENDED INDICATION/ DOSES/ ROUTE OF ADMINISTRATION

Both D.H.E. 45 and Migranal are indicated for the acute treatment of *migraine* headaches with or without aura, but only D.H.E. is indicated for the acute treatment of *cluster* headache episodes. Furthermore, both D.H.E. 45 and Migranal are not recommended for prolonged daily uses.

D.H.E. 45 (dihydroergotamine mesylate injection) should be administered in a dose of 1mg *(1 mL)* intravenously (IV), intramuscularly (IM) or subcutaneously (SC). The dose can be repeated, as needed, at 1 hour intervals to a total dose of 3 mg *(3 mL)* for IM or SC delivery or 2 mg *(2 mL)* for IV delivery in a 24 hour period. The total weekly dosage should not exceed 6 mg *(6 mL).*

Dihydroergotamine is also available as a nasal spray formulation. One spray (0.5 mg) of **Migranal** should be administered in each nostril. Fifteen minutes later, an additional spray (0.5 mg) should be administered in each nostril, for a total dosage of four sprays (2.0 mg).

C. LABELING OF CARDIAC VALVULAR DISEASE

The labeling for dihydroergotamine mesylate *(e.g. D.H.E. 45, Migranal)* does not mention any cardiac *valve-related* adverse events.

Other cardiac events are labeled as follows:

CONTRAINDICATION: D.H.E. 45 should not be given to patients with *ischemic heart disease* (angina pectoris, history of myocardial infarction, or documented silent ischemia) or to patients who have clinical symptoms or findings consistent with *coronary artery vasospasm* including Prinzmetal's variant angina. D.H.E 45 may increase blood pressure.

ADVERSE REACTIONS: Coronary vasospasm, transient MI, MI, ventricular tachycardia, ventricular fibrillation, vasospasm, hypertension, hypotension, edema, palpitation, peripheral ischemia, and angina. .

The cardiac valve-related events are listed in the Adverse Reactions section of the package insert for Cafergot (ergotamine tartrate and caffeine). For Sansert (methysergide), these events are listed in the Warnings, Contraindications, and the Adverse Reactions sections.

IV. MEDICAL LITERATURE SUMMARY:

On 1/18/01, a Medline *(Pubmed)* internet search was conducted to retrieve any published literature cases involving DHE and cardiac valve-related adverse events. Both the generic and the proprietary names of the drugs *(e.g. Migranal, DHE, dihydroergotamine)* were searched in conjunction with the following *Medline **Mesh** Terms*:

Heart valve, heart valve disease, mitral valve, aortic valve, tricuspid valve, mitral valve stenosis, aortic valve stenosis, tricuspid valve stenosis, mitral regurgitation, aortic regurgitation, tricuspid regurgitation, prolapse, and fibrosis.

The search revealed one published case report of *heart valve fibrosis* in a patient who was treated with dihydroergotamine. This case was published in the following **German** journal:

Deutsche Medizinische Wochenschrift 1992 Nov 6; 117 (45):1736

The above report was also identified in the FDA Adverse Event Reporting System (AERS) under the ISR number (#) 3075034-2. The details of this case are presented with the other identified cases in section VII of this consult.

V. SELECTION OF CASE SERIES:

Of the 397 reports of *all* adverse drug events in AERS with dihydroergotamine, we identified five cases with the search term, "Valvular heart disorders (HLGT)." Dr. Oliva provided two additional new cases that were not in AERS. These cases were selected based on the descriptions of any cardiac valve disorders, *such as valve regurgitation, insufficiency, fibrosis, prolapse, and/or stenosis,* in association with DHE use. In five cases, there was concomitant use of other drugs that are well associated with cardiac valvulopathy such as Sansert, Redux, and/or ergotamine. However, since *definitive* conclusions could not be made in terms of which drug was responsible for the adverse events, these cases were included.

A. DATABASE SEARCHES

The steps in this investigation included searches in the AERS database and the Spontaneous Reporting System (SRS) database as follows:

- On 1/9/01, we searched the **AERS** database for all reports coded with the MedDRA terms, "Valvular heart disorders (HLGT)" in association with "Dihydroergotamine%", "D.H.E.%", and "Migranal%." The search using the HLGT identified five unique cases.

- On 1/19/01, we searched the **SRS** database using the COSTART term, "STENO AORTIC," and the drug name,"Dihydroergotamine." The proprietary names, *Migranal* and *DHE 45,* were not used as search terms, since they are grouped under dihydroergotamine. *The searches in SRS did not reveal any cases of cardiac valvular disorder in association with DHE use.*

B. ADDITIONAL SOURCE OF REPORTS

On 1/8/01, OPDRA received two new cases from Dr. Oliva (HFD-120) as the basis of this consult request. These were direct reports from physicians describing cardiac valvular disorders with DHE use. These two reports will be added to the AERS database.

On 1/23/01, OPDRA received an e-mail from Dr. Oliva, containing a slide presentation from *Novartis,* listing five cases of cardiac valvular disorders with DHE use. He received this information approximately a year ago. These cases do not contain any details. One report is a duplicate foreign case that is listed in both the AERS database (ISR# 3075034-2) and the Medline (Pubmed) internet site. Two are duplicate cases in the AERS database (ISR#'s 3491669-7 & 3001354-3). The last two cases are not found in AERS, and the sources of the reports are unknown. Therefore, they are excluded from the case series.

Dr. Oliva also forwarded us a letter from a lawyer, identifying four patients who presented with cardiac valvular disorders with DHE use. Two matched the descriptions of patients from the direct reports. The last two are duplicates and are listed in AERS (ISR#'s 3544208-6 & 3491669-7). The letter contained details for only one case.

VI. DRUG USAGE DATA:

The following chart contains the projected number of total prescriptions dispensed by retail pharmacies *(chain, independent, food stores, and mail order)* in the U.S. for dihydroergotamine from the National Prescription Audit Plus of IMS Health. The data are stratified by the dosage form and the manufacturer's product, and presented by calendar year (1995 through 2000). *[Add three 000's to each figure]*

	Total (1995-2000)	2000 Total Rx	1999 Total Rx	1998 Total Rx	1997 Total Rx	1996 Total Rx	1995 Total Rx
Dihydroergotamine							
Nasal Spray Inhalant							
Amps Regular IM, IV, SC							

Source: IMS Health; National Prescription Audit Plus, On-line (Not to be used outside of FDA)
Blank field means no data
Total includes new and refill prescriptions

The following chart contains the projected number of total drug appearances during patient visits in office-based practices in the continental U.S. for dihydroergotamine. This information was retrieved from the National Disease and Therapeutic Index of IMS Health. A drug appearance roughly translates to a mention of a drug during a patient visit (unduplicated by number of diagnoses for which it may be used). A drug appearance can result from a prescription written, a refill authorized, a sample given, the drug administered in the office, a prescription issued by a dispensing physician, hospital order written, recommendation given to purchase OTC product, patient on drug and no action taken, or a combination of these. Every patient contact report is considered a patient visit, regardless of location.

The data is stratified by gender (include unspecified gender) and dosage form. *[Add three 000 to each number. Percents are absolute numbers]*

	Total (1995-2000)	Total PCT (1995-2000)	2000	2000 PCT	1999	1999 PCT	1998	1998 PCT	1997	1997 PCT	1996	1996 PCT	1995	1995 PCT
Dihydroergotamine														
Female														
Inj, mult adm reg														
Nasal, spr/aerosol														
Male														
Nasal, spr/aerosol														
Inj, mult adm reg														
Unspecified														
Inj, mult adm reg														
Nasal, spr/aerosol														

Source: IMS Health; National Disease and Therapeutic Index; CD-ROM (Not to be used outside of FDA)
Blank field means no data; a zero means less than ~ total projected
PCT = Percent

VII. SUMMARY OF CASES:

There are seven cases in this case series, five from AERS and two direct reports from Dr. Oliva. The demographic information is as follows:

Age in years:	Range 29 to 66 years old, mean 46, median 45
Gender:	Male (1), Female (6)
Time to onset:	2 years to 30 years
Dose:	0.75mg (1), 1 mg (3), 0.5- 1mg (1), Unknown (2)
Events reported:	Mitral valve fibrosis (1); Mitral/ tricuspid valve regurgitation (1); Mitral/ tricuspid valve insufficiency and regurgitation (1); Endocardial fibrosis and tricuspid valve insufficiency (1); Mitral regurgitation and prolapse, tricupid/aortic valve "damage" (1); Aortic insufficiency, tricuspid regurgitation, mitral stenosis and insufficiency (1); Mitral stenosis and regurgitation, Tricuspid regurgitation (1)
Dechallenge/Rechallenge	No information on positive dechallenge; six patients required valvular surgeries (one unknown). Rechallenge: not applicable
Outcome:	Death (1), Permanent disability (1), Required intervention (3), Other (2)
Concomitant diseases:	Obesity (3), Hypothyroidism (2), Depression (2), Asthma (2), CHF (1), Hypertension (1), DVT (1), Gangrene (1), Chronic sinusitis (1), Seizures (1), Pulmonary hypertension (1), Somatoform disorder (1), Acne (1),Retroperitoneal fibrosis (1),Ileus (1), and Viral syndrome (1).
Location:	Domestic (4), Foreign (3) *{Germany(literature report), Switzerland (literature report), Canada}*
Report type:	15-day reports (5), direct reports (2)
FDA receipt year:	1997 (1), 1998 (1), 1999 (1), 2000 (4) *{see Appendix A for event/report dates}*
Reporters:	U.S. cases: 2 lawyers, 2 physicians Foreign cases: 2 physicians, 1 unidentified healthcare professional

In these cases, the patients were predominantly female with ages ranging from 29 to 66 years with the mean and median of 46 and 45 years, respectively. There was no age for which cardiac valvulopathy was more prevalent. *(see Appendix B)*

The average dose was approximately 1 mg. The range was from 0.5 mg to 1 mg per administration. The reports indicate that the patients used 1 mg to 4.5 mg per day, which approximates 1-6 injections per day. In two patients, the doses and the frequency of use were not provided. The total weekly dose

and frequency were available for only one case where the patient used one 1mg injection/day, equaling 5-7 mg/ week. See Table 1 for more dosing details.

Table 1. DHE Use

Drug Used	No. of Patients	DHE Dose				Duration of DHE Use			Country
		Individual patient		Per day or week		Individual patient		Average	
DHE	2	unk	1 mg	unk	multiple inj/day	30 yrs	5 yrs	≈18 yrs	[redacted]
DHE + Redux	1	1 mg		3 mg/day		4 yrs		≈ 4 yrs	
DHE + Ergotamine	1	1 mg		1 mg/ day		8 yrs		≈ 8 yrs	
DHE + Ergotamine + Sansert	1	0.5 –1 mg		1 mg/ day (5-7 mg/week)		> 9 yrs		≈ 9 yrs	
DHE + Redux + Sansert	2	unk	0.75 mg	unk	4.5 mg/ day	unk	2 yrs	≈ 2 yrs	

*Unk= Unknown

DHE was most frequently delivered intramuscularly, but other routes included SC, IV, nasal, and oral. In three patients, both the injectable, *D.H.E. 45*, and the nasal spray, *Migranal*, were used *[e.g. Nasal/IV (1), Nasal/IM/IV (1), IM (2), SC (1), PO (1), IM/IV/SC/Nasal (1)]*.

The duration of use prior to the onset of symptoms ranged from 2 years to 30 years *{2 yrs, 4yrs, 5yrs, 8yrs, >9yrs, 30yrs}*. This information was not available for one patient. The mean and the median duration were 9.7 and 6.5 years, respectively. The most unusual case is the 30 year-use of DHE. This case was from a foreign literature report and did not contain any details of the events. Therefore, it is difficult to substantiate this duration of use without further details. Concomitant use of other drugs known to be associated with cardiac valvulopathy was not mentioned in the report.

In a second case, the patient used DHE for five years prior to the development of symptoms with no previous cardiac history and rheumatic fever. No concomitant use of other suspect drugs such as Redux, Sansert, and ergotamine was mentioned in this case. See below for more details.

Date of Report :11/14/00 (domestic)

Feb/2000
49 year old Caucasian female (DOB 8/23/50) with a history of severe migraine *(x 20 yrs)*, asthma, depression, and hypothyroidism presents with a 2 year history of progressive dyspnea on exertion which has progressed in the month prior to her diagnosis to one half block exertion. (2/00) Patient also started to develop lower extremity edema. Patient on chronic IV DHE for approximately 5 yrs. *[No hx of rheumatic fever]*

Medication: no prior use of Redux, Sansert, ergotamine, Imitrex

• DHE 1 mg IV x 5 yrs (mult inj/ day) – '96-'99?	• Migranal – '96-'98	• Naproxen	• Feldene
• Desipramine 100 mg QD	• Fiorinal	• Verapamil	• Vicodin prn
• Zoloft 15 mg QD	• Celebrex	• Effexor	• Tranzene
• Allegra 60 mg BID	• Reglan	• Azmacort	• Thyroid

Echocardiogram revealed normal left ventricular systolic function, rheumatic appearing valvular structures with severe mitral stenosis and regurgitation. There was also severe tricuspid valve regurgitation with markedly elevated right ventricular systolic pressure of 75 mmHg.

Transesophageal echocardiogram revealed chordal fusion and thickening of the submitral valve apparatus.

5/2000
Mitral valve replacement: during surgery, significant valvular disease w/ severe scarring and fusion of tricuspid and mitral valve apparatus noted. There was moderate shortening of subvalvular chordae. Surgeon noted unusual presentation for rheumatic dz.

5/10/200
Pathology: mitral valve surfaces tan-white, smooth, glistening, w/o areas of yellow discoloration or calcification. Valve tissue including chordae tendinae markedly thickened, ranging up to 0.3 cm. No vegetation.

Repeat ECHO: normal left ventricular systolic function. Moderate to severe tricuspid regurgitation w/ reduced pulmonary pressure of 40 mmHg.

Outcome: asymptomatic, walks 2 miles/day w/ no complaints

There were five cases where other drugs known to be associated with cardiac valvulopathy were used concomitantly with DHE. One patient used DHE for four years, and during that time, Redux was also used for 1 ½ months. Redux was discontinued approximately 4 months before the first onset of symptoms, and DHE was discontinued between two valve replacements. Another patient used Redux for approximately 14 months during the 2-year course of DHE. Redux was discontinued in the same month as the onset of symptoms, and DHE was discontinued 2 months after valve replacement. In this same patient, Sansert was used more than 9 years prior to the onset of symptoms for an unknown period of time.

In another case, DHE was used for more than 9 years, but during that time, ergotamine and Sansert were also used. Ergotamine was used sporadically for seven years, and Sansert was used for only 1½ months. DHE was discontinued when the valvular abnormality was discovered. Ergotamine was discontinued two years before the onset of symptoms. Sansert was used 7 years prior to the onset of symptoms.

In the other two cases, the duration of use and the overlap between DHE and other concomitant drugs were not available. In one case, DHE was used for 8 years and ergotamine was used "often" for an unidentified time. This was also a foreign literature report. In the second case, DHE, Redux, and Sansert were used, but no further information was given in terms of the timeline.

The patients presented with various symptoms such as shortness of breath (SOB), chest pain, tachycardia, dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, fullness in throat with a choking sensation, and/or peripheral edema. In addition to migraine, other medical conditions were listed in the reports as follows: *obesity (3), hypothyroidism (2), depression (2), asthma (2), CHF (1), hypertension (1), DVT (1), gangrene (1), chronic sinusitis (1), seizures (1), pulmonary hypertension (1), somatoform disorder (1), acne (1), retroperitoneal fibrosis (1), ileus (1), and viral syndrome (1).* The incidence of CHF and pulmonary hypertension occurred in the same patient secondary to valvular disease and/or fluid overload from steroid use. In regard to the history of hypertension in another patient, the foreign literature report did not provide any information regarding the possible role of HTN in this patient's valvular disorder.

All three patients with obesity used Redux. Moreover, there was no prior history of rheumatic fever in four patients. In the other three patients, only one case mentioned a history of rheumatic valve disease, but conflicting information was also present in the medical records. For example, in one of the documents, the patient, who was a nurse, denied any history of rheumatic fever.

There was one patient with tricuspid valve abnormality, four with both mitral and tricuspid valve abnormalities, one with only a mitral valve abnormality, and one with mitral, tricuspid, and aortic valve involvement. These reported findings were confirmed by echocardiograms in all cases. The mitral valve was the most commonly replaced valve, but tricuspid valve abnormality was also noted in all of the patients requiring mitral valve replacements. The time of onset of symptoms to surgery ranged from 7 days to 3 months. The reports indicate that valve replacements were performed in six cases. There were 5 single valve replacements, 1 double valve replacement, and 1 unknown case. There was an unusual case where a patient underwent a mitral valve replacement, but the use of DHE continued because the physician at the time did not make the connection between DHE use and valvulopathy. It was only after the tricuspid valve replacement that DHE was identified as the suspect drug. It is also noteworthy that in three patients, pulmonary hypertension was present as well.

In six cases, the cardiac valves were described as white, thickened, myxoid, fibrotic, and/or glistening in appearance. Furthermore, there were three noteworthy reports where the physician, operating surgeon, or the pathology report described the appearance of rheumatic valves. However, in one report, the pathology findings were also described as being similar to those reported in carcinoid syndrome and valvular diseases related to fen-phen or ergot-alkaloid use. Redux was concomitantly used with DHE in this patient. In another report, the diagnosis was consistent with rheumatic valvular structure, but the surgery reports indicated that it was an unusual presentation for rheumatic disease. This patient had no prior history of rheumatic disease. The third patient also displayed no prior history of rheumatic disease, but the echo and the pathology findings were consistent with rheumatic valve disease. However, the reporting physician was still not sure if the valvular disorder was related to ergots or rheumatic disease.

In four other cases, one physician attributed the valve damage to ergotamine medications. Another physician could not conclude that Redux or DHE caused the valve damage, but noted that the findings were consistent with the use of a dietary supplement. This patient had previously used Redux. There was no information in the other two cases. *(see Appendix C)*

In summary, the pathology findings were suggestive of possible drug-induced cardiac valvulopathy, but we could not conclude a causal relationship between DHE use and cardiac valvulopathy because there are many confounding factors that could challenge this association. For example, in five cases, the concomitant use of other drugs that are well associated with cardiac valvulopathy, such as Redux, Sansert, and/or ergotamine, precludes a direct association between cardiac valvulopathy and DHE use. Also, a prior history of rheumatic fever could not be ruled out in three cases. Moreover, in two cases, the concomitant use of other suspect drugs was not mentioned with DHE use, but one case lacked details to confirm the sole use of DHE.

VIII. CONCLUSION:

Since DHE was approved in 1946, only nine cases involving cardiac valvular disorders with DHE use have been received by the FDA, of which seven were selected for this case series. All cases were received in recent years, ranging from 1997-2000. It is unknown if the publicity of cardiac valvulopathy with Redux use has contributed to the awareness of drug-induced valve diseases and the reporting of such cases.

One case of cardiac valvulopathy with DHE use reported no obvious confounding factors. Six other cases had insufficient information and/or confounding factors. Although we cannot conclude from our seven cases that there is a direct association between DHE and cardiac valvulopathy, we also cannot

exclude the possibility that DHE could be associated with this adverse reaction especially since other ergot-alkaloids have shown an association with cardiac valvulopathy. Therefore, we recommend continued monitoring of cardiac valvulopathy with DHE use. We also recommend making a request to Novartis for an English translation of the two foreign literature reports and for more detailed information of the two excluded cases.

IX. BIBLIOGRAPHY:

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Signed 02-22-01

Lauren Lee, Pharm.D.
Post-Marketing Safety Evaluator

Concur:

Signed 02-22-01

Min Chen, R.Ph., M.S.
Team Leader

APPENDIX A

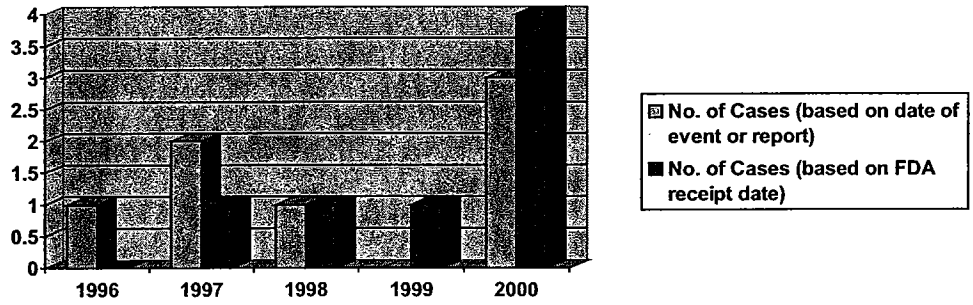
Reports of DHE Use and Cardiac Valvular Abnormality

	ISR#'s	Type of Report	*Date of Event or Report	FDA Receipt	**Serious (D/L/H/A/C/R/O) or Nonserious	U.S. or Foreign Reports
1	3491669-7	15-day	11/25/96 (Date of Event)	4/20/00	Serious; H, A, R	[redacted]
2	3001354-3	15-day	10/8/97 (Date of Report)	11/11/97	Serious: H, R	[redacted]
3	3259906-1	15-day	12/97 (Date of Event)	5/12/99	Serious: D, H, R	[redacted]
4	3075034-2	15-day	5/1/98 (Date of Report)	5/11/98	Serious: O	[redacted]
5	Not in AERS	direct report	2/00 (Date of Event)	2000	Serious: H,R	[redacted]
6	3544208-6	15-day	8/3/00 (Date of Report)	8/7/00	Serious: O	[redacted]
7	Not in AERS	direct report	10/16/00 (Date of Report)	2000	Serious: H, R	[redacted]

* Since the date of event was not provided in all of the cases, the date of the report was substituted to provide the case timeline .

** D=death; L=life-threatening; H=hospitalization (initial/prolonged); A=disability; C=congenital anomaly; R=required intervention to prevent permanent impairment/damage; O=other

*** Report from NOVARTIS, but this data was presented on a slide. See section VI(B) for detailed explanation.



APPENDIX B

Rough Data - Age/Gender

Gender	Age (years)			Source	Age (years) / Gender (male/female)
Male	57			U.S.	36F, 43F, 45F, 49F
Female	29, 36, 43, 45, 49, and 66			Foreign	29F, 57M, 66F

APPENDIX C

Synopsis of Diagnosis & Pathology

	Age (yr) Sex	Diagnosis of valve abnormality	Valve replaced	Pathology	Pulm HTN	Drug Use *D/R/ S/E/I	Country
1	57 M	Mitral valve fibrosis	UK	UK	UK	D	
2	36 F	**Rheumatic appearing mitral valve** with severe regurgitation, moderate tricuspid valve regurgitation	MIT, TRI	**MIT:** myxomatous degeneration of mitral valve; thickened with shortening and fusing of chordae tendinae **During Operation:** obvious **rheumatic valvular disease** without much calcification **TRI**: moderate myxoid degeneration and fibrosis on valve; **findings similar to those reported in fen/phen and ergot-alkaloid** related valvular diseases and in situation in which serotonin-rich blood bathes cardiac valve in the **carcinoid syndrome**	Yes	D/R	
3	43 F	Thickened/redundant mitral valve leaflets, no prolapse or stenosis; severe mitral insufficiency; mild to moderate tricuspid insufficiency; severe mitral and significant tricuspid regurgitation	MIT	**MIT:** valve leaflet thickened, white, glistening; diagnosis of fibromyxoid thickening. Physician attributed valve damage to expose to **ergotamine** medications	Yes; mild	D/R/ S/I	
4	66 F	Endocardial fibrosis; tricuspid valve insufficiency; tricuspid valve density and thickness appeared increased up to and extending into valvular ring and functionally seemed virtually rigid in open position.	TRI	**TRI:** Not provided	UK	D/E	
5	29 F	Severe mitral valve regurgitation due to degenerative mitral valve prolapse **possibly related to fen-phen;** tricuspid and aortic valve damaged but no significant leak to replace valve.	MIT (need replace again in 10yrs)	**MIT:** Thickened, white valve; fibromyxoid changes consistent w/ but not **diagnostic of valve dz secondary to amine-type dietary supplement; valve not conclusive to determine if DHE or Redux caused damage.** **During Operation:** pale valve leaflets noted; no vegetation; no torn leaflets	Yes	D/R/S	

6	45 F	Mild aortic insufficiency; mild tricuspid regurgitation; mild mitral stenosis; mitral insufficiency; mitral leaflet thickened and excursion decreased w/ tethered appearance consistent with **rheumatic valve;** subvalvular chordae also thickened from mitral valve leaflets to papillary muscle. However, rheumatic fever never diagnosed and the physician is **not clear if valvular pathology related to ergots or rheumatic dz.**	MIT	**MIT:** diffusely distributed, scant calcifications **During Operation:** fibrotic valve, moderately calcified (chunks) with total obliteration of subvalvular mechanism of post leaflet and significant obliteration of papillary muscle and cords on anterior leaflet; seem compatible with old **rheumatic dz**	UK	D/E/S /I	[redacted]
7	49 F	Severe mitral stenosis and regurgitation with **rheumatic appearing** valvular structures; cordal fusion and thickening of submitral valve apparatus; severe tricuspid regurgitation	MIT	**MIT:** fibrous thickening; surfaces tan-white, smooth, glistening w/o areas of yellow discoloration or calcification; no vegetation; chordae tendinae markedly thickened ranging up to 0.3 cm. **During Operation:** significant valvular dz w/ severe scarring; fusion of tricuspid and mitral valve apparatus noted; moderate shortening of subvalvular chordae; **unusual presentation for rheumatic dz**	No	D	[redacted]

*Concomitant drugs used: R= Redux, S= Sansert, E= Ergotamine, I= Imitrex
MIT = mitral valve; TRI= tricuspid valve
"During operation" = contains surgeon's comments during valve surgery

APPEARS THIS WAY
ON ORIGINAL

/s/

Lauren Lee
3/2/01 12:42:57 PM
PHARMACIST

Julie Beitz
3/2/01 01:43:50 PM
DIRECTOR

Appendix G - OPDRA Consult: sumatriptan and Cardiac Valvulopathy

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

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

PID#: D010075

DATE: March 1, 2001

FROM: Lauren Lee, Pharm.D.
Post-marketing Safety Evaluator
Division of Drug Risk Evaluation I, HFD-430

THROUGH: Julie Beitz, M.D., Director ***Signed 03-12-01***
Division of Drug Risk Evaluation I, HFD-430

TO: Russell Katz, M.D., Director
Division of Neuropharmacological Drug Products, HFD-120

SUBJECT: OPDRA Post-marketing Safety Review

- **Drugs:** **NDA 20-626, 20-080, 20-132 / Applicant: GLAXO WELLCOME**
  Imitrex (sumatriptan nasal spray); 5, 10, and 20 mg/ spray
  Imitrex (sumatriptan succinate injection); 6 mg/ 0.5 mL
  Imitrex (sumatriptan succinate tablets); 25 and 50 mg

- **Reaction:** **Cardiac valvulopathy**

CONFIDENTIAL: CONTAINS IMS DATA; NOT TO BE USED OUTSIDE OF THE FDA WITHOUT CLEARANCE FROM IMS.

I. EXECUTIVE SUMMARY:

This consult is in response to a January 11, 2001 request, by the Division of Neuropharmacological Drug Products, to review case reports of cardiac valvulopathy with sumatriptan use and to compare the sumatriptan and DHE case series regarding the subcutaneous and the nasal spray formulation. The association between DHE and cardiac valvular disease was addressed in a former consult dated February 27, 2001 (PID # D010004).

Among 6708 reports of *all* adverse drug events in AERS with Imitrex (sumatriptan), we reviewed 84 cases from our searches and retrieved three possible cases of cardiac valvulopathy with Imitrex use. However, based on the available information in these three cases, we cannot be certain of any association between Imitrex and cardiac valvulopathy. In one case (5183919), mitral prolapse was diagnosed during a routine medical visit in a patient who reported no problems with 17 months of Imitrex use. However, the exact frequency of injections in relation to the event was not specified. The report did not mention any significant cardiac history or concomitant use of drugs associated with cardiac valvulopathy. No outcome information was available for this case. In the second case (3471806), mitral regurgitation was diagnosed per echocardiogram in a patient who had taken Imitrex orally and developed chest pressure, increased PVC's, and an abnormal EKG. When Imitrex was discontinued, EKG abnormality resolved, but other events remained at the time of the reporting. The patient had previously experienced chest pressure with injectable Imitrex six months ago, but

symptoms resolved when the drug was discontinued. It is not clear how many doses and how frequent the oral and injectable Imitrex were used in this patient. No concomitant drugs associated with cardiac valvulopathy were used. In the third case (5287663), mitral valve regurgitation was diagnosed in a patient who presented with an *exacerbation* of "breathing problems" after one year of Imitrex use. This patient had a history of congestive heart failure and "breathing problems" from prior radiation therapy for Non-Hodgkin's disease. Since symptoms were improved with digoxin, furosemide, benazepril, flunisolide, ipratropium, albuterol, and the discontinuation of Imitrex injections, mitral valve regurgitation in this case might be secondary to the preexisting congestive heart failure. No concomitant drugs associated with cardiac valvulopathy were used.

Given the above three cases, we cannot be certain of any association between Imitrex and cardiac valvulopathy. Accordingly, a comparison between Imitrex and DHE case series regarding the subcutaneous and the nasal spray formulations could not be made.

II. DRUG INFORMATION AND LABELING:

Sumatriptan is a selective agonist for a vascular 5-hydroxytryptamine$_1$ receptor subtype (probably a member of the 5-HT $_{1D}$ family) with no significant affinity (as measured using standard radioligand binding assays) or pharmacological activity at 5-HT $_2$, 5-HT $_3$ receptor subtypes or at alpha $_1$-, alpha $_2$, or beta-adrenergic; dopamine $_1$; dopamine $_2$; muscarinic; or benzodiazepine receptors. The vascular 5-HT $_1$ receptor subtype to which sumatriptan binds selectively, and through which it presumably exerts its antimigrainous effect, has been shown to be present on the human basilar artery, and in the vasculature of the isolated dura mater. In these tissues, sumatriptan activates this receptor to cause vasoconstriction, an action correlating with the relief of migraine and cluster headache. [1]

Drug Product	NDA	Applicant	FDA Approval	Approved Strength	Supplied
Imitrex (sumatriptan succinate injection)	20-080	Glaxo Wellcome	**12/28/1992**	6 mg/ 0.5 mL (12 mg/1 mL)	0.5 mL unit single dose prefilled syringes, 6 mg single dose vials, Statdose system
Imitrex (sumatriptan succinate tablets)	20-132	Glaxo Wellcome	6/1/1995	25 and 50 mg	Blister pack of 9 tablets
Imitrex (sumatriptan nasal spray)	20-626	Glaxo Wellcome	**8/26/1997**	5, 10, and 20 mg/ spray	Unit dose sprays
D.H.E. 45 (dihydroergotamine mesylate injection)	5-929	Novartis	**4/12/1946**	1mg/ mL	1 mL sterile ampuls
Migranal (dihydroergotamine mesylate nasal spray)	20-148	Novartis	**12/8/1997**	4 mg/ mL or 0.5 mg/ spray	1 mL amber glass ampuls

Imitrex tablets, nasal spray, and injection are indicated for the acute treatment of migraine attacks with or without aura. In addition, the injectable Imitrex is indicated for the acute treatment of cluster headache episodes. However, the safety and effectiveness of Imitrex nasal spray and tablets have not been established for cluster headache.

The maximum single recommended adult dose of Imitrex injection is 6 mg. The maximum recommended dose that may be given in 24 hours is two 6 mg injections separated by at least 1 hour.

[1] Imitrex package insert

Since the injection is intended to be given subcutaneously, intramuscular or intravascular delivery should be avoided.

Imitrex nasal spray dose should be made on an individual basis. A 10 mg dose may be achieved by the administration of a single 5 mg dose in each nostril. If the headache returns, the dose may be repeated once after 2 hours, not to exceed a total daily dose of 40 mg. The safety of treating an average of more than four headaches in a 30 day period has not been established.

Similarly, Imitrex tablet dose should be made on an individual basis. If the headache returns or the patient has a partial response to the initial dose, the dose may be repeated after 2 hours, not to exceed a total daily dose of 200 mg. If a headache returns following an initial treatment with Imitrex injection, additional single Imitrex tablet (up to 100 mg/day) may be given with an interval of at least 2 hours between tablet doses. The safety of treating an average of more than 4 headaches in a 30 day period has not been established.

LABELING OF CARDIAC VALVULAR DISEASE

The labeling for sumatriptan does not mention any cardiac *valve-related* adverse events. See Appendix A for other labeled cardiac events.

III. MEDICAL LITERATURE SUMMARY:

On 1/18/01, Medline *(Pubmed)* internet searches were conducted to retrieve any published literature cases involving sumatriptan and cardiac valve-related adverse events. Both the generic and the proprietary name, Imitrex, were searched in conjunction with the following *Medline **Mesh** Terms*:

Heart valve, heart valve disease, mitral valve, aortic valve, tricuspid valve, mitral valve stenosis, aortic valve stenosis, tricuspid valve stenosis, mitral regurgitation, aortic regurgitation, tricuspid regurgitation, prolapse, and fibrosis.

The searches did not reveal any cases of cardiac valvular disorder in association with sumatriptan.

IV. DRUG USAGE DATA:

The following chart contains the projected number of total prescriptions dispensed by retail pharmacies *(chain, independent, food stores, and mail order)* in the U.S. for sumatriptan from the National Prescription Audit Plus of IMS Health. The data are stratified by the dosage form and the manufacturer's product, and presented by calendar year (1995 through 2000). *[Add three 000's to each figure]*

	Total (1995-2000)	2000 Total Rx	1999 Total Rx	1998 Total Rx	1997 Total Rx	1996 Total Rx	1995 Total Rx
Sumatriptan							
Tabs Coated							
Systemic Kits							
Nasal Spray Systemic							
Vial Regular S.C.Only							

Source: IMS Health; National Prescription Audit Plus, On-line (Not to be used outside of FDA)
Blank field means no data
Total includes new and refill prescriptions

V. SELECTION OF CASE SERIES:

On 1/20/01, we searched the old SRS database using the COSTART term, "STENO AORTIC," and the drug name, "sumatriptan." The search did not reveal any case of cardiac valvular disorder in association with sumatriptan use.

We also searched the AERS database, and among 6708 reports of *all* adverse drug events in AERS with sumatriptan, we retrieved 28 cases searched under "Valvular heart disorders" (HLGT) and 56 cases under "Cardiac Disorders NOS" (HLT). Among a total of 84 cases, there were nine reports of cardiac valvulopathy with sumatriptan use, eleven of sumatriptan use concomitantly with anorexiants, and three of sumatriptan use concomitantly with ergot-alkaloids and/or dexfenfluramine. The remaining 61 cases were either duplicates or lacked cardiac valve-related adverse events.

In the first set of nine cases of cardiac valvulopathy with sumatriptan use, we excluded six cases due to the following reasons: 1) diagnosis of a mitral valve insufficiency nine months after a single dose of Imitrex, 2) previous history of cardiac valve disease and Marfan's syndrome, 3) findings consistent with mucoid degeneration of an aortic valve in a patient who had coincidentally received a single dose of Imitrex days prior to the event, 4) transient valve regurgitation secondary to acute myocardial infarction, 5) valve insufficiency from youth, 6) valvular prolapse/insufficiency secondary to acute myocardial infarction after two doses of Imitrex.

All eleven cases where Imitrex was concomitantly used with two or more anorexiants, such as fenfluramine, phentermine, and dexfenfluramine, were excluded because these cases lacked sufficient information to establish a true temporal and causal relationship between Imitrex use and cardiac valvulopathy. Furthermore, we could not conclude that the above anorexiants did not contribute to cardiac valvulopathy in these cases. In addition, one case also mentioned a prior history of valvulopathy, and in another case, a possible history of rheumatic fever was mentioned. Hypertension was also noted in one case as a possible cause of the adverse event.

The three cases involving Imitrex use with ergot-alkaloids and/or dexfenfluramine were also excluded from the case series. One reported acute myocardial infarction and stroke following the use of Imitrex with only a mention of a "possible aortic valve disease" from an unknown laboratory finding. Cafergot was also used in this patient for at least five years, and we could not conclude that this drug did not contribute to the events of this case. Another case did not provide sufficient information regarding the details of Imitrex use in a patient who was also taking Sansert and dexfenfluramine. The third case reported "a mild myxomatous change in the mitral valve" from an autopsy report, and a valvular disorder was not confirmed. This patient had used Imitrex and dihydroergotamine. The reported event was death secondary to myocarditis of a viral origin.

The remaining three cases of mitral valve regurgitation or prolapse are in this case series and are reviewed for a possible association with cardiac valvulopathy.

VI. SUMMARY OF CASES:

The demographic information of the three cases is as follows:

	Overview (Patient 1, 2, & 3)	Patient 1	Patient 2	Patient 3
Age in years:	Range 46-54, mean 49, median 47	46	54	47
Gender:	F (n=3)	F	F	F

Time to onset:	12 and 17 months; unknown (n=1)	17 months	12 months	Unk
Dose:	6 mg (n=2), 150 mg (n=1)	6 mg prn	6 mg dose, 2 times/week	150mg (oral) unk (inj)
Route:	SC (n=2), SC then oral (n=1)	SC	SC	SC then oral *[not used together]*
Events reported:	Mitral valve regurgitation (n=2), mitral valve prolapse (n=1)	Mitral valve prolapse	Mitral valve regurgitation, exacerbation of breathing problems	Mitral valve regurgitation
Dechallenge/ Rechallenge	(+)dechallenge (n=1),(-)dechallenge (n=1), unknown (n=1)	Unknown	(+) dechallenge	(-) dechallenge
Outcome:	Other (n=2), Unk (n=1)	Unknown	Other	Other
Location:	Domestic (n=3)	Domestic	Domestic	Domestic
Report type:	Periodic (n=3)	Periodic	Periodic	Periodic
FDA receipt year:	1994 (n=1), 1995 (n=1), 1999 (n=1)	1994	1995	1999
Reporters:	Consumers (n=3)	Consumer	Consumer	Consumer

*Unk= unknown

Based on the available information of these three cases, we cannot be certain of any association between Imitrex and cardiac valvulopathy. These three consumer reports did not present sufficient evidence to support that cardiac valvulopathy was directly related to Imitrex use. In the first case (5183919), mitral prolapse was diagnosed during a routine medical visit in a 46-year old female who reported no problems with 17 months of Imitrex use. The reported dose of 6 mg was used subcutaneously. However, the exact frequency of injections in relation to the event was not specified. The report did not mention any significant cardiac history or concomitant use of drugs associated with cardiac valvulopathy. No outcome information was available for this case.

In the second case (3471806), mitral regurgitation was diagnosed per echocardiogram in a 47-year old female who had taken 150 mg of Imitrex orally and developed chest pressure, increased PVC's, and an abnormal EKG. When Imitrex was discontinued, EKG abnormality resolved, but other events remained at the time of the reporting. The patient had previously experienced chest pressure with injectable Imitrex six months ago, but symptoms resolved when the drug was discontinued. It is not clear how many doses and how frequent the oral and injectable Imitrex were used in this patient. No concomitant drugs associated with cardiac valvulopathy were used.

In the third case (5287663), mitral valve regurgitation was diagnosed in a 54-year old female who presented with an *exacerbation* of "breathing problems" after one year of Imitrex use. The patient was using 6 mg injections twice per week. This patient had a history of congestive heart failure and "breathing problems" from prior radiation therapy for Non-Hodgkin's disease. Since symptoms were improved with digoxin, furosemide, benazepril, flunisolide, ipratropium, albuterol, and the discontinuation of Imitrex, mitral valve regurgitation in this case might be secondary to the preexisting congestive heart failure. No concomitant drugs associated with cardiac valvulopathy were used.

VII. CONCLUSION:

Among 6708 reports of *all* adverse drug events in AERS with Imitrex (sumatriptan), we reviewed 84 cases from our searches and retrieved three possible cases of cardiac valvulopathy with Imitrex use. However, these three consumer reports did not present sufficient evidence to support that cardiac valvulopathy was directly related to Imitrex use. In the first two cases, the frequency of Imitrex use in relation to the adverse event is unknown. Also, symptoms were not resolved upon the discontinuation of the drug in the second case. In the third case, the reported event might be related to the preexisting

congestive heart failure. Based on the available information of these three cases, we cannot be certain of any association between Imitrex and cardiac valvulopathy at this time. Accordingly, a comparison between Imitrex and DHE case series regarding the subcutaneous and the nasal spray formulations could not be made.

Signed 03-11-01
Lauren Lee, Pharm.D.
Post-Marketing Safety Evaluator

Concur:

Signed 03-11-01
Min Chen, R.Ph., M.S.
Acting Team Leader
Associate Division Director

1 pages redacted from this section of the approval package consisted of draft labeling

/s/

Lauren Lee
3/20/01 03:16:49 PM
PHARMACIST

Julie Beitz
3/21/01 01:15:47 PM
DIRECTOR

Appendix H - Clean Running Version of Recommended Labeling

DHE 45 (NDA 05-929) and Migranal Nasal Spray (NDA 20-148)

CLINICAL PHARMACOLOGY

Pharmacokinetics: Interactions

[

]

WARNINGS

Fibrotic Complications

[

]

PRECAUTIONS

Fibrotic Complications: **see WARNINGS: Fibrotic Complications.**

Information for Patients

Administration of D.H.E. 45 (dihydroergotamine mesylate) Injection / Migranal (dihydroergotamine) Nasal Spray, USP, should not exceed the dosing guidelines and should not be used for chronic daily administration (see DOSAGE AND ADMINISTRATION).

CYP 3A4 Inhibitors [New Section – replaces "Macrolide Antibiotics"]

[

]

[

]

DOSAGE AND ADMINISTRATION
D.H.E. 45 (dihydroergotamine mesylate) Injection / Migranal (dihydroergotamine) Nasal Spray, USP, should not be used for chronic daily administration.

Cafergot Suppositories (NDA 09-000)
CLINICAL PHARMACOLOGY
Pharmacokinetics: Interactions [New Section-from Sponsor]

[redacted]

CONTRAINDICATIONS [New Section]
Coadministration of ergotamine with potent CYP 3A4 inhibitors (ritonavir, nelfinavir, indinavir, erythromycin, clarithromycin, and troleandomycin) has been associated with acute ergot toxicity (ergotism) characterized by vasospasm and ischemia of the extremities (see PRECAUTIONS: Drug Interactions), with some cases resulting in amputation. Because of the increased risk for ergotism and other serious vasospastic adverse events, ergotamine use is contraindicated with these drugs and other potent inhibitors of CYP 3A4 (e.g., ketoconazole, itraconazole) (see WARNINGS: CYP 3A4 Inhibitors).

[redacted]

CYP 3A4 Inhibitors [New Section]

[redacted]

PRECAUTIONS
Drug Interactions [New Section]
CYP3A4 Inhibitors: see CONTRAINDICATIONS and WARNINGS.

[

]

ADVERSE EVENTS
Fibrotic complications: (see WARNINGS).

DOSAGE AND ADMINISTRATION

APPEARS THIS WAY
ON ORIGINAL

/s/

Armando Oliva
3/22/01 02:22:51 PM
MEDICAL OFFICER

hard copy is in your inbox

Russell Katz
3/27/01 03:08:31 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICATION INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
NOVARTIS PHARMACEUTICALS CORPORATION	**December 23, 1999**
TELEPHONE NO. (*Include Area Code*) **(973) 781-3217**	FACSIMILE (FAX) Number (*Include Area Code*) **973-781-6325**
APPLICANT ADDRESS (*Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* **59 Route 10 East Hanover, New Jersey 07936-1080**	AUTHORIZED U.S. AGENT NAME & ADDRESS (*Number, Street, City, State, ZIP Code, telephone & FAX number*) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) **20-148**

ESTABLISHED NAME (*e.g., Proper name, USP/USAN name*)	PROPRIETARY NAME (*trade name*) IF ANY
(ergotamine USP)	**Cafergot®**

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (*If any*) | CODE NAME (*If any*)

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Suppository		

(PROPOSED) INDICATION(S) FOR USE:

APPEARS THIS WAY ON ORIGINAL

APPLICATION INFORMATION

APPLICATION TYPE
(check one) ☐ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug | Holder of Approved Application

TYPE OF SUBMISSION
(check one) ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☒ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION

PROPOSED MARKETING STATUS (check one) ☐ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 | THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Application, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: (*Check all that apply*)

	1. Index
X	2. Labeling (check one) ☒ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and control information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k) (1))
	17. Field copy certification (21 CFR 314.50 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606 and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact law.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been review and, to the best of my knowlegde are certified to be true and accurate.

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SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
M. Struck	**Martina Struck, Ph.D.** **Drug Regulatory Affairs**	**12/23/99**

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
59 Route 10 **East Hanover, New Jersey 07936-1080**	**((973) 781-3217**

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

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17-1

MEMORANDUM OF MEETING MINUTES

Meeting Date: October 20, 1999
Location: WOCII 4th Floor Conference Room
Applications: NDAs 5-929/S-032, 6-620, [redacted]S-022, 20-148/S-007
Type of Meeting: To discuss safety issues in labeling
Meeting Chair: Russell Katz, MD
Meeting Recorder: Lana Chen, RPh

FDA Attendees
Robert Temple, MD, Russell Katz, MD, Randy Levin, MD, Armando Oliva, MD, Greg Burkhart, MD, Glenna Fitzgerald, PhD, Charlene Flowers, Vijay Tammara, PhD, Lana Chen, RPh

External Constituent Attendees
T. Koestler, R. Hume, D. Ventura, J. Haas, J. Pincus, M. Struck, R. Dodsworth, S. Witham

Meeting Objectives:

The Sponsor requests discussion with the Agency regarding improving the safety of labeling regarding cardiac valvular changes and interactions with potent CYP 3A4 inhibitors,

Discussion Points (bullet format):

1. **Prolonged Chronic Daily Use:** The Agency requests that [redacted]
2. **CYP 3A4 Inhibitors:** Interactions with potent inhibitors should be included prominently in labeling, specifically in the Contraindications section. Pharmacokinetic studies may be needed to determine which drugs are potent inhibitors. May also consider including this in the patient package insert.
3. **Heparin:** Vasospasm should be included in the labeling under ergotism warnings.

Decisions (agreements) reached:

1. The Division will provide Sponsor with a response to the labeling supplements submitted in early October.

2. The Sponsor will submit pharmacokinetic information describing ergotamine and dihydroergotamine as CYP 3A4 inhibitors.

Unresolved issues or issues requiring further discussion:

None.

Action Items:

See under **Decisions reached** above.

Minutes Preparer: _____

Lana Chen, R.Ph.
Project Manager, DNDP

Chair Concurrence: _____

Randy Levin, MD
Team Leader, Neurology
(designated signatory)

APPEARS THIS WAY
ON ORIGINAL

cc: Original
HFD-120/Div. Files
HFD-120/Chen
HFD-120/Katz/Levin/Oliva/Burkhart

HFD-860/Tammara

Draft: December 2, 1999
Final: 2/4/00

C:\wpfiles\migranal\20oct99mm.doc

MEETING MINUTES

APPEARS THIS WAY
ON ORIGINAL

FOOD AND DRUG ADMINISTRATION
DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
(HFD-120)
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857
FAX (301) 594-2859

Telecopier Cover Sheet

DATE: February 9, 2000
TIME:

DELIVER TO: Ms. Martina Struck
Fax Number: 973.781.6325

FROM: Lana Chen, R. Ph.
Regulatory Management Officer.
Ph 301.594.5529

Total number of pages, including cover page: 4 (MC)
If you do not receive all pages or have any problems with receiving, call (301) 594-2850.

MESSAGE:

Martina,

Re:

DHE 45 (NDA 05-929)
Migranal Nasal Spray (NDA 20-148)
Cafergot Tablets (NDA 06-620)
[redacted]

Please see our attached labeling comments in response to your October 8, 1999 and December 22, 1999 submissions.

Thanks,
Lana

3 pages redacted from this section of the approval package consisted of draft labeling

Cc: NDA 05-929
NDA 20-148
NDA 06-620
NDA 09-000
Div Files

HFD-120/Levin/Oliva NO 2/9/00
HFD-120/Chen RLC 2/9/00

HFD-860/Tammara 2/10/00

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICATION INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
NOVARTIS PHARMACEUTICALS CORPORATION	
TELEPHONE NO. (*Include Area Code*)	FACSIMILE (FAX) Number (*Include Area Code*)
(973) 781-4149	(973) 781-6325
APPLICANT ADDRESS (*Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	AUTHORIZED U.S. AGENT NAME & ADDRESS (*Number, Street, City, State, ZIP Code, telephone & FAX number*) IF APPLICABLE
59 Route 10 East Hanover, New Jersey, 07936-1080	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) **9-000**

ESTABLISHED NAME (*e.g., Proper name, USP/USAN name*)	PROPRIETARY NAME (*trade name*) IF ANY
(ergotamine USP)	**Cafergot®**

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (*If any*)	CODE NAME (*If any*)

DOSAGE FORM	STRENGTHS	ROUTE OF ADMINISTRATION
Suppositories		

(PROPOSED) INDICATION(S) FOR USE:

APPEARS THIS WAY
ON ORIGINAL

APPLICATION INFORMATION

APPLICATION TYPE
(check one) ☐ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION
(check one) ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☒ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

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PROPOSED MARKETING STATUS (check one) ☐ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

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	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
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	16. Debarment certification (FD&C Act 306 (k) (1))
	17. Field copy certification (21 CFR 314.50 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
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2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
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SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
	Kay A Chitale, PharmD Drug Regulatory Affairs	10/14/99

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
59 Route 10 East Hanover, New Jersey, 07936-1080	(973) 781-4149

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20.1

Electronic Mail Message

N-9000

Date: 8/24/00 10:42:01 AM
From: Paul David (DNPDP/ODEI) (DAVID)
To: Savithri Chandra * (CHANDRAS)
Cc: Robbin Nighswander (NIGHSWANDER)
Cc: Lana Chen (CHENLA)
Cc: Armando Oliva (OLIVAA)
Cc: Paul David (DNPDP/ODEI) (DAVID)
Subject: 7-7-00 Submissions to NDAs 5-929, 20-148, and 9-000

Ms. Savithri,
Please administratively cancel the labeling supplements dated 7-7-00 submitted to the DHS-45 Injection (5-929/SLR-035), Migranal nasal spray (NDA 20-148/SLR-010) and Cafergot suppositories (NDA 9-000/SLR-025) NDAs.

The 7-7-00 submission should, instead of being coded as an original labeling supplement, be coded as major clinical amendments to the following supplemental applications:

5-929/SLR-032/SLR-033
20-148/SLR/007/SLR-008
9-000/SLR-022/SLR-023

This submission should then be checked out to Dr. Oliva for review.

Thank you,
Paul David

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICATION INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
NOVARTIS PHARMACEUTICALS CORPORATION	February 25, 2002
TELEPHONE NO. *(Include Area Code)*	FACSIMILE (FAX) Number *(Include Area Code)*
(973) 781-3217	(973) 781-7177
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
One Health Plaza East Hanover, New Jersey 07936-1080	

PRODUCT DESCRIPTION

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ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
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CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)* | CODE NAME *(If any)*

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Suppositories		

(PROPOSED) INDICATION(S) FOR USE:

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Name of Drug | Holder of Approved Application

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☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT

☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

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SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
M. Struck	Martina Struck, Ph.D., Associate Director Drug Regulatory Affairs	**02/25/02**

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
One Health Plaza East Hanover, New Jersey 07936-1080	(973) 781-3217

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Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICATION INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
NOVARTIS PHARMACEUTICALS CORPORATION	April 16, 2002
TELEPHONE NO. *(Include Area Code)*	FACSIMILE (FAX) Number *(Include Area Code)*
(973) 781-3217	(973) 781-7177
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
One Health Plaza East Hanover, New Jersey 07936-1080	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* **9-000/S-007, S-008**

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CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)* — CODE NAME *(If any)*

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Suppositories		

(PROPOSED) INDICATION(S) FOR USE:

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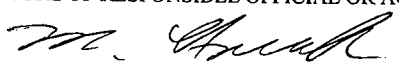
1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowlegde are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
	Martina Struck, Ph.D., Associate Director Drug Regulatory Affairs	04/16/02

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
One Health Plaza East Hanover, New Jersey 07936-1080	(973) 781-3217

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICATION INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
NOVARTIS PHARMACEUTICALS CORPORATION	November 12, 2002
TELEPHONE NO. (*Include Area Code*) (973) 781-3271	FACSIMILE (FAX) Number (*Include Area Code*) (973) 781 7177
APPLICANT ADDRESS (*Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* One Health Plaza East Hanover, New Jersey 07936-1080	AUTHORIZED U.S. AGENT NAME & ADDRESS (*Number, Street, City, State, ZIP Code, telephone & FAX number*) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* **9-000**

ESTABLISHED NAME (*e.g., Proper name, USP/USAN name*)	PROPRIETARY NAME (*trade name*) IF ANY
ergotamine tartrate and caffeine, usp	**Cafergot®**

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (*If any*) | CODE NAME (*If any*)

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Suppositories		

(PROPOSED) INDICATION(S) FOR USE:

ARCHIVE THIS WAY
ON ORIGINAL

APPLICATION INFORMATION

APPLICATION TYPE *(check one)*

☐ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)

☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION

☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT

☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Copy Of Dear Health Care Provider Letter

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 | THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: (*Check all that apply*)	
	1. Index
	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50 (d)(1); 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g., 21 CFR 314.50 (e)(2)(i); 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50 (d)(2); 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50 (d)(3); 21 CFR 601.2)
	7. Clinical Microbiology (e.g., 21 CFR 314.50 (d)(4))
	8. Clinical data section (e.g., 21 CFR 314.50 (d)(5); 21 CFR 601.2)
	9. Safety update report (e.g., 21 CFR 314.50 (d)(5)(vi)(b); 21 CFR 601.2)
	10. Statistical section (e.g., 21 CFR 314.50 (d)(6); 21 CFR 601.2)
	11. Case report tabulations (e.g., 21 CFR 314.50 (f)(1); 21 CFR 601.2)
	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b)(2) or (j)(2)(A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k)(3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. Financial Information (21 CFR Part 54)
x	20. OTHER *(Specify)* Copy of Dear Health Care Provider Letter

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowlegde are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
	Martina Struck, Ph.D., Associate Director Drug Regulatory Affairs	**11/12/02**

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
One Health Plaza East Hanover, New Jersey 07936-1080	(973) 781-3217

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

9-000/S-022/S-023

CORRESPONDENCE

NDA SUPPLEMENT

NOVARTIS ORIGINAL

October 8, 1999

NDA NO. 9-000 REF NO. SLR-022
NDA SUPPL FOR Draft Labeling

Russell Katz, MD
Acting Director
Division of Neuropharmacological
Drug Products/HFD-120
Office of Drug Evaluation I
Attn: Document Room
Center for Drug Evaluation and Research
Woodmont II, 1451 Rockville Pike
Rockville, MD 20852

NDA No. 9-000
Cafergot® (ergotamine USP) Suppositories

CENTER FOR DRUG EVALUATION AND RESEARCH

NDA Supplement: OCT 15 1999
Draft Labeling

RECEIVED HFD-120

Dear Dr. Katz:

In accordance with 21 CFR §314.70 (b)(3), Novartis Pharmaceuticals Corporation herewith submits the attached draft labeling to the CLINICAL PHARMACOLOGY and PRECAUTIONS sections of the package insert for Cafergot® (ergotamine tartrate and caffeine) Suppositories, USP. Separate "draft labeling" supplements were also submitted to the appropriate NDAs for D.H.E. 45® (dihydroergotamine mesylate) Injection, (NDA No. 5-929) and Migranal® (dihydroergotamine mesylate) Nasal Spray (NDA No. 20-148) on October 8, 1999.

Enclosed are the following documents:

- Summary of labeling changes
- Annotated package insert
- Current package insert (No. 89001301 T1999-04)
- Diskette in Word 6.0 of the proposed changes (all diskettes have been scanned for viruses using VIRUSCAN Version 3.1.4a McAfee Associates)
- Reference articles

If you have any questions, please contact me at (973) 781-4149.

Sincerely,

Kay A. Chitale, PharmD
Drug Regulatory Affairs Fellow

4 copies of "Draft Labeling" Supplement submitted to the Agency
cc: Ms. Lana Chen, Regulatory Management Officer- letter only

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

17.1

NDA 9-000/S-022

DEC - 3 1999

Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, New Jersey 07936-1080

Attention: Kay A. Chitale, Ph. D.
Drug Regulatory Affairs Fellow

Dear Ms. Chitale:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Cafergot (ergotamine USP) Suppositories

NDA Number: 9-000

Supplement Number: 022

Date of Supplement: 08-Oct-99

Date of Receipt: 15-Oct-99

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on 14-Dec-99 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Office of Drug Evaluation I
Attention: Document Control Room 4008
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

(for) 12/3/99

John S. Purvis
Chief, Project Management Staff
Division of Neuropharmacological Drug Products, HFD-120
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Original NDA 9-000/022
HFD-120/Div. Files
HFD-120/CSO/Chen

filename:

SUPPLEMENT ACKNOWLEDGEMENT

NDA NO. 9-000 REF NO. SLR-023
NDA SUPPL FOR Labeling

NOVARTIS

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 7500
Fax 973 781 6325

December 22, 1999

ORIGINAL

NDA SUPPLEMENT

Russell Katz, MD
Director
Division of Neuropharmacological
Drug Products/HFD-120
Office of Drug Evaluation I
Attn: Document Room
Center for Drug Evaluation and Research
Woodmont II, 1451 Rockville Pike
Rockville, MD 20852

NDA No. 9-000
Cafergot® (ergotamine USP) Suppositories

CENTER FOR DRUG EVALUATION AND RESEARCH

DEC 27 1999

RECEIVED HFD-120

NDA Supplement:
Draft Labeling

Dear Dr. Katz:

In accordance with 21 CFR §314.70 (b)(3) and per discussions at the October 20, 1999 meeting with the Division, Novartis Pharmaceuticals Corporation herewith submits the attached draft labeling with modifications to the WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION sections of the package insert for Cafergot® (ergotamine tartrate and caffeine) Suppositories, USP. Separate "draft labeling" supplements were also submitted to the appropriate NDAs for D.H.E. 45® (dihydroergotamine mesylate) Injection, (NDA No. 5-929) and Migranal® (dihydroergotamine mesylate) Nasal Spray (NDA No. 20-148) on December 22, 1999.

Enclosed are the following documents:

- Summary of labeling changes
- Annotated package insert
- Current package insert (No. 89001301 T1999-04)
- Diskette in Word 6.0 of the proposed changes (all diskettes have been scanned for viruses using Network Associates (formerly McAfee) Version 4.0.3a

If you have any questions, please contact me at (973) 781-3217.

Sincerely,

M. Struck

Martina Struck, PhD
Associate Director, Drug Regulatory Affairs

4 copies of "Draft Labeling" Supplement submitted to the Agency

cc: Ms. Lana Chen, Regulatory Management Officer- letter only

APPEARS THIS WAY
ON ORIGINAL

19.1

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 9-000/S-023

DEC 29 1999

Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936-1080

Attention: Martina Struck, Ph.D.
Associate Director, Regulatory Affairs

Dear Dr. Struck:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Cafergot Suppository

NDA Number: 9-000

Supplement Number: 023

Date of Supplement: 22-Dec-99

Date of Receipt: 27-Dec-99

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on 25-Feb-2000 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Office of Drug Evaluation I
Attention: Document Control Room 4008
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

(for) 12/29/99

John S. Purvis
Chief, Project Management Staff
Division of Neuropharmacological Drug Products, HFD-120
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Original NDA 9-000/023
HFD-120/Div. Files
HFD-120/CSO/Chen

filename:

SUPPLEMENT ACKNOWLEDGEMENT

~~NDA SUPPLEMENT~~

Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 8300

NOVARTIS 5-929 SLR-032 SLR-033
9-000 SLR-025
NDA NO. 20148 REF NO. SLR-010
NDA SUPPL FOR ~~Label Comp~~

~~BM~~ AM
5929/SLR-32/33
9-000/SLR-22/23
20-148/SLR-7/8

July 7, 2000

ORIGINAL
~~ORIGINAL~~

NDA SUPP AMEND

Russell Katz, MD, Director
Division of Neuropharmacological Drug Products, HFD-120
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Woodmont II
1451 Rockville Pike
Rockville, Maryland 20852

CENTER FOR DRUG EVALUATION AND RESEARCH RECD JUL 10 2000 DDMAC

AM
SLR-032 ~~BM~~
SLR-033 ~~BM~~ AM
SLR-007 ~~BM~~ AM
SLR-008 ~~BM~~

CENTER FOR DRUG EVALUATION AND RESEARCH

SLR-022 ~~BM~~ AM
SLR-023 ~~BM~~ AM

AUG 11 2000

RECEIVED HFD-120

Re: D.H.E. 45® Injection (NDA 05-929)
Migranal® Nasal Spray (NDA 20-148)
Cafergot® Suppositories (NDA 09-000)

Dear Dr. Katz:

Thank you for your communication of February 9, 2000 concerning the Food and Drug Administration staff's proposed revisions of the package inserts for the above-listed products. This letter provides our detailed comments on the February 9 proposal.

In general, we are amenable to the proposed package insert changes with respect to drug interactions, with minor changes described below. The proposed changes with respect to fibrotic events and dosage, however, do not reflect the discussions and agreements that we had reached at our October 20, 1999 meeting. Accordingly, we would like to request another meeting to discuss these issues.[1]

CENTER FOR DRUG EVALUATION AND RESEARCH

AUG 11 2000

RECEIVED HFD-120

I. BACKGROUND: THE OCTOBER 20 MEETING

At the outset, we thought it useful to recap the events that led to our October 20 meeting and our discussions at the meeting. In August of last year, after reviewing a law firm's press release announcing that FDA had commenced an investigation into a possible association between D.H.E.45® Injection and heart valve disease, Novartis contacted FDA to inquire whether such an investigation was in fact underway. FDA responded that it was indeed reviewing the labels for several of Novartis' migraine medications to determine whether changes were warranted with respect to possible cardiac valvular effects and, shortly thereafter, sent Novartis certain proposed label changes. The proposed changes

[1]For your convenience, we have enclosed copies of our submissions dated October 8, 1999 (Attachment A-1 through A-3, without enclosures), October 21, 1999 (Attachment B), November 4, 1999 (Attachment C), and December 22, 1999 (Attachments D-1 through D-3) and your communication of February 9, 2000 (Attachment E). To facilitate our next meeting, we are also providing a copy of this letter and its attachments to Dr. Temple.

In an ensuing telephone call on August 26, 1999, Novartis reminded FDA that the existing labels for Cafergot® (ergotamine tartrate and caffeine) already advised of rare reports of fibrotic thickening of the cardiac valves with long-term, continuous use of Cafergot® and inquired whether FDA was aware of any case reports that suggested a similar label warning was warranted for D.H.E.45® Injection and Migranal® Nasal Spray (dihydroergotamine mesylate). FDA responded that, in the case of both dihydroergotamine mesylate products, the sole basis for the requested label change was a single case report that had been forwarded to FDA by Novartis in connection with a lawsuit filed by the attorney who had issued the press release.[2] FDA also stated that it had obtained additional information regarding this case report from the patient's attorney, who apparently issued the press release following his conversation with FDA.

Because of the unusual circumstances of FDA's requested label changes and the apparent absence of any justification for them, Novartis requested a meeting with FDA to discuss the proposals. The meeting, which was held on October 20, was productive, and the discussions were summarized in minutes that Novartis provided to FDA on November 4, 1999. See Attachment C. We received no comments on the minutes from FDA staff and so believe that they fairly describe the meeting. The minutes reflect the following agreements reached in the meeting. First, the FDA representatives, including Dr. Temple, agreed that neither the single report relied upon by FDA staff in drafting the initial proposed label change nor the four other reports of cardiac valve changes located by Novartis should precipitate any label change for the dihydroergotamine mesylate products (D.H.E. 45® Injection and Migranal® Nasal Spray) with respect to cardiac valvular fibrosis. Second, although the package inserts already warn against chronic or prolonged daily use, Novartis agreed that it would propose labeling further stressing this point, because FDA was concerned about off-label chronic or prolonged use. Finally, FDA agreed that it would respond to Novartis' proposed language regarding possible drug interactions.

The FDA proposals included in the February 9 communication, however, do not take into

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[2] The lawsuit in question was filed in April of last year against American Home Products Corporation, Wyeth Laboratories, Novartis, a pharmacy and several treating physicians, alleging that the plaintiff had been prescribed Redux® and D.H.E.45® Injection and as a result had suffered cardiac valvular damage and pulmonary artery hypertension. Novartis reported the complaint's allegations to FDA (MedWatch Form USA/99/00843/DHE). FDA staff thereafter contacted the plaintiff's attorney to inquire about the report. Following that telephone call, the plaintiff's counsel (a) issued a press release announcing that FDA had commenced an investigation into a possible association between D.H.E.45® Injection and heart valve disease and that counsel were commencing their own scientific investigation into that question, (b) established an Internet website which, among other things, discussed FDA's purported investigation and solicited persons who had taken D.H.E.45® Injection (and related products) to complete an investigation questionnaire, and (c) placed advertisements in a number of national and local newspapers announcing their availability to represent persons who may have been injured as a result of taking D.H.E.45® Injection and inviting such persons to contact them.

consideration our discussions and agreements at the October meeting. Indeed, FDA's latest proposal does not differ significantly from its originally suggested changes of August 1999 concerning fibrotic effects and does not appear to reflect the results of our October 20 meeting. Below, we summarize our concerns in greater detail, together with our proposals, which we would like to discuss with you in a meeting to reach agreement on these issues.

II. D.H.E. 45® INJECTION (NDA 05-929) and MIGRANAL® NASAL SPRAY (NDA 20-148)

A. Fibrotic Complications

1. Current label: The **ADVERSE REACTIONS/Post-introduction Reports** sections of the package inserts state that:

> The following events derived from postmarketing experience have been occasionally reported in patients receiving D.H.E. 45® (dihydroergotamine mesylate) Injection, USP: . . . pleural and retroperitoneal fibrosis following long-term use of dihydroergotamine.

2. December 22, 1999 Novartis proposal: Revise the package inserts to add text to the [redacted] section stating:

> There have been reports of pleural and retroperitoneal fibrosis following prolonged daily use of injectable dihydroergotamine mesylate.

3. February 9, 2000 FDA proposal: Add new language to the **WARNINGS** section concerning reports of pleural and retroperitoneal fibrosis following prolonged use of dihydroergotamine mesylate and cardiac valvular fibrosis allegedly associated with "[redacted]" add a reference to "fibrotic complications" in the **ADVERSE EVENTS** section, and add a cross-reference to the **WARNINGS** section in the **DOSAGE AND ADMINISTRATION** section, as follows:

APPEARS THIS WAY
ON ORIGINAL

WARNINGS
Fibrotic Complications

[redacted]

DOSAGE AND ADMINISTRATION

[redacted]

3. Novartis comments: At our October 20 meeting, we reported that our review of our world-wide safety database and over 50 years of marketing experience disclosed only four cases of cardiac valvular changes in patients receiving D.H.E. 45® Injection and that three of these four (including the lawsuit-related case report that precipitated FDA's interest) involved co-medications labeled for valvular changes. All of the cases lacked sufficient information regarding the patient's medical histories. There was one case of valvular changes in a patient who had taken D.H.E. 45® oral tablets (only available in Europe) on a daily basis for 30 years. There were no reported cases of cardiac valve changes for Migranal® Nasal Spray, which has been marketed in some European countries since 1987.

In the above mentioned meeting, FDA agreed that the few cases of cardiac valvular changes reported involving D.H.E. 45® Injection could not be attributed to the drug and that those four cases (including the lawsuit-related event) and the one reported case for D.H.E. 45® oral tablets would not precipitate a labeling revision. As FDA staff is aware, different ergot alkaloids have different chemical structures and properties that result in different mechanisms of action, and there is not a sufficient basis for concluding that dihydroergotamine mesylate may cause

[redacted]

B. **Dosage**

1. Current label: The D.H.E. 45® Injection package insert **INDICATIONS AND USAGE** section provides that:

D.H.E. 45® (dihydroergotamine mesylate) Injection, USP is indicated for the acute treatment of migraine headaches with or without aura and the acute treatment of cluster headache episodes.

In addition, the **DOSAGE AND ADMINISTRATION** section states that:

[redacted]

The Migranal package insert **INDICATIONS AND USAGE** section advises that:

Migranal® (dihydroergotamine mesylate, USP) Nasal Spray is indicated for the acute treatment of migraine headaches with or without aura.

Migranal® (dihydroergotamine mesylate, USP) Nasal Spray is not intended for the prophylactic therapy of migraine or for the management of hemiplegic or basilar migraine.

In addition, the **DOSAGE AND ADMINISTRATION** section reads as follow:

The solution used in Migranal® (dihydroergotamine mesylate, USP) Nasal Spray (4 mg/mL) is intended for intranasal use and must not be injected.

In clinical trials, Migranal® (dihydroergotamine mesylate, USP) Nasal Spray has been effective for the acute treatment of migraine headaches with or without aura. One spray (0.5 mg) of Migranal® (dihydroergotamine mesylate, USP) Nasal Spray should be administered in each nostril. Fifteen minutes later, an additional one spray (0.5 mg) of Migranal® (dihydroergotamine mesylate, USP) Nasal Spray should be administered in each nostril, for a total dosage of four sprays (2.0 mg) of Migranal® (dihydroergotamine mesylate, USP) Nasal Spray. Studies have shown no additional benefit from acute doses greater than 2.0 mg for a single migraine administration. The safety of doses greater than 3.0 mg in a 24 hour period and 4.0 mg in a 7 day period has not been established.

The indications and dosage recommendations for both products are reinforced by the following sections, which provide in pertinent part:

DRUG ABUSE AND DEPENDENCE
Currently available data have not demonstrated drug abuse or psychological dependence with dihydroergotamine. However, cases of drug abuse and psychological dependence in patients on other forms of ergot therapy have been reported. Thus, due to the chronicity of vascular headaches, it is imperative that patients be advised not to exceed recommended dosages.

OVERDOSAGE
To date, there have been no reports of acute overdosage with this drug. Due to the risk of vascular spasm, exceeding the recommended dosages of D.H.E. 45® (dihydroergotamine mesylate) Injection, USP [Migranal® (dihydroergotamine mesylate, USP) Nasal Spray] is to be avoided. Excessive doses of dihydroergotamine may result in peripheral signs and symptoms of ergotism. Treatment includes discontinuance of the drug, local application of warmth to the affected area, the administration of

vasodilators, and nursing care to prevent tissue damage.

2. December 22, 1999 Novartis proposal: Add the following language to the **PRECAUTIONS/ General** and **PRECAUTIONS/Information for Patients** and **Dosage and Administration** sections:

D.H.E. 45® Injection

PRECAUTIONS

[ ]

Information for Patients
Administration of D.H.E. 45® (dihydroergotamine mesylate) Injection, USP, should not exceed the dosing guidelines and should not be used for chronic daily administration (see **DOSAGE AND ADMINISTRATION**).

DOSAGE AND ADMINISTRATION
D.H.E.® (dihydroergotamine mesylate) Injection, USP, should not be used for chronic daily administration.

Migranal® Nasal Spray

PRECAUTIONS
General
Migranal® (dihydroergotamine mesylate) Nasal Spray, USP, should not be used for chronic daily administration (see **DOSAGE AND ADMINISTRATION**).

Information for Patients
Administration of Migranal® (dihydroergotamine mesylate) Nasal spray, USP, should not exceed the dosing guidelines and should not be used for chronic daily administration (see **DOSAGE AND ADMINISTRATION**).

DOSAGE AND ADMINISTRATION
Migranal® (dihydroergotamine mesylate) Nasal Spray, USP, should not be used for chronic daily administration

3. February 9, 2000 FDA proposal: Add the statement that the drugs should not be used to treat more than two headaches per week in the **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION** sections and the statement that dihydroergotamine "is not for prolonged daily use" in the **WARNINGS** section:

WARNINGS

[redacted]

AND ADMINISTRATION).

PRECAUTIONS
Information for Patients
D.H.E. 45® (dihydroergotamine mesylate) Injection, USP, should not be used to treat more than two headaches per week (see **DOSAGE AND ADMINISTRATION**).

DOSAGE AND ADMINISTRATION
The drug should not be used to treat more than two headaches per week (see **WARNINGS: Fibrotic Complications**).

4. Novartis comments: During our telephone conference with FDA staff on August 26, 1999, FDA staff suggested that the package inserts be revised to strengthen the current wording that informs physicians that these products are to be used intermittently to treat acute migraines and are not for chronic daily use. Novartis recommended adding additional language to the **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION** sections stating that D.H.E. 45® and Migranal® "should not be used for chronic daily administration." We believe that this proposal, in addition to the current label language, is appropriate to caution against chronic or prolonged daily use of D.H.E. 45® and Migranal®, and we believe that it is unnecessary to add this wording to the **WARNINGS** section as well. Similarly, we believe the existing indications and dosage instructions are appropriate based on clinical and post-introduction experience and can discern no basis for the alternate limitation to treatment of two headaches per week, as suggested by FDA. In our view, the relevant criterion is not the weekly number of

13 **pages redacted from this section of the approval package consisted of draft labeling**

We trust that these comments are helpful in framing the issues that remain to be resolved. We respectfully request a meeting with you and appropriate members of your staff at your convenience to discuss these issues in greater detail. We further request that Dr. Temple be included in any such meeting given his previous participation. Should you have any questions or comments concerning this correspondence, please contact the undersigned at 973-781-3250. Thank you for your consideration.

Sincerely,

Roy W. Dodsworth
Executive Director
Drug Regulatory Affairs
Global Therapeutic Area Head
Nervous System Drugs

Submitted in duplicate to:

NDA No.	05-929
NDA No.	20-148
NDA No.	09-000

Attachment

cc: Robert Temple, MD, Director
Office of Drug Evaluation I, HFD-100

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 05-929/S-032, S-033
NDA 09-000/S-022, S-023
NDA 20-148/S-007, S-008

Novartis Pharmaceuticals Corporation
Attention: Roy Dodsworth
59 Route 10
East Hanover, NJ 07936-1080

Dear Mr. Dodsworth:

Please refer to your supplemental new drug applications dated July 7, 2000, received July 10, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for DHE 45, Cafergot Suppositories, and Migranal Nasal Spray.

We acknowledge receipt of your submissions dated October 8, 1999 and December 22, 1999.

These supplements propose changes with regard to drug interactions with CYP3A4 inhibitors and the potential risk of cardiac valvular fibrosis.

We have completed the review of these applications, as amended, and they are approvable. Before these applications may be approved, however, it will be necessary for you to address the following:

We propose that you incorporate stronger language than previously suggested to the Warnings section of DHE 45 and Migranal Nasal Spray for the following reasons.

1. We have received two additional reports which we believe support the association between prolonged daily use of dihydroergotamine (DHE) and cardiac valvular fibrosis. You may request details of these cases through our Freedom of Information Office (http://www.fda.gov/cder/foi/index.htm) by referencing the following ISR numbers: 3692194-0, 3692199-x.

2. We also note that prolonged daily use of DHE is associated with fibrosis elsewhere in the body. Furthermore, DHE is a member of a class of compounds of which other members are associated with cardiac valvular fibrosis.

We believe that the information from these two cases, taken together with these additional facts, do support the proposed labeling change.

In addition, it will be necessary for you to submit final printed labeling (FPL) for the drug. The labeling should be identical in content to the enclosed labeling (text for the package insert). All previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes

that are being made.

Please submit the copies of final printed labeling (FPL) electronically (to each application) according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL (to each application), ten of which individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of these drugs becomes available, revision of the labeling may be required.

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

These products may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if they are marketed with these changes prior to approval of these supplemental applications.

If you have any questions, call Lana Chen, R.Ph., Regulatory Management Officer, at (301) 594-5529.

Sincerely,

{See appended electronic signature page}

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

2 pages redacted from this section of the approval package consisted of draft labeling

PRECAUTIONS
Drug Interactions
CYP3A4 Inhibitors: see CONTRAINDICATIONS and WARNINGS.

Information for Patients
Administration of CAFERGOT (ergotamine tartrate) suppositories should not exceed the dosing guidelines and should not be used for chronic daily administration (see DOSAGE AND ADMINISTRATION).

ADVERSE EVENTS
Fibrotic complications: (see WARNINGS).

DOSAGE AND ADMINISTRATION
CAFERGOT (ergotamine tartrate) suppositories should not be used for chronic daily administration.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz
6/29/01 01:15:31 PM

APPEARS THIS WAY
ON ORIGINAL

Martina Struck, PhD
Regulatory Affairs Manager
Therapeutic Area:
Nervous System

Novartis Pharmaceuticals Corp.
Drug Regulatory Affairs
419/1164
59 Route 10
East Hanover, NJ, 07936

Tel (001) 973 7813217
Fax (001) 973 7817177
Internet: martina.struck
@pharma.novartis.com

NOVARTIS

DUPLICATE

SLR-032,033 (BL)
007,008 (BL)
022,023 (BL)

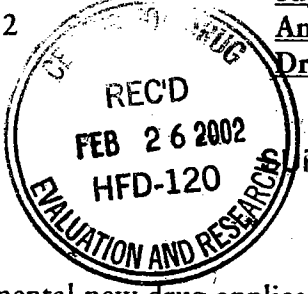
WAT
3/6/02

February 25, 2002

Russell Katz, MD
Acting Director
Division of Neuropharmacological
Drug Products/HFD-120
Office of Drug Evaluation I
Attn.: Document Control Room
Center for Drug Evaluation and Research
Woodmont II, 1451 Rockville Pike
Rockville, Maryland 20852

DHE 45 Injection (NDA 05-929)/S-032, S-033 (BL)
Migranal Nasal Spray (NDA 20-148)/~~S-022, S-023~~ S-007,008 (BL)
Cafergot Suppositories (NDA 09-000)/S-~~007~~,S-~~008~~
022,023 (BL)

Supplemental New Drug Applications:
Amendment to a Pending Application
Draft Labeling



RECEIVED
SUPPLEMENT AMENDMENT FEB 26 2002
CDR/CDER

Dear Dr. Katz,

Please refer to our supplemental new drug applications dated July 7, 2000 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for DHE 45, Cafergot Suppositories, and Migranal Nasal Spray. Reference is also made to your Division's correspondence dated June 29, 2001, and our notice of intent to amend the above mentioned applications of July 19, 2001, as well as the teleconference of December 6, 2001 between your Division and Novartis with regard to interactions with potent CYP 3A4 inhibitors.

Please refer also to our submissions dated October 8, 1999 and December 22, 1999.

Novartis hereby amends the above mentioned pending supplemental applications with new draft labeling to strengthen for the warnings with regard to interactions with potent CYP 3A4 inhibitors. The changes reflect our discussions of the December 6, 2001 teleconference.

Please note that the issue of cardiac valvular changes will be discussed at the meeting with your Division scheduled for March 6, 2002, and is not subject of this submission.

If you have any questions or comments please contact me at (973) 781-3217.

Sincerely,

M. Struck

Martina Struck, Ph.D.
Associate Director
Drug Regulatory Affairs

Martina Struck, PhD
Regulatory Affairs Manager
Therapeutic Area:
Nervous System

Novartis Pharmaceuticals Corp.
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NOVARTIS

ORIGINAL
SUPPLEMENT AMENDMENT

February 25, 2002

Russell Katz, MD
Acting Director
Division of Neuropharmacological
Drug Products/HFD-120
Office of Drug Evaluation I
Attn.: Document Control Room
Center for Drug Evaluation and Research
Woodmont II, 1451 Rockville Pike
Rockville, Maryland 20852

DHE 45 Injection (NDA 05-929)/S-032, S-033
Migranal Nasal Spray (NDA 20-148)/S-~~022~~, S-~~023~~ 007, 008
Cafergot Suppositories (NDA 09-000)/S-~~007~~,S-~~008~~ 022, 023

SLR-022/023 (BL)

Supplemental New Drug Applications:
Amendment to a Pending Application
Draft Labeling

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
FEB 26 2002
HFD-120

RECEIVED
FEB 26 2002
CDR/CDER

ORIGINAL

Dear Dr. Katz,

Please refer to our supplemental new drug applications dated July 7, 2000 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for DHE 45, Cafergot Suppositories, and Migranal Nasal Spray. Reference is also made to your Division's correspondence dated June 29, 2001, and our notice of intent to amend the above mentioned applications of July 19, 2001, as well as the teleconference of December 6, 2001 between your Division and Novartis with regard to interactions with potent CYP 3A4 inhibitors.

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If you have any questions or comments please contact me at (973) 781-3217.

Sincerely,

M. Struck

Martina Struck, Ph.D.
Associate Director
Drug Regulatory Affairs

Submitted in Duplicate to NDA 05-929, NDA 20-148, NDA 09-000
Attachment: CD-ROM
Cc: Ms. Lana Cheng, R.Ph., Regulatory Management Office – letter only

Martina Struck, PhD
Regulatory Affairs Manager
Therapeutic Area:
Nervous System

Novartis Pharmaceuticals Corp.
Drug Regulatory Affairs
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NOVARTIS

April 16, 2002

ORIGINAL

Russell Katz, MD
Acting Director
Division of Neuropharmacological
Drug Products/HFD-120
Office of Drug Evaluation I
Attn.: Document Control Room
Center for Drug Evaluation and Research
Woodmont II, 1451 Rockville Pike
Rockville, Maryland 20852

Cafergot® Suppositories
(NDA 09-000) / S-~~007~~, S-008
S-022, S-023

Supplemental New Drug Applications:
Amendment to a Pending Application
Final Draft Labeling

SUPPLEMENT AMENDMENT

SLR-022 (~~BL~~) AL
SLR-023 (~~BL~~) AL

Dear Dr. Katz,

Please refer to our supplemental new drug application dated July 27, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cafergot® Suppositories. Reference is also made to your Division's correspondence dated June 29, 2001, our notice of intent to amend the above mentioned application of July 19, 2001, as well as the teleconference of December 6, 2001 between your Division and Novartis with regard to interactions with potent CYP 3A4 inhibitors, our submission of new draft labeling of February 25, 2002, and your Division's response of March 25, 2002, as well as the meeting of March 6, 2002 between your Division and Novartis to discuss the issue of cardiac valvular changes.

Please refer also to our submissions dated October 8, 1999 and December 22, 1999.

Novartis hereby amends the above mentioned pending supplemental application with final draft labeling to address both the issues of interactions with potent CYP 3A4 inhibitors, as well as the issue of cardiac valvular changes.

In reference to your letter of March 25, 2002, we hereby commit to issue a Dear Doctor letter to alert precribers of the label change with regard to interactions with potent CYP 3A4 inhibitors and the new black box warning. The proposed text of the Dear Doctor letter will be submitted under separate cover.

If you have any questions or comments please contact me at (973) 781-3217.

Sincerely,

Martina Struck, Ph.D.
Associate Director
Drug Regulatory Affairs

Submitted in Duplicate to NDA 09-000
Attachment: CD-ROM
Cc: Ms. Lana Cheng, R.Ph., Regulatory Management Office – letter only

NOVARTIS

Martina Struck, PhD
Regulatory Affairs Manager
Therapeutic Area:
Nervous System

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PM note: NAT. Med watch notified 11/18/02. CCA 11/18/02

AD NAT 11/19/02

November 12, 2002

DUPLICATE

Russell Katz, MD
Director
Division of Neuropharmacological
Drug Products/HFD-120
Office of Drug Evaluation I
Attn.: Document Control Room
Center for Drug Evaluation and Research
Woodmont II, 1451 Rockville Pike
Rockville, Maryland 20852

Cafergot® Suppositories (NDA 09-000)

GENERAL CORRESPONDENCE:
DEAR HEALTHCARE
PROVIDER LETTER

RECEIVED
NOV 1 3 2002
HFD-120/CDER

NEW CORRESPONDENCE

Dear Dr. Katz,

SLR-022(C) / SLR-023(C)

Reference is made to the approval letter of June 05, 2002 for the supplemental new drug applications S-022 and S-023. As requested, please find enclosed a copy of the Dear Health Care Provider letter, which was sent to Health Care Providers together with the labels of Cafergot® (ergotamine tartrate and caffeine) suppositories and tablets to inform about a new boxed warning section related to interactions with potent CYP 3A4 inhibitors.

If you have any questions or comments please contact me at (973) 781-3217.

Sincerely,

M. Struck

Martina Struck, Ph.D.
Associate Director
Drug Regulatory Affairs

Submitted in Duplicate
Attachment

Copy: MEDWATCH
Electronic Document Room (EDR): included in FPL submission

Martina Struck, PhD
Regulatory Affairs Manager
Therapeutic Area:
Nervous System

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NOVARTIS

November 12, 2002

ORIGINAL

Russell Katz, MD
Director
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Office of Drug Evaluation I
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Woodmont II, 1451 Rockville Pike
Rockville, Maryland 20852

Cafergot® Suppositories (NDA 09-000)

GENERAL CORRESPONDENCE:
DEAR HEALTHCARE
PROVIDER LETTER

RECEIVED
NOV 1 3 2002
HFD-120/CDER

NEW CORRESPONDENCE SLR-022(C)/SLR-023(C)

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If you have any questions or comments please contact me at (973) 781-3217.

Sincerely,

M. Struck

Martina Struck, Ph.D.
Associate Director
Drug Regulatory Affairs

Submitted in Duplicate
Attachment

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Electronic Document Room (EDR): included in FPL submission