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

CLINICAL PHARMACOLOGY

Pharmacokinetics: Interactions

Pharmacokinetic interactions have been reported in patients treated orally with other ergot alkaloids (e.g., increased levels of ergotamine) and macrolide antibiotics, principally troleandomycin, presumably due to inhibition of cytochrome P450 3A metabolism of the alkaloids by troleandomycin. Dihydroergotamine has also been shown to be an inhibitor of cytochrome P450 3A catalyzed reactions. No pharmacokinetic interactions involving other cytochrome P450 isoenzymes are known.

WARNINGS

Fibrotic Complications

There have been reports of pleural and retroperitoneal fibrosis in patients following prolonged daily use of injectable dihydroergotamine mesylate. In addition, prolonged daily use of dihydroergotamine has been associated, in at least two reports, with cardiac valvular fibrosis. The mitral and tricuspid valves were affected and both patients required mitral valve replacement. 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).

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"]

Although there have been no reports of serious adverse events in connection with the coadministration of dihydroergotamine and potent CYP 3A4 inhibitors, there is a potential risk for increased blood levels and serious toxicity including vasospasm when these drugs are used in combination. The use of potent CYP 3A4 inhibitors with dihydroergotamine should therefore be avoided. Examples of some of the more potent CYP 3A4 inhibitors include: anti-fungals ketoconazole and itraconazole, the protease inhibitors ritonavir, nelfinavir, and indinavir, and macrolide antibiotics erythromycin, clarithromycin, and troleandomycin. Other less potent CYP 3A4 inhibitors should be administered with caution. Less potent inhibitors include saquinavir, nefazodone, fluconazole, grapefruit juice, fluoxetine, fluvoxamine, zileuton, 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 dihydroergotamine.

ADVERSE EVENTS

Fibrotic complications have been associated with long term dihydroergotamine use (see WARNINGS: Fibrotic Complications).

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

Pharmacokinetic interactions (increased blood levels of ergotamine) have been reported in patients treated orally with ergotamine and macrolide antibiotics (e.g., troleandomycin, clarithromycin, erythromycin} presumably due to inhibition of cytochrome P450 3A metabolism of ergotamine by the macrolide. 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.

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. 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).

WARNINGS

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).

CYP 3A4 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, and PRECAUTIONS: Drug Interactions). 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 dihydroergotamine.

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.