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HEALTH PROFESSIONAL SUMMARY INFORMATION - PAVOSIC™

INDICATIONS AND CLINICAL USE

Pavosic™ is indicated for the treatment of pain (analgesic) and/or the treatment of insomnia (hypnotic and sedative).

Use 1 capsule of Pavosic™ at night for the management of night pain (pain-associated insomnia).
Use 1 capsule of Pavosic™ at night as a sleep aid (hypnotic).

Pediatrics (18 < years of age):
The product is only approved for use in adults. There is no clinical data supporting the use in children and adolescents.

COMPOSITION

Route of Administration	Dosage Form / Strength	Active Ingredient	Non medicinal Ingredients
oral	Capsule 600 mg extract equivalent to 3 g of the dried herb top of California poppy	Extract standardized to 0.8% isoquinoline alkaloids (based on HPLC analysis).	Magnesium stearate, cellulose, hypromellose

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action[1]

Pavosic™ is standardized to contain 0.8% of the three isoquinoline alkaloids californidine, escholtzine and protopine.
The following is a summary of the animal pharmacology data that confirmed the sedative, anxiolytic and some of the analgesic effects of a 5:1 extract of California poppy:

- The sedative effects of the extract were partly antagonized by Flumazenil (benzodiazepine receptor antagonist). The extract produced similar effects to Midazolam (Versed®).
- The anxiolytic effects of the extract were antagonized by Flumazenil (benzodiazepine receptor antagonist). The effects were similar to those obtained with Clorazepate dipotassium.
- No anticonvulsant or myorelaxant effects were observed. Dose-dependent anticonvulsant and myorelaxant effects are seen with Clorazepate in this study.
- No protective effect was observed against dexamphetamine produced mortality. Whereas, a protective effect was observed with Chlorpromazine.
- A dose-response was observed. The extract significantly increased the stereotyped behaviour effects of dexamphetamine whereas Chlorpromazine significantly decreased these effects.
- The extract had no effect against reserpine-induced ptosis, akinesia or hypothermia. Whereas, amitryptiline significantly reduced ptosis and hypothermia.
- The extract had no effect against the anticholinergic effects of Oxotremorine. Whereas, Imipramine significantly reduced these effects.
- A dose-response effect was observed for peripheral analgesia against acetic acid writhing. Protection against writing was 70% and 85% with the extract whereas acetylsalicylic acid, paracetamol and morphine sulphate gave protection at 60%, 60% and 70% respectively.

Pharmacodynamics/Pharmacokinetics

Onset of action: Oral: 15-30 minutes.
Duration of action (based on observations in clinical trials): Oral: 4-6 hours
The absorption-distribution-metabolism and excretion (ADME) of Pavosic™ currently cannot be performed since the product contains hundreds of ingredients and the analytical methodology is not sufficiently sensitive to follow the three main isoquinoline alkaloids at the plasma levels found in the human body.

THERAPEUTIC INFORMATION

GENERAL:

Dependence

There is no known dependence or addiction to Pavosic™. Pavosic™ is not classified as a narcotic or controlled drug.

Tolerance

There are no reports of a tolerance to the hypnotic or analgesic effect of Pavosic™. Theoretically, based on the pharmacology of the alkaloids, tolerance is expected in some patients.

Potential Drug Interactions[2,3]

Pavosic™ may have an additive sedative effect when used with sedatives, tranquilizers, hypnotics, analgesics, antidepressants, antipsychotics or alcohol.

Drug-Drug Interactions[4,5]

In vitro studies performed using pure synthetic forms of the known ingredients of California poppy revealed that Escholtzine (MM = 323 g/mole) had strong inhibition of CYP3A4 (IC50 = 13.4 ± 4.7 uM); the other alkaloids only had weak inhibition. Pavosic™ contains 0.4 to 1.2 mg of Escholtzine. Assuming 100% bioavailability, for a 70 kg human subject (i.e., 5 litres of blood), this represents a maximum blood level of 0.24 ug/ml (0.74 uM). At the recommended dosage, or when given twice a day, Pavosic™ should not cause significant CYP3A4 inhibition.

CONTRAINDICATIONS[2,3]

Pregnancy

Do not use during pregnancy.

Maternal

There is no clinical evidence supporting the safe use of Pavosic™ in women breastfeeding. In addition, Pavosic™ is a concentrated extract derived from California poppy (*Eschscholzia californica*) and may contain ingredients that are harmful to the newborn.

Allergy

Do not use Pavosic™ in patients with known allergy/hypersensitivity to California poppy (*Eschscholzia californica*), its constituents (codeine or morphine and their derivatives), or related members of the Papaveraceae (Poppy) family. Allergic reactions have been reported in people allergic to codeine or morphine.

PRECAUTIONS

Cardiovascular

Pavosic™ has anxiolytic effects in patients. Theoretically, Pavosic™ may have a hypotensive effect when used in combination with hypertensive medications or sedatives/tranquilizers.

Geriatrics (≥90 years of age):

Pavosic™ has anxiolytic therapeutic activity and may have a hypotensive effect when used in combination with other opioid analgesics and or tranquilizer, sedative or hypertensive medications.

Hepatic

Use cautiously in patients with liver insufficiency since the metabolism of Pavosic™ is not known and molecules can accumulate causing increased therapeutic and adverse effects.

Renal

Use cautiously in patients with renal dysfunction/insufficiency since the metabolites of Pavosic™ can accumulate causing therapeutic and adverse effects.

SIDE EFFECTS

Potential Adverse Drug Reactions[6]

The following Adverse Drug Reactions have been observed/reported:

- **Altered Dreaming:** frequently reported by patients as pleasant or strange dreams (fantastic dreams). Does not cause nightmares.
- **Drowsiness:** frequently reported by patients taking Pavosic™ during the day time.
- **Hypotension:** A hypotensive effect was reported in an elderly bedridden patient taking the equivalent of an extract of California poppy as a sleep aid. The patient was on several medications including hypertension, anti-nausea and analgesic drugs.
- **Excitation/Insomnia:** low incidence but is known to occur in some patients.

STORAGE AND STABILITY

Pavosic™ capsules should be stored at room temperature. The medicinal ingredient is stable for 2 to 3 years.

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[1] **Rolland A et al. Neurophysiological Effects of an Extract of *Eschscholzia californica* Cham. (*Papaveraceae*)** *Phytother. Res.* **15**, 377–381 (2001).

[2] **Health Canada**. Monographs prepared by the Natural Health Products Directorate, Health Canada.

[3] **Natural Standard database**. *Evidence-based Systematic Reviews of herbs* by the Natural Standard Research Collaboration. Copyright ® 2011.

[4] Salminen KA et al. Inhibition of human drug metabolizing cytochrome P450 enzymes by plant isoquinoline alkaloids. Phytomedicine 2011 Apr 15;18(6):533-8.

[5] Gafner S. et al. Alkaloids from Eschscholzia californica and their capacity to inhibit binding of [3H]8-Hydroxy-2-(di-N-propylamino)tetralin to 5-HT1A receptors in Vitro. J Nat Prod. 2006 Mar;69(3):432-5.

[6] Chamberland G, Clinical report- Pavosic. 2012.