28 January 2015
EMA/HMPC/680375/2013
Committee on Herbal Medicinal Products (HMPC)

# Assessment report on *Eschscholzia californica* Cham., herba

Based on Article 16d(1), Article 16f and Article 16h of Directive 2001/83/EC as amended (traditional use)

**Final**

| | |
|---|---|
| Herbal substance(s) (binomial scientific name of the plant, including plant part) | *Eschscholzia californica* Cham., herba |
| Herbal preparation(s) | Powdered herbal substance |
| Pharmaceutical forms | Herbal preparation in solid dosage forms for oral use |
| Rapporteur | O. Palomino |
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# 1. Introduction

## *1.1. Description of the herbal substance(s), herbal preparation(s) or combinations thereof*

- Herbal substance(s)

*Eschscholzia californica* Cham. is a component part of the French Pharmacopoeia. The following monograph exists:

- *Eschscholzia californica* Cham., **French Pharmacopoeia, 10th ed.** (Fr. Ph. Jan 1996): Dried flowering aerial parts of *Eschscholzia californica* Cham. Content: not less than 0.50 per cent and not more than 1.20 per cent of total alkaloids, expressed as californidine ($C_{20}H_{20}NO_4^+$; $M_T$ 338.4) (dried herbal substance).
- Eschscholzia (poudre d'), **French Pharmacopoeia, 10th ed.** (Fr. Ph. Jan 1996): Dried and powdered flowering aerial parts of *Eschscholzia californica* Cham. Content: not less than 0.50 per cent and not more than 1.20 per cent of total alkaloids, expressed as californidine ($C_{20}H_{20}NO_4^+$; $M_T$ 338.4) (dried herbal substance).

*Eschscholzia californica* Cham. (Fam. *Papaveraceae*) is a perennial and annual plant growing approximately 30 cm high with alternately branching glaucous blue-green foliage. The leaves are ternately divided into round, lobed segments. The flowers are solitary on long stems, silky-textured, with four petals, each petal 2–6 cm long and broad; their colour ranges from yellow to orange. The petals close at night or in cold, windy weather and open again the following morning, although they may remain closed in cloudy weather. The plant is prolific, with numerous black or dark brown coloured seeds held in the centre of the flower within slender, ribbed single celled seed capsules (3-9 cm long) **(Bruneton, 1998).**

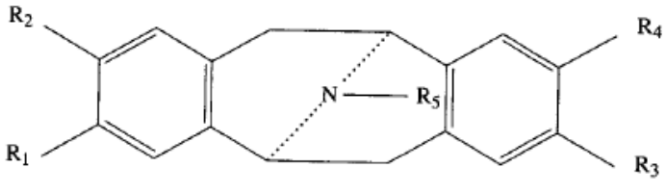
Both aerial parts and roots contain alkaloids, the latter being richer than the former (up to 1.6% alkaloids) (Fleurentin *et al*., 1996).

Synonyms: California poppy

Constituents **(Bartram, 1995; Bruneton, 1998; 1999; Cheney, 1963; Felter and Lloyd, 1898 in Mills and Bone, 2000; Fleurentin *et al.*, 1996; Greunwald *et al*., 2004 ; Klvana *et al.*, 2006; Mills and Bone, 2005; Vogel *et al*., 2010):**

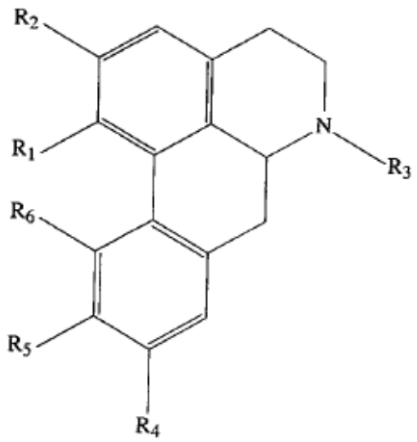
Alkaloids: 0.50-1.20 per cent of total alkaloids, expressed as californidine; six different groups of alkaloids have been described.

Pavin alkaloids in the aerial parts (most abundant and characteristic of this genus):



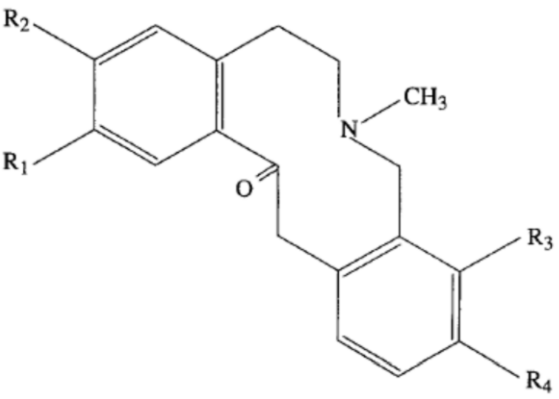

| | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $N–R_5$ |
|---|---|---|---|---|---|
| Bisnorargemonine | $OCH_3$ – | OH | $–OCH_3$ | –OH | $–CH_3$ |
| Eschsholtzine (ou californine) | \O–$CH_2$–O/ | | \O–$CH_2$–O/ | | $–CH_3$ |
| Californidine | \O–$CH_2$–O/ | | \O–$CH_2$–O/ | | \ / $(CH_3)_2$ |
| Eschsholtzidine | \O–$CH_2$–O/ | | $–OCH_3$ | $–OCH_3$ | $–CH_3$ |
| Norargemonine | \OH | $–OCH_3$ | $–OCH_3$ | $–OCH_3$ | $–CH_3$ |

Aporphine alkaloids: laurotetamine and N-methyl laurotetamine are present in the whole plant, glaucine can be found within the aerial parts **(Fleurentin *et al.*, 1996):**



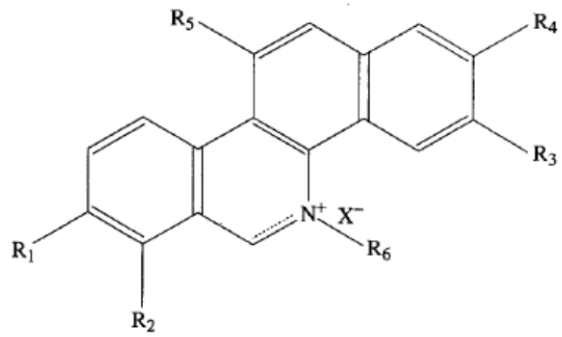

| | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ |
|---|---|---|---|---|---|---|
| Laurotétamine | $–OCH_3$ | $–OCH_3$ | –H | –OH | $–OCH_3$ | –H |
| N–méthyl laurotétamine (ou lauroscholzine) | $–OCH_3$ | $–OCH_3$ | $–CH_3$ | –OH | $–OCH_3$ | –H |
| Glaucine | $–OCH_3$ | $–OCH_3$ | $–CH_3$ | $–OCH_3$ | $–OCH_3$ | –H |

Protopine alkaloids: protopine, cryptopine and α-cryptopine are found in the whole plant, leaves and stem **(Fleurentin *et al.*, 1996):**



| | $R_1$ | $R_2$ | $R_3$ | $R_4$ |
|---|---|---|---|---|
| Protopine (ou macleyine ou fumarine) | \O–$CH_2$–O/ | | \O–$CH_2$–O/ | |
| Cryptopine | O–$CH_3$ | –$OCH_3$ | \O–$CH_2$–O/ | |
| α–allacryptopine | \O–$CH_2$–O/ | | \$OCH_3$ | –$OCH_3$ |

Benzo-phenanthridin alkaloids: Chelirubine, chelidonine and homochelidonine are present in the whole plant, chelilutine can be found in aerial parts:



| | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | N–$R_6$ |
|---|---|---|---|---|---|---|
| Chélirubine | –O–$CH_2$–O | | –O–$CH_2$–O | | –$OCH_3$ | –$CH_3$ |
| Chélilutine | –$OCH_3$ | –$OCH_3$ | –O–$CH_2$–O | | –$OCH_3$ | –$CH_3$ |
| Chélidonine | –O–$CH_2$–O | | –O–$CH_2$–O | | –$OCH_3$ | $CH_3$ |
| Homochélidonine | –$OCH_3$ | –$OCH_3$ | –O–$CH_2$–O | | –OH | $CH_3$ |

The group of benzo-C-phenanthridin alkaloids, and mainly sanguinarine and chelerythrine, are present in very low quantities in aerial parts **(Fleurentin *et al.*, 1996),** but are more abundant in the roots**.** According to **Guédon *et al*. (1990)**, the total alkaloid content in the aerial parts is close to the minimum amount cited in the Pharmacopoeia monograph:

| **Alkaloid** | **Aerial parts content (µg/ml)** | **Percentage** |
|---|---|---|
| N-methyllaurotetanina | 0.050 | 8.9% |
| Protopine | 0.035 | 6.27% |
| Allocryptopine | < 0.001 | 0.18% |
| Eschscholzine | 0.103 | 18.49% |
| Californidine | 0.350 | 65% |
| Sanguinarine | 0.015 | 2.6% |
| Chelerythrine | 0.005 | 0.89% |
| Total content | 0.558 | 100% |

The presence of quaternary benzophenanthridine alkaloids (sanguinarine and chelerythrine) is controversial. Colombo and Tomé (1991) identified both alkaloids in aerial parts of California poppy, but these results came from an experimental culture in controlled conditions under continuous light: no quantitative data were given. So these results could not reflect the real content of these alkaloids in natural growing plants.

Others: Flowers contain rutin and a purple-red pigment eschscholtz-xanthin **(Duke, 2001)**.

- Combinations of herbal substance(s) and/or herbal preparation(s) including a description of vitamin(s) and/or mineral(s) as ingredients of traditional combination herbal medicinal products assessed, where applicable.

Not applicable.

## *1.2. Information about products on the market in the Member States*

**France: Traditional use**

1. Powdered herbal substance
2. Dry extract, solvent water (DER: 4-6:1)

| Since when on the market? | Pharmaceutical form | Posology / daily dosage |
|---|---|---|
| 1. 1982 | Hard capsules | Adults: 2 capsules twice daily (1200 mg), up to 5 capsules, if necessary<br>Adolescents > 12 years: 1 capsule twice daily<br>1 hard capsule contains 300 mg powder with 0.8% eschscholzine |
| 2. 1996 | Hard capsules | Adults and children > 6 years: 2 capsules twice daily<br>1 hard capsule contains 200 mg extract |

Indications:

1 and 2: Traditionally used in the symptomatic treatment of neurotonic conditions of adults and children, notably in cases of mild disorders of sleep.

**Spain: Traditional use**

1. Powdered herbal substance

| Since when on the market? | pharmaceutical form | Posology / daily dosage |
|---|---|---|
| 1. 1982 | Hard capsules | 2 capsules twice daily (960 mg) |

Indications:

1) Traditional herbal medicinal product to relieve nervousness and anxiety.

2) Traditional herbal medicinal product to improve sleep quality.

## Regulatory status overview

| Member State | Regulatory Status | | | | Comments |
|---|---|---|---|---|---|
| Austria | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No products in the market |
| Belgium | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No products in the market |
| Bulgaria | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No information available |
| Cyprus | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No information available |
| Czech Republic | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No products in the market |
| Denmark | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No products in the market |
| Estonia | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No products in the market |
| Finland | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No products in the market |
| France | ☐ MA | ☒ TRAD | ☐ Other TRAD | ☐ Other Specify: | |
| Germany | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No products in the market |
| Greece | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No products in the market |
| Hungary | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No information available |
| Iceland | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No information available |
| Ireland | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No information available |
| Italy | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No products in the market |
| Latvia | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☒ Other Specify: | Combination products |
| Liechtenstein | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No information available |
| Lithuania | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No information available |
| Luxemburg | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No information available |
| Malta | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No information available |

| Member State | Regulatory Status | | | | Comments |
|---|---|---|---|---|---|
| The Netherlands | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No products in the market |
| Norway | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No information available |
| Poland | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No products in the market |
| Portugal | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No information available |
| Romania | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No products in the market |
| Slovak Republic | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No information available |
| Slovenia | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No information available |
| Spain | ☐ MA | ☒ TRAD | ☐ Other TRAD | ☐ Other Specify: | |
| Sweden | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No information available |
| United Kingdom | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No products in the market |

MA: Marketing Authorisation
TRAD: Traditional Use Registration
Other TRAD: Other national Traditional systems of registration
This regulatory overview is not legally binding and does not necessarily reflect the legal status of the products in the MSs concerned.

## *1.3. Search and assessment methodology*

Available literature on *Eschscholzia californica* in the electronic databases PubMed, Toxline and The Cochraine Library was used for a literature search. Articles were filtered by using the following terms: *Eschscholzia californica*, California poppy. No restrictions to language were applied. The search was performed twice: March 2012 and July 2013. References provided by interested parties upon the call for scientific data were also considered.

***Results in PubMed***

Search term "*Eschscholzia californica*": 93 references were obtained in 2013.

Search term "California poppy": 113 results.

***Results in Toxline***

Search term "*Eschscholzia californica*": 11 references.

Search term "California poppy": 2 results.

***The Cochrane Library***

No references were obtained for both search terms (*Eschscholzia californica* and California poppy).

***Toxicity data for alkaloids from Eschscholzia californica***

Toxnet (http://toxnet.nlm.nih.gov/ ):

Search term “protopine”: 5 results.

Search term “cryptopine”: 1 result.

Search term “chelidonine”: 7 results.

Search term “d-glaucine”: 6 results.

Only articles found to be relevant for assessment are included in the list of references.

# 2. Data on medicinal use

## *2.1. Information on period of medicinal use in the European Union*

According to the information provided by the National Competent Authorities, no preparations within *Eschscholzia californica* Cham., herb with a “well-established use” can be found in the European Union.

Based on the data provided by the National Competent Authorities, some *Eschscholzia californica* herb products have a “traditional use”.

Powdered dry herb

This herbal preparation is recognised as a traditional herbal preparation in several monographs and handbooks and can be found in the European market since 1982, so traditional use in Europe is proven.

## *2.2. Information on traditional/current indications and specified substances/preparations*

California poppy is a traditional medicinal plant of the American Indian population, nowadays being used for its mild analgesic and sedative properties (and as the state flower of California) **(Baldacci, 1990; Bocek, 1984; Mills and Bone, 2000)** without the dangers of opiates **(Felter and Lloyd, 1898 in Mills and Bone, 2000)**.

This species is native to California (USA) and North of Mexico and has perfectly been adapted to several European countries where it is frequently cultivated in ornamental gardens. It is traditionally used by the rural population of western USA as analgesic and sedative **(Fleurentin, 1993).**

California poppy is traditionally known as a soporific remedy which is harmless **(Baldacci, 1990; Bocek, 1984)** and considered to be an excellent soporific, particularly for children suffering from whooping cough; for adults it was prescribed as an antineuralgicum possessing hypnotic, anodyne and analgesic properties.

The monograph from the **Commission E (Blumenthal *et al.*, 1998)** describes the following pharmacological properties: reduction in spontaneous motility and prolongation of pentobarbital-induced sleep (in mice) as well as prevention of spasms induced by $BaCl_2$ (isolated jejunum). Combinations of California poppy herb with other components (valerian root, St. John's wort, passionflower herb, lemon balm leaf and others) are traditionally used for several disorders such as "Reactive, agitated and masked depressions, melancholy, neurasthenia, neuropathy, organ neurosis, vegetative-dystonic disturbances, imbalances, constitutional lability of the nervous system", as well as a sleep-inductor and sedative tea. This monograph also indicates that it should be avoided during pregnancy due to its pharmacological activity and the lack of experiments pertaining to the use in this period.

According to the **Handbook of Medicinal Herbs (Duke, 2001),** California poppy is reported to be analgesic, anodyne, diaphoretic, diuretic, soporific and spasmolytic, the alkaloids present in the roots are said to have feeble narcotic and respiratory effects.

Also the **Encyclopedia of Herbal Medicine (Bartram, 1995)** includes similar therapeutic uses: insomnia, migraine, stressful conditions, nervous bowel, anxiety, depression, neuralgia. It combines well with passionflower for hyperactivity and sleeplessness.

The **Avis aux fabricants concernant les demandes d'autorisation de mise sur le marché de spécialités pharmaceutiques a base de plantes (**Cahiers de L'Agence N°3, **Ministry of Health and Family, France, 1998)** includes the therapeutic indication « traditionally used in the symptomatic treatment of neurotonic disturbances in adults and children, mainly for minor sleep disorders » for *Eschscholzia californica*.

The reference in the **Pharmacognosie. Phytochimie. Plantes médicinales** handbook **(Bruneton, 1998)** for *Eschscholzia californica* lists the following traditional use: symptomatic treatment of neurotonic disturbances in adults and children, mainly for minor sleep disorders. It is frequently used in association with other plants such as passionflower herb or valerian root.

The monograph included in the **PDR for Herbal Medicines (Gruenwald *et al.*, 2004)** describes the internal use of preparations of the herbal substance in the treatment of insomnia, aches, nervous agitation, enuresis nocturna in children, diseases of the bladder and liver, reactive agitative and masked depressions, melancholia, neurasthenia, neuropathy, organic neuroses, vegetative-dystonic disorders, mood swings, weather sensitivity, vasomotor dysfunctions, vegetative-endocrine syndrome, constitutional weakness of the nervous system, and vasomotor cephalgia. The tea is used as a sedative. Also its homeopathic use to treat insomnia is cited. Not to be used during pregnancy.

A recent review on Plant-based medicines for anxiety disorders **(Sarris *et al.*, 2013)** includes *Eschscholzia californica* as a plant with preclinical evidence of anxiolytic activity.

**Mills and Bone (2005)**, in **The Essential Guide to Herbal Safety** list the traditional use of California poppy in Western herbal medicine to reduce pain and to assist sleep. Indications include insomnia, neuralgia, anxiety, stress migraine and nervous bowel. No contraindications are included, except for lactation without professional advice. It was used by the women of the tribes Mendocino, Pomo, Yuki and Kashaya to decrease and stop milk production by rubbing the mashed seed pods on the mother's breast **(Adams and Garcia, 2006).**

The Canadian monograph **(2008)** lists two medicinal uses for California poppy aerial parts: traditionally used as a mild sedative and/or sleep aid (hypnotic) and traditionally used as an analgesic **(Mills and Bone, 2005; Hoffmann, 2003; Felter and Lloyd, 1988, in Mills and Bone, 2000).** Use during pregnancy is contraindicated.

According to the **Adverse Effects of Herbal Drugs** handbook **(De Smet *et al.*, 1993)**, aerial parts are permitted for oral use, although use during pregnancy should be avoided, as the major alkaloid cryptopine showed a stimulating effect on guinea pig uterus *in vitro.*

In Belgium, the use of aerial parts of California poppy is allowed with no dose restrictions, under the Food Supplements national legislation since 1997 **(Royal Decree of 29 August 1997, 21st November 1997).**

### *2.3. Specified strength / posology / route of administration / duration of use for relevant preparations and indications*

See section 1.2.

**Traditional use**

| **Strength (name)** | **Posology** | **Route of administration / duration of use** |
|---|---|---|
| 300 mg powdered dry herb | Adults: 2 capsules 2 times daily. Up to 5 capsules, if necessary<br>Adolescents > 12 years: 1 capsule 2 times daily<br>Indication: Traditionally used in the symptomatic treatment of neurotonic conditions of adults and children, notably in cases of mild disorders of sleep | Oral administration |
| 240 mg powdered dry herb | Adults<br>Indication 1): 2 capsules 2 times daily (breakfast and dinner)<br>Indication 2): 2 capsules 2 times daily (dinner and before sleep time) | Oral administration / 4 weeks |

# 3. Non-Clinical Data

Many studies have demonstrated the *in vivo* and *in vitro* pharmacological activity of *Eschscholzia californica* herba. Those studies with relevance for the clinical efficacy are included.

### *3.1. Overview of available pharmacological data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof*

The main components in *Eschscholzia californica* herba are isoquinoline alkaloids (such as californidine and eschscholzine) that are responsible for the sedative, anxiolytic and minor analgesic effects observed **(Bruneton, 1998; Cheney, 1963; Fleurentin *et al.*, 1996; Mills and Bone, 2005)**. Isolated californidine has sleep-inducing, sedative, anxiolytic and spasmolytic effects **(Gruenwald *et al.*, 2004-PDR)**.

### 3.1.1. Primary pharmacodynamics

***In vitro studies***

Aqueous-alcoholic extracts from *Eschscholzia californica* inhibited the enzymatic degradation of catecholamines as well as the synthesis of adrenaline, dopamine beta-hydroxylase and monoamine oxidase **(Mills and Bone, 2000)**.

A 70% ethanol extract of California poppy is able to bind the 5-HT(1A) and 5-HT(7) receptors at 100 µg/ml. The main alkaloids in this extract were californidine, escholzine, N-methyllaurotanine, caryachine and O-methylcaryachine, along with a new pavine alkaloid, 6*S*,12*S*-neocaryachine-7-O-methyl ether N-metho salt **(Gafner *et al.*, 2006).**

***In vivo studies***

The intraperitoneal administration of the aqueous extract of the plant at 25 mg/kg in mice exerted an anxiolytic action, as proved by changes in behavioural parameters; at higher levels, the effect became more sedative **(Mills and Bone, 2000)**.

A study performed by **Rolland *et al.*, (1991)** intended to validate the traditional sedative indications of *Eschscholzia californica* by pharmacological investigations. Thus, several doses of the aqueous extract from aerial parts of the plant (from 25 to 400 mg/kg) were tested to determine the possible sedative and/or anxiolytic effects on the behaviour of mice subjected to several experimental situations. Naive male mice (Swiss) weighing 30-35 g were used for behavioural tests (two compartments test, sleep induction test, staircase test) while naive male and female Swiss mice were used for acute toxicity determination.

With respect to the first experiment, *Eschscholzia californica* induced a dose-dependent decrease of the number of rearing and the total locomotion from the dose of 100 mg/kg while the novelty preference was significantly affected only from 200mg/kg. $ED_{50}$ was estimated to be 151 mg/kg for the locomotion reduction and 108 mg/kg for the rearing reduction.

In the second study, California poppy aqueous extract induced a dose-dependent sleep induction from the dose of 100 mg/kg. The sleeping induction $ED_{50}$ was estimated to be 106 mg/kg. In the same conditions, dipotassium clorazepate as the reference compound, induced significantly and dose-dependent sleep in mice from the dose of 5 mg/kg (50% of sleeping mice). The results obtained after the exposition of mice to the staircase test demonstrated that *Eschscholzia californica* significantly decreased the number of steps climbed and the number of rearings affected by mice, from 200 mg/kg (at lower dose of 25 mg/kg, the effects were reversed). $ED_{50}$ was estimated to be 254 mg/kg for the rearings and 153 mg/kg for the steps climbed; data obtained for the reference compound, dipotassium clorazepate, were a sedative $ED_{50}$ of 13 mg/kg and 23 mg/kg for the rearings and the steps climbed, respectively. Also *Eschscholzia californica* significantly increased the time spent by mice in the lit box at the dose of 25 mg/kg.

The authors concluded that the anxiolytic and sedative effects exerted by *Eschscholzia californica* were proven and that these results validated the traditional therapeutic indication of this specie **(Rolland *et al.*, 1991)**.

The same research group evaluated the benzodiazepine, neuroleptic, antidepressant, antihistaminic and analgesic properties of an aqueous alcohol extract of *Eschscholzia californica* **(Rolland *et al.*, 2001).** The plant extract did not protect mice against the convulsing effects of pentylenetetrazol, and did not cause muscle relaxation but appeared to possess an affinity for the benzodiazepine receptor: thus, flumazenil, an antagonist of these receptors, suppressed the sedative and anxiolytic effects of the

extract. The Ec extract induced peripheral analgesic effects in mice but did not possess antidepressant, neuroleptic or antihistaminic effects. The authors concluded that the anxiolytic and sedative effects of *Eschscholzia californica* were caused by affinity for GABA receptors, as showed by suppression of anxiolytic and sedative effects following pre-treatment with flumazenil.

Table 1 summarizes the pharmacological studies with *Eschscholzia californica* or any of its components.

Table 1. Summary of the pharmacodynamic studies

| Author | Design | Tested product | Dose | Effect | Result |
|---|---|---|---|---|---|
| Gafner *et al*., 2006 | *in vitro* | 70 % ethanol extract of *Eschscholzia californica* | 100 µg/ml | Binding to 5-HT(1A) and 5-HT(7) receptors at 100 µg/ml | Not specified |
| Rolland *et al*., 2001 | Mice, rats | Aqueous-alcohol extract of *Eschscholzia californica* | 200 mg/kg<br>800 mg/kg | Affinity for the benzodiazepine receptors | Sedative and anxiolytic effect, induction of peripheral analgesic effects |
| Kleber *et al*., 1995 | Not specified | Aqueous-alcoholic extracts from *Eschscholzia californica* | Not specified | Inhibition of the enzymatic degradation of catecholamines as well as synthesis of adrenaline | Sedative, antidepressive and hypnotic activities |
| Rey *et al*., 1991 | Not specified | Californine and protopine/ Aqueous alcoholic preparation of *Eschscholzia* | Not specified | Sedative and spasmolytic effects | Determination of both alkaloids by HPLC |
| Rolland *et al*, 1991 | Mice | Aqueous extract of *Eschscholzia californica* | 100 mg/kg (familiar environment)<br>200 mg/kg | Sedative properties | Sleeping induction at doses above 100 mg/kg |
| | | | 25 mg/kg | | Anxiolytic action |
| Vincieri *et al*., 1988 | Not specified | *Eschscholzia* | Not specified | Not specified | Hypnotic and spasmolytic effect |
| Kardos *et al*., 1986 | Rat | Protopine, cryptopine, allocrytopine | No information | Enhance 3H-gamma-aminobutyric acid (3H-GABA) binding to brain synaptic receptors | Benzodiazepine-like activity |

## 3.1.2. Secondary pharmacodynamic

***In vitro studies***

The isolated alkaloid chelerythrine was reported to be a protein-kinase C inhibitor with antitumor activity that caused significant reduction of nociceptive responses in one study, attenuated the development of morphine dependence and showed potent antinflammatory activity **(Mills and Bone, 2000)**.

Chelerythrine and sanguinarine exhibited affinity for rat liver vasopressin V1 receptors and were shown to be competitive inhibitors of [3H]-vasopressin binding **(Mills and Bone, 2000)**.

The isoquinoline alkaloids hennemanine and norsanguinarine were isolated from a methanolic extract of the whole plant of *Eschscholzia californica* and checked for their antifungal activity against phytopathogenic fungi *Alternaria melongenae, Alternaria brassicola, Alternaria brassicae, Curvularia lunata, Curvularia maculans, Helminthosporium pennisetti, Helminthosporium oryzae, Helminthosporium turcium, Fusarium undum* and *Fusarium lini*. Hunnemanine exhibited 100% inhibition of spore germination of *A. brassicae, H. pennisetti* and *F. lini* at 1000 ppm, whereas norsanguinarine exhibited 100% inhibition of *A. brassicola* and *C. maculans* at this concentration **(Singh *et al.*, 2009)**.

***In vivo studies***

No data available.

## 3.1.3. Safety pharmacology

No data available.

## 3.1.4. Pharmacodynamic interactions

No data available.

## 3.1.5. Conclusions

Pharmacodynamic studies have been performed with *Eschscholzia californica* herba or some isolated compounds. The observed anxiolytic and sedative effects after *in vitro* and *in vivo* tests were related to its affinity for GABA receptors and were in accordance with the traditional use of this species.

There is no information available on the safety and pharmacodynamic interactions of *Eschscholzia californica* herba.

## *3.2. Overview of available pharmacokinetic data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof*

No data are available related to California poppy.

Only some data related to the metabolism of the isolated alkaloids californine and protopine have been published **(Paul and Maurer, 2003; Paul *et al.*, 2004)**. Both alkaloids underwent hepatic metabolism through the cytochrome P450 (CYP). Californine is metabolised by N-demethylation and/or single or double demethylenation by CYP3A2 and CYP2D1-CYP2C11, respectively; this was followed by catechol-O-methylation of one of the hydroxyl groups. Protopine underwent demethylenation of the 2,3-methylenedioxy group followed by catechol-O-methylation, but not N-demethylation of the former. All phenolic hydroxyl metabolites were partially conjugated and detected in human urine **(Paul and Maurer, 2003)**.

## *3.3. Overview of available toxicological data regarding the herbal substance(s)/herbal preparation(s) and constituents thereof*

### 3.3.1. Single dose toxicity

The administration of the aqueous or 60% hydroalcoholic extract of the plant at doses of 5000 mg/kg/i.p. to mice did not cause any mortality (**Fleurentin *et al.*, 1996).**

Powdered plant (aerial parts) did not cause any toxicological reaction after acute or subacute toxicity studies in rat (oral administration of 300-900 mg/kg and 2000 mg/kg for 4 weeks) **(Fleurentin *et al.*, 1996).**

The aqueous extract of *Eschscholzia californica* did not induce the mortality up to the dose of 8 mg/kg after *i.p*. and *per os* administration. Animals did not show any toxic manifestation on the studied parameters. The evolution of body weight was normal, despite a small decrease in the first four hours when eyes were closed, this effect corresponding to the sedative activity **(Rolland *et al.*, 1991)**.

Toxicological assessment of California poppy is hampered by the lack of relevant toxicity studies performed by the herbal preparations or by the individual alkaloids. There are relatively old rodent $LD_{50}$ studies from 1950's to 1983 on alkaloids present in aerial parts of California poppy, i.e. protopine, cryptopine, chelidonine and d-glaucine indicating moderate to low toxicity, values in excess of 100 mg/kg bw after peritoneal, oral, or subcutaneous administration and <100 mg/kg after intravenous administration. The value of these studies in risk assessment is negligible. However, the observation that the acute and subacute toxicity studies with aqueous or hydroalcoholic extracts, demonstrating no toxicological effects at high doses (up to 2000 mg/kg for 4 weeks), suggests a certain degree of safety in agreement with a long-term traditional use of California poppy extracts (**Kelentey, 1960**).

### 3.3.2. Repeated dose toxicity

No data available.

### 3.3.3. Genotoxicity

No data available.

### 3.3.4. Carcinogenicity

No data available.

### 3.3.5. Reproductive and developmental toxicity

No data on reproductive and developmental toxicity are available from the literature.

### 3.3.6. Local tolerance

No data are available from the literature.

### 3.3.7. Other special studies

Not available.

## *3.4. Overall conclusions on non-clinical data*

The scientific information available on the pharmacological activity of *Eschscholzia californica*, herba supports the traditional use.

Nearly 85% of the alkaloid content in California poppy corresponds to pavine alkaloids (californidine and eschscholzine), with unknown toxicity. Toxicity data for the other isolated alkaloids indicate a low toxicity: taking into account the low percentage of these compounds in *Eschscholzia californica* aerial parts, toxicity in humans, when taken at the recommended doses, is not expected. There might be possible effects of other constituents of the plant on the absorption of the active principles, but no further details are available.

These data are in accordance with the traditional use of the plant, which can be found in the European market for more than 30 years without any safety concern.

Non-clinical information on the safety of *Eschscholzia californica* herba is scarce. As there is no information on reproductive and developmental toxicity the use during pregnancy and lactation cannot be recommended. Due to the lack of genotoxicity studies, a list entry cannot be recommended.

# 4. Clinical Data

## *4.1. Clinical Pharmacology*

### 4.1.1. Overview of pharmacodynamic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents

No data available.

### 4.1.2. Overview of pharmacokinetic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents

No data available.

## *4.2. Clinical Efficacy*

Only a few clinical studies have been published with *Eschscholzia californica* herba. The most relevant data are summarized in this section..

### 4.2.1. Dose response studies

No data available.

### 4.2.2. Clinical studies (case studies and clinical trials)

An open study including 60 patiens (2 children, 38 women, 20 men) suffering from sleep disorders and treated with California popy has been published. Adults received 2 g of one marketed product with *E. californica* as a nebulizer (2 capsules of 0.50 g at dinner and before sleep time), while children received a total dose of 0.5 g. Treatment duration was 6 months. After this period, 43% patients reported excellent results, mainly for sleep quality; 43% patients reported good results, while 14% gave up the study because of the lack of efficacy. Authors concluded that *E. californica* exerts a positive, effective and constant action on sleep disorders **(Baldacci, 1984).**

Only two clinical trials have been reported with the aim of studying the efficacy of *Eschscholzia californica* in anxiety disorders. a) The main objective was to assess the clinical efficacy of a neurotonic component containing fixed quantities of two plant extracts (*Crataegus oxyacantha* and *Eschscholzia californica*) and magnesium *versus* placebo in mild-to-moderate anxiety disorders with associated functional disturbances: 75 mg of dry hydro-alcoholic extract of the flowering head of *Crataegus oxyacantha*, 20 mg of dry aqueous extract of *Eschscholzia californica* and 75 mg of elemental magnesium (i.e. 124.35 mg of heavy magnesium oxide) (Hanus *et al.,* 2004). A total of 264 patients (81% female; mean age: 44.6 years) presenting with generalised anxiety (DSM-III-R) of mild-to-moderate intensity (total Hamilton anxiety scale score between 16 and 28) were included in a double-blind, randomised, placebo-controlled trial. Patients were randomly assigned to two groups: 130 received the study drug and 134 received a placebo (two tablets twice daily for 3 months). Efficacy and safety data were recorded before first administration and 7, 14, 30, 60 and 90 days after start of treatment.

With respect to the main outcome measures, **efficacy** was assessed by (a) change in Hamilton anxiety scale total and somatic scores; (b) change in patient self-assessment; (c) number and percentage of responsive subjects (reduction of at least 50% in Hamilton or self-assessment score); and (d) the physician's clinical global impression. **Tolerance** was assessed by undesirable events spontaneously reported by the patients over the study period. Results showed a Total and somatic Hamilton scale scores and subjective patient-rated anxiety fell during treatment, indicating clinical improvement. The decrease was greater in the study drug than in the placebo group. End of treatment clinical improvement, as measured by the mean difference between final and pre-treatment scores, was, for the study drug and placebo groups: -10.6 and -8.9 on the total anxiety score, respectively ($p = 0.005$); -6.5 and -5.7 on the somatic score, respectively ($p = 0.054$); and -38.5 and -29.2 for subjectively assessed anxiety, respectively ($p = 0.005$). The risk/benefit ratio as judged by the investigating physicians was also significantly better in the study drug than in the placebo group. In all, 15 patients (11.5%) in the study drug group and 13 patients (9.7%) in the placebo group experienced 22 and 15 adverse events, respectively. Undesirable events were mainly mild or moderate digestive or psychopathological disorders.

Authors concluded that the preparation containing fixed quantities of *Crataegus oxyacantha, Eschscholzia californica*, and magnesium proved safe and more effective than placebo in treating mild-to-moderate anxiety disorders **(Hanus *et al.,* 2004).**

**b)** One product containing 3 grams of the dried herb standardized to 0.8% isoquinoline alkaloids (californidine, escholtzine and protopine) is authorised by Health Canada and marketed as an analgesic and mild sedative (hypnotic) to be used as an analgesic or co-analgesic in the management of chronic pain **(Chamberland, 2012).**

This open-label trial was carried out in order to obtain analgesic proof-of-concept and preliminary safety and efficacy information on the product. Two studies were performed: a 7-day and 30-day study with ten patients per study. A total of 20 men and women between 18 to 80 years of age with chronic pain were enrolled into the study. Three clinics participated in the trial. The product was administered either once a day or twice a day and daily for up to 1 month. Subjects were excluded from the study if: they were allergic to California poppy; if there was clinical evidence for severe renal/liver/pulmonary, neurologic, cardiovascular, metabolic, haematological, or psychiatric condition which in the Investigator's opinion contraindicated treatment with California poppy; if the subject had heart or liver disease or was taking heart medication; had taken an investigational drug (i.e., participated in a pharmaceutical drug clinical trial) within 30 days prior to screening; was pregnant or breastfeeding. The efficacy was measured using patient questionnaires at baseline and during an interim and final visit after 1 month of treatment . The short form of the McGill Pain scale was used to record the degree of severity of pain as measured by the Pain Visual Analog Outcome Scale. A questionnaire was used to record insomnia. Adverse events and concomitant medication were recorded.

The authors concluded, that the standardized extract of California poppy can be used in the management of chronic pain and as a hypnotic-mild-sedative for the management of pain-related insomnia. It can be used as a co-analgesic in combination with other pain medications to help reduce the intensity/severity of pain to a tolerable level (dosage: 1 capsule BID). It was well tolerated in combination with the majority of other pain medications; insomnia (excitation) and urticaria were the only observed adverse events. The data also demonstrated that the studied product can be used as an analgesic-hypnotic in cases of mild-to-moderate night pain (dosage: 1 capsule at bedtime, according the Health Canada monograph for California poppy).

### *4.3. Clinical studies in special populations (e.g. elderly and children)*

Not found.

### *4.4. Overall conclusions on clinical pharmacology and efficacy*

The existing data do not meet the criteria for "well established medicinal use" in accordance with Directive 2001/83/EC. The plausibilitiy of efficacy of the medicinal product is only based on long-standing use and experience and allows the development of a European Union herbal monograph on the traditional use of *Eschscholzia californica* herba.

## 5. Clinical Safety/Pharmacovigilance

No data available.

### 5.1. Overview of toxicological/safety data from clinical trials in humans

No data available

### 5.2. Patient exposure

No data available

### 5.3. Adverse events, serious adverse events and deaths

No data available

### 5.4. Laboratory findings

No data available

### 5.5. Safety in special populations and situations

No data available on: use in children and adolescent; contraindications; special warnings and precautions for use; drug interactions and other forms of interactions; fertility, pregnancy and lactation; overdose; effects on ability to drive or operate machinery or impairment of mental ability; safety in other special situations.

### 5.6. Overall conclusions on clinical safety

No data available

## 6. Overall conclusions

Well-established use can not be accepted for *Eschscholzia californica* Cham., herba, due to the lack of data on clinical efficacy, in accordance with Directive 2001/83/EC.

There exist no data in relation to reproductive and developmental safety, therefore, the use of California poppy in pregnancy is not recommended. Also, because of the lack of data on genotoxicity, a list entry is not suggested.

Some data related to the toxicity of some isolated alkaloids from *E. californica* have been published. Most of the studies were performed more than 40 years ago and do not fulfil the current guidelines for toxicity studies. Moreover, the obtained data for every isolated compound demonstrate a very low toxicity risk after oral intake. Safety of California poppy has been investigated and because of the long-standing use, no major safety concerns can be derived in relation to the use of *E. californica* in the recommended posology and conditions of use.

The traditional medicinal use of *Eschscholzia californica* Cham., herba, is well documented in several handbooks throughout a period of at least 30 years (15 years in the European Union) under Directive 2001/83/EC as powdered substance. A traditional use as soporific, sleep-inducing, analgesic and sedative has been described for *Eschscholzia californica* Cham., herba. The long-standing use has shown that *Eschscholzia californica*, herba can be recognized as safe when used in recommended dosages under the conditions specified in the monograph.

In conclusion, a monograph *Eschscholzia californica* Cham., herba, for oral use is recommended with the following indications:

1) Traditional herbal medicinal product for relief of mild symptoms of mental stress.

2) Traditional herbal medicinal product to aid sleep.

# Annex

## *List of references*