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SCIENCE MEDICINES HEALTH

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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)

Draft

Herbal substance(s) (binomial scientific name of the plant, including plant part)	<i>Eschscholzia californica</i> Cham., herba
Herbal preparation(s)	
Pharmaceutical forms	Powdered herbal substance
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Note: This draft assessment report is published to support the release for public consultation of the draft Community herbal monograph on *Eschscholzia californica* Cham., herba. It should be noted that this document is a working document, not yet edited, and which shall be further developed after the release for consultation of the monograph. Interested parties are welcome to submit comments to the HMPC secretariat, which the Rapporteur and the MLWP will take into consideration but no 'overview of comments received during the public consultation' will be prepared in relation to the comments that will be received on this assessment report. The publication of this draft assessment report has been agreed to facilitate the understanding by Interested Parties of the assessment that has been carried out so far and led to the preparation of the draft monograph.



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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 (C₂₀H₂₀NO₄⁺; M_r 338.4) (dried drug).
- *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 (C₂₀H₂₀NO₄⁺; M_r 338.4) (dried drug).

Eschscholzia californica Cham. (Fam. *Papaveraceae*) is a perennial and annual plant growing approx 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 color 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 colored seeds held in the center of the flower within slender, ribbed single celled seed capsules (3-9cm long) (**Bruneton, 1998**).

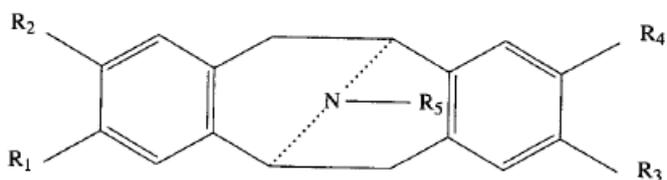
Both aerial parts and roots contain alkaloids, the latter being richer than the former (up to 1.6% alkaloids) (Fleurentin *et al.*, 1996).

Synonyms: California poppy

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

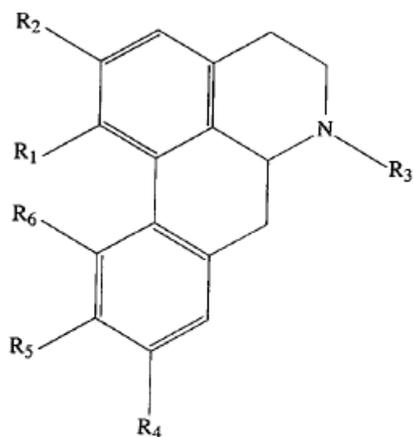
Alkaloids: 0.50-1.20 per cent of total alkaloids, expressed as californidine; six different groups of alkaloids have been described.

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



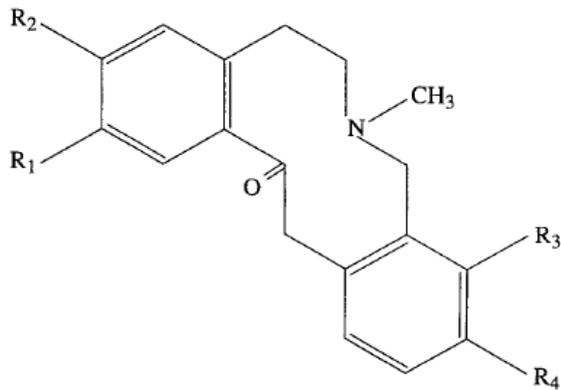
	R ₁	R ₂	R ₃	R ₄	N-R ₅
Bisnorargemonine	OCH ₃ -	OH	-OCH ₃	-OH	-CH ₃
Eschsholtzine (ou californine)	\O-CH ₂ -O/		\O-CH ₂ -O/		-CH ₃
Californidine	\O-CH ₂ -O/		\O-CH ₂ -O/		(CH ₃) ₂
Eschsholtzidine	\O-CH ₂ -O/		-OCH ₃ -OCH ₃		-CH ₃
Norargemonine	\OH-OCH ₃		-OCH ₃ -OCH ₃		-CH ₃

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**)



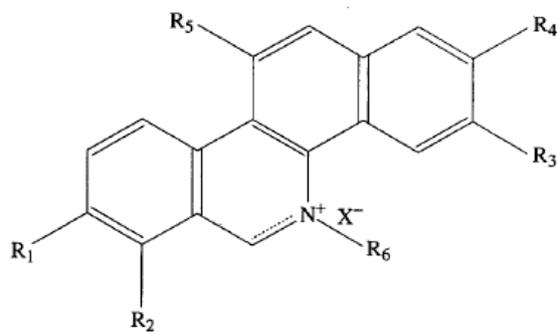
	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆
Laurotétamine	-OCH ₃	-OCH ₃	-H	-OH	-OCH ₃	-H
N-méthyl laurotétamine (ou lauroscholzine)	-OCH ₃	-OCH ₃	-CH ₃	-OH	-OCH ₃	-H
Glaucine	-OCH ₃	-OCH ₃	-CH ₃	-OCH ₃	-OCH ₃	-H

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/	\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 being 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	-O-CH ₂ -O	-OCH ₃	-CH ₃	
Chélilutine	-OCH ₃ -OCH ₃	-O-CH ₂ -O	-O-CH ₂ -O	-OCH ₃	-CH ₃	
Chélidonine	-O-CH ₂ -O	-O-CH ₂ -O	-O-CH ₂ -O	-OCH ₃	CH ₃	
Homochélidonine	-OCH ₃ -OCH ₃	-O-CH ₂ -O	-O-CH ₂ -O	-OH	CH ₃	
Chélilutine	-OCH ₃ -OCH ₃	-O-CH ₂ -O	-O-CH ₂ -O	-OCH ₃	-CH ₃	
Chélidonine	-O-CH ₂ -O	-O-CH ₂ -O	-O-CH ₂ -O	-OCH ₃	CH ₃	
Homochélidonine	-OCH ₃ -OCH ₃	-O-CH ₂ -O	-O-CH ₂ -O	-OH	CH ₃	

The group of benzo-C-phenanthridin alkaloids, and mainly sanguinarine and chelerythrine, are not present in aerial parts (**Fleurentin et al., 1996**). According to **Guedon et al. (1990)**, the total alkaloids content in the aerial parts is close to the minimum amount cited in the Pharmacopoeia monograph:

Alkaloid	Aerial parts content (µg/ml)	Percentage
N-methylaurotetanina	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 et Tome (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 drug
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 (1200mg), up to 5 capsules, if necessary Adolescents > 12 years: 1 capsule

		twice daily 1 hard capsule contains 300mg powder with 0.8% eschscholzine
2. 1996	Hard capsules	Adults and children > 6 years: 2 capsules twice daily 1 hard capsule contains 200mg extract

Indications:

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

Herbal substance is on the market.

Spain: Traditional use

1. Powdered drug

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

Indications:

- 1) Traditional herbal medicinal product to relieve nervousness and anxiety
- 2) Traditional herbal medicinal product to improve sleep quality

Herbal substance is on the market.

Regulatory status overview

Member State	Regulatory Status				Comments
Austria	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products in the market
Belgium	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No information available
Bulgaria	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No information available
Cyprus	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No information available
Czech Republic	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products in the market
Denmark	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products in the market
Estonia	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products in the market
Finland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products in the market
France	<input type="checkbox"/> MA	<input checked="" type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	

Member State	Regulatory Status				Comments
Germany	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products in the market
Greece	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products in the market
Hungary	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No information available
Iceland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No information available
Ireland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No information available
Italy	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products in the market
Latvia	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input checked="" type="checkbox"/> Other Specify:	Combination products
Liechtenstein	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No information available
Lithuania	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No information available
Luxemburg	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No information available
Malta	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No information available
The Netherlands	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products in the market
Norway	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No information available
Poland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products in the market
Portugal	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No information available
Romania	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products in the market
Slovak Republic	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No information available
Slovenia	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No information available
Spain	<input type="checkbox"/> MA	<input checked="" type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Sweden	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No information available
United Kingdom	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products in the market

MA: Marketing Authorisation

TRAD: Traditional Use Registration

Other TRAD: Other national Traditional systems of registration

Other: If known, it should be specified or otherwise add 'Not Known'

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* at the electronic databases PubMed, Toxline and The Cochrane Library and the incoming, on the "call for scientific data for use in HMPC assessment work on *Eschscholzia californica* Cham., herba", 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.

Results in PubMed

Search term "*Eschscholzia californica*": 93 references 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. Historical data on medicinal use

2.1. Information on period of medicinal use in the Community

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 Community.

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

1. Powdered dry herb

This product is recognized as a traditional product 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 from North-american Indian population, nowadays being used for its mild analgesic and sedative properties (and as the state flower of California) (**Bocek, 1984; Mills and Bone, 2000**) without the dangers attending opiates (**Felter and Lloyd, 1898**).

This specie is native to California (USA) and North area of Mexico and has perfectly been adapted to several European countries where it is frequently cultivated in ornamental gardens. 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 (**Boericke, 1901**) and considered 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 **Comission E (Blumenthal, 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 BaCl₂ (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, 2004)** describes the internal use of preparations of the drug 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 Mendocino, Pomo, Yuki and Kashaya women 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, 1983 [1898]**). Use during pregnancy is contraindicated.

In 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 shows 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 (Belgian State Journal on 21st November 1997)

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

See section 1.2.

Insert table with different extracts

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 Adolescents > 12 years: 1 capsule 2 times daily 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 and adolescents > 18 years Indication 1): 2 capsules 2	Oral administration / 4 weeks

	<p>times daily (breakfast and dinner)</p> <p>Indication 2): 2 capsules 2 times daily (dinner and before sleep time)</p>	
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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 of 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 pharmacodynamic

In vitro studies

Aqueous-alcoholic extracts from *E. californica* inhibit 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 100µg/ml. The main alkaloids in this extract were californidine, escholzine, N-methylaurotanine, caryachine and O-methylcaryachine, along with a new pavine alkaloid, 6S,12S-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 25mg/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).

The study performed by Rolland *et al.*, (1991) intended to validate the traditional sedative indications of *E. californica* by pharmacological investigations. Thus, several doses of the aqueous extract from aerial parts of the plant (from 25 to 400mg/kg) were tested to dertermine the possible sedative and/or anxiolytic effects on the behaviour of mice subjected to several experimental situations. Naive male mice (Swiss) weighing 30-35g 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, *E. californica* induces a dose-dependent decrease of the number of rearing and the total locomotion from the dose of 100mg/kg while the novelty preference is significantly affected only from 200mg/kg. ED₅₀ is estimated to be 151mg/kg for the locomotion reduction and 108mg/kg for the rearing reduction. In the sleep induction test, California poppy aqueous extract induced a dose-dependent sleep induction from the dose of 100mg/kg. The sleeping induction ED₅₀ was estimated to be 106mg/kg. In the same conditions, dipotassium clorazepate as the reference compound, induced significantly and dose-dependent sleep in mice from the dose of 5mg/kg (50% of sleeping mice). The results obtained after the exposition of mice to the staircase test demonstrated that *E. californica* significantly decreased the number of steps climbed and the number of rearings affected by mice, from 200mg/kg (at lower dose of 25mg/kg, the effects were reversed). ED₅₀ was estimated to be 254mg/kg for the rearings and 153mg/kg for the steps climbed; data obtained for the reference compound, dipotassium clorazepate, were a sedative ED₅₀ of 13mg/kg and 23mg/kg for the rearings and the steps climbed, respectively. Also *E. californica* significantly increased the time spent by mice in the lit box at the dose of 25mg/kg.

In relation to the acute toxicity test, the aqueous extract of *E. californica* did not induced the mortality up to the dose of 8mg/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.

The authors conclude that the anxiolity and sedative effects exerted by *E. 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 convulsant effects of pentylenetetrazol, and did not cause muscle relaxant effects 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. So the anxiolytic and sedative effects of *E. californica* are caused by affinity for GABA receptors, as evidenced by suppression of anxiolytic and sedative effects following pre-treatment with flumazenil.

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

Table 1. Summary of the pharmacodynamic studies

Author	Design	Tested product	Dose	Effect	Result
Gafner et al., 2006	/	70 % ethanol extract of <i>Eschscholzia californica</i>	/	Binding to 5-HT(1A) and 5-HT(7) receptors at 100µg/ ml	/
Rolland et al., 2001	Mice	Aqueous-alcohol extract of <i>Eschscholzia californica</i>	/	Affinity for the benzodiazepine receptors	Sedative and anxiolytic effect, induction of peripheral analgesic effects
Kleber et al., 1995	/	Aqueous-alcoholic extracts from <i>Eschscholzia californica</i>	/	Inhibition of the enzymatic degradation of catecholamines as well as synthesis of adrenaline	Sedative, antidepressive and hypnotic activities
Rey et al., 1991	/	Californine and protopine/ Aqueous alcoholic preparation of <i>Eschscholzia</i>	/	Sedative and spasmolytic effects	Determination of both alkaloids by HPLC
Rolland et al., 1991	Mice	Aqueous extract of <i>Eschscholzia californica</i>	100 mg/kg (familiar environment) 200 mg/kg 25 mg/kg	Sedative properties /	Sleeping induction at doses above 100 mg/kg Anxiolytic action
Vincieri et al., 1988	/	<i>Eschscholzia</i>	/	/	Hypnotic and spasmolytic effect
Kardos et al., 1986	Rat	Protopine, cryptopine, allocryptopine	/	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 is a protein-kinase C inhibitor with antitumour activity that produced significant reduction of nociceptive responses in one study, attenuated the development of morphine dependence and showed potent antiinflammatory activity (**Mills and Bone, 2000**).

Chelerythrine and sanguinarine exhibit affinity for rat liver vasopressin V1 receptors and are competitive inhibitors of [3H]-vasopressin binding (**Mills and Bone, 2000**).

The isoquinoline alkaloids hennemanine and norsanguinarine were isolated from methanolic extract of the whole plant of *E. californica* and checked for their antifungal activity against phytopathogenic fungi *Alternaria melongenae*, *A. brassicola*, *A. brassicae*, *Curvularia lunata*, *C. maculans*, *Helminthosporium pennisetii*, *H. oryzae*, *H. turcium*, *Fusarium undum* and *F. lini*. Hunnemanine exhibited 100% inhibition of spore germination of *A. brassicae*, *H. pennisetii* and *F. lini* at 1000ppm, 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.

3.2. 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 undergo hepatic metabolism through the cytochrome P450 (CYP). Californine is metabolized by N-demethylation and/or single or double demethylenation by CYP3A2 and CYP2D1-CYP2C11, respectively; this is followed by catechol-O-methylation of one of the hydroxyl groups. Protopine undergoes demethylenation of the 2,3-methylenedioxy group followed by catechol-O-methylation, but not N-demethylation of the former. All phenolic hydroxyl metabolites are 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 5000mg/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 300-900mg/kg and 2000mg/kg for 4 weeks) (**Fleurentin et al., 1996**).

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 LD50 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 100mg/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 (**Dil, 1973; 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 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 *Eschscholzia californica* herba pharmacological activity agrees with the traditional use.

Nearly 85% of the alkaloid content in California poppy corresponds to pavine alkaloids (californidine and eschscholzine), with not known toxicity. Toxicity data for the other isolated alkaloids indicate a low toxicity: taking in account the low percentage of these compounds in *E. californica* aerial parts, toxicity in humans, when taken at the recommended doses, is not expected. Also the possible effects of other constituents of the plant on the active principles absorption should be taken in account.

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, the 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

No clinical studies testing the efficacy of *Eschscholzia californica* herba alone have been published.

4.2.1. Clinical studies (case studies and clinical trials)

Only two clinical trials have been reported with the aim of studying the efficacy of *E. 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: 75mg of dry hydro-alcoholic extract of the flowering head of *Crataegus oxyacantha*, 20mg of dry aqueous extract of *Eschscholzia californica* and 75mg of elemental magnesium (i.e. 124.35mg 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 authorized 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.

An 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, hematological, 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 collected.

Results showed 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).

4.2.2. Clinical studies in special populations (e.g. elderly and children)

Not found.

4.3. 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 plausibility of efficacy of the medicinal product is only based on long-standing use and experience and allows the development of a Community herbal monograph on the traditional use of *Eschscholzia californica* herba.

5. Clinical Safety/Pharmacovigilance

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, so 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 so, 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 the MLWP has a positive opinion on this issue, so no safety concerns exist in relation to the use of *E. californica* in the recommended posology and conditions of use.

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 Community) under Directive 2001/83/EC as herbal tea or powdered substance. A traditional use as soporific, sleep-inducing, analgesic and sedative has been described for *Eschscholzia californica* Cham., herba. Traditional 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