EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

16 December 2011
EMA/HMPC/277791/2009
Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Oenothera biennis* L., *Oenothera lamarckiana* L., oleum

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)	n/a
Herbal preparation(s)	Oil from the seeds of *Oenothera biennis* L. or *Oenothera lamarckiana* L.
Pharmaceutical form(s)	Solid dosage forms such as capsules
Rapporteur(s)	Gert Laekeman
Assessor(s)	Veerle Pellens and Leslie Vroman

Table of contents

1. Introduction

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

- Herbal substance(s)

The HMPC has established a Community herbal monograph on the oil obtained from the seeds of *Oenothera biennis* L. or *Oenothera lamarckiana* L. The monograph does not cover the herbal substance itself, i.e. the seeds from the two species.

- Herbal preparation(s)

The fatty oil is obtained from seeds of *Oenothera biennis* L. or *Oenothera lamarckiana* L. by extraction and/or expression. It contains at least 65% (cis)linoleic acid, 7-14% (cis)gamma-linolenic acid (γ-linolenic acid) and a maximum of 0.5% is alpha-linolenic acid. Other substances are 5-12% oleic acid, 1-4% stearic acid, 4-10% palmitic acid and a maximum of 0.3% saturated fatty acids of chain length less than C_{16} (European Pharmacopoeia 2010).

The oil of Oenothera *biennis* and Oenothera *lamarckiana* is a fatty oil obtained by cold pressing of the seeds. This oil is more reactive and less stable than most other fatty oils. Besides oxidation after exposure to air and light, the oil is also sensitive to heat and humidity. Consequently, it should be stored in a cool, dark place (Price & Price 2007).

- 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

Denmark

According to the Drogelist DK at least 5 g oil is accepted in food supplements. These products were very popular 10-15 years ago for the treatment of mastalgia (breast pain), eczema and high levels of cholesterol.

Germany

Code	Pharmaceutical form On the market since	Posology, use and therapeutic indications
1	Soft capsules 1990 500 mg oil per capsule	Children 1-12 years: 2 times daily 2-4 capsules Adults: 2 times daily 4-6 capsules For the treatment and symptomatic relief of neurodermatitis, especially of the associated pruritus. It is recommended to start the treatment with the highest indicated dose. It is possible that in some patients only after 8-12 weeks of use an amelioration of symptoms can be observed. As soon as a therapeutic success appears the treatment can be continued with a lower dose or can be stopped.
2	Soft capsules 1993	Children 1-12 years: 2 times daily 2-4 capsules Adults: 2 times daily 4-6 capsules

	500 mg oil per capsule	For the treatment of neurodermatitis with a positive influence on the symptom complex, especially on the pruritus. It is recommended to start the treatment with the highest indicated dose. It is possible that in some patients only after 8-12 weeks of use an amelioration of symptoms can be observed. As soon as a therapeutic success appears the treatment can be continued with a lower dose or can be stopped.
3	Soft capsules 1994 1000 mg oil per capsule	Children 1-12 years: 2 times daily 1-2 capsules Adults: 2 times daily 2-3 capsules For the treatment and symptomatic relief of neurodermatitis, especially of the associated pruritus. It is recommended to start the treatment with the highest indicated dose. It is possible that in some patients only after 8-12 weeks of use an amelioration of symptoms can be observed. As soon as a therapeutic success appears the treatment can be continued with a lower dose or can be stopped.
4	Soft capsules 1994 500 mg oil per capsule	Children 1-12 years: 2 times daily 2-4 capsules Adults: 2 times daily 4-6 capsules For the treatment of neurodermatitis with a positive influence on the symptom complex, especially on the pruritus. It is recommended to start the treatment with the highest indicated dose. It is possible that in some patients only after 8-12 weeks of use an amelioration of symptoms can be observed. As soon as a therapeutic success appears the treatment can be continued with a lower dose or can be stopped.
5	Cream 1999 20 g oil per 100 g cream	Topical use: 2-3 times daily (or more frequently) applied on the affected areas. For the symptomatic relief of acute and chronic dry skin conditions, to restore hydration and improve skin smoothness.

Preparations 1-5, side-effects: Uncommon: nausea, dyspeptic complaints, headache.
Rare: hypersensitive reactions like exanthema, abdominal pain and very rare rise in temperature.

Preparations 1-5, interactions: occurrence of, to date unknown, epileptic seizures (temporal epilepsy), especially in schizophrenic patients and in patients taking medicinal products, which can cause epilepsy (e.g. phenothiazine).

Hungary

1 capsule contains 500 mg Oenotherae biennis oleum, minimum gamma linolenic acid content 9%.

On the market since 1992.

Oral use. For adults and adolescents above 12 years of age 3 times 1-2 capsules daily.

Indications: atopic eczema, symptoms associated with menstruation, prevention of vascular diseases, as adjuvant treatment of rheumatic arthritic inflammation and multiple sclerosis.

Undesired effects: rarely nausea, diarrhoea, vomiting, bloating.

In case of adverse effects occur the dose should be reduced.

Apart from this licensed preparation, more than 5 combination products are on the market.

Ireland

Oenothera fatty oil is used in a licensed cream with a full marketing authorisation. It is indicated as an occlusive, emollient cream, which restores hydration and improves skin smoothness in chronic dry skin conditions.

Spain

There are some food supplements on the Spanish market, usually soft gelatine caps of 500 mg (2-6 capsules a day). There are also combinations of "Onagra (Spanish name) 500 mg" and vitamin E (5 mg) in capsules available in the food market.

United Kingdom

Pharmaceutical form	Posology and use	Therapeutic indications
Cream containing 20 g Oenothera fatty oil per 100 g.	To be applied on the affected areas of the skin: 2-3 times daily.	Occlusive emollient cream for the symptomatic relief of acute and chronic dry skin conditions, to restore hydration and improve skin smoothness.

Undesirable effects: Mild and transient irritation to the site of application has been reported rarely. Contact dermatitis and urticaria has been reported in individual cases.

Regulatory status overview

Member State	Regulatory Status				Comments
Austria	☐ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify:	Food supplements
Belgium	☐ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify:	Food supplements
Bulgaria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorised or registered products
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information
Czech Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorised or registered products
Denmark	☐ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify:	Food supplements + see detailed information
Estonia	☐ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify:	Food supplements
Finland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorised or registered products
France	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information
Germany	☒MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	See detailed information
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information
Hungary	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Licensed product + see detailed information
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorised or registered products
Ireland	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	See detailed information

Member State	Regulatory Status				Comments
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorised or registered products
Latvia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information
Liechtenstein	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information
Lithuania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorised or registered products
Luxemburg	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information
Malta	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorised or registered products
The Netherlands	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorised or registered products
Norway	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorised or registered products
Poland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information
Portugal	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorised or registered products
Romania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information
Slovak Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorised or registered products
Slovenia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorised or registered products
Spain	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Only food supplements + see detailed information
Sweden	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorised or registered products
United Kingdom	☒MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Licensed products + see detailed information

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

The following basic sources were searched:

Herbal Medicines (Barnes et al. 2007)

Phytotherapy (Capasso et al. 2003)

European Pharmacopoeia (2008, 2010)

Hagers Handbuch der pharmazeutischer Praxis (Hänsel 1993)

Pubmed and Embase were searched from February 2009 to March 2011 on the following keywords (separate or combined):

Oenothera biennis or *lamarckiana* primrose fatty oil, skin, disorders, atopic, dermatitis, eczema, children, patient, premenstrual, syndrome, oral, topical, premenstrual syndrome = PMS, mastalgia, menopausal, menopause, hormonal, Sjögren, Raynaud, safety, quality, mutagenicity, mutagenic, side effects, adverse, event.

2. Historical data on medicinal use

2.1. Information on period of medicinal use in the Community

Oenothera biennis was first grown by North American Indians. They used the plant as treatment for swelling in the body and other health problems.

Before the arrival of the Pilgrim Fathers, Oenothera species oil was used by the Indians in poultices to relieve skin disorders. In 1614, botanists from Virginia brought it to Europe, in order to study it. English herbalist Nicholas Culpeper wrote in 1650: *"It opens obstructions of the liver and spleen, provokes urine, is good for dropsy (oedema) if infused in common drink."*
It was introduced to Europe by the name 'king's cure-all', which made it popular in Britain. At this time it was a popular folk remedy.
Since then it was ignored for centuries, even though old herbal text books described it as astringent and sedative, with its oil being 'helpful in treating gastro-intestinal disorders, whooping cough, asthma, female complaints and wound healing'.
The German scientist Unger discovered that the oil can be extracted from the seeds, which contain 15% oil, using light petroleum. In 1919, an unusual linolenic acid was found by Heiduschka and Lüft when they analysed the seed oil; they named it γ-linolenic acid (GLA). British scientists started to examine the effects of the oil in the 1960s with medical experiments carried out in rats. These experiments demonstrated that the human body metabolised this GLA far more effectively than linoleic acid (LA). Other trials found that GLA could also control cholesterol levels (Cottier 1996; Senapati et al. 2008).

Modern usage of *Oenothera biennis* oil

Interest in *Oenothera biennis* oil increased in the late 1970s when the oil was proposed to treat various ailments. *Oenothera biennis* oil products were marketed as a supplement for the treatment of PMS, alcoholism, pregnancy-induced hypertension, atopic eczema, elevated cholesterol levels, hypertension, scleroderma, multiple sclerosis, rheumatoid arthritis, mastalgia and other problems. Products containing *Oenothera biennis* oil were investigated in clinical trials during the following decades. Initially, results looked promising, however, subsequent reviews called into question the standards of efficacy seen in the clinical studies.

In 2002, the UK Medicines Agency withdrew all marketing authorisations for oral evening primrose oil capsules. This followed a review by the UK Medicines Agency of all the relevant information, including new studies and statistical analyses. The UK Medicines Agency concluded that the data did not support the current standards of efficacy required for authorisation of these products as medicines for the treatment of eczema and mastalgia (Anonymous 2002).

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

See 1.2. Information about products on the European market and 2.3. Relevant preparations and indications.

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

Posology

Based on the posology published in handbooks, the dosages for atopic eczema for adults and children are 6-8 g daily and 2-4 g daily, respectively. The dosage used for mastalgia is 3-4 g a day (Barnes et al. 2007). The doses for PMS and menopausal complaints are 3-6 g a day (Capasso et al. 2003). Based on clinical trials, the dosages for atopic eczema for children and adults are 2-4.5 g a day and 4-8 g a day, respectively. One gram of Oenothera oil contains approximately 80-116 mg GLA. The dosages used for mastalgia, menopause and PMS are 3 g, 4 g and 4-6 g, respectively. The daily dosage in diabetic patients with diabetic neuropathy is 4 to 8 g (Halat & Dennehy 2003). Patients with rheumatoid arthritis received a daily dosage of 6 g EPO, which contains 540 mg GLA (Brzeski et al. 1991; Belch et al. 1988). Subjects with Raynaud's phenomenon and Sjögren syndrome received 6 g Evening Primerose Oil (EPO) (540 mg GLA) and 1.5–3 g EPO (9% GLA), respectively (Belch & Hill 2000; Oxholm et al. 1986). In children with attention deficit hyperactivity disorder (ADHD), a daily dosage of 3 g is administered (Aman et al. 1987).

Duration of use

Three months of therapy is usually required before a full therapeutic effect is noticed (Bédard 2003). Results of clinical studies on atopic eczema demonstrated a clinical effect after 3-5 months of oral use. In trials reporting positive results, a treatment duration of 6-12 months was usually required for diabetic neuropathy patients (Halat & Dennehy 2003).

3. Non-Clinical Data

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

Abou El-Ela (1987) took 40-day old female Sprague-Dawley rats for his research. They could eat and drink *ad libitum*. A single intragastric dose of 5 or 10 mg DMBA (71212-dimethylbenz(a)anthracene) in 0.5 ml corn oil was given to induce mammary tumour development. In the first study, the rats received 10 mg DMBA and were divided in two groups of each 18 animals. Twenty-one days after DMBA-administration, 18 animals received a diet with 20% corn oil, the others with 20% Oenothera fatty oil. Three rats, who had received a corn oil diet, died before the end of the experiment, while only one died who had received an EPO diet. In study 2, no rats died previously. In the second study, the rats received 5 mg DMBA and were divided in two groups of each 30 animals. Fourteen days after administration of DMBA, the same is done as in study 1 with 30 rats instead of 18. At 16 or 13 weeks post-DMBA, the surviving rats were killed. Blood was drawn from the heart for plasma lipid analysis and the tumours were analysed.
There was no significant difference in weight gain between the two diets. The average number of tumours and tumour-burden per tumour-bearing rat in study 1 was significantly greater than in study 2. The average latency period was significantly longer in study 1 than in study 2. When rats received an Oenothera feeding, there is a significantly decreased of malignant tumours in comparison with feeding corn oil. The lineolate level in the plasma is similar in both feedings. GLA and arachidonic acid

(AA) levels were significantly higher, and oleic acid levels were significantly lower in rats who received an Oenothera feeding compared with a corn oil feeding. DMBA–induced mammary tumorigenesis was dose-dependent in rats fed both Oenothera and corn oil diets. The mammary tumour promoting effect of a diet containing 20% fat can be diminished by substituting Oenothera EPO for corn oil. The promoting effect on mammary cancer by a high-fat diet could be depressed by feeding a source of GLA.

Abou El-Ela (1988) used female Sprague-Dawley rats, which were forty days old. At the age of 50 days, all the rats received a single intragastric dose of 10 mg DMBA in 0.5 ml corn oil. Twenty-one days after the DMBA administration, the rats were divided in 3 groups of 26 and received a fed diet containing either 20% corn oil (CO), Oenothera fatty oil or menhaden oil (MO). The controls rats were divided into 3 groups of 10 rats each and received the same diets. The 20% CO and Oenothera diet contained respectively 12% linolenic acid and 16.8% linolenic acid + GLA. The 20% MO diet contained 0.8% essential fatty acid (EFA). Weekly, the rats were weighed and palpated for the presence of the tumours. The size and location of each tumour was noted. One rat who received the CO-diet and one who received the MO-diet, died previously. After 16 weeks, every rat was killed and analysed. Although tumour incidence was similar in rats fed the MO, Oenothera and CO diets, the number of malignant tumours was reduced by 24% and 21% in the MO- and Oenothera-fed rats, respectively, compared with malignant tumours recovered from rats fed the 20%-CO diet. Moreover, the frequency of mitosis and the extent of necrosis and inflammation within tumours were higher in CO-fed rats compared with MO- or Oenothera-fed rats. These changes denote a more rapid tumour growth and a greater, although altered, immunologic reactivity. Feeding a 20%-Oenothera diet significantly extended tumour latency and reduced tumour burden compared with feeding the 20%-CO diet. Although tumour incidence was unchanged with any of the three diets, rats who received an Oenothera diet had 21% fewer malignant tumours, longer latency and reduced tumour burden. This can be mediated by an increased synthesis of prostaglandin E_1 (PGE_1) that may, in turn, alter the immune responses by opposing leukotriene B_4 (LTB_4). The finding that a MO diet favours the immunologic generation of LTB_5, which has attenuated biological activity compared with LTB_4, suggests that eicosapentaenoic acid (EPA)-enriched tissues may exhibit less proinflammatory activity than EPA-poor tissues. Oenothera fatty acid diet may decrease malignancy by altering eicosanoid profiles.

De La Cruz et al. (1997) performed a study of 6 weeks. Animals used were forty male white New Zealand rabbits of 2 months and had a body weight of 2498 ±36 g. Four groups were made with each ten rabbits. The first group received a normal diet and was seen as controls. The second group received an atherogenic diet. The following group had to eat a normal diet with 15% Oenothera. The last group of rabbits received an atherogenic diet with 15% Oenothera. The rabbits received their meal periodically. Serum lipid profile, platelet aggregation in whole blood, tromboxane B2 production and platelet lipid peroxide were measured. Oenothera fatty oil reduced platelet production. The oil also inhibited the lipid peroxide production. The cholesterol was reduced by 25%, the triglyceride value by 51% and the HDL-cholesterol was raised by 64%. Oenothera fatty oil reduced platelet hyperaggregability in rabbits fed an atherogenic diet.

Al – Shabanah (1997) used Wistar albino rats of both sexes, approximately the same age and weighing 150-200 g. They were feeding on a standard rat chow. The rats in the control groups received orally 10 ml corn oil/kg body weight. The non-control groups received orally 5 or 10 ml Oenothera. The ulcerogenic drugs used were aspirin and indomethacin.
In the first study, pylorus ligation-induced ulcers were tested. The rats were deprived of food for 36 hours with free access to water until the morning of the experiment. Under anaesthetic a small midline abdominal incision was made. Immediately after pylorus ligation, the Oenothera or the corn oil were given intragastrically. Six hours after pylorus ligation, the rats were killed and their stomachs were analysed. Pylorus ligation for 6 hours in fasted rats caused an increase in gastric acid secretion and

acidity output. Oenothera reduced the volume of gastric secretion, free acid and total acid output significantly, compared with controls.
The second study proceeded NSAID-induced gastric ulcers. The Oenothera or corn oil were administered intragastrically, 30 minutes before the ulcerogenic drugs. Aspirin and indomethacin were administered orally after fasted 40 hours. The dose of aspirin was 200 mg/kg (0.5 ml/kg) body weight and the rats were killed after 4 hours administration of aspirin. The dose of indomethacin was 30 mg/kg body weight (0.5 ml/100 g). The rats were killed after 6 hours administration of indomethacin. Each stomach was examined. Phenylbutazone induced gastric lesions. Two hundred mg/kg phenylbutazone was given intraperitoneal to rats who had fasted 24 hours. After 6 hours of administration, the rats were killed. The results are: pre-treatment with Oenothera produced a dose-dependent decrease in the gastric ulceration induced by aspirin and phenylbutazone whereas, in the indomethacin-treated group of rats, Oenothera significantly inhibited gastric ulceration at the dose of 10 ml/kg only. The inhibition of gastric erosions was in the range of 32 to 95%. The maximum inhibition of gastric erosion following Oenothera administration was in the phenylbutazone group at the dose of 10 ml Oenothera/kg.
The third study proceeded hypothermic restraint stress-induced ulcers. The rats were fasted for 36 hours with access to water *ad libitum*. One hour after receiving the Oenothera or corn oil treatment, the rats were immobilised in restraint cages and placed inside a ventilated refrigerator at a temperature of 2-4°C for 2 hours and further they were killed. The stomachs were analysed. The results of the treatment with Oenothera was a dose-dependently decreased intraluminal bleeding in comparison with the control rats, whereas Oenothera (10 ml/kg body weight), produced also a significant reduction in gastric ulceration with an inhibition of ulceration index by 85%, relative to the control values.
The last study consisted of gastric ulcers induced by necrotising agents (cytoprotective studies). After fasting 36 hours with access to water *ad libitum*, 1 ml of necrotising agent (0.6 M HCl, 0.2 M NaOH, 25% NaCl or 80% (v/v) aqueous ethanol) was given intragastrically. Oenothera or corn oil was administered 30 minutes before the necrotising agents. One hour after the administration of necrotising agents, the rats were killed and their stomachs were examined. The inhibitory action exerted by Oenothera on the ulcers induced by HCl and ethanol was dose-dependent and highly significant, the inhibition of ulceration being in the range of 36-84%. Those ulcers induced by HCl and NaOH were prevented by Oenothera at a dose of 10 ml/kg only, with the percentage inhibition in the range of 33-84%.

The results show that Oenothera oil prevents an increase in acid secretion in pylorus-ligated rats, and inhibits formation of gastric ulcers induced by different ulcerogenic drugs, by cytodestructive agents and by stress caused by hypothermic restraint. Oenothera exerts a dose-dependent inhibitory action on gastric mucosal lesions caused by various necrotising agents. In this study, Oenothera has a significant anti-ulcer and cytoprotective effect on various experimentally induced gastric lesions. Data suggest that γ-linolenic acid, administered as Oenothera oil, can prevent or reverse diabetic neuropathy in animal models (Barnes et al. 2007).

Riaz Azra et al. (2009) assessed the effect of Oenothera on coagulation parameters in healthy rabbits. Oenothera fatty oil contained 73% linoleic acid, 9% γ-linolenic acid, 8.6% oleic acid, 6.3% palmitic acid, 1.9% stearic acid and 10 IU vitamin E. The study was carried out on 50 healthy white rabbits of either sex weighing 1 to 15 kg. The rabbits were divided in 5 groups of each 10 animals. Three groups were administered normal (90 µl/kg daily), moderate (180 µl/kg daily) and high doses (360 µl/kg daily) of Oenothera. As a standard, 0.54 mg/kg warfarin sodium was used. The control animals were administered with water equivalent to the corresponding dose of Oenothera. Blood samples were collected once at 30 days and once at 60 days on the end of the study. Haematological parameters, red blood cell (RBC), white blood cell (WBC), platelet (PLT) and haemoglobin (Hb) were measured. Thrombin time (TT), prothrombin time (PT), activated prothromboplastin time (aPTT) and

fibrinogen time (Fg) were measured to monitor the influence of Oenothera on the blood coagulation process.
After 30 days of treatment a significant increase was found in PT and TT at normal, moderate and high doses and at standard drug warfarin. Also a significant increase in aPTT was observed at normal, moderate and high dose of Oenothera and standard drug warfarin.
After 60 days significant increase in TT and in PT were found at all doses. Fibrinogen time was not significantly affected at any dose. This study concluded that Oenothera has anticoagulant properties and its anticoagulant activity is supported by its anti-inflammatory effect. These effects along with antiplatelet activity suggest that Oenothera may be of value in cardiovascular diseases.

Anti-tumoural

Pellegrina et al. (2005): A phenolic fraction from *Oenothera biennis* showed potent and selective cytotoxic effects against bone marrow-derived tumour cells *in vitro* and *in vivo*, where it delayed the growth of established tumours.

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

No data available.

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

Chronic toxicity

Everett et al. (1988a) studied the toxic effects of Oenothera oil in a long-term study carried out on dogs (52 weeks) and rats (53 weeks).
Twenty male and 20 female beagle dogs received a daily dose of 5 ml/kg oil by oral gavage. A natural vitamin E was added to the oils. There were 4 groups with a different dose of Efamol® (0, 1, 3, 5 ml/kg) and corn oil. Food consumption was measured every week, body weight every 4 weeks and ophtalmoscopic examination was performed at 0, 25 and 52 weeks. Haematology analysis, clinical chemistry analysis and urinalysis were carried out at 0, 12, 26 and 50 weeks. After 52 weeks, the animals were killed and a *post mortem* examination was carried out. One dog died during the study, after administration of an intermediate dose of Efamol, was also examined. A histopathologic examination was performed on internal and external body parts. These data were analysed and the Efamol® treatment was compared with the control group. No significant differences were found in food consumption, clinical signs or body weight changes neither in haematology, urinalysis nor clinical chemistry. No differences were found in the necroscopical or histopathological examination.

Male and female Sprague-Dawley rats (n=100 in each group), 5-6 weeks old, received a daily dose of 2.5 ml/kg oil by oral gavage, which contained 0, 0.3, 1 or 2.5 ml/kg Efamol®. Examinations were the same for all rats. Only the ophtalmoscopic examination was carried out at 0 and 50 weeks and the *post mortem* was carried out at 53 weeks. Eleven rats died, 5 in the control and 6 in the Efamol® group. A significant increase in potassium level was found in female high dose rats. No other significant differences were found.
No important adverse effects were found in comparison with corn oil. Therefore, it is safe to use Efamol® as a nutritional supplement.

Carcinogenicity

Everett et al. (1988b) performed a long-term study on a total number of 500 rats randomly assigned to 4 treatment groups and 1 placebo group. Two hundred male and 200 female Sprague-Dawley rats were administered with 2.5 ml/kg/d oil during 5-6 weeks, 50 animals from each gender received a daily dose of 0.3 ml/kg, 1 ml/kg or 2.5 ml/kg Oenothera oil. The lower doses were diluted to 2.5 ml with corn germ oil. The remaining 50 males and females were given 2.5 ml corn germ oil as a control. Fifty other animals from each gender received a normal laboratory diet. After 104 weeks, the surviving and deceased animals were subjected to a *post mortem* histopathologic examination. An identical experiment with CD-1 mice, where the *post mortem* histopathologic examination was conducted after 78 weeks because of the short life expectation of the animals, showed the same results. These experiments did not find any significant difference in the nature and the frequency of the tumours between the animals with a different dose of Oenothera and the control animals (Hänsel et al. 1993).

Genotoxicity

No specific genotoxicity or mutagenicity testing was performed.

Teratogenicity

In animal studies, Oenothera oil was found not to be teratogenic (Barnes et al. 2007).

3.4. Overall conclusions on non-clinical data

Pharmacology

The activity of Oenothera oil has been studied in experimental *in vivo* cancer models. It seems to protect the animals against development of experimentally-induced tumours. These experiments can however not replace genotoxicity investigation. Possible antiplatelet activity seen in rabbits may be taken into consideration for cardiovascular patients. Gastric protection was seen in provocative experiments by possible inhibition of acid secretion. Pharmacological investigation does not provide a direct link to the therapeutic application in atopic dermatitis.

Toxicology

There was no chronic toxic, carcinogenic or teratogenic effect observed in the studies.

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

Linoleic acid (LA) is an essential fatty acid that is metabolised by delta-6-desaturase (D6D) and elongase, which forms dihomo-γ-linolenic acid (DGLA). The D6D step is time and rate-limiting. Through delta-5-desaturase, AA is formed (Figure 1). Cyclooxygenase (COX) transforms DGLA and AA into serie 1 and serie 2 prostaglandines and thromboxanes, respectively. Leukotrienes are formed by the metabolisation of AA by lipoxygenase (Martens-Lobenhoffer & Meyer 1998).
Only the cis-configuration of linoleic acid and its metabolites are biologically active. The D6D activity depends on different factors: ATP, insulin and protein-rich diet are activating; factors with inhibitory effect include c-AMP, glucagons, glucocorticoids and thyroxine (Hänsel et al. 1993).

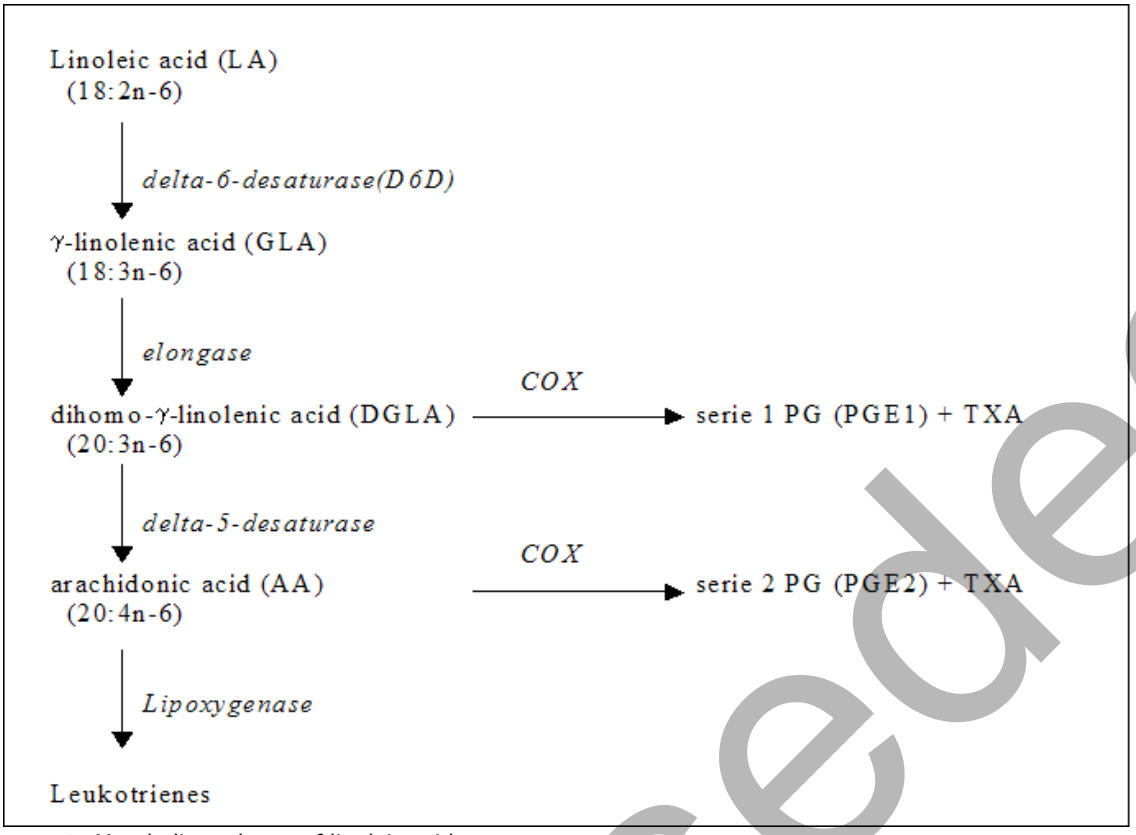


Figure 1: Metabolic pathway of linoleic acid.

There is a deficit of D6D enzyme in atopic eczema and PMS. This causes an increase of LA and a decrease of GLA and DGLA.
An increased sensitivity for prolactin and other hormones during the luteal phase in PMS might be caused by the abnormal fatty acid metabolism (Collins et al. 1993).
Because of this D6D deficit in atopic eczema, there is a lower concentration of PGE_1 and PGE_2. The decrease of PGE_1 causes an increased IgE concentration which leads to a release of mediators including histamine from leukocytes, mast cells and basophils. A decrease of PGE_2 results in less activation of T-suppressor lymphocytes (= T-regulatory cells). These cells discriminate self from non-self antigens. Because of a reduction in T-suppressor lymphocytes, self antigens will be recognised as non-self antigens and will activate helper T cells. These cells will produce interleukin-2 (IL-2), which leads to stimulation of cytotoxic T cells. Helper T cells will also activate B cells, which produce IgE, which will once more lead to more release of histamine and other mediators. The shortage of EFA also plays a role in the skin disorder because it is necessary for the maintenance of the epithelial barrier which causes an increased permeability (Kerscher & Korting 1992).

Assessor's overall conclusions on pharmacodynamics

Patients with atopic eczema and premenstrual syndrome have a deficit in D6D, the enzyme that converts linoleic acid in γ-linolenic acid. Oenothera oil contains γ-linolenic acid. Based on this biochemistry, its therapeutic use can be hypothesised in patients with atopic eczema and PMS with a D6D deficit.

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

Martens-Lobenhoffer & Meyer (1998) investigated the pharmacokinetics of GLA with and without (control) the administration of Oenothera oil (Epogam®). Three male and female volunteers between

21-25 years old participated in the study. From 6 volunteers, serum concentration time curves of fatty acids were profiled 24 hours with and without the administration of Epogam®. The volunteers took 6 capsules of Epogam® at 7 am and 7 pm. Six capsules contain a total amount of 240 mg GLA, resulting in a daily amount of 480 mg GLA. The volunteers were on a low fat diet during the experiment. On the days without Epogam®, blood samples were taken every 2 hours. Blood samples were taken before and 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 9 and 11.5 hours after the beginning of the first treatment at 7 am and 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 9 and 12 hours after the second treatment at 7 pm. A significantly higher concentration of GLA was noticed compared to the baseline levels. Non-significant elevations in AA, DGLA and LA were detected. In the average of all administrations, C_{max} is about 4.5 times higher than the baseline in the related volunteer. The study also observed a much slower uptake of GLA in the morning. In the morning, the mean time to reach the maximum concentration of γ-linolenic acid takes 4.4 ± 1.9 hours, in the evening this takes only 2.7 ± 1.2 hours (Table 1). Bioavailability was not calculated.

Table 1: Pharmacokinetic parameters of γ-linolenic acid (Martens-Lobenhoffer & Meyer 1998).

Volunteer	t_{max} AM (h)	C_{max} AM ($\mu g \times ml^{-1}$)	t_{max} PM (h)	C_{max} PM ($\mu g \times ml^{-1}$)	AUC_{12h} AM ($\mu g \times ml^{-1} \times h$)	AUC_{12h} PM ($\mu g \times ml^{-1} \times h$)	AUC_{24h} ($\mu g \times ml^{-1} \times h$)
Mean (SD)	4.4 (1.9)[a]	22.6 (16.9)	2.7 (1.2)	20.7 (12.2)	119.0 (103.1)	155.1 (131.3)	274.1 (232.8)[b]

[a] Significantly higher than t_{max} PM ($p < 0.05$).

[b] Significantly higher than AUC_{24h} of the baseline concentration of γ-linolenic acid (114.5 ± 87.6 $\mu g \times ml^{-1} \times h$, $p < 0.05$).

Assessor's overall conclusions on pharmacokinetics

GLA, administered as Oenothera oil (Epogam®), is absorbed from the gastro-intestinal tract, without significant elevations in AA, DGLA and LA when compared to baseline levels.

4.2 Clinical Efficacy

4.2.1. Dose response studies

There are no dose response studies available.

4.2.2 Clinical studies (case studies and clinical trials)

Grade system for quality assessment

The GRADE system for randomised clinical trials, reviews and meta-analyses takes into account the following factors:

Study design	+4	Randomised controlled trial (RCT)
	+2	Observational
	+1	Expert opinion
Study quality	-1	Serious limitation to study quality
	-2	Very Serious limitation to study quality
Consistency*	-1	Important inconsistency
Directness**	-1	Some uncertainty about directness
	-2	Major uncertainty about directness
Imprecision***	-1	Imprecise or sparse data
Publication bias	-1	High probability of publication bias

For observational studies	Evidence of association	+1	Strong evidence of association (RR of >2 or <0.5)
		+2	Very Strong evidence of association (RR of >5 or <0.2)
	Dose response gradient	+1	Evidence of a dose response gradient (+1)
	Confounders	+1	All plausible confounders would have reduced the effect
SUM		4	HIGH quality of evidence
		3	MODERATE quality of evidence
		2	LOW quality of evidence
		1	VERY LOW quality of evidence

*** Consistency**: refers to the similarity of estimates of effect across studies. If there is important unexplained inconsistency in the results, our confidence in the estimate of effect for that outcome decreases. Differences in the direction of effect, the size of the differences in effect, and the significance of the differences guide the (inevitably somewhat arbitrary) decision about whether important inconsistency exists.

**** Directness**: there are two types of indirectness of evidence. The first occurs when considering, for example, use of one of two active drugs. Although randomised comparisons of the drugs may be unavailable, randomised trials may have compared one drug with placebo and the other with placebo. Such trials allow indirect comparisons of the magnitude of effect of both drugs. Such evidence is of lower quality than would be provided by head to head comparisons of the drugs.

The second type of indirectness of evidence includes differences between the population, intervention, comparator to the intervention, and outcome of interest, and those included in the relevant studies.

***** Imprecision**: When studies include relatively few patients and few events and thus have wide confidence intervals, a guideline panel will judge the quality of the evidence to be lower.

For more information: http://www.gradeworkinggroup.org

- **Atopic eczema**

'Atopic eczema/dermatitis syndrome' is the summarised term for 'atopic dermatitis', 'atopic eczema' and 'prurigo Besnier'. This disease is a chronic inflammatory of the skin, which can appear everywhere on the body. Mostly it begins in childhood. Frequently, it is related to other atopic diseases such as asthma. Both genetic and socio-economic factors play an important role. A deficiency of the immune system can provoke atopic eczema. A shortage of structural lipids like ceramid, which can hold water in the stratum corneum, and a shortage of EFA can also be the cause of atopic dermatitis. The diagnosis is clinically established and based on a variety of sensitive and specific symptoms and signs (Schmidt et al. 2003).

Cutaneous application

Anstey et al. (1990) performed a randomised, double-blind, placebo-controlled trial over a period of 2 weeks. Twelve patients between 4 and 46 years old, 6 women and 6 men, with mild or moderate atopic eczema were included in this pilot study. During a period of 14 days, the patients applied an Oenothera cream (water-in-oil -w/o- emulsion) or the placebo (E45 cream®). The subjects could only treat themselves with the given cream during the entire trial. One patient left the study. Self-assessment scores from the patients indicated significant better results for the Oenothera cream compared to the placebo cream. However, the physician's scores did not reveal any significant difference between the Oenothera cream or the placebo cream.

Grading: 4 –1 (limited number of patients) –1 (inconsistency patients/physicians) –1 (assessment scale?) = 1
Very low quality of evidence.

Gehring et al. (1999) conducted a vehicle-controlled, randomised, double-blind trial with a two within-person right/left forearm parallel design. Transepidermal water loss (TEWL) and stratum corneum hydration were the epidermal barrier function parameters investigated. For the barrier function test 0.1N sodium lauryl sulphate (SLS), as hydrophilic irritant, and nicotinic acid, as lipophilic irritant, were used. Two studies were performed during 5 weeks, based on 4 weeks treatment following by a 1-week treatment-free period. Each study included 20 study subjects (age = 19-42 years) with an **atopy score of 10 or more**. In the first study, an amphiphilic oil-in-water emulsion of 20% Oenothera fatty oil was used. The placebo was a vehicle with 20 % miglyol. This population consisted of 14 females and 6 males with an average age of 25.1 years (range: 19 to 42 years; median of 24 years). After four weeks a reduction of TEWL and an improvement in stratum corneum hydratation was noticed. The curves were parallel as well as in the vehicle with and without Oenothera fatty oil. The barrier function tests of these 2 formulations were indistinguishable. The barrier function assessed in various ways was improved equally in both groups. In the second study, a stable w/o emulsion of 20% Oenothera fatty oil was used. The vehicle of the comparator was liquid paraffin. Eighteen females and 2 males of a mean age of 22.9 years (range: 18 to 42 years; median of 23.5 years) took part in this study. Only one female dropped out because of an acute exacerbation of atopic eczema. The effect of TEWL was significantly improved through the application of the vehicle with Oenothera fatty oil. The barrier function test with nicotinic acid ester noticed a statistic significant difference between vehicle with or without Oenothera fatty oil. While there was no difference found in the barrier function test with SLS. The latter study confirms the positive effect of Oenothera on the stability of the stratum corneum barrier. Generally, this vehicle controlled trial highlighted that the efficacy of Oenothera fatty oil in a cream depends on the choice of the vehicle. The study also proved that the onset of a prolonged interaction with the epidermal barrier lipids, above and beyond the physical properties of Oenothera fatty oil, is slow (Hoare et al. 2000).

Grading: 4 –1 (limited number of patients) –1 (indirect measure) = 2
Low quality of evidence.

Oral intake

Lovell et al. carried out a randomised, double-blind, placebo-controlled cross-over study during 6 weeks with 32 patients. There were 17 children (18 months to 13 years) and 15 adults (14 to 32 years). The subjects had **atopic eczema** for at least 6 months. Adults and children received twice a day 4 and 2 Efamol® capsules, respectively for 3 weeks per treatment period. These capsules contained 500 mg evening primrose oil, including 45 mg γ-linolenic acid. The placebo was liquid paraffin. All patients were allowed to continue the use of a mild topical steroid preparation. Patients or their relatives and a doctor were asked to score the severity of the eczema on a continuous 10 cm linear scale, at the beginning and the end of the treatment periods. The authors concluded that the patients receiving Efamol® showed a modest but significant improvement on both the doctor's ($P < 0.01$) and their own assessment ($P < 0.05$).

Grading: 4 –1 (limited number of patients) –1 (assessment scale?) = 2
Low quality of evidence.

Wright & Burton (1982: cited by Berth-Jones & Graham-Brown 1993; Hoare et al. 2000) studied 99 patients, among them adults (n=60; 15-58 years) and children (n=39; 8 months to 14 years) with moderate to **severe atopic dermatitis**. The researchers used a cross-over design during

12 weeks in a blocked randomisation with approximately equal numbers.
Efamol® containing 500 mg evening primrose oil (= 360 mg LA, 45 mg GLA) was administered in different doses. Adult patients received 3 different doses: 2 capsules 2 times daily, 4 capsules 2 times daily and 6 capsules 2 times daily. Children received 2 different doses: 1 capsule 2 times daily and 2 capsules 2 times daily. The placebo was 500 mg liquid paraffin. The use of mild topical steroids, emollients, oral antihistamines was allowed. Sixteen adults and 3 children dropped out early.

In the lowest dose groups for children and adults, itch was the only symptom which improved more with Oenothera as compared to placebo ($P < 0.05$). In the higher dose groups, a significant clinical improvement was found on a 10 cm linear scale. The patient assessment is significantly superior to the placebo in itch, scaling and general impression of severity ($P < 0.01$ to 0.002). There was also a beneficial effect shown in the doctor's assessments ($P < 0.002$). There was a mean improvement of about 30% of the overall severity of the eczema.

Grading: 4 –1 (imprecision: scale?) = 3
Moderate quality of evidence.

Bamford et al. (1985) conducted a double-blind, blocked cross-over trial with random controlled assignment to treatment groups. The study lasted 6 months. One hundred fifty four individuals started the study and 123 remained, of which 49 children (2-16 years) and 74 adults (16-66 years). These people had **atopic eczema** and used a prescribed topical steroid but they did not use systemic steroids or chemotherapy. One group started with Oenothera for 3 months, the other group with placebo. After these 3 months, they were treated 3 months with respectively placebo and Oenothera. Some of the individuals received a high dose, the others a lower dose. Thirty-three children were administered the lowest dose of Oenothera (2 capsules twice daily). The 16 other children swallowed 4 capsules twice a day. Forty adults took 6 capsules twice daily, the 34 others took 8 capsules twice a day. Each capsule contained 500 mg Oenothera (9% = 45 mg GLA and 72% = 360 mg LA) and 10 IU d-alpha tocopheryl acetate. The placebo capsules contained 500 mg liquid paraffin oil and 10 IU d-alpha tocopheryl acetate. During the study, the patients could use emollients, topical steroids or oral antihistamines. Of the 31 persons who dropped out, 14 were taking Oenothera and 17, placebo. Twenty-nine dropped out for personal reasons, 3 had an allergic reaction to the capsules, 1 adult discontinued because of increased dermatitis. One child (placebo) discontinued because of a developing hyperactivity.
Side effects were minor and temporary. The complaints were equal in both groups: nausea and bloating (5 subjects using Oenothera versus 1 subject using placebo), hyperactivity (3 children placebo versus 1 Oenothera).
Eighty patients achieved a compliance of 50%, 56 patients achieved 75%. Both patients (or parents of child patients) and physicians had a similar rating of the average appearance of lesions. The patients had 3 evaluation visits, namely before the trial, and 3 and 6 months after the beginning of the study. No changes in weight, triceps, skin-fold thickness, blood pressure, appetite and stress were observed. Erythema, scale, excoriation, lichenification or overall severity had marked no significant effect. There were no advantages found in the Oenothera treatment with atopic eczema patients, although a 50% and 33% higher dose was respectively used in adults and children compared to the trial of Wright and Burton.

Grading: 4 –1 (limited compliance) = 3
Moderate quality of evidence.

Schalin-Karrila et al. (1987) investigated 25 young adults (9 men, 16 women, 19-31 years) with **moderate to severe atopic dermatitis** in a 12 weeks continuous parallel double-blind, randomised, placebo-controlled trial. These persons had a family history of atopy or had atopic respiratory symptoms. An Oenothera capsule (Efamol®) contained 360 mg LA, 50 mg oleic acid and 45 mg GLA. A

placebo-capsule consisted of 500 mg liquid paraffin. Fourteen subjects received four capsules of Oenothera twice a day and 11 subjects received four capsules of placebo. One person of the Oenothera group dropped out because of an allergic reaction due to topical dequaline chloride. Patients did not change diets. Two weeks before the start of the trial, topical or systemic treatments were changed to an emollient cream of which they could use as much as needed. If not sufficient, a topical cream or oral antihistamines could exceptionally be employed. Potent steroids or systemic steroid therapy were not used. Before the start of the trial and every 3 weeks the clinical parameters were evaluated. At the beginning of the study, at 6 and at 12 weeks a blood sample was taken.
All the clinical parameters (overall severity and grade of inflammation, dryness and itch, reduction surface area) significantly improved in patients treated with Oenothera. These patients used less topical steroids than the placebo groups. The latter had a significant reduction in inflammation. Patients treated with Oenothera had a more significant reduction in inflammation than the placebo group.
The DGLA concentration increased significantly after 6 weeks of treatment with Oenothera. However, PGE_1, a metabolite of DGLA, did not rise. The ratio of PGE_1 to PGE_2 was unaltered. A clinical improvement in the patients suggested that the increased DGLA level may play a role in the effects of Oenothera. The use of topical steroid during Efamol® treatment could be reduced to about 30% (Morse & Clough 2006).

Grading: 4 –1 (limited number of patients) = 3
Moderate quality of evidence.

Morse et al. (1989) reported on a meta-analysis of 9 controlled trials, which were carried out in 8 centres. Four had a parallel design and 5 a cross-over design. Approximately 200 persons with atopic dermatitis were included during 8 to 12 weeks. They received a daily dose between 2 and 6 g, which is equal to 160–480 mg GLA.
In the parallel trials, patient's and doctor's score had a highly significant improvement of the symptoms like inflammation grade, dryness, scaliness, itching and overall skin involvement. Furthermore, the authors noticed a dose-dependent treatment response and a positive relation between improvement of the clinical symptoms and the plasma concentration of DGLA and AA. The effect on itch was particularly striking. A similar conclusion was made in the cross-over trials, although there was no significant improvement in the doctor score.

A significant after-effect was noticed in cross-over treated Oenothera patients and was interpreted as an evidence of the therapeutic effect (Schulz et al. 2004). The use of Oenothera fatty oil in atopic dermatitis patients was concluded as having a modest beneficial effect (Hoare et al. 2000). Patients with the greatest increase in blood levels of GLA, DGLA and AA had the greatest progress in their skin condition.

Grading: 4 –1 (publication bias: forest plot & funnel plot necessary) = 3
Moderate quality of evidence.

Berth-Jones & Graham-Brown (1993) included 123 patients with **atopic eczema** in a double blind placebo randomised controlled trial with a parallel design. The study took 16 weeks, followed by a wash out period of 8 weeks. Twenty-one persons dropped out during the trial and another 6 during the wash out period. The patients were older than 12 years and were divided in 3 groups based on gender, age and disease severity. One group received Epogam® capsules, which contained 500 mg Oenothera, which consisted of 321 mg LA and 40 mg GLA. Another group received Efamol® marine capsules, which contained 430 mg Oenothera and 107 mg marine fish oil. The latter group was the placebo group and received capsules with liquid paraffin for the adults and olive oil for the children. The patients were administered 6 capsules twice a day. Children who could not swallow the capsule were allowed to open them. The patients could use topical steroids and emollients during the treatment. Patients taking

antihistamines could continue their treatment. The study demonstrated no improvement in the active treatment and no effect of EFA supplementation in atopic dermatitis patients.

Grading: 4 –1 (assessment scale?) = 3
Moderate quality of evidence.

Humphreys et al. (1994) carried out a double-blind, parallel, placebo-controlled study with 58 adult persons with **moderately severe atopic eczema.** The patients were divided in 3 groups: 26 women with premenstrual exacerbation of eczema, 17 women without the premenstrual exacerbation of eczema and a group of 15 men. They were separated based on sex, age and duration of eczema. The whole study comprised 30 weeks, with 4 weeks of run-in, 16 weeks of treatment and 8 weeks of evaluations. The patients continued their usual treatment with topical corticosteroids, emollients or/and systemic treatment. Fifty two patients completed the trial. Four patients of the placebo and 2 of the active group were withdrawn. During the active treatment the patients received 12 Epogam® capsules a day, with 500 mg Oenothera and 10 mg vitamin E. The placebo group received capsules containing 500 mg liquid paraffin and 10 mg vitamin E.
Results of the study demonstrated that there was no conclusive evidence for the two female groups regarding the different reactions in the different stages of the menstrual cycle. A highly significant difference is marked in erythema and surface damage between Oenothera and placebo after 4 months and post treatment. There was no significant effect in lichenification. A more sustained fall of serum soluble IL-2 receptor levels was noted in treated patients with Oenothera. No significant difference was seen in the use of topical corticosteroid between Oenothera and placebo. Women with a premenstrual flare had the greatest improvement of the eczema with GLA. In patients with chronic atopic dermatitis, adjunctive therapy with Oenothera should be considered.

Grading: 4–1 (limited number of patients) –1 (consistency: variability among patients) =2
Low quality of evidence.

Senapati et al. (2008) performed a randomised placebo-controlled trial with Indian people, suffering from mild, moderate or severe **atopic dermatitis**. Sixty eight persons entered the trial. The subjects received Oenothera or placebo capsules (Table 2). An Oenothera capsule contained 500 mg Oenothera, of which 8-10% GLA and 10 IU vitamin E. The placebo capsule consisted of 300 mg sunflower oil and 10 IU vitamin E. Twenty-six out of 29 patients of the Oenothera group and 27 of 36 patients of the placebo group ended the study. The study took 5 months and included young and old persons with atopic eczema. At the end of the first month, the intensity and itching were significantly reduced. At the end of the study, 96% of the Oenothera group marked an improvement compared to 32% in the placebo group.

Table 2: The amount of capsules given twice a day dependent on the age.

Age (Year)	Amount capsules a day
1	1-4
2-5	5-6
6-10	7-8
11-16	9-10
> 16	12

Grading: 4 –1 (limited number of patients) –1 (diversity of patients) = 2
Low quality of evidence.

Table 3: *Oenothera biennis* oil: oral intake in adults for the indication 'atopic dermatitis'

Ref.	Patients	Intervention	Therapeutic Outcomes	Adverse

				outcomes/ complications (side effects)
Lovell et al., 1981	n = 32 A (14-32 y) and Ch (1.5-13 y) Incl.: AD for at least 6 m	R, DB, PC, CO-study: Efamol® caps vs. liquid paraffin 1 caps = 500 mg OB/Pl Posology: 4 caps 2x/d (A), 2 caps 2x/d (C) Duration: 6 w	Modest but significant improvement on both doctor's and their own assessment. Quality of evidence **LOW**	
Wright & Burton, 1982	n = 99 A (15-58 y) and Ch (8 m-11 y) Incl.: moderate to severe AD	CO- design: Efamol® vs. liquid paraffin Placebo: 1 caps = 500 mg paraffin Posology: 3 different doses for A, 2 different doses for Ch Duration: 12 w	In high dose: significant clinical improvement. In low dose: itch was the only symptom which improved; In high dose: itch, scaling, and general impression of severity were improved. A significant improvement of 43% in clinical signs of AE with children was found. Quality of evidence **MODERATE**	Drop out: 16 A and 3 Ch
Bamford et al., 1985	n = 154 at the start, n = 123 at the end A (74) and Ch (49) between 16-66 y and 2-16 y Incl.: AD + used a prescribed topical CS Excl.: patients having used systemic corticosteroids or chemotherapy	DB, RC, blocked CO trial: OB caps vs. liquid paraffin 1 caps = 500 mg OB/Pl + 10 IU d-alpha tocopheryl acetate Posology: group low (33 Ch): 2 caps 2x/d group high (16 Ch): 4 caps 2x/d group low (40 A): 6 caps 2x/d group high (34 A): 8 caps 2x/d Duration: 6 m (3 m OB and 3 m Pl)	There were no advantages found in the *ob* treatment, although a 50% and 33% higher dose was respectively used in adults and children compared to the trial of Wright and Burton. Quality of evidence **MODERATE**	31 dropped out: 14 OB, 17 Pl
Schalin-	n = 25	Continuous parallel	Clinical parameters	1 person of

Karrila et al., 1987	young A (9 M/16 F) between 19-31 y Incl.: moderate to severe AD with family history of atopy (18 A) or atopic respiratory symptoms (20 A)	DB, R, PC trial: Efamol® caps (14 A) vs. liquid paraffin (11 A) 1 caps = 500 mg OB/Pl Posology: 4 caps 2x/d Duration: 12 w	improved significantly. OB-patients had a significant greater reduction in inflammation than Pl. The DGLA-concentration increased significantly after 6 w treatment with OB. Quality of evidence **MODERATE**	OB-group dropped out because of a severe allergic reaction not due to OB. No side effects due to OB
Morse et al., 1989	n = 200 Incl.: AD	Meta-analysis of 9 C trials: 4 parallel design and 5 CO-design Posology: 2-6 g/d Duration: 8-12 w	Parallel: significant improvement of the symptoms, especially itch. Noticed a dose dependent treatment response and a positive relation between improvement of clinical symptoms and plasma concentration of DGLA and AA. CO: similar, although no significant improvement in the doctor score. A significant after-effect was noticed. Quality of evidence **MODERATE**	
Berth-Jones & Graham-Brown, 1993	n = 123 (A and C) 12+ y Incl.: AD + use topical corticosteroids and emollients during treatment + antihistaminics	DB, PC, R with parallel design: Epogam® caps vs Efamol marine® caps vs. liquid paraffin (A) or olive oil 1caps = 500 mg OB/OB marine/Pl Posology: 6 caps 2x/d Duration: 16 w + 8 w wash-out	No improvement in the active treatment. Quality of evidence **MODERATE**	21 dropped out during trial + 6 during wash-out
Humphreys et al., 1994	n = 58 A (26 F with premenstrual exacerbation of eczema, 17 F	DB, parallel, PC trial: Epogam® caps vs. liquid paraffin 1 caps = 500 mg OB/Pl + 10 mg Vit E	A highly significant difference in erythema and surface damage after 4 m and post-treatment. No significant effect in	6 dropped out: 4 Pl-group and 2 OB-group

	without, 15 M) Incl.: moderately severe AD	posology: 12 caps/d Duration: 30 w (4 w run-in, 16 w treatment, 8 w evaluation)	lichenification. No conclusive evidence for the different reactions in the different stages of the menstrual cycle. Quality of evidence **LOW**	
Senapati et al., 2008	n = 65 (A and Ch) from 1 year on Incl.: mild, moderate or severe AD Indian patients diagnosed by Hanifin and Rajka criteria Excl.: Pregnant and lactating women, epilepsy patients, patients with history of peptic ulceration, intake of phenothiazines, patients who received UV-B photoherapy or photo-chemotherapy in the last 1 m, patients who received systemic CS or other immunosuppressive drugs in the last 3 m	R, PC trial: OB vs. sunflower oil 1 caps = 500 mg OB / 300 mg Pl + 10 IU Vit E Posology: ≤ 1 y: 1-4 caps/d 2-5 y: 5-6 caps/d 6-10 y: 7-8 caps/d 11-16 y: 9-10 caps/d > 16 y: 12 caps/d Duration: 5 m	96% of OB Group marked an improvement compared to 32% in the Pl group Quality of evidence **LOW**	12 dropped out: 3 of OB Group, 9 of Pl group No significant adverse effects

Abbreviations:

A: adult(s)
AD: atopic dermatitis
C: Controlled
Caps: capsules
Ch: children
CO: Cross-over
DB: Double-blind
Excl.: exclusion criteria
F: female(s)
Incl.: inclusion criteria
M: man/men
m: month(s)
OB: *Oenothera biennis*
PC: Placebo-controlled
Pl: Placebo
R: Randomised
vs: versus
w: week(s)

- **Other dermatological studies**

Chalmers & Shuster (1983) first performed an uncontrolled pilot study. Six children with atopic dermatitis participated in the trial and there was a benefit response seen in 2 patients with ichthyosis vulgaris, but not with atopic eczema. The researchers expanded this study to a randomised, double-blind trial with 30 patients with ichthyosis vulgaris. Twenty patients (3 to 35 years) were atopic: 11 had active eczema, 6 had a history of atopic eczema and 3 had rhinitis or asthma. Ten other patients (6 to 69 years) were not atopic. The trial took 9 weeks. The placebo was liquid paraffin. The adults were administered 3 g daily, while the children received only 2 g a day. There were no patients with severe eczema. Patients topically treated could continue their therapy.
A slight improvement in the mean scores of ichthyosis vulgaris was seen in all groups. No progress was seen in the eczema patients, both Oenothera (6 subjects) and placebo (5 subjects) treated. In both atopic and non atopic patients, there was no improvement in ichthyosis vulgaris noted. In atopic eczema treated with Oenothera, no benefit was remarked.

Grading: 4 –1 (limited number of variable patients) –1 (inconsistency in results) -1 (different assessment scales) = 1
Very low quality of evidence.

Whitaker et al. (1996) studied 39 patients with stable chronic hand dermatitis during 24 weeks. The patients were between 19 and 75 years. During 16 weeks, 20 of them took 12 capsules of 500 mg Oenothera, which is equal to 50 mg GLA. The other 19 subjects received capsules of 500 mg sunflower. After the treatment, the study was continued by a wash out period of 8 weeks. The patients could take unlimited amounts of standard emollients and limited amounts of a semi potent group III topical steroid cream. Five patients dropped out, of which 1 from the Oenothera group and 4 from the placebo group.
After 16 weeks, no statistically significant difference was noted in both groups. At the end of week 24, the Oenothera group gave statistically significant clinical improvement in all parameters, while the placebo group did not. The study demonstrated an improvement of clinical parameters in Oenothera and placebo, but no significant difference between the two groups. During the treatments, there was no change in lipid composition of plasma RBC or the epidermis. This double-blind placebo-controlled trial with parallel design demonstrated that GLA has no superior therapeutic value to the placebo.

Grading: 4 –1 (design: comedication) –1 (limited number of patients) –1 (assessment scales) = 1
Very low quality of evidence.

Muggli (2005) studied the biophysical skin parameters in 22 healthy volunteers. Twenty-two non-pregnant women and 18 men between 32 and 56 years participated in a 12 week continuous randomised, double-blind, placebo-controlled study. The active treatment group received Efamol® soft gel capsules which contained 500 mg Oenothera and 8 mg dl-alpha tocopherol acetate. The placebo and the Oenothera group received 3 capsules twice a day, each time during the meal, which means that the active groups received 345 mg GLA a day. The **subjects did not suffer from any skin disease**. They could not use topical preparations on the treated skin area 1 week before the study until the end. Only water or mild synthetic detergent could be used for washing the skin.
There was no significant difference between baseline and 4 weeks in both groups. After 12 weeks, skin moisture, transepidermal water loss, firmless, elasticity, fatigue resistance and roughness improved in the Oenothera group compared to the placebo group. There was no significant improvement for redness.

Grading: 4 –1 (limited number of healthy volunteers) = 3
Moderate quality of evidence. This study is not a clinical trial for medicinal use, as there was no real therapeutic indication.

- **Premenstrual syndrome**

PMS is a condition characterised by a number of physical and mental symptoms during the luteal phase of the menstrual cycle; this is between 7 and 14 days before the onset of the menstrual period. A lot of symptoms are attributed to PMS, the most common are headache, backache, swollen abdomen, breast discomfort (including mastalgia), irritability, depression, anxiety, changes in sexual drive and lack of energy (Larsson et al. 1989, Wang et al. 2008).

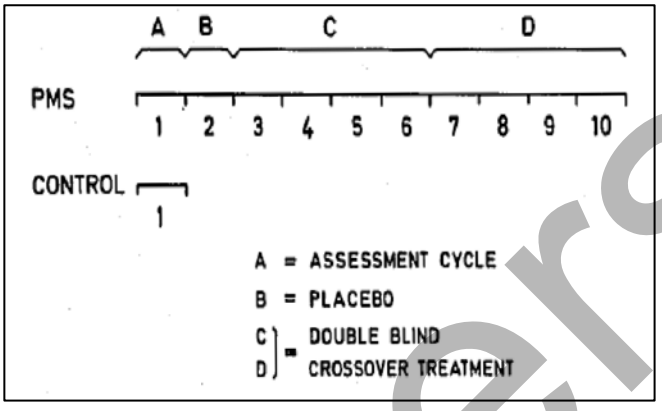
Puolakka et al. (1985) carried out a placebo controlled, randomised cross-over study over 4 cycles to investigate the value of Oenothera in premenstrual tension. Thirty subjects, suffering from severe premenstrual syndrome, took 3 Efamol® capsules twice a day, from the 15th day of the cycle until the next menstrual period. Nineteen symptoms were recorded and scored. The comparison of Efamol with placebo suggested no difference in effectiveness as both decreased the PMS score. The authors concluded that more patients obtained relief on Efamol® than on placebo.

Casper (1987) studied 66 patients with PMS in a double-blind, placebo-controlled cross-over trial. The premenstrual self-rating scores were reduced at 3 months with both placebo and Oenothera, but no difference was found between placebo and Oenothera.

Larsson et al. (1989) studied the effects of Oenothera fatty oil in a pilot study with 19 women between 25 and 48 years old. Two women left the study. The subjects received 4 capsules of Oenothera in the morning and 4 in the evening during the last 2 weeks before menstruation in 5 consecutive cycles. There were 8 premenstrual symptoms listed and scored every day: irritability, swollen abdomen, breast discomfort, depression, anxiety, swollen fingers or ankles, tiredness and headache. The symptom scores were significantly lower for 6 symptoms during the treatment cycles 1 and 2 compared to control. The scores were lower for 7 symptoms during the 5th cycle. Also the total PMS score was significantly lower in the 5th cycle compared to the pre-treatment cycle.

Khoo et al. (1990) studied the therapeutic effectiveness of Oenothera fatty oil (Efamol®). Thirty-eight women, age 20-40 years, with PMS were observed for 7 menstrual cycles of which one pre-treatment cycle. The preparation, containing 72% linoleic acid and 12% oleic acid, was studied in a randomised, double-blind placebo-controlled, cross-over study. Ten symptoms associated with PMS and menstrual symptoms were studied in categories: (a) fluid retention, (b) breast and (c) mood changes. Subjects taking systemic steroids and non-steroidal anti-inflammatory drugs were excluded from the trial because these drugs interfere with the essential fatty acid metabolism. The patients were randomly assigned to two treatments A or B. The placebo treatment consisted of liquid paraffin capsules. The subjects took 8 capsules a day, four in the morning and four in the evening. On the first day of the first cycle, the placebo or Oenothera treatment was started and was continued until the end of the third cycle. The other treatment was started on the first day of the fourth cycle and continued for 3 cycles. Before the onset of the trial, every subject filled in an assessment report. A four-point scoring system was used to rate the severity of the 10 symptoms, menstrual pain and blood loss. Body weight was measured in the beginning and at the end in order to count the weight gain. There were no dropouts in this study. There was no significant difference found in the scores between the two treatment groups. There was a possible carry-over effect in the data. This was tested and there was no carry-over noticed. Oenothera fatty oil had no advantage over placebo in the scoring of the 10 symptoms of PMS or menstrual symptoms. The scores increased in the fourth cycle after the cross-over independently from active or placebo treatment. This suggested that the improvements were due to a placebo effect.

Collins et al. (1993) carried out a randomised, double-blind, cross-over study with 27 women suffering from PMS to evaluate the effect of essential fatty acids. The age of the subjects ranged from 30 to 45 years. Thirty-eight subjects completed the study, but 11 women were excluded due to non-significant cyclicity or due to the absence of ovulation during the assessment cycle. The symptoms were self-reported by the women throughout the study, which consisted of 10 cycles for the women with PMS and 1 cycle for the controls: 1) happiness and feelings of well-being, 2) depressed feelings and crying spells, 3) irritability and short temper, 4) breast swelling and discomfort, 5) headache, 6) fatigue, 7) sexual need and positive feelings toward sex, 8) energetic feelings, and 9) tension and anxiety were rated. The subjects received 12 capsules of Efamol® every day which contained 4.32 g linoleic acid and 0.54 g γ-linoleic acid. The placebo contained 500 mg paraffin oil and was given 3 times a day. The drug-first group started the treatment in cycle 3 of the study, while the placebo-first group started treatment with Efamol® in cycle 7. (Figure 2) Blood samples were taken in the assessment cycle and in cycles 1,5,6,9 and 10. The samples were drawn 1 time during the follicular phase (cycle days 3-5) and 3 times in the luteal phase (cycle days 22-26) and were set for hormone analysis. The results showed no significant effect for mood ratings, but there was an effect in time noticed for tension and anxiety, irritability and short temper, depression and crying spells. The longer the women stayed in the study, the better they felt, independently of the treatment they were receiving, which indicates a placebo-effect.



- **Mastalgia**

A lot of women suffer from cyclical premenstrual breast pain, which resolves with menstruation. It is physiological, hormonally driven and normal. Non-cyclical breast pain with nodularity is more severe and can interfere with the daily activities, it is considered to be clinically relevant (Qureshi & Sultan 2005).

Pashby et al. (1979: cited by Anonymous 1981) investigated the effect of Oenothera fatty oil in mastalgia in 73 patients in a randomised double-blind cross-over study. Over 3 months, the subjects took Oenothera. Nineteen patients dropped out of the experiment. Pain and tenderness were significantly reduced in the non-cyclical group. This was less marked in the cyclical group.

Blommers et al. (2002) carried out a randomised, double-blind, controlled trial to evaluate the effect of Oenothera fatty oil and fish oil on breast pain in premenopausal women with severe chronic mastalgia. One hundred twenty women were randomly assigned to 4 groups: (1) fish oil and control oil (FC), (2) Oenothera fatty oil and control oil (EC), (3) fish and Oenothera fatty oils (EF), or (4) both control oils (CC). The control oils were corn oil and corn oil with wheat germ oil. The study took 6 months. The subjects were categorised in cyclic (94 patients) or non-cyclic mastalgia (26 patients). Every day the women received 3 g of two oils. The capsules with Oenothera fatty oil contained 9.6% γ-linoleic acid, 71.2% linoleic acid and 5 mg of vitamin E. Vitamin E was added to every oil to prevent oxidation. Patients did not change their diet during the trial. The patients had to fill in a questionnaire

about the changes in their breast complaints at the time of randomisation and after 3 and 6 months. There was a significant decrease of percentage of days with pain found for the total study population. The severity of pain was not significantly decreased. Oenothera showed less decrease in the percentage of pain days than the control oils. However, none of these results were significant.

Srivastava et al. (2007) conducted a meta-analysis on randomised trials on mastalgia. The studies of Pashby et al. (1979), Blommers et al. (2002), Preece et al. (1982) and the trial of Goyal and Mansel (2005) were evaluated. The results indicated that Oenothera is ineffective.

- Menopause

Chenoy et al. (1994) evaluated the efficacy of oral GLA provided by Oenothera fatty oil on menopausal flushing in a double-blind, placebo-controlled study. The study consisted of 56 women who had hot flushes at least 3 times a day, and increased gonadotrophin concentrations and/or women with amenorrhoea for at least 6 months. In the first month the women did not receive any treatment in order to establish a baseline level. The placebo group received 500 mg of liquid paraffin and the treatment group received 500 mg Oenothera fatty oil with 10 mg of natural vitamin E. The subjects took 4 capsules twice a day for 24 weeks. The severity and the amount of sweating episodes during the day and night were written on diary cards. Eighteen women receiving Oenothera and 17 receiving placebo completed the study. The frequency of daytime hot flashes decreased in the placebo group, but not in the treatment group. The night time hot flashes were decreased in both groups. The trial shows that Oenothera offers no benefit over placebo for the vasomotor symptoms of the menopause.

- **Rheumatoid arthritis**

Rheumatoid arthritis (RA) is a chronic inflammatory disease of the synovium. This causes pain, stiffness, swelling, deformity and eventually loss of function in the joints (Soeken et al. 2003).

Jäntti et al. (1989) studied the effect of 10 ml of Oenothera fatty oil and olive oil in 18 patients with RA. Twenty patients were randomly assigned to two groups of 10 patients, each group with 9 women and 1 man. One group (mean age of 50 years) received Oenothera containing 9% of γ-linolenic acid twice a day. The other group took olive oil (mean age of 38 years). The duration of RA was 13 years in the Oenothera group and 10 years in the olive oil group. In each group, one patient left the study. Blood was collected from the antecubital vein and the plasma PGE_2, 6-keto-$PGF_{1\alpha}$ and TxB_2 were measured. Urine was collected over a 24-hour period. No significant changes in Erythrocyte sedimentation rate (ESR), blood hemoglobin or platelet count, serum C reactive protein (CRP) or immunoglobulin concentrations were seen in either of the treatment group; neither in the number of swollen or tender joints, pain, duration of morning stiffness or grip strength of hands. PGE_2 decreased and TxB_2 increased more in the Oenothera group, but the changes between the groups in plasma prostanoids, PGE_2, TxB_2 and 6-keto $PGF_{1\alpha}$ concentrations were not statistically significant. Neither the urinary excretion of these products changed significantly.

Brzeski et al. (1991) carried out a 6-month double-blind placebo-controlled study on 40 patients with rheumatoid arthritis and upper gastrointestinal lesions due to non-steroidal anti-inflammatory drugs. The subjects had classical or definite RA, and were between 16 and 75 years old. The NSAIDs, H_2 blockers and analgesia medication was not stopped during the trial. The patients were divided into 2 groups, 19 of them received Oenothera fatty oil 6 g a day, 21 others received placebo, olive oil 6 g a day, in identical capsules. The Oenothera fatty oil contained 540 mg GLA and 10mg of alpha-tocopherol as antioxidant a day. Six subjects from the Oenothera group and 4 from the placebo group withdrew from the study. At 0, 3 and 6 months, assessments were performed of the daily use of NSAID and analgesia, morning stiffness, pain and well-being, Ritchie articular index (AI) and health assessment questionnaire, haemoglobine (Hb), platelets, ESR, CRP, globulins and plasma fatty acid analysis. After 3 months the patients tried to reduce the NSAID and analgesic medication. In each

group, 3 subjects reduced their NSAID dose with one tablet. In the Oenothera treated patients the morning stiffness was significantly reduced at 6 months, in the placebo treated patients the AI was significantly reduced at 6 months. The trial found that only 23% of the subjects receiving Oenothera treatment could reduce their NSAID dose and none could stop, which was the same for the placebo group.

Belch et al. (1988) treated patients (age between 28 and 74) with 12 capsules Oenothera or Oenothera/fish oil daily for 12 months to determine whether Oenothera or Oenothera/fish oil could replace NSAID treatment in RA. Liquid paraffin was used as placebo (18 patients). Sixteen and 15 patients received 540 mg GLA or 240 mg EPA, respectively, plus 450 mg GLA a day. There was a wash out phase from 12 to 15 months. All patients received placebo capsules without vitamin E to assess whether any improvement was due to the antioxidant and radical scavenging effect of the vitamin E. From three months the patients were instructed to decrease or stop their NSAID and from 12 to 15 months they were told to maintain the dose, if possible.
One patient in the Oenothera group and two in the Oenothera/fish oil group were withdrawn. Assessment of morning stiffness, grip strength and the Ritchie articular index was performed at 0, 3, 6, 12, and 15 months, also blood samples were taken at these times, ESR, CRP, Hb and rheumatoid factor estimation were measured.
Eleven Oenothera treated patients and 12 Oenothera/fish oil treated patients reduced or stopped their NSAIDs by 12 months compared to 5 out of 15 patients from the placebo group. No significant changes were noted in the laboratory and clinical measurements. After the 3 months placebo phase, almost all patients from the Oenothera and Oenothera/fish oil groups returned to baseline or became worse compared to 14% of the placebo group.
The results showed that it is possible to reduce or stop the NSAID medication in some RA patients by using Oenothera or Oenothera/fish oil treatment. The improvement, however, is purely subjective as there are no measurements found to support it. Therefore, the authors claim that it is unlikely that long-term therapy with these EFAs would alter the course or prognosis of the disease (Belch & Hill 2000).

- **Sjögren syndrome**

Sjögren syndrome (SS) is a common systemic autoimmune disease. It occurs most in menopausal women, frequent symptoms are fatigue, oral and ocular dryness. The secondary Sjögren syndrome is often associated with RA. In these patients, the GLA concentrations are reduced (Belch & Hill 2000, Theander et al. 2002).

Manthorpe et al. (1984) evaluated 36 patients in a randomised, double-blind, cross-over study. A week wash out period was used which is not long enough, when EFA therapy is evaluated. Nevertheless, 3 capsules Efamol® (500 mg with 9% GLA and 73% LA) or 3 tablets of Efavit® (125 mg vitamin C, 25 mg pyridoxine, 25 mg niacin, 5 mg zinc sulfate) twice a day improved results during the treatment period compared to placebo.

Oxholm et al. (1986) carried out a randomised, double-blind, placebo-controlled cross-over trial in order to determine whether long-term Efamol® treatment of patients with primary SS would improve their clinical status. Furthermore, the increase of the levels of EFA in plasma and erythrocytes during the treatment with Efamol® was investigated.
Twenty-four women and 4 men with a mean age of 51 years entered the study. All the subjects had keratoconjunctivitis sicca (KCS) and xerostomia. The subjects were treated with 3 g Efamol® (73% cis-LA, 9% GLA) a day, 6 capsules, for a period of 8 weeks and, for another 8 weeks, they received placebo capsules.
The patients' ocular and oral status, fatty acid levels in plasma and erythrocytes were evaluated after 0, 4, 8, 12 and 16 weeks. The values after 8 weeks of Efamol® treatment were compared with scores

after placebo treatment and the values after 8 weeks of Efamol® treatment were compared with Efamol® start values.
Significant improvements were found in the ocular status when start values were compared with values after Efamol treatment. Results of the fatty acid analyses showed a pronounced increase of DGLA values after Oenothera treatment, although compared to the placebo treatment it is thought not to be significant. No significant difference was observed between DGLA erythrocyte values at the end of placebo and Efamol® treatments. The authors concluded that, in the absence of further data, this treatment cannot be recommended to patients with Sjögren syndrome (Belch & Hill 2000).

- **Raynaud's phenomenon**

Raynaud's phenomenon is characterised by local vasospasm, cyanosis and rubor. It is evoked by cold or emotions and bloodflow, mainly in the limbs, slows down due to vasospasms, most often followed by hyperemia. Enhanced platelet aggregation, decreased RBC deformability, increased leukocyte aggregation and release are also associated with Raynaud's phenomenon (Belch & Hill 2000).

Belch et al. (1986) assessed the effect of Oenothera on the manifestations of Raynaud's phenomenon (RP) in 21 patients in a double-blind placebo-controlled trial. All subjects endured a 2 week run-in period, taking 12 placebo capsules a day. Eleven patients received 12 Oenothera capsules daily for 8 weeks (540 mg GLA), 6 of them suffered from Raynaud's syndrome (RS) associated with SS and 5 from Raynaud's disease (RD). The other 10 subjects, 5 RS with SS and 5 RD, took placebo capsules 12 times daily. One subject was withdrawn.
The Oenothera group experienced less and shorter vasospastic attacks then the control group when the weather became colder. There was no significant improvement in hand temperature and cold challenge, both measured to indicate the blood flow. The drug appears to be able to stimulate production of PGE_2 and decrease production of TxB_2, possibly leading to some antiplatelet effect.
The trial demonstrated that some patients with RP experience benefit from Oenothera treatment, but larger controlled studies are needed.

- **Diabetic neuropathy**

Peripheral neuropathy is a complication of both insulin dependent (type 1) and non-insulin-dependent (type 2) diabetes mellitus. It is characterised by a progressive loss of nerve fibres which leads to painful or insensitive extremities, neuropathic ulceration and finally amputation. It was caused by a long-term elevated plasma glucose levels. Elevated plasma and nerve glucose levels contribute to nerve degradation by a number of proposed mechanism (Halat & Dennehy 2003).

Three randomised, double-blind, placebo-controlled trials were completed with type 1 and 2 diabetes mellitus patients (Halat & Dennehy 2003).

Jamal & Carmichael (1990: cited by Halat & Dennehy 2003) included 22 diabetic patients with also a mild distal diabetic neuropathy for a mean of 3 years. Twelve subjects received 360 mg Oenothera fatty oil daily, 10 subjects got a placebo during a period of 6 months. The Oenothera treated patients had statistical significant improvements in nerve function measurements, wrist and ankle heat threshold values and overall symptoms scores. Glycohemoglobin (HbA_{1C}) was not significantly different between the 2 groups and indicated that GLA had no effect on glucose control.

NOTE: In view of the fact that one of the investigators in this study was found guilty of research fraud in the clinical trials on Evening Primrose oil for diabetic neuropathy. The HMPC considers that no further use should be made of this publication and it is included here solely for completeness. ***BMJ 2003;326:730.2***
http://www.bmj.com/content/326/7392/730.2

Keen et al. (1993: cited by Halat & Dennehy 2003) included 111 diabetic patients with a mild or moderate neuropathy. They received 480 mg Oenothera a day or a placebo (liquid paraffin) during 12 months. Eighty-four patients left the study. It was noted that 13 neural function parameters improved more in the intervention group. The improvements were significantly greater in patients with HbA_{1C} values of less than 10%.

Purewal et al. (1997: cited by Halat & Dennehy 2003) studied 51 diabetic patients with autonomic peripheral neuropathy for 12 months. They administered a dose of 480 mg daily of Oenothera or placebo. No improvements were shown in the vibratory perception threshold compared to placebo.

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

- **Atopic eczema**

Cutaneous application

Ferreira et al. (1998: cited by Hoare et al. 2000) examined 23 patients, aged 3 to 15 years, for 4 months in a randomised controlled trial with a parallel design. The patients had an **atopic dermatitis which was in remission**. Two patients were withdrawn from the study. The emollients contain 10% GLA versus borage oil (24% GLA) versus rose hip oil (35%-40% GLA). The placebo was an emollient without EFA (Atoderm®).

Clinical assessment of xerosis and pruritis revealed improvement in all 4 groups, slightly more pronounced in the 3 GLA groups. The changes were not statistically significant.

Also see 4.2.2 for studies on children Anstey et al. (1990).

Oral intake

Bordoni et al. (1987) studied 24 children with **atopic dermatitis**, of which 14 boys and 10 girls aged 2 to 4 years. The children were divided in 2 equal groups. One group received 6 capsules of Efamol® a day. The other group swallowed the same amount capsules which contained 0.5 g of olive oil. An Oenothera capsule consisted of 0.5 g Oenothera fatty oil, of which 74.7% LA; 8.9% GLA; 6.8% palmitic acid and 1.9% stearic acid. During the parallel, double-blind, randomised, placebo-controlled trial, the patients continued to take emollients and weak topical steroids.

Only in the Oenothera treated children, there was an increase of DGLA and AA and a decrease of 18:2/20:4 ratio measured.

After 4 weeks, the trial showed an improvement of 2/3 of clinical symptoms in EFA-treated children in comparison with that of placebo-treated children. No side effects were noticed.

Grading: 4–1 (limited number of patients) –1 (imprecision of outcome measures) = 2
Low quality of evidence.

Biagi et al. (1988) studied 12 children, 8 boys and 4 girls, with **atopic dermatitis** between 2 and 4 year during 20 weeks in a double-blind, parallel, placebo-controlled trial. They took 6 capsules every day with 0.5 g Oenothera, which contains 74.7% LA and 8.9% GLA. The patients could continuously make use of emollients and also topical steroids, if necessary. Blood samples were taken at the beginning of the trial and after 4 and 20 weeks. AA levels, plasma LA/AA ratio and other fatty acids were measured. No important side effects were noticed. The results proved a significant improvement of the clinical status of atopic eczema after 4 weeks of treatment. There was no improvement between week 4 and 20 of the treatment.

Grading: 4 –1 (limited number of patients) –1 (outcome measures: after 4 weeks no further improvement) = 2
Low quality of evidence.

Hederos & Berg (1996) studied children, between 1 and 16 years, with **atopic dermatitis,** who met the criteria of Hanifin and Rajka and who needed the regular treatment with topical skin corticosteroids. Sixty children started the study and were divided in 2 equal groups. Two subjects group dropped out of the study. Twenty-two of the patients also had asthma symptoms. The double-blind, randomised, placebo-controlled trial with a parallel design took 16 weeks. The placebo capsules contained 50 mg sunflower oil and 10mg vitamin E. An Oenothera capsule contained 500 mg Oenothera fatty oil (= 40 mg GLA) and 10 mg vitamin E. Children between 1 and 12 years took 4 capsules twice a day. Children above 12 years took 6 capsules twice daily. The use of topical steroids, antihistamines and asthma medication was allowed. Children, who could not swallow the capsule were allowed to open it. Two patients dropped out of the study: 1 because of the taste and 1 refused to undergo further assessments. Some side effects (5 of Oenothera group and 6 of the placebo group) were mentioned, but these effects were not considered as serious. Over the 16 weeks, a compliance of minimum 87% was obtained in each patient. In the Oenothera group, there was a highly significant raise of DGLA and AA concentration in the blood analyses. Both groups improved with respect to the baseline, but no significant differences were found between both groups. Furthermore, the use of asthma medication and topical steroids showed no differences between the groups.

Grading: 4 –1 (limited number of patients) –1 (indirect measure) = 2
Low quality of evidence.

Yoon et al. (2002) studied 14 children with **atopic eczema**, which had an itchy dry scale skin. The persons, who had an apparent erythema or oozing were excluded. Five boys and 9 girls, with an average age of 5.5 years, participated in the trial. Seven of them had a mild atopic dermatitis; the other 7 had a severe atopic dermatitis. They received 2 capsules twice a day. Each capsule contained 40 mg GLA. The control group consisted of 4 boys and 2 girls, with an average age of 7.2 years. Before the start of the study the serum interferon γ was lower and the serum IgE concentration was higher than these of the normal group. After 2 weeks treatment with Oenothera, there was a significant raise of serum interferon γ and decrease of serum IgE found. The study marked a reduced level of skin lesions and pruritus. No serious side effects were noticed. This study demonstrated that both supplementation of GLA and modulation of immunological abnormalities improved atopic dermatitis.

Grading: 2 (Observational study with pilot character) –1 (limited number of patients) = 1
Very low quality of evidence.

Also see 4.2.2 for studies on children: Lovell et al. (1981), Wright & Burton (1982), Bamford et al. (1985), Berth-Jones & Graham-Brown (1993), Senapati et al. (2008).

Table 4: *Oenothera biennis* oil: Oral intake in children for the indication 'atopic dermatitis'

Ref.	Patients	Intervention	Therapeutic Outcomes	Adverse outcomes /complications (side effects)
Bordoni et al., 1987	n = 24 Ch: 14 M, 10 F 2-4 y Incl.: AD	DB, parallel, R, PC trial: 500 mg OB vs. 500 mg olive oil Posology: 6 caps daily Duration: 4 w	Primary: Improvement of 2/3 of the symptoms after 4 w of treatment. Secondary: increase of DGLA and AA levels.	No side effects

			Quality of evidence **LOW**	
Biagi et al., 1988	n = 12, Ch (8 M, 4 F) 2-4 y Incl.: AD	DB, parallel, PC trial 1 caps = 500 mg OB Posology: 6 caps daily Duration: 20 w	Significant improvement of the clinical status of AD after 4 w of treatment. Quality of evidence **LOW**	No important side effects
Hederos & Berg, 1996	n = 60 Ch (1-16 y) Incl.: AD and need the regular treatment with topical skin corticosteroids 22 Ch had asthma symptoms	DB, parallel, R, PC trial. Posology: <12 y: 4 caps twice a day >12 y: 6 caps twice a day 1 caps = 500 mg OB + vit E placebo = 50 mg sunflower oil + 10 mg vit E Duration: 16 w	Both groups improved with respect to the baseline, but no significant differences were found. Use of asthma medication and topical steroids showed no differences. Quality of evidence **LOW**	2 patients dropped out of the OB group
Yoon et al., 2002	n = 14 Ch (5 M, 9 F) average age: 5.5 y control group: (4 M, 2 F) average age: 7.2 y Incl.: 7 mild AD, 7 severe AD and free from treatment for the last 2 months. Excl.: inflammatory signs such as erythema or oozing	Posology: 2 caps 2x/day containing 40 mg GLA	Reduction of skin lesions and pruritus. After 2 w of treatment: significant raise of serum interferon γ and decrease of serum IgE. Both supplementation of GLA and modulation of immunological abnormalities improved AD. Quality of evidence **VERY LOW**	No serious side effects

Abbreviations:

OB: *Oenothera biennis*
AD: atopic dermatitis
Incl.: inclusion criteria
Excl.: exclusion criteria
DB: Double-blind
PC: Placebo-controlled
R: Randomised
CO: Cross-over
Pl: Placebo
C: Controlled
M: man/men, male
F: female(s)
A: adult(s)
Ch: children
Caps: capsules
vs: versus
w: week(s)
m: month(s)

- **Other skin studies**

See 4.2.2 for studies on children Chalmers & Shuster (1983)

- **Attention deficit hyperactivity disorder**

ADHD is a development and behaviour disorder. The three principal symptoms are hyperactivity, concentration problems and impulsiveness. To date, the mechanism is unprecedented.

Aman et al. (1987) conducted a study with 31 hyperactive children (4 girls and 27 boys; age not specified) in Australia. Twenty-six had attention problems and 5 had an attention deficit disorder with or without hyperactivity. Six children had a history of febrile convulsions and one of epilepsy. The children did not swallow medication and they had no neurological disorders. The double-blind, placebo-controlled, cross-over study took 4 weeks. Three capsules twice a day were given to each patient. An Oenothera capsule contained 360 mg LA and 45 mg GLA. The placebo consisted of 500 mg liquid paraffin. A wash out period of 1 week took place.
Blood samples were taken and analysed. The results showed a significant decrease of palmitoleic acid and a 14% increase of DGLA during Oenothera treatment. Other EFA did not change, but there was a non-significant trend of decreased alpha-LA. Some measurements showed treatment-related changes, but the majority of measurements failed to show an effect in psychomotor improvements.

4.3. Overall conclusions on clinical pharmacology and efficacy

A difference must be made between the pathological conditions for which Oenothera oil has been used. Most of the studies concern with patients suffering from moderate or severe atopic dermatitis. Personal characteristics of these patients were representative for a usual population. The age varied from 8 months to 66 years. A total of 740 patients were included in 9 studies. The number of patients per study varied from 12 to 200. In most cases, a double-blind, placebo controlled, parallel or cross-over design was chosen.
The patients received an equivalent to 360 mg LA and 45 mg GLA, mostly as soft capsules containing 500 ml of Oenothera (Efamol®). Treatment periods were up to 6 months.
In 7 out of 9 trials, a positive clinical outcome was seen. When measured, plasma levels of DGLA, GLA and AA were increased. There seemed to be a relation between the increase in these plasma levels and the clinical outcome. The level of evidence is **LOW to MODERATE**.

Four small scale studies were done with children between 1 and 16 years old (n=88), suffering from atopic dermatitis or eczema. Two of these studies – of which one with an open design - resulted in a positive outcome. However, the number of subjects in these studies is lower, compared to studies with adults. It should be noted that children were also included in the other clinical trials mentioned before. The level of evidence is **LOW to VERY LOW**.

Other indications were non specified dermatitis, PMS, mastalgia, menopausal complaints, RA, SS, Raynaud's phenomenon and diabetic neuropathy. It is notable that the results in the case of PMS (the most common indication for Oenothera) failed to show efficacy. In 3 double-blind, placebo-controlled studies, there was no significant difference between Oenothera and placebo with regard to clinical outcomes. In one study, only partial results were obtained. In most cases, the condition of all patients improved, therefore the therapeutic efficacy was considered to be due to a placebo effect. The same can be concluded when patients with mastalgia were studied, and when Oenothera was used in case of RA. Clinical trials in the other conditions mentioned did not create perspective for a well-established use.
There were no serious adverse events reported during the clinical trials taken into consideration.

Outcomes described in patients with Raynaud's phenomenon may point to possible antiaggregating effects on blood platelets.

Overall conclusions on clinical efficacy of the oil of *Oenothera biennis*:

- Positive outcomes were only seen for eczema/atopic dermatitis. The evidence generated by the studies is graded very low to moderate even by using a less conservative approach with respect to some of the parameters applied. One study with moderate evidence had a negative outcome.

- Negative results were reported for studies on other therapeutic uses including non specified dermatitis, PMS, mastalgia, menopausal complaints, RA, SS, Raynaud's phenomenon and diabetic neuropathy.

- Although several hundreds of patients participated in the clinical studies, the number is low in the individual studies. Furthermore, in most cases children and adults are included in the same study which makes the study population diverse and the drawing of conclusions difficult.

- Most studies have involved preparations of 500 mg oil of *Oenothera biennis* which facilitates comparison between studies.

- The instruments used for therapeutic evaluation are diverse and subjective.

In conclusion, the evidence for a well-established use in the case of eczema/atopic dermatitis is not sufficient. A traditional use can be considered for oral use as Efamol® was on the market before 1981 and plausibility is supported by some clinical studies.
With regard to the use of cutaneous preparations, the studies fail to support a well-established medicinal use. In addition, there is no evidence to demonstrate 30 years of cutaneous use, therefore traditional use is not substantiated for this route of administration.

5. Clinical Safety / Pharmacovigilance

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

See sections below.

5.2. Patient exposure

More than 800 patients (of whom more than 100 children) were exposed in clinical studies dealing with atopic dermatitis. For other conditions (e.g. PMS, menopausal complaints, SS, Raynaud, diabetes, inflammatory conditions) another 600 patients were involved.

5.3. Adverse events

The World Health Organization's Uppsala Monitoring Centre (WHO-UMC) received 291 reports from national pharmacovigilance centres of 12 different countries. These reports describe 489 suspected adverse drug reactions for products reported to contain Oenothera fatty oil as the active ingredient (Table 5 in appendix). Only mild adverse effects are reported when Oenothera fatty oil is taken in the recommended dosage. The most common are gastro-intestinal effects, indigestion, nausea, softening of stool and headache (Barnes et al. 2007).

5.4. Serious adverse events and deaths

No serious adverse events were reported in the above-mentioned clinical studies.

The most serious side effects reported in the above-mentioned WHO-UMC database (Table 5 in appendix) related to the use Oenothera oil were convulsions, hepatitis, bronchospasms and interference with platelet function.

5.5. Laboratory findings

None reported.

5.6. Safety in special populations and situations

Intrinsic (including elderly and children) / extrinsic factors

Puri (2007) criticises the fact that 2 trials concluded that Oenothera leads to a higher risk of epileptic seizures in schizophrenic patients.
The first trial, which was performed by **Vaddadi (1981: cited by Puri 2007)**, was an open study. Three long-term hospitalised schizophrenic patients, for whom conventional therapy failed, participated in the trial. The 3 subjects took phenothiazine-type antipsychotics while being treated with Oenothera. They had a history of abnormal electroencephalographs and loss of consciousness. All developed characteristics of temporal lobe epilepsy.
The second trial was carried out by **Holman & Bell (1983: cited by Puri 2007)**. It was a double-blind placebo-controlled study with 23 schizophrenic patients. Three patients generated epileptic seizures, 1 from the placebo and 2 from the Oenothera group. One Oenothera and one placebo treated patient had tonic-clonic seizures. These patients were administered with phenothiazines, which are known to decrease the attack threshold. Therefore, Puri concluded that Oenothera is not a risk for having epileptic seizures.
In rats, researchers demonstrated that a long-term oral intake of LA and GLA protects rats of seizures and that Oenothera-derived omega-6 fatty acid arachidonic acid inhibits sodium ion currents and synaptic transmission. Oenothera-derived eicosanoid PGE_1 seems to have an anticonvulsive activity. Therefore, according to the author, Oenothera can be seen as a safe product which does not cause epileptic attacks as side effects.

Drug interactions

There may be an increased risk of seizure in schizophrenic patients, temporal lobe epileptic patients and others who take epileptogenic drugs such as phenothiazines. Patients with a history of these illnesses should use Oenothera products with caution (Barnes et al. 2007).

Also see paragraph above Puri (2007) for studies on phenothiazines.

Assessor's comment: There is no consensus whether a drug-drug interaction with phenothiazine-type antipsychotics exists in schizophrenic patients, lowering the convulsive threshold.

Patients taking antiplatelet or anticoagulant medications should use Oenothera with caution or should not use it at all. Oenothera consumption decreases thromboxane formation and increases PGE_1 formation, which leads to an inhibition of the platelet aggregation with increased risk of bleeding (Halat & Dennehy 2003).

Assessor's comment: Use of Oenothera oil concomitantly with antiplatelet drugs could enhance the effect of the latter. This combination should be discouraged.

Theoretically, there is a risk of interaction with anti-inflammatory drugs, corticosteroids, beta-blockers and antipsychotics (Huntley 2004).

Morse & Clough (2006) made a meta-analysis of 26 clinical RCTs of Oenothera oil. The open, not placebo-controlled or ongoing trials were not included in the meta-analysis. A number of 1207 patients participated in these studies: in the parallel trial 616 patients took Oenothera and 591 placebo; in the cross-over studies there were respectively 212 and 217 patients in both groups. The number of patients per study was between 15 and 154. The patients of the studies differ from age, sex, baseline severity of eczema and nationality. The placebos used in the trials were different: liquid paraffin, olive oil, safflower oil or sunflower oil. The duration of the trials was between 3-16 weeks. The dose (in mg GLA a day) taken was between 2 to 16 capsules of 500 mg Oenothera a day (160-480 mg GLA). The most important potential factor of heterogeneity between the trials was the use of steroids. The patients in the trial were classified as 'low' users or as 'high' users. The low users were the ones taking mild to moderate potent steroids. High users took potent, very potent or oral steroids. If a study consisted of less than 25% of the high users, it was considered as a 'low' usage. If more than 25% were high users in a trial, it was regarded as a 'high' usage trial. Twelve studies used low steroids, 13 were high use trials. The meta-analysis noted that, in the presence of low steroid usage, there is a beneficial effect of Oenothera for itching and this is apparent between 4 to 8 weeks. Other parameters like sleep loss, crusting, excoriation and oedema showed a trend in favour of Oenothera. The magnitude of the effects is reduced in association with an increased frequency of potent steroid use.

Use in pregnancy and lactation

Oral treatment given to atopic pregnant and nursing mothers and Oenothera given to newborns with an increased risk of atopic eczema may prevent atopic dermatitis. During the growth of the thymus, it can compensate the D6D deficit and the lack of lymphocytic PGE receptors (Kerscher & Korting 1992). However, not enough data are available on the safety of Oenothera during pregnancy and therefore it is not recommended to use Oenothera products during pregnancy. Oenothera treatment is, however, possible during pregnancy when the potential benefits outweigh the potential harms, but attention should be paid to high doses, above 4 g daily (Barnes et al. 2007; Bédard 2003).

Dove & Johnsons (1999) studied the effect of oral Oenothera fatty oil on the length of pregnancy and selected *intrapartum* outcomes in low-risk nulliparous women. Fifty-four women received a standard dose of Oenothera. At week 37, they received 500 mg 3 times a day for 1 week, then once a day 500 mg until labour started. The control group consisted of 54 women who did not take Oenothera during their pregnancy. One subject was withdrawn of the study. There were no significant differences found in age, Apgar score and days of gestation between the control group and the Oenothera group. A borderline significant difference was observed in birth weight: the Oenothera group infants were on average 156 g heavier. A significant variation was observed on the 5-minute Apgar score and length of labour between the Oenothera and control groups. Women administered with Oenothera had a longer labour as compared to the control group. The Oenothera group had a tendency to a greater risk of more protracted active phase, prolonged rupture of membranes, oxytocin augmentation, and arrest of descent.

Overdose

Symptoms of overdosage are loose stool and abdominal pain, treatment is not necessary (Barnes et al. 2007).

Drug abuse

None reported.

Withdrawal and rebound

None reported.

Effects on ability to drive or operate machinery or impairment of mental ability

None reported.

5.7. Overall conclusions on clinical safety

There are no major concerns related to serious adverse reactions. Possible implication of Oenothera fatty oil (Oenothera) lowering the convulsive threshold is debated. The HMPC did not consider that the data justify including in the monograph a statement on drug interactions during the use of Oenothera in patients taking anticonvulsive drugs or antipsychotics. Oenothera has been used during pregnancy without major problems. Use during in the perinatal period is not recommended, due to interference with delivering. The HMPC concluded that safety during pregnancy and lactation has not been established; in the absence of sufficient data, the use during pregnancy and lactation is not recommended.

6. Overall conclusions

- **Quality**

The herbal preparation is a fatty oil, described in the European Pharmacopoeia. It contains unsaturated fatty acids. Besides oxidation after exposure to air and light, the oil is sensitive to heat and humidity. Consequently, the storage conditions (cool dark place) are important. There are no cases of contamination or adulteration mentioned in literature, but the quality parameters/specifications for Oenothera oil are referred to in the European Pharmacopoeia, especially as far as the percentage non oxidized linoleic acid is concerned.

- **Safety**

The use of Oenothera oil can be considered as well known, as its use has been reported in the 17th century in Europe, coming from North America (Indians). In the Vigisearch database of the World Health Organization's Uppsala Monitoring Centre reported side effects are listed. As most serious side effects, convulsions, hepatitis, bronchospasms and interference with platelet function were related to the use Oenothera oil. A variety of minor side effects was also collected in the database. The type of preparation and the dose are not always specified. Ingestion of overdoses can lead to fatty diarrhoea. This effect may be considered as self-limiting when ingesting large doses.
There is no consensus whether a drug-drug interaction with phenothiazine-type antipsychotics exists in schizophrenic patients, lowering the convulsive threshold.
Use of Oenothera oil concomitantly with antiplatelet drugs could enhance the effect of the latter. This combination should be considered carefully. The HMPC decided that the data do not justify including a statement in the monograph.
There is limited information from clinical observations in pregnant women. Oenothera oil did not cause any harm, but more systematically gathered reports are needed, also in case of breast-feeding.
There is a suggestion from animal experiments that Oenothera oil can protect animals (rats) against induced breast cancer. In chronic feeding experiments with rats, no carcinogenic potential could be seen. No specific genotoxicity or mutagenicity testing was performed.
As Ames testing has not been performed on the oil, no list entry can be granted.

Conclusion: taking into consideration available information on side effects and drug-drug interactions, the use of Oenothera oil in the specified conditions of use is safe.

- **Efficacy**

Oenothera oil has been studied for atopic dermatitis in more than 400 adults and more than 100 children (from 8 months of age). The quality of evidence varied from very low to moderate. The outcome was not consistent but was mainly negative for other indications such as premenstrual syndrom, rheumatoid arthritis, mastalgia, menopausal symptoms, Sjögren syndrome, Raynaud's phenomenon, ADHD and diabetic neuropathy. Concerns have been raised about the quality of the evidence to support the therapeutic claims for Oenothera oil. In 2002, the UK Medicines Agency withdrew all marketing authorisations for oral evening primrose oil capsules. This followed a review by the UK Medicines Agency of all the relevant information, including new studies and statistical analyses. The UK Medicines Agency concluded that the data did not support the current standards of efficacy required for authorisation of these products as medicines for the treatment of eczema and mastalgia (Anonymous 2002).

Studies on the use of Oenothera oil for diabetic neuropathy have been marred by the fact that one of the investigators in the studies was found guilty of research fraud in the clinical trials.

In view of the uncertainties concerning the available bibliographic data together with the poor quality of the evidence of efficacy in the published studies, the HMPC considers that there is insufficient evidence on which to base a 'well-established use' indication for Oenothera oil. Clinical studies with commercial Oenothera oil preparations were reported from 1981 onwards, and a traditional use of the oil in atopic dermatological conditions (for the symptomatic relief of itching in acute and chronic dry skin conditions) can be accepted.

In the absence of adequate genotoxicity testing, no Community list entry can be established.

Appendix

Table 5

Annexes

List of references

Table 5: Summary of spontaneous reports (n=187) of suspected adverse drug reactions associated with single-ingredient *Oenothera biennis* preparations held in the Vigisearch database of the World Health Organization's Uppsala Monitoring Centre for the period up to end of 2005 (Barnes et al. 2007).

System organ class. Adverse drug reaction name (number)[a,b]	**TOTAL**
Body as a whole - general disorders. Including allergic reaction (4); therapeutic response decreased (5); condition aggravated (5); fatigue (4); fever (6); malaise (7); pain (7); withdrawal syndrome (3).	65
Cardiovascular disorders, general. Including hypertension (3).	5
Central and peripheral nervous system disorders. Including convulsions (16); convulsions, aggravated (8); dizziness (5); headache (27); paraesthesia (9).	84
Endocrine disorders.	2
Foetal disorders.	1
Gastrointestinal system disorders. Including abdominal pain (18); constipation (3); diarrhoea (12); dyspepsia (7); eructation (3); flatulence (5); nausea (19); vomiting (5).	74
Heart rate and rhythm disorders.	2
Liver and biliary system disorders. Including hepatic function abnormal (4); hepatitis (3).	11
Metabolic and nutritional disorders. Including thirst (3); weight decrease (3).	15
Musculo-skeletal system disorders. Including arthralgia (3); myalgia (3).	8
Neoplasm.	2
Platelet, bleeding and clotting disorders. Including purpura (3).	13
Psychiatric disorders. Including nervousness (4); aggressive reaction (3); confusion (3).	38
Red blood cell disorders.	1
Reproductive disorders, female and male. Including menorrhagia (4); menstrual disorder (3).	17
Resistance mechanism disorders.	1
Respiratory system disorders. Including bronchospasm, aggravated (4); dyspnoea (4).	18
Skin and appendages disorders. Including acne (4); alopecia (3); eczema (5); pruritus (11); skin exfoliation (4); sweating increased (4); rash (9); rash, erythematous (11); rash, macropapular (5); urticaria (16).	96
Urinary system disorders. Including face oedema (5).	13
Vascular (extracardiac) disorders. Including flushing (4).	6
Vision disorders. Including abnormal vision (4).	12
White cell and RES* disorders.	1
Other reactions described using terms not included in database.	4
Total number of suspected adverse drug reactions	**489**

[a] Specific reactions described where n=3 or more.

[b] Caveat statement. These data were obtained from the Vigisearch database held by the WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden. The information is not homogeneous at least with respect to origin or likelihood that the pharmaceutical product caused the adverse reaction. Any information included in this report does not represent the opinion of the World Health Organization.

* RES - Reticuloendothelial system