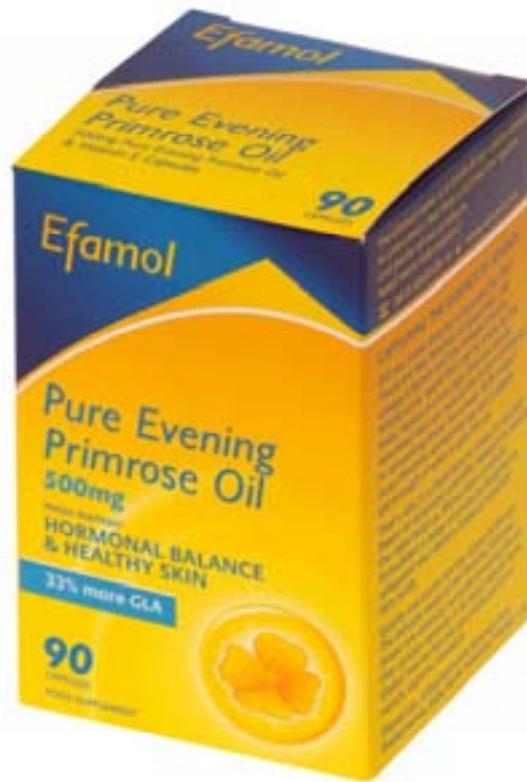




# **Efamol<sup>®</sup>**

## **Pure Evening Primrose Oil**



## **A Product Monograph**

### **Skin Health**

## INTRODUCTION

Efamol Pure Evening Primrose Oil is an entirely new approach to the management of atopic eczema. It is an oral medication containing GLA-gamma-linolenic acid, in the form of the seed oil from specially selected varieties of the evening primrose *Oenothera spp.* GLA is one of a family of substances known as essential (EFAs) which are required for normal healthy skin structure and function. Levels of GLA and its metabolites have been found to be reduced in patients with atopic eczema. The administration of Efamol<sup>®</sup> Pure Evening Primrose Oil is therefore directed at

what appears to be a fundamental biochemical abnormality in this disease.

In a series of randomized, double blind, placebo-controlled trials, Efamol<sup>®</sup> Pure Evening Primrose Oil has been found to be effective in resolving the symptoms of atopic eczema especially in relieving itch. The administration of Efamol<sup>®</sup> Pure Evening Primrose Oil is associated with very few side effects, and those, which do occur, are mild and transient. Efamol<sup>®</sup> Pure Evening Primrose Oil has not been shown to cause any drowsiness.

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## Section I: Medical Background

### Atopic Eczema

Atopy is a general term which indicates an increased risk of developing one of the group of atopic disorders, including eczema, asthma and allergic rhinitis. The risk of being atopic is present at birth, and is indicated by an increased IgE level in umbilical cord blood. However, the development of overt atopic eczema depends on an interaction between constitutional and environmental factors, since the pattern of disease is similar in only about half of all pairs of identical twins.

Atopic eczema, or atopic dermatitis, is a condition, which usually begins in infancy. In some, but by no means all patients, the condition wanes during late childhood and adolescence. Other less fortunate individuals may suffer from moderate to severe atopic eczema throughout their lives.

Eczematous skin disorders can also develop in middle and later life in people who, as young adults, appear to have had healthy skin. A careful history often reveals that these patients may have experienced atopic eczema in early childhood. The later emergence of the skin problem is therefore likely to represent a recurrence of atopic disease.

Atopic eczema is usually observed to run in families, which suggests a genetic implication. In spite of much investigation, the mode of inheritance is not yet clear. Asthma, hay fever and various disorders believed to have an allergic basis, are common both in patients with atopic eczema and in their near relatives. Despite reports of numerous abnormalities in the immune system, the precise relationship to the dermatitis is uncertain. The most consistently described immunological changes are elevated blood levels of IgE and reduced numbers of mature T lymphocytes, especially T suppressor cells. There is some evidence of impaired beta-adrenergic function, and also of reduced cyclic AMP levels in lymphocytes and other tissues.

### Symptoms

Atopic eczema involves the typical inflammatory response of the skin, which is familiar to every doctor. The dermatitis commonly fluctuates in an erratic and unpredictable fashion, hence it is particularly important to conduct double blind trials when assessing new medications. Eczematous lesions can occur at any place on the skin, although in infants the face and exposed areas of the limbs, including the elbow and knee flexures, are most likely to be involved. In adults the lesions can be

anywhere, but again the flexures, the face, the fingers and the toes are commonly affected. The more severe persistent lesions frequently become infected.

Even though the inflamed skin is unsightly and unpleasant, it is often the itch, which is the worst symptom from the patient's point of view. Although the itching is worse when the skin is inflamed, patients frequently suffer from generalized pruritis, affecting even those areas of skin, which visually appear normal. Many dermatologists express the view that itch is the primary feature of the disease and that it is the scratching of pruritic areas of skin, which precipitates the development of frank dermatitis.

Apart from itching, the non-inflamed areas of skin in patients with atopic eczema often feel rough and dry. This is also an important problem from the patient's point of view.

### Current Treatments

Treatment of atopic eczema usually begins with advice about avoidance of unsuitable clothing and reducing exposure to potential irritants. Simple emollients are also widely prescribed at this stage. The search for specific antigens, which may precipitate the disease, is occasionally helpful but often unrewarding, since patients may react to a large number of different substances, making avoidance impractical.

These simple initial approaches can be effective, but many patients find that they provide incomplete relief and additional medication is required. The mainstays of treatment are the topical steroids which are classified into four potency groups relating both to their clinical efficacy and to their potential for producing side effects, such as skin atrophy and adrenal suppression<sup>1</sup>. Oral antihistamines are prescribed for some patients in an attempt to relieve the itch. Unfortunately, the relief from pruritis appears to be associated with the potential for sedation. While the sedating antihistamines are effective, in relieving itch in some skin disorders, the only placebo-controlled trial of their use in the itch of atopic eczema found no significant effect<sup>2</sup>.

Infected atopic eczema often requires the use of topical or systemic antibiotics. Patients with very severe eczema, refractory to topical treatment, may require oral steroids to control their conditions. Those who are unresponsive to all the usual common treatments may be tried on antimetabolites and immunosuppressants.

Although current treatment is moderately effective in controlling atopic eczema, there are many patients who

do not experience a satisfactorily complete response. While topical steroids frequently produce excellent local relief, there are no systemically active agents which are beneficial for the generalized pruritis, skin dryness and roughness.

### Essential Fatty Acids (EFAs)

The Essential Fatty Acids (EFAs), like vitamins, are essential nutrients which cannot be manufactured in the body but must be provided in the food. There are two families of EFAs, the n-6 or omega-6 family, starting with linoleic acid and the n-3 or omega-3 family starting with alpha-linolenic acid (a substance quite different from gamma-linolenic acid and not interchangeable with it). Dietary linoleic acid and alpha-linolenic acid are metabolised within the body by the reaction sequence shown in Figure 1. In order to exert their full biological effects, it is essential that the parent dietary EFAs are metabolized, as alone they have only very limited effects.

In general, the EFAs have two fundamental roles within the body. First they are essential components of all membranes, conferring properties of fluidity and flexibility. By modulating membrane properties, the EFAs also modulate the behaviors of membrane associated proteins such as receptors, enzymes, ion channels and messenger systems.

In addition to this structural role, with its functional consequences, the EFAs also act as the precursors of a whole variety of short-term mediators, which regulate many aspects of cellular function. These mediators include several different prostaglandins, leukotrienes and thromboxanes, together with various other types of oxygenated EFA derivatives. Some of these mediators such as prostaglandin E1 (PGE1), formed from dihom-

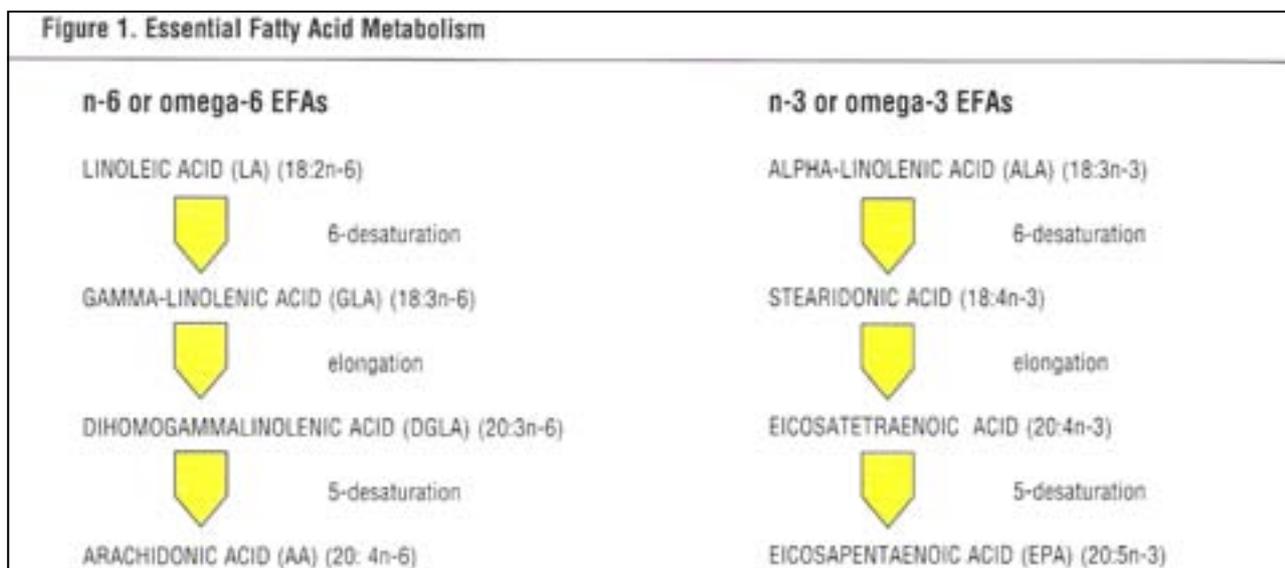
mogammalinolenic acid (DGLA); prostacyclin, formed from arachidonic acid (AA); and prostaglandin  $1_3$  (PGE<sub>3</sub>), formed from eicosapentaenoic acid (EPA), have a wide range of desirable effects. Other EFA derivatives, such as PGF<sub>2a</sub>, thromboxane A<sub>2</sub> and the leukotrienes derived from arachidonic acid, have potentially undesirable actions, including the promotion of inflammation, thrombosis and vasoconstriction.

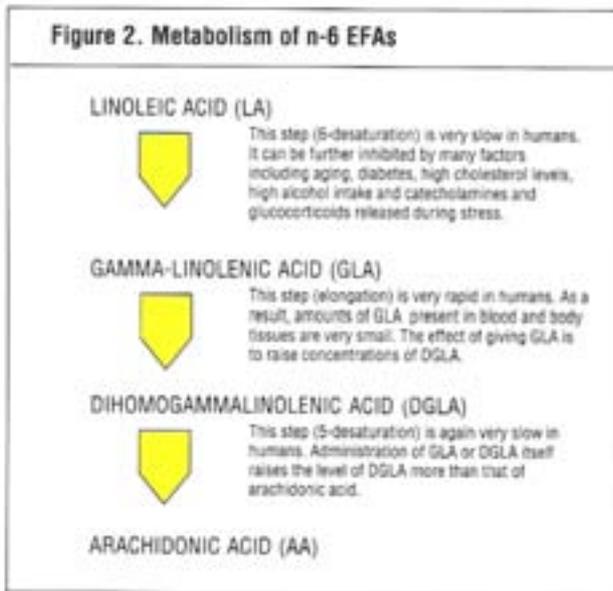
### Effects of deficiency of n-6 and n-3 EFAs

Studies in both animals and humans have shown that the n-6 EFAs are very much more important than the n-3 EFAs for certain functions. When animals are deprived of all EFAs, almost every system of the body, particularly the skin, is severely affected. This is not surprising given the fundamental roles of EFAs in membrane structure and in the generation of regulatory molecules. If the n-3 EFAs alone are then administered, it is difficult to demonstrate the correction of all abnormality. In contrast, provision of the n-6 EFAs alone normalizes most body systems, although n-3 EFAs are also required to show improvements in retinal, cerebral and other nervous system functions. For almost everything else, in particular the skin, it is the n-6 EFAs that are important.

### EFAs and the skin

When either animals or humans are deprived of EFAs, skin changes are among the first abnormalities to be detected<sup>3,4</sup>. These abnormalities include: loss of hair; development of a scaly, rough epidermis which sheds dandruff like scales; development of an eczema-like dermatitis; weakening of cutaneous capillaries; failure of normal wound healing; high susceptibility to infection and greatly increased trans-epidermal water loss with failure of the normal water-permeability barrier of the skin. All these abnormalities are rapidly corrected by





the administration of n-6 EFAs. The n-3 EFAs are ineffective and may make the skin worse<sup>3,4</sup>. It is therefore appropriate to concentrate on the n-6 EFAs.

The n-6 EFA metabolic pathway is summarized in Figure 2. The two desaturase steps, conversion of linoleic acid to gamma-inolenic acid, GLA and conversion of dihomogammalinolenic acid (DGLA) to arachidonic acid (AA), are very slow, especially in humans. In contrast, the conversion of GLA to DGLA is rapid. These conclusions are illustrated by the fact that it is very difficult in adult humans to raise the blood levels of LA, DGLA or AA by greatly increasing the amount of linoleic acid in the diet<sup>5</sup>. In contrast, administration of GLA in the form of Efamol<sup>®</sup> Pure Evening Primrose Oil consistently and significantly raises the level of DGLA in the blood. The concentration of GLA itself does not change much because of the very rapid conversion to DGLA.

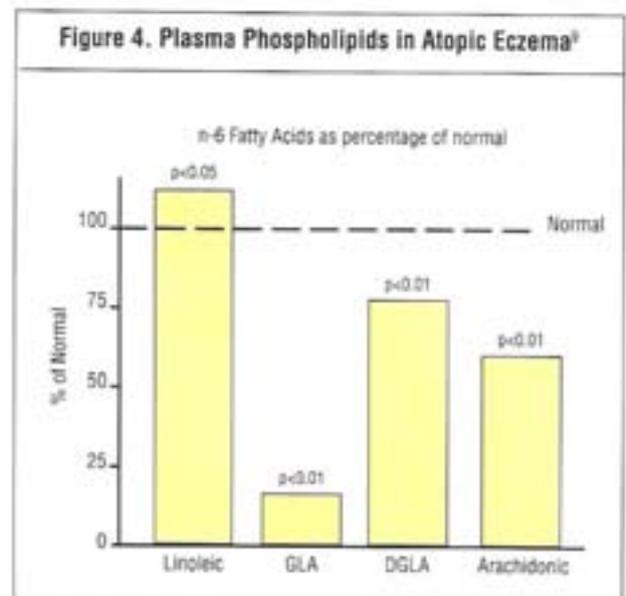
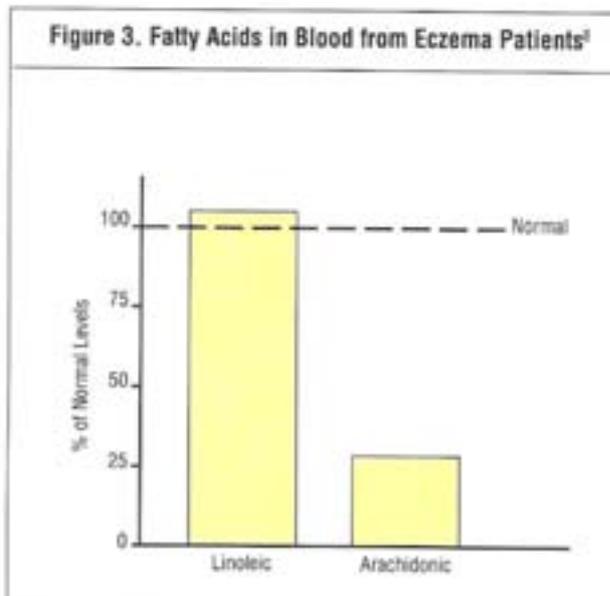
Efamol Pure Evening Primrose Oil produces a much smaller rise in AA because of the very slow conversion of DGLA to AA in humans. The slow metabolism of linoleic acid in humans may explain why human milk, unlike milk from most other species, contains substantial amounts of GLA, DGLA and AA as well as linoleic acid. Cows' milk, in contrast, contains only linoleic acid. The breast-fed human infant has direct access to all the important n-6 EFAs in the diet, without the need to metabolise linoleic acid itself. In contrast, the infant receiving cows' milk, or artificial formulae, must make its own GLA, DGLA and AA from linoleic acid in the milk.

Many factors have been found to retard the conversion of linoleic acid to GLA<sup>6,7</sup>. These include aging, catecholamines and glucocorticoids released during stress, diabetes, high cholesterol levels, and high alcohol intake. As will be demonstrated in the next section, conversion of linoleic acid to GLA may also be slower in patients with atopic eczema than in normal individuals.

### Atopic Eczema and Essential Fatty Acids

The effects of EFAs on the skin were discovered at the University of Minnesota in 1928-30 by Hansen, a pediatrician, who saw EFA deficient animals and noted that their skin lesions resembled the dermatitis of atopic eczema. This observation led to the suggestion that atopic eczema might be related to a deficiency of EFAs.

Using the crude technology available at the time, he measured EFA levels in the blood of atopic eczema patients. In patients consuming substantial amounts of linoleic acid, he found that linoleic acid levels were near normal, whereas arachidonic acid levels were far below normal (Figure 3)<sup>8</sup>.



There appear to have been no attempts to repeat Hansen's work on blood EFA levels in eczema for over forty years. Then in the early 1980's a group of investigators from The Efamol<sup>®</sup> Research Institute, working with Dr. Stephen Wright and Dr. John Burton, clinicians from the University of Bristol Medical School, compared plasma phospholipids EFA levels in adult atopic eczema patients with normal controls. The results are summarized in Figure 4<sup>9</sup>. Linoleic acid levels were slightly above normal, indicating normal intake and absorption in levels in the eczema patients. In contrast, the levels of metabolites GLA, DGLA and arachidonic acid, were all well below normal.

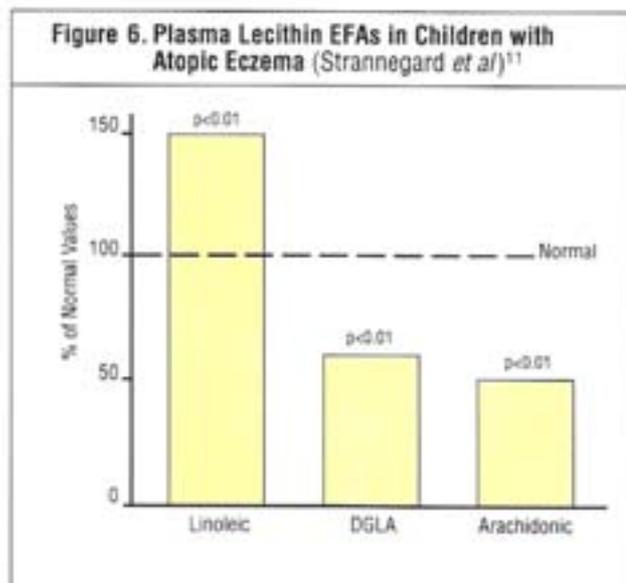
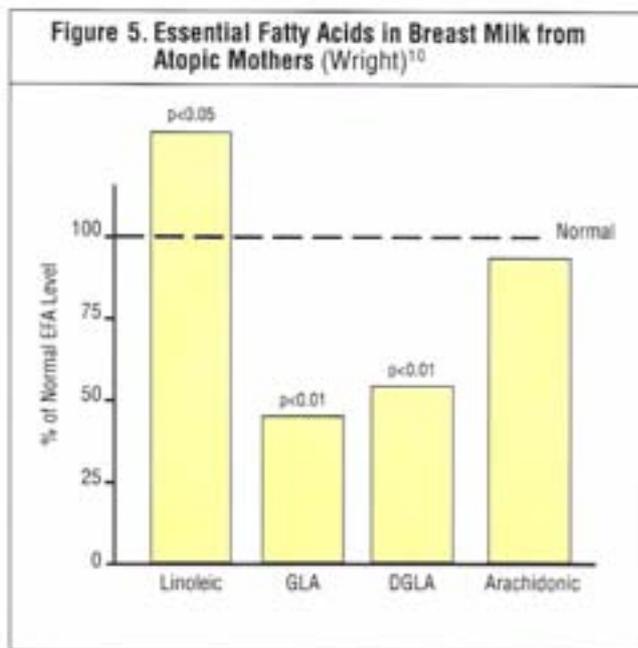
Wright reasoned that because human milk contains substantial amounts of linoleic acid, GLA, DGLA and AA, the amounts of these fatty acids present might represent the amounts biologically available to the mother and her infant. Wright therefore collected milk samples from mothers with and without atopic eczema and measured the EFAs in the milk. The results are summarized in Figure 5. Linoleic acid levels were above normal in the milk from eczematous mothers, whereas the levels of all the linoleic acid metabolites were below normal<sup>10</sup>.

Strannegard et al, from the University of Uppsala in Sweden, reasoned that, if there is an abnormality of EFA metabolism in atopic eczema, it should be present in children with the disease as well as in adults. They therefore compared plasma phosphatidyl-choline EFA levels in children with atopic eczema and in normal children<sup>11</sup>. The results were similar to those from the Bristol study but the deviation of linoleic acid from normal was considerably more striking (Figure 6). Linoleic acid

concentrations were substantially elevated, whereas DGLA and AA were markedly reduced (GLA was not measured because of the small amounts present). Arguing that, if the abnormality is important in atopic eczema, it might be detectable at birth, they measured linoleic acid levels and IgE levels in umbilical cord blood. The conclusions drawn from this must be cautious since cord blood EFAs are in part derived from the mother and so may be limited as a guide to the infants EFA metabolism. IgE levels were used as an indicator of the risk of development of an atopic disorder. There was a significant correlation between linoleic acid level and IgE concentration (Figure 7). In infants at risk of atopy, an EFA abnormality can therefore be demonstrated even before the emergence of any skin lesions. This shows that the EFA problem is not a consequence of the skin inflammation and raises the possibility that the EFA defect could be the underlying cause of atopic eczema.

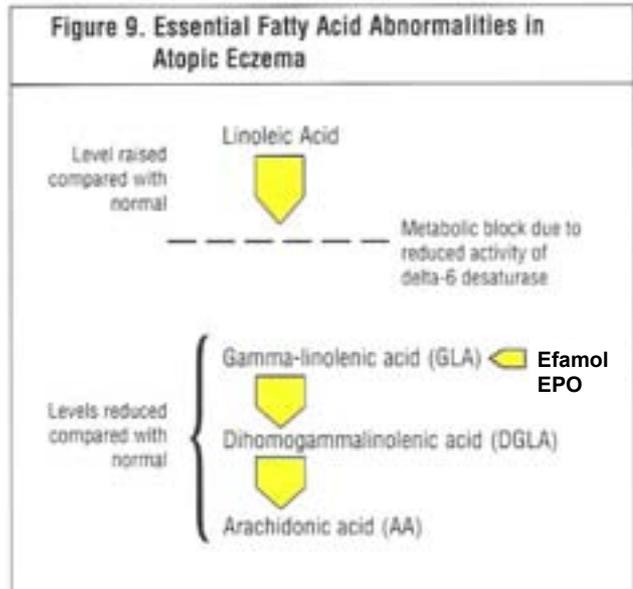
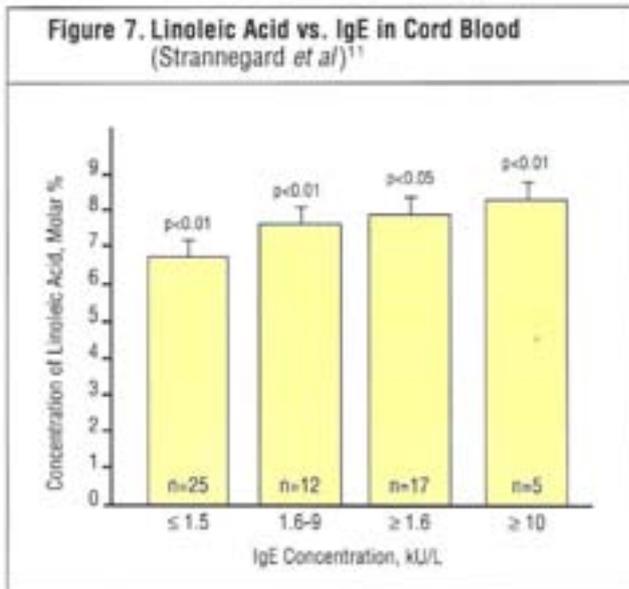
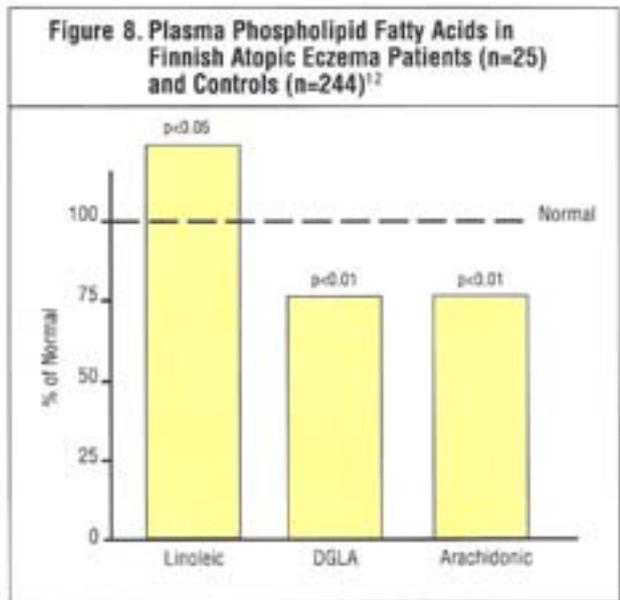
Jansen et al in Turku, Finland, also compared EFA levels in the plasma phospholipids of atopic eczema patients with those in normal individuals. They looked at only seven controls and could find no significant differences between the normal and eczematous individuals<sup>12</sup>. However, these normal values varied substantially from other normal published values. When the eczema patients were compared with a much larger number of 244 normal Finnish controls, linoleic acid was again seen to be elevated in the eczema patients, while DGLA and AA were reduced (Figure 8).

There is now a substantial body of evidence supporting the view that, in atopic eczema, linoleic acid levels are either normal or above normal, indicating normal EFA intake. In contrast, the levels of the metabolites of linoleic acid are consistently and substantially reduced.



These results strongly suggest that there is an abnormality in the conversion of linoleic acid to GLA in atopic eczema patients. As a result, linoleic acid tends to accumulate whereas the concentrations of GLA and its metabolites, DGLA and AA are reduced below normal levels (Figure 9).

Since the conversion of linoleic acid to GLA is indeed slow under normal circumstances, then atopic eczema patients are deprived of a series of EFAs known to have very important actions on the skin. This raises the possibility that the direct administration of GLA, to by pass the apparent metabolic block, will have beneficial effects. GLA can be conveniently and effectively administered in the form of Efamol<sup>®</sup> Pure Evening Primrose Oil.



## Section 2: Clinical Evidence

### Preliminary Observations

The first anecdotal evidence for a beneficial effect of evening primrose oil in atopic eczema came from the child of a member of a group involved in evening primrose oil research. The one-year-old boy had extremely severe atopic eczema, which was uncontrollable, even by oral steroids. Evening primrose oil was given to the child at a daily dose of 2 g and produced a dramatic therapeutic response. Within about 4 weeks the child's skin was almost clear and the improvement was maintained as long as the therapy was continued.

A pilot double-blind, placebo-controlled trial was then set up at the University of Bristol<sup>13</sup>. This was a crossover study, with each patient being given Efamol<sup>®</sup> Pure Evening Primrose Oil or placebo for three weeks in random order. The Efamol<sup>®</sup> Pure Evening Primrose Oil group demonstrated greater improvement than the placebo group. Several patients who chose to continue on active therapy improved further following the end of the trial. Limited open studies indicated that, while most patients began to show some effect within four weeks, the full response was often not achieved for two to six months. It was therefore decided to set up larger trials over longer time periods.

### Double-Blind, Placebo Controlled Trials

Sixteen double-blind, placebo-controlled trials of Efamol<sup>®</sup> Pure Evening Primrose Oil in atopic eczema have now been completed<sup>12,13,14,15,16,17,18,19,20,21,22,26,27</sup>. Nine of these studies are summarized in Table 1 (Those published up to 1989). Five of these trials were crossover in design and four were parallel. In each trial, doctors regularly assessed their patients, particularly noting inflammation, scaliness, dryness and overall skin involvement. In some of the trials, patients made similar as-

Study	Study Design	Duration (weeks)	Number of Patients Entered*	
			EPO	Placebo
Burton <sup>14</sup> (adults)	Crossover	12 + 12	29	31
Burton <sup>14</sup> (children)	Crossover	12 + 12	18	21
Gould <sup>15</sup>	Crossover	12 + 12	20	22
Allen <sup>16</sup>	Crossover	8 + 8	23	24
Wexler <sup>17</sup>	Crossover	12 + 12	9	5
Jansen <sup>18</sup>	Parallel	8	14	11
Holt <sup>19</sup>	Parallel	12	19	18
Meiger <sup>20</sup>	Parallel	12	18	7
Bordon <sup>21</sup>	Parallel	4	10	12

\*First treatment only if crossover study

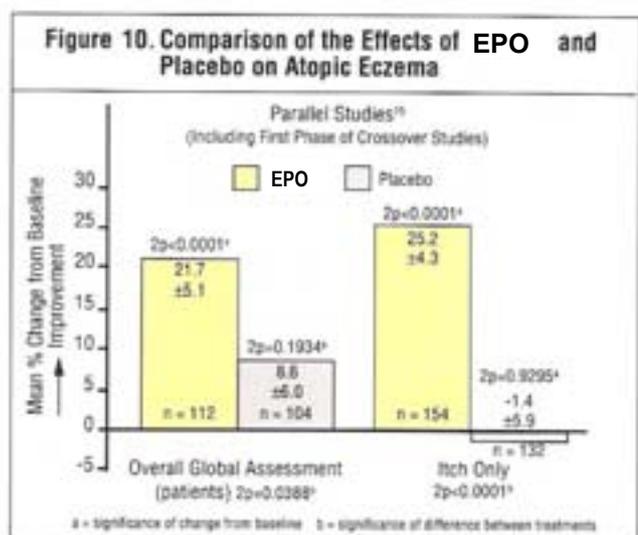
sessments. In all the trials, doctors and patients together made an assessment of the severity of the key symptom of itch.

In order to analyse the trials, for individual patients at each assessment point a global score was constructed. This global score included all the assessments made by both patients and doctors. The effect of Efamol<sup>®</sup> Pure Evening Primrose Oil or placebo was assessed by noting the percentage change in global score from either the start of the trial or the crossover point. In addition, because of its central importance in atopic eczema, the single symptom of itch was assessed separately.

### Patients in the trials

127 children and 204 adults completed the placebo-controlled trials. The patients entered into the studies all demonstrated mild to moderate atopic eczema. Almost all were using topical steroids, often in association with emollients. The atopic eczema in each patient had persisted in spite of continued use of these medications. At the start of each trial, the patients were all considered to be receiving the best available treatment for their grade of eczema, consistent with efficacy and long-term acceptability. The patients continued to use their existing treatments during the trials of Efamol<sup>®</sup> Pure Evening Primrose Oil. In all but two studies, they were instructed to maintain their pre-existing treatment unchanged throughout the trial. In the other studies, variation in the dosage and amount of symptomatic therapy used was employed as a measure of the response to Efamol<sup>®</sup> Pure Evening Primrose Oil or placebo.

It is important to emphasise that all improvements in these Efamol<sup>®</sup> Pure Evening Primrose Oil trials were over and above those achieved with conventional long term maintenance therapy.



### Overall results

The overall results, with all patients and all dose levels grouped together, are shown in Figure 10 and 11. Figure 10 shows the effects obtained in all the trials, including both the trials set up as parallel studies and the first parallel phases of the trials set up as crossover studies. Figure 11 shows the results in the crossover studies only. The overall results of the two types of analysis reveal almost identical outcomes<sup>15</sup>.

As in all trials in atopic eczema, the overall global score shows a substantial placebo response. However, the effect of Efamol<sup>®</sup> Pure Evening Primrose Oil was more than double the effect of placebo and the difference between the two was highly significant statistically.

The effect of Efamol<sup>®</sup> Pure Evening Primrose Oil on the key symptom of itch was particularly clear cut. Surprisingly, there was no placebo effect, demonstrating unequivocally that this symptom has a physical rather than a psychological basis. In contrast, there was a large therapeutic response to Efamol<sup>®</sup> Pure Evening Primrose Oil. Moreover, not a single patient noticed and drowsiness a consequence of taking Efamol<sup>®</sup> Pure Evening Primrose Oil. This indicates that the mechanism of the anti-pruritic effect of Efamol<sup>®</sup> Pure Evening Primrose Oil is different from that of the antihistamines.

In all the trials together, comparisons of 126 parameters were made. For each one an assessment was made as to whether the results with Efamol<sup>®</sup> Pure Evening Primrose Oil were better than the results on placebo or vice versa. These results are summarized in Figure 12. It is clear from the doctor and patient assessments as well as objective measurements that Efamol<sup>®</sup> Pure Evening Primrose Oil is superior to placebo.

### Timing of improvement

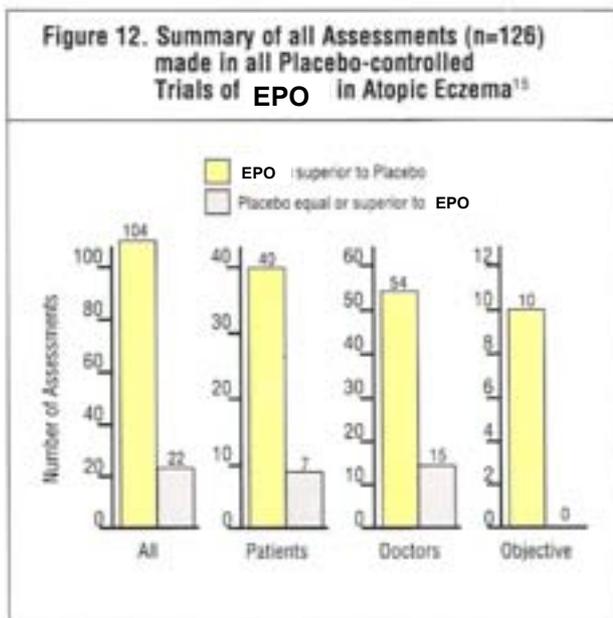
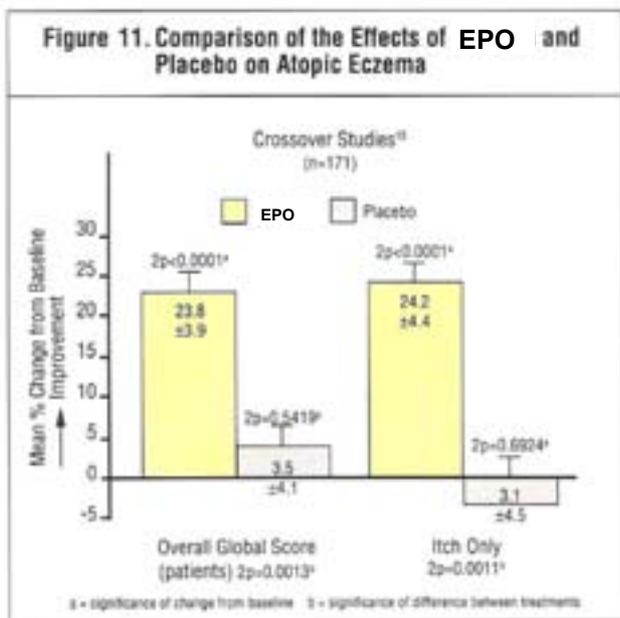
A comparison of the improvements in clinical score at the first and last assessment points in the trials is shown in Figure 13. With the exception of a short 4 week trial, the first assessment points were always 3 or 4 weeks after starting treatment, while the last assessment was at 12 weeks, except in one trial when it was 8 weeks. The figure shows that the degree of improvement is consistently greater at the last assessment than at the first.

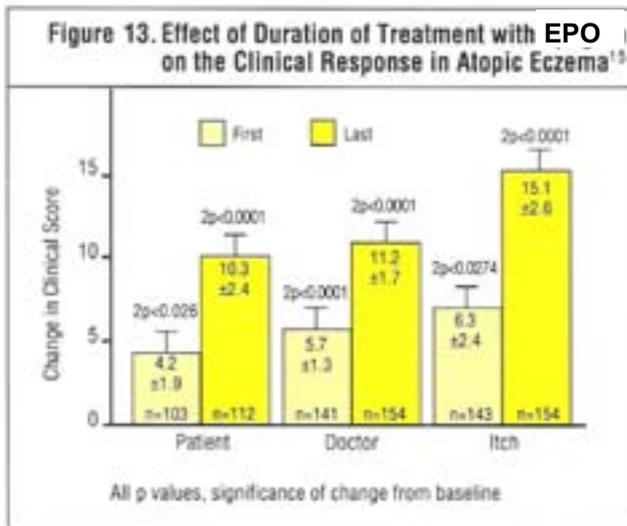
This result emphasizes the fact that Efamol<sup>®</sup> Pure Evening Primrose Oil generally does not produce a short term, rapid, symptomatic response. The effect is slow to develop and is much greater after three months than after one month. This is presumably because changes in the fatty acid composition of the relevant cells in the skin and in the immune system are gradual and take time to build-up.

### Relapse on stopping treatment

The effect of stopping Efamol<sup>®</sup> Pure Evening Primrose Oil can readily be seen by looking at the changes in the trials in those patients who received Efamol<sup>®</sup> Pure Evening Primrose Oil first. The changes in itch scores in these trials are shown in Figure 14. The improvement achieved at the end of the first phase in those who received Efamol<sup>®</sup> Pure Evening Primrose Oil first was not lost over the three months of the second phase.

Longer term open observations suggest that relapse does occur in most patients, three to six months after stopping Efamol<sup>®</sup> Pure Evening Primrose Oil. This may be reversed by a second course of Efamol<sup>®</sup> Pure Evening Primrose Oil or prevented by continuing Efamol<sup>®</sup> Pure Evening Primrose Oil on a maintenance basis at a reduced dose.



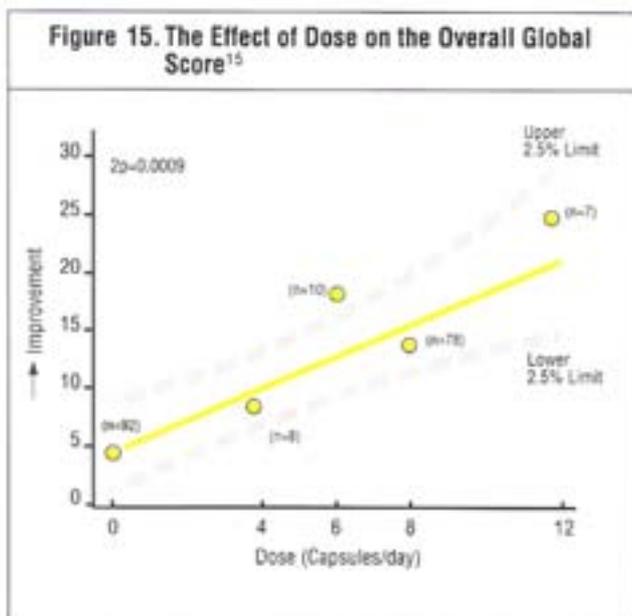


### Dosage

Analyses of the effects of individual doses used in the trials suggest that, in adults, there is a progressive dose/response effect (Figure 15). A dosage of 6 Efamol<sup>®</sup> Pure Evening Primrose Oil 1g capsules per day is more effective than 3 or 4, which in turn is more effective than 2 capsules per day.

### Use in children

Animal studies have shown that EFA requirements are highest during growth. The needs of pre-pubertal animals are therefore greater than those of adults. It is now known that a similar situation is true in humans. The highest dose of Efamol<sup>®</sup> Pure Evening Primrose Oil given to children with atopic eczema has been 3 (1g) capsules per day in 1 to 4 year olds<sup>16</sup>. The dose was highly effective clinically and produced no noticeable adverse events. This lack of adverse events, even in very small children given relatively large doses, is not altogether surprising. A fully-breast fed infant in fact, is



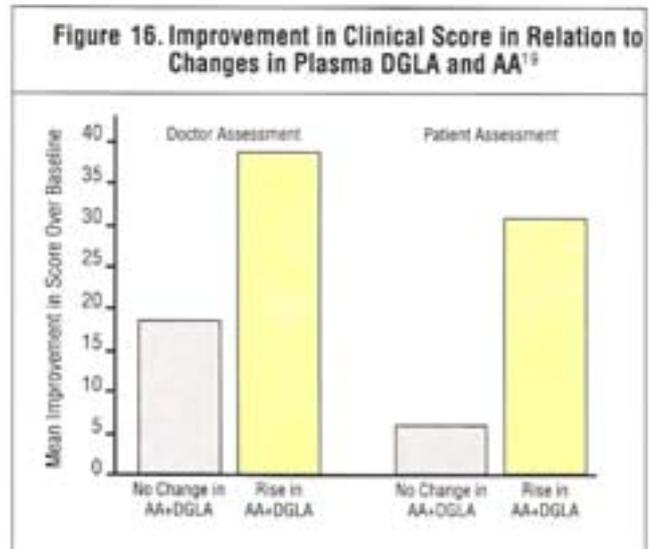
ingesting the equivalent of one or two Efamol<sup>®</sup> Pure Evening Primrose Oil capsules per day.

In children with cystic fibrosis the equivalent of 25 capsules per day of Efamol<sup>®</sup> Pure Evening Primrose Oil has been administered for one year without any adverse affects other than an occasional gastrointestinal upset in about one third of the children.

Many children with atopic eczema are observed to be hyperactive and fidgety. The reason for this is unknown, but itching probably plays a substantial part. In a study by Guenther and Wexler, this issue was addressed specifically. Efamol<sup>®</sup> Pure Evening Primrose Oil was found to produce a significantly greater improvement in hyperactivity than placebo<sup>22</sup>.

### Adverse events

Adverse events in both the Efamol<sup>®</sup> Pure Evening Primrose Oil and the placebo groups were infrequent and mild. No single serious adverse event was recorded in either group. The only event which appeared consis-



tently more frequent in the Efamol<sup>®</sup> Pure Evening Primrose Oil group than in the placebo group was mild gastrointestinal upset. There were eight such episodes in patients on Efamol<sup>®</sup> Pure Evening Primrose Oil and two in patients on placebo. The commonest event was slight nausea, probably attributable to taking capsules on an empty stomach. This could usually be avoided by taking Efamol<sup>®</sup> Pure Evening Primrose Oil after meals.

### Relationship of response and blood EFAs

In some of the studies, blood samples were taken at the beginning and end of treatment. Plasma phospholipids DGLA and AA were measured and related to the clinical response. As shown in Figure 16, patients who showed no change in AA + DGLA showed little clinical response. Those patients whose AA and DGLA levels rose, showed a substantially and significantly greater response.

### Objective Studies

In most trials of treatment of atopic eczema, all assessments, whether by patients or by doctors, are by necessity subjective attempts to measure the severity of the disease. Four investigators have evaluated objectively the effects of Efamol<sup>®</sup> Pure Evening Primrose Oil, employing either records of the amount of use of topical steroids, or measurement of physical changes in the skin such as roughness.

### Skin roughness - Marshall and Evans Study<sup>23</sup>

Skin roughness was measured by macrophotography of a defined area of non-inflamed skin, followed by computer-assisted densitometric analysis of the image. Five different measures of skin roughness were obtained. All showed a significant improvement in smoothness with Efamol<sup>®</sup> Pure Evening Primrose Oil but no significant improvement in response to placebo.

### Skin roughness - Nissen study<sup>24</sup>

Nissen et al used a somewhat different technique to

measure the roughness of a defined area of non-inflamed skin on the ventral forearm. A fine silicone rubber impression was taken of a defined skin area before and after treatment with three 1000 mg capsules per day of Efamol<sup>®</sup> Pure Evening Primrose Oil for four weeks. Both normal individuals and patients with atopic eczema were studied. The roughness of the defined area was then measured by running a stylus over it.

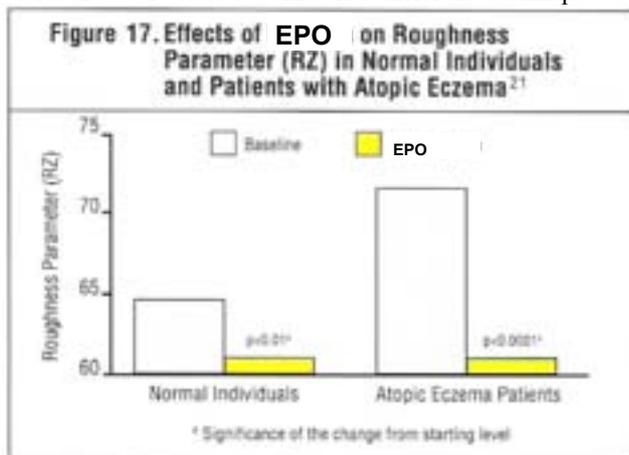
The upward and downward movement of the stylus generated an electronic signal which was converted by a computer into various measures of roughness. The results for parameter RZ (the mean peak to valley height over a defined track) are shown in Figure 17.

Prior to treatment with Efamol<sup>®</sup> Pure Evening Primrose Oil, the skin in patients with atopic eczema was significantly rougher than the skin in the normal control group. Efamol<sup>®</sup> produced a significant reduction in roughness in both groups but the improvement was much greater in the atopic eczema patients. At the end of Efamol<sup>®</sup> Pure Evening Primrose Oil treatment there was no measurable difference between the skin smoothness in patients and in controls.

### Skin roughness - Muggli study<sup>25</sup>

Muggli further investigated the beneficial effects of Efamol<sup>®</sup> Pure Evening Primrose Oil on healthy skin as a follow up to the observations reported in the Nissen trial. The randomized, double-blind, placebo controlled, parallel trial included 40 healthy males and females between the ages of 32 and 56 years of age that were randomly assigned to take either six 500 mg capsules per day of Efamol<sup>®</sup> Pure Evening Primrose Oil or an inert placebo for 84 days.

At the start of the trial, skin on the forearm of all participants was assessed for skin moisture, redness, trans epidermal water loss (TEWL – the rate at which water escapes from the body through the skin), roughness and biomechanical properties including elasticity, firmness and fatigue. The same tests were repeated after 28 and



TREATMENT	Patients Requiring Treatment	
	BEFORE EPO	AFTER EPO
Antihistamines	62	17
Antibiotics	34	6
Systemic Steroids	22	6
Moderate and High Potency Topical Steroids	125	60

84 days. The results obtained in the middle and the end of the study were compared to those obtained prior to treatment with either Efamol<sup>®</sup> Pure Evening Primrose Oil or the inert placebo.

After 84 days of treatment there was a statistically significant improvement from baseline in skin moisture (18%), TEWL (8%), roughness (18%), elasticity (7%), firmness (16%) and fatigue (12%). These same improvements although apparent, were not significant following only 28 days of treatment. This delay in response highlights the need to allow time for Efamol<sup>®</sup> Pure Evening Primrose Oil to work. There was no improvement in any of these parameters following treatment with placebo. There was no significant reduction in redness from the start (baseline) of the study to the end in either the Efamol<sup>®</sup> Pure Evening Primrose Oil or the placebo group because there was no appreciable redness detected in the healthy skin at the start of the study.

This study confirmed that Efamol<sup>®</sup> Pure Evening Primrose Oil could enhance skin structure and function in healthy subjects through improving its moisture content and retention, elasticity, firmness, strength and smoothness. These improvements tighten skin, reduce wrinkles and dryness, and give a more youthful glow to normal healthy skin.

#### **Topical steroid use - Jansen study<sup>12</sup>**

In a trial by Jansen, all patients were given supplies of the same mild topical steroid and told to vary its use as required. The amounts of steroid ointment used were assessed by weighing the tubes. In the Efamol<sup>®</sup> Pure Evening Primrose Oil group, the mean amount used over 12 weeks was 60 +/- 10 g per patient. In the placebo group the amount used was 200 +/- 60 g per patient. At the end of the trial, the clinical status of the Efamol<sup>®</sup> Evening Primrose Oil group had improved to a significantly greater extent than the placebo group, although the latter had used more than three times as much steroid.

#### **Open Studies in Severe Atopic Eczema**

Chronic severe atopic eczema is usually defined as the long-term requirement for the use of potent or moderately potent topical steroids.

Thirteen dermatologists collaborated in a study of 179 patients with severe atopic eczema<sup>26</sup>. Most of these patients received four 1000 mg capsules of Efamol<sup>®</sup> Pure Evening Primrose Oil per day. Of the 179 patients, 116 were assessed as being improved as a result of taking Efamol<sup>®</sup> Pure Evening Primrose Oil. Of these patients,

46% first noted some improvement between 1 and 4 weeks after starting Efamol<sup>®</sup> Pure Evening Primrose Oil, and 44% between 4 and 12 weeks after starting.

Once improvements had begun it was sustained for the duration of treatment. Of these patients 89% received Efamol<sup>®</sup> Pure Evening Primrose Oil for four months or more and 48% for one year or more. Only two adverse events were recorded. One patient developed stomach pains and another mild fluid retention, although it is uncertain whether these events were related to Efamol<sup>®</sup> Pure Evening Primrose Oil use.

Some patients in this study who had previously suffered lifelong intractable eczema experienced complete or near complete remission of all symptoms of the disease.

#### **Use of other drugs**

The effect of Efamol<sup>®</sup> Pure Evening Primrose Oil in these moderately to severely affected patients is perhaps most clearly illustrated by the changes in requirements for other drugs which have potentially serious side effects (Table 2). There was a 73% reduction in use of antihistamines, an 82% reduction in antibiotic use, a 73% reduction in oral steroid use and a 52% reduction in the use of moderate and high-potency topical steroids.

#### **Adverse Drug Interactions**

There were no reports of any adverse interactions with any of the drugs used in the trials of Efamol<sup>®</sup> Pure Evening Primrose Oil in atopic eczema. Efamol<sup>®</sup> Pure Evening Primrose Oil can therefore be used with other conventional atopic eczema treatments.

Analyses of the results in patients using steroids showed that they do not interfere with the action of Efamol<sup>®</sup> Pure Evening Primrose Oil.

#### **Inconclusive Studies**

One placebo-controlled study has been published which failed to show any benefit of Efamol<sup>®</sup> Pure Evening Primrose Oil over placebo<sup>27</sup>. However fatty acid analysis of blood samples from these patients has provided strong evidence that, in this study, active and placebo capsules were mixed inadvertently<sup>15</sup>. Some patients who were supposed to be receiving Efamol<sup>®</sup> Pure Evening Primrose Oil were in fact taking placebo and vice versa, so rendering the conclusion of this study meaningless.

### **Section 3: Technical Background**

#### **Chemistry**

Efamol<sup>®</sup> Pure Evening Primrose Oil consists of the seed

oil from a selected strain of the evening primrose, *Oenothera spp.* called Rigel. Since all the other constituents of this oil are already present in large amounts in food, it is believed that the major active constituent is gamma-linolenic acid, GLA. The seed oil from which Efamol<sup>®</sup> Pure Evening Primrose Oil is prepared is derived from a strain of plant developed through standard agricultural selected techniques, to give oil of consistent quality and composition. The oil is then subjected to quality control which rejects all oil batches which do not meet the required specifications for GLA and other fatty acids. Each 1000 mg capsule of Efamol<sup>®</sup> Pure Evening Primrose Oil capsule contains 115 mg of GLA.

### Clinical Pharmacology

Efamol<sup>®</sup> Pure Evening Primrose Oil does not demonstrate acute pharmacological effects. As there are no accepted animal models for atopic eczema, it is somewhat unclear as to which pharmacological studies are relevant to its human use. It is believed that Efamol<sup>®</sup> Pure Evening Primrose Oil may act in two main ways to achieve its therapeutic effects:

1. It produces a progressive change in the structure of the phospholipids of the blood and of cell membranes, so changing the behaviour of the cells. Human studies have shown that Efamol<sup>®</sup> Pure Evening Primrose Oil consistently elevates the amount of DGLA in the phospholipids fraction<sup>5</sup>.
2. It produces desirable alterations in the levels of pro- and anti-inflammatory mediators.

It is therefore relevant to consider the effects of Efamol<sup>®</sup> Pure Evening Primrose Oil on the levels of anti-inflammatory mediators. It is also important to consider the effects of Efamol<sup>®</sup> Pure Evening Primrose Oil on other types of inflammation both in animals and humans. While each type of inflammation is different in detail, inflammatory reactions have many common features.

<b>Common name</b>	Gamma-linolenic acid, GLA.
<b>Chemical name</b>	c,c,c-6,9,12-octadecatrienoic acid.
<b>Chemical designation</b>	18:3n-6 or 18:3 omega-6
<b>Molecular formula</b>	C <sub>18</sub> H <sub>30</sub> O <sub>2</sub>
<b>Molecular weight</b>	284

### Changes in inflammatory mediators

Ziboh and his colleagues have shown that administration of evening primrose oil to guinea pigs raises the concentrations in the skin of two mediators which are known to have anti-inflammatory effects<sup>28,29</sup>. These are prostaglandin E<sub>1</sub> (PGE<sub>1</sub>) and 15-hydroxy-DGLA. PGE<sub>1</sub> stimulates cyclic AMP formation, inhibits activity of phospholipase A<sub>2</sub>, and inhibits chemotaxis, all actions which would be expected to be anti-inflammatory. PGE<sub>1</sub> has also been shown to be anti-inflammatory in a wide range of in vivo and in vitro models. 15-hydroxy-DGLA has been shown to inhibit the 5-lipoxygenase and 12-lipoxygenase enzymes which produce leukotrienes and other pro-inflammatory metabolites from arachidonic acid.

Zurier and his colleagues have shown similar results in cultured human monocytes following addition of GLA or its metabolite DGLA<sup>30</sup>. Production of PGE<sub>1</sub> is increased, while the formation of pro-inflammatory metabolites of arachidonic acid, including leukotrienes, is reduced.

Administration of Efamol<sup>®</sup> Pure Evening Primrose Oil therefore results in a beneficial effect on the levels of various mediators. It increases the rate of formation of the anti-inflammatory PGE<sub>1</sub> while reducing the formation of mediators known to be pro-inflammatory.

### Models of inflammation

Administration of evening primrose oil has been found to exert a substantial inhibitory effect on the inflammatory responses in adjuvant arthritis (a possible model of human rheumatoid arthritis), experimental allergic encephalomyelitis (a possible model of human multiple sclerosis) and of urate-induced inflammation (a possible model of gout)<sup>31,32,33</sup>.

### Human inflammatory disorders

Two studies have been performed on the use of Efamol<sup>®</sup> Pure Evening Primrose Oil in patients with rheumatoid arthritis<sup>34,35</sup>. In one study of twenty patients, treatment with non-steroidal anti-inflammatory drugs (NSAIDs) was stopped abruptly, and treatment commenced with Efamol<sup>®</sup> Pure Evening Primrose Oil, 4 capsules per day for 12 weeks<sup>30</sup>. There were no significant changes in any subjective or objective measures of rheumatoid arthritis. Only two relapses occurred indicating that, for many patients, Efamol<sup>®</sup> Pure Evening Primrose Oil was as effective as NSAIDs in controlling symptoms.

In this study, as a measure of the cutaneous inflamma-

tory response, different areas of skin were exposed to increasing intensities of UV light and the minimum UV dose required to induce an erythematous response 24 hours later was noted. During Efamol<sup>®</sup> Pure Evening Primrose Oil treatment, the dose of UV light required almost doubled, a statistically significant change, indicating increased resistance to inflammation.

Because of the slow onset of action of Efamol<sup>®</sup> Pure Evening Primrose Oil in inflammation, a longer study in rheumatoid arthritis was conducted<sup>31</sup>. Eighteen patients with stable rheumatoid arthritis were given placebo and 16 received Efamol<sup>®</sup> Pure Evening Primrose Oil, twelve 500 mg capsules per day on a randomised, double-blind basis. After 3 months treatment and for the subsequent 9 months, attempts were made to reduce the NSAID dose in all patients. After 12 months, all patients were switched to placebo on a single blind basis.

During the first 12 months, 10 of the 18 patients in the placebo group were withdrawn from the study because of worsening arthritis. Only 1 of the 16 Efamol<sup>®</sup> Pure Evening Primrose Oil patients was withdrawn for this reason. In 12 patients in the Efamol<sup>®</sup> Pure Evening Primrose Oil group, NSAIDs were substantially reduced or stopped. At the same time patients reported a subjective improvement in their condition. Only 5 patients in the placebo group could reduce or stop NSAID treatment.

Fifteen of the 16 Efamol<sup>®</sup> Pure Evening Primrose Oil patients rated themselves improved compared with only 5 of the 18 placebo patients. When the improved patients were switched to placebo in the single blind phase of the trial, all 15 in the Efamol<sup>®</sup> Pure Evening Primrose Oil group relapsed but only 1 of the patients in the placebo group relapsed. There were no subjective improvements, other than the changes in drug dosage, in the Efamol<sup>®</sup> Pure Evening Primrose Oil group.

## **Dosage Information**

### **Presentation**

**500 mg capsules** -Clear oval soft gelatin capsules

**1000 mg capsules** -Clear oblong soft gelatin capsules

**Liquid** -30 ml oil in an amber glass dropper bottle.

### **Directions for use**

	<b>Intake per day with food or drink</b>	
	<b>First time user</b>	<b>After 12 weeks</b>
500 mg capsules	6	2
1000 mg capsules	3	1
Liquid	32 drops	16 drops

### **Precautions**

Do not exceed the recommended intake. Food supplements should not be used as a substitute for a varied diet. Those with a history of epilepsy or taking any medication should consult their doctor before using this product.

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