SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

<[Invented name]> 20 micrograms /ml solution for blood fraction modification

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml solution contains 20 micrograms of
methoxsalen.
One 5 ml ampoule contains 100 micrograms of methoxsalen.
Excipients with known effect: 200 mg ethanol 96%, 17.2 mg sodium per ampoule.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for blood fraction modification
Clear, colorless solution.
pH: 4.00 – 5.00

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

<[Invented name]> is indicated in adults for extracorporeal use in the palliative treatment of advanced stage cutaneous T-cell lymphoma (CTCL) in patients who have not been responsive to other forms of treatment.

4.2 Posology and method of administration

Posology

Adults
<[Invented name]> is used in conjunction with photopheresis systems, according to the specific manual of use and clinical protocol.
During each photopheresis treatment, the dosage of methoxsalen must be calculated according to the treatment volume, using the following formula:

Treatment volume x 0.017 ml of <[Invented name]> for each treatment
For example: Treatment volume = 240 ml x 0.017 = 4.1 ml of <[Invented name]>

The prescribed amount of <[Invented name]> is injected into the recirculation bag prior to the photoactivation phase.

Method of administration
Extracorporeal use.
The content of the ampoule must not be injected directly into the patient as there are no studies with direct injection of <[Invented name]> in humans.

In the photopheresis process the components of the whole-blood are separated. The erythrocytes and excess plasma are returned to the patient immediately, while the buffy coat (leucocyte-enriched blood) and some plasma are collected into the photoactivation bag. Here <[Invented name]> is added, UVA light radiation is performed and everything is reinfused into the patient.

General principle of extracorporeal photopheresis procedure:

- % of the haematocrit of the separate blood fraction should be determined since RBC (red blood cells) contamination interferes with UVA light access to WBCs (white blood cells).
- before radiation with UVA light [in the photoactivation bag], anticoagulant, isotonic saline solution and the prescribed amount of <[Invented name]> are added to the leucocytes;
- the quantities collected for therapy may vary depending on body weight, blood volume and method used for therapy (on-line or off-line method);
- during photoactivation, the leucocyte-enriched blood is radiated with UVA light (1-2 J/cm^2);
- at the end of the photoactivation cycle, the photoactivated cells are reinfused via intravenous drip. The recommended duration of reinfusion is within 20 minutes;
- the buffy coat collection cycle is repeated up to six times, and the complete photopheresis procedure lasts approximately 1.5 to 4 hours;
- during therapy blood pressure, heart rate and body temperature should be monitored

Duration of treatment
During the first three months it is recommended to carry out the treatment in two consecutive days every 2 to 4 weeks. After that, two-day treatment cycles are recommended every 3-4 weeks.
It has been shown that higher treatment frequencies do not lead to better treatment results.
As soon as the maximum treatment response is achieved, intervals should be gradually extended to 4-8 weeks and then continued as a maintenance therapy every 8 weeks.

The duration of photopheresis therapy should be at least 6 months. In patients who respond well to treatment or whose disease can be stabilized offering them good quality of life, photopheresis may be carried out for 2 years or more.

The above recommendations are a general guideline. Therapy cycles may be adapted individually to the specific clinical picture and the patient's response.

Note:
Extracorporeal photochemotherapy must be carried out only by specially trained staff and in institutions having the suitable equipment for this treatment.
Psoralen and UV irradiation therapy should take place under constant supervision by a physician appropriately trained. The working instructions, provided by the company manufacturing the photopheresis system and/or the recent guidelines about the procedure, must be strictly followed.

Paediatric population (under 18 years of age)
The safety and efficacy of <[Invented name]> in children and adolescents have not been established for this indication.

Hepatic or renal impairment
<[Invented name]> has not been clinically tested in patients with renal or hepatic impairment.
Liver enzymes should be monitored regularly before and during therapy (see section 4.4).

4.3 Contraindications

- Hypersensitivity to the active substance, other psoralen compounds or to any of the excipients listed in section 6.1
- Co-existing malignant skin tumor (e.g. melanoma, basalioma or squamous cell carcinoma)
- Photosensitive disease (e.g. porphyria, systemic lupus erythematosus or albinism)
- Use by sexually active men and women of childbearing potential unless adequate contraception is used during treatment (see section 4.6)
- Aphakia
- Pregnancy and lactation

Contraindications to the photopheresis procedure:
- Inability to tolerate the transitory volume loss (e.g. because of severe cardiac disease, severe anaemia etc.)
- Previous splenectomy
- Coagulation disorders (e.g. history of heparin-induced thrombocytopenia)
- Leucocyte count above 25,000/mm³

4.4 Special warnings and precautions for use

Extracorporeal photochemotherapy must be carried out only by specially trained staff persons and in institutions having the suitable equipment for this treatment.
Psoralen and UV irradiation therapy should take place under constant supervision by a physician with the appropriate training.
Because of the possibility of irreversible eye damage occurring as a side effect, the patient should be fully informed about the risks inherent in this therapy.

<[Invented name]> should be used only *ex vivo* and added directly to the separated leucocytes. If there is a possibility that the blood has been damaged during the procedure, it should only be reinfused into the patient if haemolysis has not occurred.

Contraceptive precautions
Both men and women who are being treated with <[Invented name]> should take adequate contraceptive precautions both during and after completion of photopheresis therapy.

Hypotension
Transient hypotension may occur in some patients during therapy. In most patients it is asymptomatic and disappears after reinfusion of the blood. Occasionally, normal saline solution must be infused during photopheresis to stabilize blood pressure. Patients regularly taking anti-hypertensives should wait until the end of the photopheresis procedure to take the medicine (see section 4.8).

Hypertriglyceridemia
In patients with increased blood triglyceride levels the efficacy of the procedure might be limited because the photopheresis instruments cannot separate white blood cells from fat-rich blood. Therefore patients about to get a photopheresis treatment should fast before the therapy – their triglyceride level should be lower than 300 mg/dl at the start of treatment.

Cataractogenicity
Exposure to large doses of UVA light causes cataracts in animals, an effect enhanced by the administration of oral methoxsalen. As the concentration of methoxsalen in the human lens is proportional to the serum level, the concentration will be substantially lower following *ex vivo* methoxsalen treatment compared to the concentration seen after oral administration. Nevertheless, if the lens is exposed to UVA light during the time methoxsalen is present in the lens, photochemical action may lead to irreversible binding of methoxsalen to protein and DNA components of the lens. For this reason, the patients' eyes should be protected from UVA light wearing wrap-around, UVA-opaque sunglasses during the treatment cycle and during the following 24 hours (see section 4.8).

Adverse effects on the skin
Following oral administration of psoralen (where serum concentrations may exceed 200 ng/ml), exposure to sunlight or UV radiation (even through window glass) may result in serious burns and, over the long term, 'premature aging' of the skin.
Extracorporeal use of <[Invented name]> is associated with a much lower systemic exposure to methoxsalen. However, the amount of phototoxicity of these levels has not been investigated systematically. Therefore, as a precaution, patients should avoid exposure to sunlight during the 24 hours following photopheresis treatment.
Therapy may lead to increased risk of skin cancer (basal cell, melanoma and squamous cell); this risk may be increased with fair skin or prior exposure to prolonged tar and UVB treatment, ionizing

radiation, or arsenic.

Hepatic impairment
No specific information is available on the use of photopheresis with methoxsalen in patients with hepatic impairment. As hepatic biotransformation is necessary for urinary excretion, it is possible that hepatic impairment may result in an extended half-life of methoxsalen. This may result in prolonged photosensitivity. In patients with hepatic diseases, precautions against exposure to sunlight should therefore be prolonged where required.

Renal impairment
Although several renal transplant recipients with poor renal function have been treated with photopheresis, little additional information is available on the use of methoxsalen in renally-impaired patients. No extra precautions, such as dose reduction or prolongation of protection from UV light, were taken in the few renal transplant recipients who have undergone photopheresis treatment and the procedures were well tolerated and effective.

Information about certain excipients
<[Invented name]> contains 5% of ethanol (alcohol) i.e. up to 162 mg per an assumed treatment volume of 240 ml (4.1 ml of <[Invented name]>). . The amount in volume of this medicine is equivalent to 4 ml beer or 1.6 ml wine.With extracorporeal administration systemic exposure expected to be low and clinical effect has not been evident, however Prescriber's should be aware of the potential effect other medicines and caution is advised in liver disease, alcoholism, epilepsy, brain injury or disease.<[Invented name]> contains less than 1 mmol sodium (23 mg) per ml, i.e. it is essentially 'sodium-free'.
This medicinal product contains 17,2 mg sodium per one ampoule (5 ml), equivalent to 0,86 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Phenytoin
Phenytoin may induce the metabolism of psoralens. Failure of methoxsalen therapy may be attributed to this interaction if they are administered concomitantly.

Tolbutamide
Methoxsalen is highly bound to serum albumin but it can also be displaced particularly by tolbutamide. Concomitant use of methoxsalen and tolbutamide may lead to enhanced photosensitivity.

Cytochrome P450
Methoxsalen is metabolised via cytochrome P450 (CYP1A2). Therefore, caution is required if medicinal products that are metabolised predominantly by CYP1A2 (melatonin, xanthines such as caffeine, theophylline) are administered concomitantly. Co-administration may prolong the half-life of methoxsalen and result in prolonged photosensitivity.

Although methoxsalen has been shown to be capable of both induction and inhibition of hepatic enzymes, in humans it seems to act primarily as a potent inhibitor of microsomal oxidative metabolic processes. It is therefore to be expected that interactions will occur between methoxsalen and other medicinal products whose metabolism involves the cytochrome P450 system (particularly CYP1A2). The clearance rates of caffeine were markedly reduced after methoxsalen treatment. Both conjugated and unconjugated metabolites have been identified, but neither of them showed pharmacologically relevant activity.

Photosensitising agents
Caution is also required in patients taking cytotoxic or other photosensitising agents concomitantly: fluoroquinolones, furosemide, retinoids, sulfonylureas, anthralin, coal tar, griseofulvin, nalidixic acid, sulfonamides, tetracyclines, halogenated salicyl aniline derivatives, thiazides, phenothiazines, methylene blue, tolonium chloride, rose Bengal, methyl orange, oral coumarin anticoagulants.

4.6 Fertility, pregnancy and lactation

Both men and women treated with <[Invented name]> have to take adequate contraceptive precautions, both during and after completion of photopheresis therapy.

Pregnancy
To date, there are no or a limited amount of data from the use of methoxsalen in pregnant women.
Preclinical data indicate that methoxsalen may possibly damage the foetus when it is used in pregnant animals.
Therefore, <[Invented name]> is contraindicated in women who are or may become pregnant (see section 4.3).

Breast-feeding
It is not known whether methoxsalen is excreted in human milk, therefore <[Invented name]> is contraindicated during breast-feeding.

Fertility
No clinical fertility data are available.
Preclinical data indicate that long-term exposure to high-dosed oral psoralens may have negative effects on male and female fertility.

4.7 Effects on ability to drive and use machines

Because of the possibility of transient cardiovascular instability and the recommendation that following photopheresis patients wear sunglasses, patients should not drive or use machines immediately following photopheresis treatment.

4.8 Undesirable effects

During the course of the therapy, patients experienced mild and transient adverse events with extracorporeal use of methoxsalen, frequency of undesirable effects may decline and generally do not require discontinuation of the therapy.
Adverse events associated with extracorporeal administration of methoxsalen are as follow:

The frequencies used in the table below are the following:
Very common: ≥1/10
Common: ≥1/100 to <1/10
Uncommon: ≥1/1,000 to <1/100
Rare: ≥1/10,000 to <1/1,000
Very rare: <1/10,000
Frequency not known: frequency cannot be estimated from the available data

Body system	**Frequency**	**Adverse reaction(s)**
Infections and infestations	Common	Infections
Eye disorders	Frequency not known	Phototoxic reactions, e.g. cataract formation, chorioretinitis (see section 4.4).
Central nervous system	Frequency not known	Depression, dizziness, headache, insomnia, malaise, nervousness, vertigo
Vascular disorders	Common	Hypotension Edema
Gastrointestinal disorders	Common	Nausea Vomiting
Skin and subcutaneous tissue disorders	Frequency not known	Phototoxic reactions, e.g. pruritus or erythema (see section 4.4)
General disorders and	Frequency not	Fever (1 to 12 hours after therapy low

administration site conditions	known	grade fever may occur)
Injury, poisoning and procedural complications	Common	Venous access complication after repeated venipuncture

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Dangerous overdosage of extracorporeal methoxsalen is highly unlikely – to date, there are no known cases.
Acute toxicity of methoxsalen after a single oral administration of 850 mg has been reported. The toxicity was very low. Patient experienced nausea, vomiting and severe dizziness.
In the event of methoxsalen overdose, the patient should be kept in a darkened room for at least 24 hours.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antineoplastic and immunomodulating agents, others immunostimulants, ATC code: L03AX

Mechanism of action

Methoxsalen is a member of a family of photoactivated compounds (furocoumarin derivatives), which may inhibit DNA and RNA synthesis through formation of monofunctional or bifunctional thymine adducts, gene mutations, or sister chromatid exchanges. The cross-strand formed between DNA strands results in a halt in cell division, as well as oxidative damage to cytoplasmic organelles and cell membranes. These drugs are active only if the tissue containing the psoralen compound is exposed to ultraviolet A (UVA).
The general assumption is that the molecular processes which lead to apoptotic cell death involve the intercalating of methoxsalen into the double-stranded DNA molecule within the nucleus. The nucleic acid-furocoumarin complexes formed in this intercalation process involve weak bonding forces such as van der Waals' forces, hydrogen bonding and hydrophilic forces. These bonding forces are easily reversed and, in the absence of photoactivation, they are without pharmacological consequence. However, upon activation by absorption of UVA light, methoxsalen binds to the pyrimidine bases of the nucleic acid (thymine, cytosine and uracil) and forms covalent cross-links between the two DNA strands. The reaction occurs in a few microseconds, and when the radiation is turned off, the active substance returns to its inert form immediately.

Despite the safe and effective use of photopheresis, the precise mechanism of action continues to be explored. There is good evidence that photopheresis induces an immune-mediated response to the malignant T-cell clone The early observation that significant cutaneous and hematologic responses could be induced by monthly exposure of less than 10% of peripheral blood to UVA and methoxsalen lead to the assertion that extracorporeal photopheresis must be an immunomodulating procedure.
The proposed mechanism of action involves the following processes: (1) the induction of apoptosis of malignant T cells, (2) the conversion of circulating monocytes to immature dendritic cells (DCs), (3) the presentation of tumor-loaded DCs to cytotoxic T cells, and (4) expansion of a population of cytotoxic T cells against the malignant T-cell clone.

Pharmacodynamic effects
The formation of photoadducts results in the proliferative arrest of lymphocytes and, over a period of

about 72 hours, they die. This acute effect on the T-cell is probably a minor effect with regard to therapeutic efficacy. There is an increasingly large body of evidence suggesting that photopheresis may act as an immune-modulator leading to the augmentation of systemic anti-tumor responses.

Extracorporeal photochemotherapy (photopheresis) combines phototherapy with leukophoresis and is based on the DNA damaging effect of light combined with photoactivated methoxsalen on pathogenic T-lymphocytes.

Clinical efficacy and safety
A study evaluated the safety and efficacy of extracorporeal photopheresis in patients suffering from different stages of CTCL: 17 patients, 3 with erythroderma and 14 with plaque or tumor stages. Patients were treated predominantly with ECP alone; only a few patients received concomitant therapy. Partial responses were achieved not only in patients with early CTCL (stage Ib) but also in those with far progressed tumors (stage IVa). After treatment for 6 months partial responders showed an increase in the number of NK cells in their peripheral blood ($P < 0.01$). Overall, these results indicated that extracorporeal photopheresis is a safe and effective regimen for the treatment of all stages of CTCL.
One single-arm open label study was performed to evaluate the effectiveness of photopheresis in the treatment of the skin manifestations of Cutaneous T-Cell Lymphoma (CTCL).
In the study, 51 patients were treated with methoxsalen in conjunction with a photopheresis System, 33% reported an adequate clinical response, 15 of the 17 responses were seen within six months of treatment.
Overall skin scores were used in the clinical studies of extracorporeal photopheresis (ECP) to assess the patient's response to treatment. A 25% reduction in skin score maintained for four consecutive weeks was considered a successful response to photopheresis therapy.

5.2 Pharmacokinetic properties

Administration
Extracorporeal photopheresis is a process in which extracorporeal peripheral blood mononuclear cells are exposed to UVA radiation in the presence of methoxsalen. The treated lymphocytes are returned to the patient undergoing apoptosis over 48-72 hours. In an investigation conducted in 16 patients, the quantity of methoxsalen required for extracorporeal use was compared to the quantity of oral methoxsalen required in order to achieve similar levels of active substance in the leucocyte fraction. It was shown that for the extracorporeal procedure, between 1/250 and 1/500 of the oral quantity were used.
In a clinical study, methoxsalen level in plasma was measured 30 minutes after reinfusion of the photoactivated cells, concentration were less than 10ng/ml in 82% of the 754 samples measured with a mean plasma level of approximately 25 ng/ml.

Distribution
During extracorporeal photopheresis, the cellular uptake of methoxsalen showed that the equilibrium between cells and plasma is reached within 2 minutes.
Following topical application, methoxsalen penetrates rapidly into epidermis and dermis, and the high concentrations reached remain constant over a period of 16 h. The relative distribution volume ranges between 1 and 9 L/kg. In the studies on man 88-91% of the orally administered radioactive methoxsalen was found to be protein bound. This holds for a concentration range of 50-2000 ng equivalents of methoxsalen/ml plasma. These concentrations were obtained after therapeutic dosage.

Biotransformation
Methoxsalen has a serum t 1/2 of -1 hour, but the skin remains sensitive to light for 8-12 hours. The drug has a high but variable intrinsic metabolic clearance and is almost completely metabolised.
Methoxsalen is almost completely metabolised in the liver by hydroxylation and glucuronidation.

Elimination
Methoxsalen is extensively metabolized, and no unchanged drug is excreted in the urine. Serum elimination half-life is in the order of 0.5 to 2 hours.
Approximately 80% of the dose is excreted in the urine within 8 h. Other authors reported an elimination

to the extent of 90 % in man over a period of 12 h.

Specific pharmacokinetic studies in patients with hepatic or renal insufficiency, elderly patients or the paediatric population have not been conducted.

5.3 Preclinical safety data

Preclinical effects were observed only at exposures significantly in excess of the maximum human exposure indicating little relevance to clinical use.

Methoxsalen has been studied in mice by different routes of administration including skin application or intraperitoneal injection in combination with exposure to UVA.
In a developmental toxicity study, pregnant rabbits were given gavage doses of 40, 80, or 105 mg/kg/day of methoxsalen on gestational days 6–19. The results indicate the LOAEL for methoxsalen-induced maternal toxicity was 80 mg/kg/day. The developmental toxicity NOAEL was greater than or equal to 105 mg/kg. Thus methoxsalen, at doses which cause minor maternal toxicity, does not affect fetal growth, viability, or morphological development.
The lowest of these doses, 80 mg/kg/day, is over 4000 times greater than a single dose of <[Invented name]> on a mg/m^2 basis.
Methoxsalen has been shown to be a mutagen in *Salmonella*, and in rodent carcinogenicity studies positive results in *Salmonella* have been shown to correlate with the presence of tumors in rats.
In bacterial mutagenicity tests, methoxsalen produced a positive response in four strains of *Salmonella typhimurium* in the presence of S9.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Propylene Glycol
Sodium Chloride
Sodium Acetate Trihydrate
Ethanol 96%
Glacial Acetic Acid
Water for injections

6.2 Incompatibilities

Methoxsalen can sorb onto PVC and other synthetic materials.
Once <[Invented name]> solution is drawn into a plastic syringe it should be immediately injected into the photoactivation bag.
This medicinal product must not be mixed with other medicinal products or infusion solutions.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store in the original package in order to protect from light.
This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

Amber glass ampoules (type I), 5 ml
Pack size: pack of 5 ampoules

6.6 Special precautions for disposal

<[Invented name]> must not be diluted.
The content of the ampoule should be injected into the photopheresis system immediately after being drawn up into a syringe.
The contents of the ampoule must not be injected directly into patients.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

S.A.L.F. S.p.A. Laboratorio Farmacologico – Via Marconi, 2 – 24069 Cenate Sotto (BG)

8. MARKETING AUTHORISATION NUMBER(S)

<{Name of the Member State}> <{Name of the medicineal product}>
<{Name of the Member State}> <{Name of the medicineal product}>
<{Name of the Member State}> <{Name of the medicineal product}>
<{Name of the Member State}> <{Name of the medicineal product}>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: {DD month YYYY}

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}