SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Methoxsalen G.L. Pharma 20 micrograms/ml solution for blood fraction modification

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml solution contains 20 micrograms methoxsalen.
One 5 ml ampoule contains 100 micrograms methoxsalen.

Excipients with known effect: 10.4 mg ethanol 96%, 17.7 mg sodium per ampoule

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for blood fraction modification
Clear, colourless solution
pH 5.0 to 7.0

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Methoxsalen G.L. Pharma 20 micrograms/ml solution is indicated in adults for extracorporeal use in the palliative treatment of advanced stage cutaneous T-cell lymphoma in patients who have not been responsive to other forms of treatment.

4.2 Posology and method of administration

Posology

Adults
During each photopheresis treatment with methoxsalen, the dosage is calculated according to the treatment volume, using the formula below:

Treatment volume x 0.017 ml of Methoxsalen G.L. Pharma for each treatment

For example: Treatment volume = 240 ml x 0.017 = 4.1 ml of Methoxsalen G.L. Pharma

Paediatric population (under 18 years of age)
The safety and efficacy of Methoxsalen G.L. Pharma in children and adolescents have not been established for this indication.

Hepatic or renal impairment
Methoxsalen G.L. Pharma 20 micrograms/ml solution 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).

Method of administration
Extracorporeal use.

Note:
Extracorporeal photochemotherapy is to be carried out only by persons with special training and in institutions disposing of the suitable equipment for this treatment.

Psoralen and UV irradiation therapy should take place under constant supervision by a physician with the appropriate training.
The working instructions for the procedure (according to the company manufacturing the equipment in use and/or to recent guidelines) must be followed strictly.

The content of the ampoule must not be injected directly into the patient as there are no studies with direct injection of Methoxsalen G.L. Pharma 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, Methoxsalen G.L. Pharma is added, radiated wih UV light and then reinfused into the patient.

The following basic rules should be observed:
- The haematocrit of the separated blood fraction should not exceed 5%, in order not to block exposure to the UVA radiation and thus lower the efficacy of treatment.
- Before radiation with UVA light (in the radiation bag) heparin, isotonic saline solution and the prescribed amount of Methoxsalen G.L. Pharma are added to the leucocytes.
- The quantities collected for therapy may vary (from 120 to 540 ml) depending on body weight, blood volume and therapy method used (on-line or off-line method).
- During photoactivation the leucocyte-enriched blood is radiated with UVA light (1 to 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 15 to 20 minutes.
- The buffy coat collection cycle is repeated up to six times, and the complete photopheresis procedure lasts approximately 3 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 treatment on two successive days every 2 to 4 weeks. After that, two-day treatment cycles every 3 to 4 weeks are recommended.
It has been shown that higher treatment frequencies do not lead to better treatment results.
As soon as maximum treatment response is achieved, intervals should be gradually extended to 4 to 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 stabilised 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.

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 tumour (e.g. melanoma, basalioma)
- 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 disorder
- Leucocyte count above 25,000/mm³.

4.4 Special warnings and precautions for use

Extracorporeal photochemotherapy is to be carried out only by persons with special training and in institutions disposing of 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 of this type of therapy.

Methoxsalen G.L. Pharma should only be used *ex vivo* and is to be 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.

Hypotension
Transient hypotension may occur in some patients during therapy. In most patients it stays asymptomatic and disappears after reinfusion of the blood. Occasionally, normal saline solution must be infused during photopheresis to stabilise blood pressure. Patients regularly taking anti-hypertensives should wait with the intake until the end of the photopheresis procedure (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.

Formation of cataracts
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 (with Methoxsalen G.L. Pharma) 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 by 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 Methoxsalen G.L. Pharma 20 micrograms/ml solution is associated with a much lower systemic exposure to methoxsalen (more than 80 % of the blood samples taken 30 minutes after reinfusion of the photoactivated buffy coat exhibited methoxsalen levels < 10 ng/ml and the average methoxsalen concentration in plasma was about 25 ng/ml). 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.

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.
No specific information is available on the use of photopheresis with Methoxsalen G.L. Pharma in patients with hepatic impairment.

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
This medicinal product contains small amounts of ethanol (alcohol): At an assumed treatment volume of 240 ml the patient is exposed to 4.1 ml of Methoxsalen G.L. Pharma and therefore to 8.528 mg alcohol (2.08 mg alcohol/ml).
With extracorporeal administration systemic exposure is expected to be low, and clinical effects have not been observed yet. However, the prescribing physician should bear in mind possible interactions with other medicinal products. Special caution is advised in hepatic disease, alcoholism, epilepsy, brain injury or brain disease.

This medicinal product contains less than 1 mmol sodium (23 mg) per millilitre, that is to say essentially 'sodium-free'.

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 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 Methoxsalen G.L. Pharma have to use suitable methods of contraception, 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. Therefore, methoxsalen is contraindicated during pregnancy.
Preclinical data indicate that methoxsalen may possibly damage the foetus when it is used in pregnant animals.

Breast-feeding
It is not known whether methoxsalen is excreted in human milk, therefore it 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

As a result of the special mode of administration (extracorporeal use), transient cardiovascular instability may occur. In addition, patients should wear sunglasses following photopheresis treatment (see section 4.4). Therefore, patients should not drive or use machines immediately following photopheresis treatment.

4.8 Undesirable effects

The most commonly reported side effects with extracorporea use of methoxsalen were phototoxic reactions, nausea, vomiting, congestive heart failure and hypotension. During the course of therapy, the severity and frequency of undesirable effects may decline and generally do not require discontinuation of the therapy.

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
Not known: Frequency cannot be estimated from the available data

Common (≥ 1/100 to < 1/10)	**Not known** (Frequency cannot be estimated from the available data)
Infections and infestations	
Infections	
Eye disorders	
	Phototoxic reactions, e.g. cataract formation, chorioretinitis (see section 4.4)
Vascular disorders	
Hypotension Dizziness	
Gastrointestinal disorders	
Nausea Vomiting	
Skin and subcutaneous tissue disorders	
	Phototoxic reactions, e.g. pruritus or erythema (see

Common (≥ 1/100 to < 1/10)	**Not known** (Frequency cannot be estimated from the available data)
Infections and infestations	
Infections	
Eye disorders	
	Phototoxic reactions, e.g. cataract formation, chorioretinitis (see section 4.4)
Vascular disorders	
Hypotension Dizziness	
Gastrointestinal disorders	
Nausea Vomiting	
	section 4.4)
General disorders and administration site conditions	
	Fever (2 to 12 hours after therapy low grade fever may occur)
Injury, poisoning and procedural complications	
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 : Yellow Card Scheme

Website: www.mhra.gov.uk/yellowcard

4.9 Overdose

Dangerous overdosage of extracorporeal methoxsalen is highly unlikely – to date, there are no known cases.

With oral intoxication, the symptoms most likely to occur are nausea, intense vomiting and 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, immunostimulants, ATC code: L03AX

Mechanism of action
Methoxsalen is a photosensitising agent. Although photochemotherapy has been used clinically for many years, the mechanism by which the therapy is effective remains to be fully elucidated. 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 micro-seconds, and when the radiation is turned off, the active substance returns to its inert form immediately.

The mechanism by which the photopheresis procedure acts was investigated by observing certain proteins which induce apoptosis (*bcl-2 a*nd *fas*). Lymphocytes present in peripheral blood were isolated immediately before and 24 hours after treatment, and the numbers of *bcl-2* and *fas* were recorded in comparison to an untreated control group. It was shown that the portion of *fas*-proteins was significantly higher after treatment, whereas that of *bcl-2* remained unchanged. The photopheresis procedure was also shown to increase the portion of apoptotic cells in cultured lymphocytes. These apoptotic cells appear to be absorbed by dendritic cells and presented as antigens so that a specific cell-mediated immune response is triggered and put into operation immediately.
The exact mechanism has not been elucidated in detail.

Pharmakodynamic 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-tumour responses.

Clinical efficacy and safety
41 patients with various diseases (CTCL, GVHD, systemic sclerosis) had a total of 1,210 photopheresis treatments. The CTCL patients with erythroderma and intact immune competence were the ones who responded most favourably, but even advanced tumour-stage CTCL was treated successfully.

5.2 Pharmacokinetic properties

Administration
During photopheresis the whole-blood components are separated. Erythrocytes and excess plasma are reinfused into the patient immediately, while the buffy coat (leucocyte-enriched blood) and some plasma are collected, treated with methoxsalen, exposed to UVA light (320 to 400 nm) and then reinjected or reinfused into the patient.

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 technique, between 1/250 and 1/500 of the oral quantity were used.

Distribution and biotransformation
Plasma half-life is approximately 2 hours.
Methoxsalen is almost completely metabolised in the liver by hydroxylation and glucuronidation.

Elimination
The metabolites are eliminated predominantly via the kidneys. 90% of the dose administered is found in the urine after 6 to 8 hours.

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.

Chronic administration of 12 mg/kg daily in mice over 1 year has not yielded any toxic effects.

Chronic intraperitoneal administration of 4 mg methoxsalen in combination with UV light (320 to 400 nm) has led to toxic reactions of the skin and liver. Oculotoxic effects have been observed for methoxsalen in combination with UVA light.

The potential for phototoxicity has been extensively studied in animal models. Manifestations of phototoxic reactions have been identified in the skin and eye after oral dosing and in the liver after intraperitoneal dosing. Studies in humans have shown that phototoxic responses are unlikely to occur unless systemic exposure amounts to at least 30 ng/ml.

Daily doses between 15 and 150 mg/kg resulted in dose-dependent impairment of reproductivity in rats. Foetal growth, viability and morphological development were adversely affected.

Experimental studies have indicated that methoxsalen may increase susceptibility to skin carcinogenesis as a result of exposure to UV light. Methoxsalen is reported to have induced an increase in renal, subcutaneous and lung tumours in male rats after oral administration at doses of 37.5 and 75 mg/kg/day for up to two years.

Non-photoactivated methoxsalen has been shown to induce gene mutations in bacteria as well as chromosomal aberrations and sister chromatid exchanges in mammalian cells.

Based on its mechanism of action, the possibility of teratogenic or embryotoxic effects cannot be ruled out for methoxsalen.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Ethanol 96%
Water for injection

6.2 Incompatibilities

Methoxsalen can sorb onto PVC and other synthetic materials.
Once Methoxsalen G.L. Pharma 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

5 years

6.4 Special precautions for storage

Store in the original package in order to protect from light.

6.5 Nature and contents of container

Amber glass ampoules (type I), 5 ml
Pack size: packs of 5, 25, 50 and 5 x 25 ampoules (multipack)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Methoxsalen G.L. Pharma must not be diluted.
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

G.L. Pharma GmbH, Schlossplatz 1, 8502 Lannach, Austria

8. MARKETING AUTHORISATION NUMBER(S)

PL 21597/0027

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20/10/2019

10 DATE OF REVISION OF THE TEXT

20/10/2019