1. NAME OF THE MEDICINAL NEW CHEMICAL ENTITY (NCE)

The active pharmaceutical ingredient is:

ALUMINUM-PHTHALOCYANINE DISULFONATE SODIUM (ALPCS2)

The NCE consists of the active pharmaceutical ingredient in colloidal suspension

ALUMINUM-PHTHALOCYANINE DISULFONATE SODIUM (ALPCS2) FLUID 0.1 MG/ML IN LIPOSOMAL SUSPENSION

The medicine is a blue-green liposomal suspension of phthalocyanine sensitiser available in three forms

a) Fluid for Infusion
b) Fluid to be added to a fatty drink such as chocolate milk
c) Gel for topical administration

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The suspension contains 0.1 mg of aluminium-phthalocyanine disulfonate sodium per ml

Excipients make it a liposomal suspension. Phthalocyanine is brought into a liposomal suspension with polyethylenic and phosphatidylcholine molecules, see section 6.1

3. PHARMACEUTICAL FORM

Blue-green suspension for infusion, oral ingestion or topical application

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATION

Phthalocyanine sensitiser is indicated as a follow up consolidation treatment for patients with advanced cancer failing regular therapies or unlikely to be cured by regular therapies.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

The suspension must only be administered under expert supervision.

The phthalocyanine sensitiser must be activated by light.

POSOLOGY

The dose of sensitiser for intravenous and oral use is 0.1 mg/kg body weight. The dose for gel application is liberal.

The dose of light has not yet been defined

Paediatric population

There has been no reported experience in children

METHOD OF ADMINISTRATION

The blue-green colour of the suspension is clear. Clarity should be checked against a light for particulates. The liposomal suspension can be diluted in sodium chloride or other aqueous suspension. With topical application the phthalocyanine sensitiser is absorbed through the skin into the lymphatic system. For intravenous use the fluid should be warmed to 40^{o} Centigrade. Light activation can begin

after the sensitiser has been given. Wherever possible, the illuminated area must extend beyond the tumour margin by a distance of 0.5 cm.

For topical administration an area of the skin well away from the tumour must be selected. The skin should first be washed with soap. The area of administration should be dried with a hairdryer. The patient is not allowed to wash the skin area for three days. The applicant should wear plastic gloves to protect administration to the hands.

The medicine should be shielded from light

4.3 CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Tumours known to be eroding into a major blood vessel.
- A planned surgical procedure within the next 90 days.
- Co-existing ophthalmic disease likely to require slit-lamp examination within the next 90 days.
- Pregnancy

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

At this date no patients have been treated with phthalocyanine as a follow up consolidation treatment. Therefore, no safety profile is defined. In the process of scaling up from rodent experience a few humans have been treated with phthalocyanine. We warn of the likelihood of very serious side effects that are hitherto unknown.

The phthalocyanine sensitiser may provoke a little tingling of the tongue, gums, fingers and sometimes also nausea. After 12 hours up to 3 days, most side effects disappear.

All patients will become temporarily photosensitive to sunlight. Precautions must be taken to avoid exposure of skin and eyes to direct sunlight or bright indoor light as long as the treatment is ongoing. Skin photosensitivity reactions are caused by visible light; therefore ultraviolet sunscreens provide no protection. It is important that patients are re-introduced to normal light gradually in order to reduce light when symptoms occur. For 12 months following treatment prolonged direct sunlight exposure shall be avoided. As a precautionary measure, if prolonged outdoor activity is planned, the body should be protected by wearing a hat, a long sleeved, coloured shirt and trousers. Be aware that most of the toxicities associated with are local effects seen as consequence of light-activation.

Skin reactions, typically a burning sensation, limit the illumination time. Care must be taken to ensure that no area of skin tissue receives more than a tolerable light dose. Tissue outside the target area must be shielded completely to avoid unnecessary skin reactions by scattered or reflected light. Whenever severe skin reactions occur, corticosteroids should be considered.

Illumination of airways may lead to local inflammation and oedema. The resulting complications, i.e. dyspnoea or even airway obstruction leading to, for instance, intubation or tracheotomy, should be anticipated. Prophylactic treatment with corticosteroids should be considered.

Pain in the cancer may require the use of NSAIDs or opiate analgesics for weeks following treatment. When the immune effects are too strong, corticosteroids should be considered.

Most of the toxicity associated with light therapy are local effects seen as consequence of immune reaction against the tumour. There is an acute inflammatory response at the illuminated site that is immediately followed by a chronic inflammatory response at all sites where tumour is present. That reaction may increase in strength for weeks without further light. The response is commonly associated

with oedema and pain, followed by swelling of the tumour. Adverse reactions such as cholangitis, cholecystitis, liver abscess and oesophageal perforation may occur after the light has been applied to malignant strictures. Similarly, inflammation and obstruction may be anticipated in adenocarcinoma of the lung, etcetera. There may be a risk of damage of the surrounding area following light treatment. The patient may experience nausea when abdominal cancer is cleared. The patient may, for a period require feeding through an enteral tube or a parenteral line.

Serious side effects should be controlled with drugs such as corticosteroids that suppress the immune reaction. This may also be indicated when the immune reaction of the body against the cancer is too strong and causes oedema of the cancer in an area of the body where this may become dangerous, such as the brain, the lung, or the liver.

Before repeated doses are used, chelation must be administered. Without chelation there will be accumulation of the sensitiser seen as a blue colouration of the skin and/or dizziness, nightmares or restlessness.

When the immune system continually attacks the cancer, it will cause significant swelling. The swelling is the immune system causing inflammation/oedema of the cancer. The larger the cancer, the more difficult it is for the healing process to clear. When cancer marker measures such as PSA start to fall back, the cancer is in regression. When PSA measures become normal a patient can elect to have a PET-CT scan to confirm the complete regression.

Unplanned or emergency surgical procedures must be undertaken when necessary.

Precautions must be taken to avoid direct illumination of the patient with surgical lamps. The use of headlamps is recommended instead. Some pulse oximeters may produce light of a wavelength close to that used for the photo-activation of the sensitiser. Oximeters must be repositioned at least every 10-15 minutes to avoid the risk of local skin burns. Pain, other than injection site pain, listed in section 4.8 may require the use of NSAIDs or opiate analgesics for a short time following treatment. Pain may occur after illumination. Illumination of airways may lead to local inflammation and oedema. The resulting complications (i.e. dyspnoea or even airway obstruction leading to, for instance, intubation or tracheotomy) should be anticipated. Prophylactic treatment with corticosteroids should be considered.

Time after phthalocyanine sensitiser administration

Immediately after administration and continuing for 3 days the urine may colour. The colour may be blue-green, which is the colour of aluminum-phthalocyanine disulfonate sodium.

After application of light has ended, subjects should get proper detoxification with chelation and full spectral mineral replacement for a year. In the meantime burns from sunlight should be prevented. During light treatment subjects should stay indoors in a darkened room: the curtains drawn and using light bulbs of 60 W or less. They should avoid exposure to direct sunlight. When detoxification has started the subject can gradually return to normal indoor lighting. They should be reminded to avoid direct sunlight coming through the window or direct light from household appliances such as reading lamps. They may watch television and go outdoors after dusk. If it is absolutely necessary to go outdoors during the hours of daylight, they must be careful to cover up including face and hands and wear dark glasses. The type of clothes are: • Wide-brimmed hat: for head, neck, nose and ears. • Scarf: for head and neck. • Sunglasses with side panels: for eyes and skin around eyes. • Long sleeved top: for upper body/arms. • Long trousers: for lower body/legs. • Gloves: for hands, wrist and fingers. • Socks: for feet and ankles. • Closed shoes: for feet. • Thin clothing is useless, because it will not protect from strong light. They should wear dark, closely woven clothing. • If exposure to light by mistake occurs, it may

result in a prickly or burning feeling on the skin. The subject should get out of the light immediately. The eyes may be very sensitive to bright lights. They may get eye pain or headache when lights are switched on. If this problem occurs, they should wear dark glasses.

After light treatment, detoxification should be intense with daily chelation capsules. When detoxification has progressed beyond a week and there are no undesired side effects, the subject can begin to go outside during daylight hours. They should stay in shaded areas or go out when it is cloudy and continue to wear dark, closely woven clothing. They should start with 10-15 minutes outdoors. If they do not see any skin redness in the next 24 hours, subjects can gradually increase time outdoors.

They should avoid direct sunlight or strong indoor lighting and stay in the shade. After a month of detoxification the sensitivity to light may seems to be gradually getting back to normal. For this they should be warned, because it is partially due to avoidance. Subjects must test their sensitivity carefully by exposing the back of their hand to the sun for 5 minutes and wait 24 hours to see if there is any redness. If there is redness, the subject should avoid direct sunlight for another week and then repeat the test. If there is no redness, the subject can gradually increase exposure to sunlight day by day. Most people will be able to go back to their normal routine after a month of detoxification, others may take longer. Do not stay in the sunlight for periods of more than 15 minutes in the first year after being treated.

After a month of daily taking detoxification capsules, detoxification should be continued on a once a weekly basis for at least a year. If at any time the subject notices a prickly or burning feeling or see skin reddening after exposure to sun, he should wait until this disappears before exposing the skin to light for this length of time again.

For a month following phthalocyanine sensitiser treatment, avoid eye tests that use bright lights.

For 12 months following phthalocyanine sensitiser treatment, avoid UV tanning beds. Do not sunbathe.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

There is potential for exacerbation of skin photosensitivity if phthalocyanine sensitiser is used with other photosensitising active substances. No interactions have been observed.

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy

There are no data from the use of phthalocyanine sensitiser in pregnant women. Phthalocyanine sensitiser should not be used during pregnancy unless the clinical condition of the woman requires treatment. Women of childbearing potential have to use effective contraception during and up to 3 months after treatment.

Breast-feeding

A risk to the new-borns/infants cannot be excluded. Breast-feeding should be discontinued for at least a year following phthalocyanine sensitiser use.

Fertility

The effects of phthalocyanine sensitiser on fertility in humans have not been studied.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

On the basis of the pharmacodynamic profile, phthalocyanine sensitiser is presumed to be safe or unlikely to produce an effect on the ability to drive. To avoid photosensitivity problems, it is advised not to drive during the treatment and the first week thereafter, and to use machines only if it is practical to do so under subdued lighting conditions according to the recommended lighting precautions (see section 4.4). Driving and use of machines may resume under normal lighting or daylight conditions once photosensitivity has been shown to have subsided.

4.8 UNDESIRABLE EFFECTS

At this date no patients have been treated with phthalocyanine as a follow up consolidation treatment. Therefore, no safety profile is defined. In the process of scaling up from rodent experience a few humans have been treated with phthalocyanine.

All patients who receive phthalocyanine sensitiser will become temporarily sensitive to light and must be instructed to observe precautions to avoid sunlight and bright indoor light. Regarding the expected adverse reactions, skin reactions and administration site conditions are the most likely. Most of the expected toxicities associated with the therapy are local effects seen in the region of illumination and occasionally in surrounding tissues. They are an effect of the lighting and consist of acute local tissue inflammatory response induced by light-activation and commonly include oedema and pain. In the next hours, possibly days to even weeks a generalized immune reaction against the cancer may occur. Most of the toxicities are likely to be associated with the immune reaction against the cancer. Immune reaction to the cancer may have uncommon systematic effects such as asthma when lung metastasis is present, whereby corticosteroids should always be considered.

4.9 OVERDOSE

In the event of an overdose of sensitiser, light will result in a more intense immune reaction than would be expected with the recommended dose. Illumination of the tumour should only be carried out if the potential benefit justifies the potential risk of excessive reaction. Chelation may be considered first. The adverse reactions associated with overdose would be expected to be limited to photosensitivity.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antineoplastic agents, other antineoplastic agents, ATC code: L01XD05. phthalocyanine is a sensitising agent used in the light-activated immune-therapy of tumours. The pharmacodynamical hypothesis of light therapy with phthalocyanine sensitiser is that the host immune system is educated to recognise the cancer.

5.2 PHARMACOKINETIC PROPERTIES

Phthalocyanine liposomal suspension is designed to circulate undisturbed for days. No pharmacokinetic studies have been done.

5.3 PRECLINICAL SAFETY DATA

In repeated dose toxicity studies in rodents, the main undesirable effects of phthalocyanine were phototoxicity and adverse injection site reactions. Local irritancy of phthalocyanine suspension for injection after intravenous administration occurred with all doses. No other signs of toxicity were found, while rodents were treated with doses exceeding those of humans. Genotoxicity has not been studied.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Polyethylenic Molecules; Phosphatidylcholine Molecules

6.2 INCOMPATIBILITIES

In the absence of compatibility studies, this NCE must not be mixed with other medicinal products. Phthalocyanine sensitiser can be diluted with aqueous suspensions.

6.3 SHELF LIFE

The shelf life has not been tested. Once opened, the suspension must be used immediately.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 25° C.

Store in the original package to protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Bags are prepared for immediate use.

Type I amber glass vials with a bromobutyl elastomer stopper and aluminium seal for longer term storage. Each pack contains 1 vial.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Appropriate precaution must be taken when handling this medicinal NCE. It has been shown that phthalocyanine sensitiser is non-irritant. Each vial represents a single dose and any unused suspension must be discarded.

Phthalocyanine sensitiser is photosensitive. Once removed from its packaging it must be administered immediately.

Where delay is unavoidable, the suspension must be protected from light.

Any unused medicinal NCE or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Not applicable.

8. MARKETING AUTHORISATION NUMBER(S)

No market authorisation has been obtained.

Intellectual properties of the NCE are owned by:

Hugo Intellectual Properties BV
The Netherlands

9. REGULATORY STATUS

The regulatory status is that phthalocyanine-aluminium is registered in Russia.

10. DATE OF REVISION OF THE TEXT

24 April 2018