ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

TOOKAD 183 mg powder for solution for injection
TOOKAD 366 mg powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TOOKAD 183 mg powder for solution for injection
Each vial contains 183 mg of padeliporfin (as di-potassium salt).

TOOKAD 366 mg powder for solution for injection
Each vial contains 366 mg of padeliporfin (as di-potassium salt).

1 mL of reconstituted solution contains 9.15 mg of padeliporfin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection. The powder is a dark lyophilisate.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TOOKAD is indicated as monotherapy for adult patients with previously untreated, unilateral, low-risk, adenocarcinoma of the prostate with a life expectancy ≥ 10 years and:
- Clinical stage T1c or T2a,
- Gleason Score ≤ 6, based on high-resolution biopsy strategies,
- PSA ≤ 10 ng/mL,
- 3 positive cancer cores with a maximum cancer core length of 5 mm in any one core or 1-2 positive cancer cores with ≥ 50 % cancer involvement in any one core or a PSA density ≥ 0.15 ng/mL/cm^3.

4.2 Posology and method of administration

TOOKAD is restricted to hospital use only. It should only be used by personnel trained in the Vascular-Targeted Photodynamic therapy (VTP) procedure.

Posology
The recommended posology of TOOKAD is one single dose of 3.66 mg/kg of padeliporfin.

TOOKAD is administered as part of focal VTP. The VTP procedure is performed under general anaesthetic after rectal preparation. Prophylactic antibiotics and alpha-blockers may be prescribed at the physician's discretion.
Retreatment of the same lobe or sequential treatment of the contralateral lobe of the prostate are not recommended (see section 4.4).

Special populations

Hepatic impairment
No data are available in patients with hepatic impairment. Exposure to padeliporfin is expected to be increased and/or prolonged in patients with hepatic impairment. No specific dosage recommendation can be given. TOOKAD should be used with caution in patients with severe hepatic impairment.

TOOKAD is contraindicated in patients who have been diagnosed with cholestasis (see section 4.3).

Renal impairment
There is minimal renal excretion of TOOKAD so no adjustment in dose is required in patients with renal impairment.
This medicinal product contains potassium. This should be taken into consideration (see section 4.4).

Elderly
No specific posology adjustment is necessary in this population (see section 5.2).

Paediatric population
There is no relevant use of TOOKAD in the paediatric population in the treatment of low-risk localised prostate cancer.

Method of administration
TOOKAD is for intravenous use. For instructions on reconstitution of TOOKAD before administration, see section 6.6.

Illumination for photoactivation of TOOKAD
The solution is administered by intravenous injection over 10 minutes. Then the prostate is illuminated immediately for 22 minutes 15 seconds by laser light at 753 nm delivered via interstitial optical fibres from a laser device at a power of 150 mW/cm of fibre, delivering an energy of 200 J/cm.
Planning of optical fibre positioning should be performed at the beginning of the procedure using the treatment guidance software. During the procedure, the number and the length of the optical fibres are selected depending on the shape and the size of the prostate and the optical fibres are positioned transperineally into the prostate gland under ultrasound guidance to achieve a Light Density Index (LDI) ≥ 1 in the targeted tissue. Treatment should not be undertaken in patients where an LDI ≥ 1 cannot be achieved (see section 5.1).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Any previous prostatic interventions where the internal urinary sphincter may have been damaged, including trans-urethral resection of the prostate (TURP) for benign prostatic hypertrophy.

Current or prior treatment for prostate cancer.

Patients who have been diagnosed with cholestasis.

Current exacerbation of rectal inflammatory bowel disease (see section 4.4).

Any medical condition that precludes the administration of a general anaesthetic or invasive procedures.

4.4 Special warnings and precautions for use

Tumour localisation
Before treatment, the tumour must be accurately located and confirmed as unilateral using high-resolution biopsy strategies based on current best practice, such as multi-parametric MRI-based strategies or template-based biopsy procedures.

Simultaneous treatment of both prostate lobes was associated with an inferior outcome in clinical trials and should not be performed.
Insufficient patients underwent retreatment of the ipsilateral lobe or sequential treatment of the contralateral lobe to determine the efficacy and safety of a second TOOKAD-VTP procedure.

Follow-up post TOOKAD-VTP
There is limited biopsy data beyond 2 years after TOOKAD treatment, so long-term efficacy has not been determined. Residual tumour has been found on follow-up biopsy of the treated lobe at 12 and 24 months, usually outside of the treated volume, but occasionally within the area of necrosis.

There is limited data on long-term outcomes and on potential consequences of post-TOOKAD local scarring in case of disease progression.

At present TOOKAD-VTP has been shown to defer the need for radical therapy and its associated toxicity. Longer follow-up will be required to determine whether TOOKAD-VTP will be curative in a proportion of patients.

Following TOOKAD VTP, patients should undergo digital rectal examination (DRE) and have their serum PSA monitored, including an assessment of PSA dynamics (PSA doubling time and PSA velocity). PSA should be tested every 3 months for first 2 years post VTP and every 6-months thereafter in order to assess PSA dynamics (PSA Doubling Time (DT), PSA velocity). Digital Rectal Examination (DRE) is recommended to be performed at least once a year and more often if clinically justified.Routine biopsy is recommended at 2-4 years and 7 years post VTP, with additional biopsies based on clinical/ PSA assessment. mpMRI may be used to improve the decision making but not, at present, to replace biopsy. In case of positive biopsies, patients who exceed the threshold for low risk disease (i.e. have GS > 6, > 3 positive cores or any single core length > 5mm) should receive a treatment recommendation for radical therapy.

Radical therapy post VTP procedure
The safety and efficacy of subsequent radical therapy (surgery or radiotherapy) is uncertain. Limited information is available regarding the safety and efficacy of radical prostatectomy after TOOKAD-VTP. In small surgical series, there have been reports of T3 tumours, positive margins and impotence. In the 24 months of the pivotal European Phase III study, no patients underwent radical radiotherapy post TOOKAD-VTP.

Photosensitivity
There is a risk of skin and eye photosensitivity with exposure to light post TOOKAD-VTP.

It is important that all patients follow the light precautions below for 48 hours post-procedure to minimize the risk of damage to the skin and eyes.

Patients should avoid exposure to direct sunlight (including through windows) and all bright light sources, both indoors and outdoors. This includes sunbeds, bright computer monitor screens and medical examination lights, such as ophthalmoscopes, otoscopes and endoscopy equipment, for 48 hours following the VTP procedure.

Sunscreen creams do not protect against near infra-red light and, therefore, do not provide adequate protection.

If the patient reports discomfort to the skin or eyes during hospitalisation, reduce the level of lighting and take extra care to shield the patient from artificial and natural light.

First 12 hours after VTP procedure
The patient should wear protective goggles and be kept under medical surveillance for at least 6 hours in a room with dimmed light.

The patient may be discharged in the evening of the same day at the physician's discretion.

The patient must stay in a dimmed light environment without any direct exposure of the skin and the eyes to daylight. The patient may only use incandescent light bulbs with a maximum power of 60 watts or equivalent (i.e. 6 watts for LED lights, 12 watts for fluorescent low-energy lights).

The patient may watch television from a distance of 2 metres and, from 6 hours onwards, may use electronic devices such as smartphones, tablets and computers. If the patient must go outdoors during daylight hours, he should wear protective clothes and high protection goggles to shield his skin and eyes.

12-48 hours after VTP procedure
The patient may go outdoors during daylight hours but only in shaded areas or when it is overcast. He should wear dark clothes and take care when exposing hands and face to the sun.

The patient can return to normal activity and tolerate direct sunlight 48 hours after the procedure.

No patients with photosensitive dermatitis, skin conditions such as porphyria or a history of sensitivity to sunlight have received TOOKAD in clinical studies. However, the short duration of action of TOOKAD means that the risk of enhanced phototoxicity is expected to be low provided these patients strictly follow the precautions against light exposure.

There could be an additional risk of eye photosensitivity in patients who have received intra-occular anti-VEGF therapy. Patients who have received prior VEGF therapy should take particular care to protect the eyes from light for 48 hours post TOOKAD injection. Concomitant use of systemic VEGF inhibitors is not recommended with TOOKAD.

See section 4.5 for interactions with photosensitizing medicinal products.

Erectile dysfunction
Erectile dysfunction may occur even if radical prostatectomy is avoided.
Some degree of erectile dysfunction is possible soon after the procedure and may last for more than 6 months (see section 4.8).

Extraprostatic necrosis
There may be extraprostatic necrosis in the peri-prostatic fat not associated with clinical symptoms.

Excessive extraprostatic necrosis occurred as a result of incorrect calibration of the laser or placement of the light fibres (see section 4.8). In consequence there is a potential risk of damage to adjacent structures, such as the bladder and/or rectum, and development of a recto-urethral or external fistula. A urinary fistula has occurred in one case due to incorrect fibre placement.

The equipment should be carefully calibrated and use the treatment guidance software to reduce the risk of clinically significant extraprostatic necrosis.

Urinary retention/urethral stricture
Patients with a history of urethral stricture or with urinary flow problems may be at increased risk of poor flow and urinary retention post the TOOKAD-VTP procedure. Urinary retention immediately post procedure has been attributed to transient prostatic oedema and generally only short term recatheterisation was required.

Poor urinary flow due to urethral stricture developed some months post procedure. In certain cases, the bulbar location suggested that the stenosis was caused by urinary catheterisation. In other cases, urethral stenosis may have been a late consequence of TOOKAD-VTP induced necrosis.

Although they were excluded from the clinical trials, there is a potential risk of increased stenosis post the TOOKAD-VTP procedure in patients with pre-existing stenosis (see section 4.8).

Urinary incontinence
The risk of sphincter damage can be minimised by careful planning of the fibre placement using the treatment guidance software. Severe long-term urinary incontinence was observed in a patient who underwent a previous transurethral prostatectomy (TURP). This event was not considered to be related to a faulty procedure but rather the pre-existing damage to the internal urethral sphincter from the TURP. The TOOKAD-VTP procedure is contraindicated in patients with any previous prostatic interventions where the internal urinary sphincter may have been damaged, including transurethral resection of the prostate (TURP) for benign prostatic hypertrophy (see section 4.3).

Inflammatory bowel disease
TOOKAD-VTP should only be administered after careful clinical evaluation, to patients with a history of active rectal inflammatory bowel disease or any condition that may increase the risk of recto-urethral fistula formation (see section 4.3).

Use in patients with abnormal clotting
Patients with abnormal clotting may develop excessive bleeding due to the insertion of the needles required to position the light fibres. This may also cause bruising, haematuria and/or local pain. It is not expected that a delay in clotting will reduce the effectiveness of the TOOKAD-VTP treatment ; however, it is recommended that drugs that affect clotting are stopped prior to and for the immediate period following the VTP procedure (see section 4.5).

Use in patients on a controlled potassium diet
This medicinal product contains potassium and in general the dose (3.66 mg/kg) will be less than 1 mmol (39 mg) i.e. essentially 'potassium free'. However, this will be exceeded in patients heavier than 115 kg. This should be taken into consideration in patients with reduced kidney function or patients on a controlled potassium diet where a rise in serum potassium would be considered detrimental (see section 4.2).

4.5 Interaction with other medicinal products and other forms of interaction

OATP1B1 and OATP1B3 transporters
In vitro studies predict that TOOKAD at therapeutic concentrations is unlikely to inhibit cytochrome P450 enzymes but could inhibit OATP1B1 and OATP1B3 transporters (see section 5.2).

The magnitude of interaction has not been investigated clinically but a transient increase in the plasma concentration of co-administered substrates of OATP1B1 and OATP1B3 cannot be ruled out. The use of medicinal products that are substrates of OATP1B1 or OATP1B3 (repaglinide, atorvastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin, bosentan, glyburide) for which concentration-dependent serious adverse events have been observed should be avoided on the day of TOOKAD infusion and for at least 24 hours after administration. Co-administration should be done with caution and close monitoring is recommended.

Photosensitisers
Medicinal products which have potential photosensitising effects (such as tetracyclines, sulphonamides, quinolones, phenothiazines, sulfonylurea hypoglycaemic agents, thiazide diuretics, griseofulvin or amiodarone) should be stopped at least 10 days before the procedure with TOOKAD and for at least 3 days after the procedure or replaced by other treatments without photosensitizing properties. If it is not possible to stop a photosensitising medicinal product (such as amiodarone), the patient should be advised that increased sensitivity to sunlight may occur and they may need to protect themselves from direct light exposure for a longer period (see section 4.2).

Anticoagulants and antiplatelet agents
Anticoagulant medicinal products and those that decrease platelet aggregation (e.g. acetylsalicylic acid) should be stopped at least 10 days before the procedure with TOOKAD. Medicinal products that prevent or reduce platelet aggregation should not be started for at least 3 days after the procedure.

4.6 Fertility, pregnancy and lactation

Contraception
If the patient is sexually active with women who are capable of getting pregnant, he and/or his partner should use an effective form of birth control to prevent getting pregnant during a period of 90 days after the VTP procedure.

Pregnancy and breast-feeding
TOOKAD is not indicated for the treatment of women.

Fertility
Padeliporfin has not been tested for reproductive toxicity and fertility.
However, all stages of spermatogenesis have been observed in animal. Minimal seminiferous epithelial degeneration was also recorded in one high-dose male with vacuolation. All these changes were considered to be incidental and probably related to the intravenous administration procedure.

4.7 Effects on ability to drive and use machines

TOOKAD has no influence on the ability to drive or use machines. However, as the procedure includes general anaesthesia, patients should not perform complex tasks like driving or using machines until 24 hours after a general anaesthetic is employed.

4.8 Undesirable effects

Summary of the safety profile
The most frequently reported adverse reactions in the Phase II and III clinical studies were urinary and reproductive system disorders: dysuria (25.1 %), erectile dysfunction (21.1 %), haematuria (19.6 %), perineal pain/haematoma (15.3 %), urinary retention (13.3 %), micturition urgency (9.0 %), pollakiuria (7.3 %), urinary tract infection (5.5 %), incontinence (5.3 %) and ejaculation failure (5.0 %).

Unspecific adverse events probably linked to the general anaesthesia were also observed: transient global amnesia, bradycardia, sinus arrhythmia, atrial fibrillation, hypotension, bronchospasm, pharyngeal inflammation, respiratory tract congestion, nausea, vomiting, constipation, pyrexia, procedural hypotension. Some cases of hepatotoxicity (1.5 %), such as elevation of transaminases, were also reported. All of them were mild in intensity.

Tabulated list of adverse reactions
Adverse reactions reported are listed below in Table 1 by organ class and frequency. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100).

Table 1: Summary of adverse reactions considered related to TOOKAD and/or the study device and/or the study procedure in the pooled safety analysis (N=398)

System Organ Class	Frequency	Adverse reaction
Infections and infestations	Common	Genito-urinary tract infection[1]
	Uncommon	Prostatic abscess
Psychiatric disorders	Uncommon	Libido decreased
		Affective disorder
		Encopresis
Nervous system disorders	Uncommon	Headache
		Dizziness
		Sciatica
		Sensory disturbance
		Formication
Eye disorders	Uncommon	Eye irritation
		Photophobia
Vascular disorders	Common	Haematoma
		Hypertension
Respiratory, thoracic and mediastinal disorders	Uncommon	Exertional dyspnoea
Gastrointestinal disorders	Common	Haemorrhoids
		Anorectal discomfort[2]
		Abdominal pain
		Rectal haemorrhage[3]
	Uncommon	Abdominal discomfort
		Abnormal faeces
		Diarrhoea
Hepatobiliary disorders	Common	Hepatotoxicity[4]
Skin and subcutaneous tissue disorders	Common	Ecchymosis
	Uncommon	Rash
		Erythema
		Dry skin
		Pruritus
		Skin depigmentation
		Skin reaction
Muscular and connective tissue disorders	Common	Back pain[5]
	Uncommon	Groin pain
		Muscle haemorrhage
		Haemarthrosis
		Musculoskeletal pain
		Pain in extremity
Renal and urinary disorders	Very common	Urinary retention
		Haematuria
		Dysuria[6]
		Micturition disorders[7]
	Common	Urethral stenosis
		Urinary incontinence[8]
	Uncommon	Ureteric haemorrhage
		Urethral haemorrhage
		Urinary tract disorders
Reproductive system and breast disorders	Very common	Perineal pain[9]
		Male sexual dysfunction[10]
	Common	Prostatitis
		Genital pain[11]
		Prostatic pain[12]

System Organ Class	Frequency	Adverse reaction
		Haematospermia
	Uncommon	Genital haemorrhage
		Penile swelling[13]
		Prostatic haemorrhage
		Testicular swelling
General disorders and administration site conditions	Common	Fatigue
	Uncommon	Asthenia
		Catheter site pain
		Laser device failure
		Infusion site bruising
		Nodule
		Pain
		Application site erythema
Investigations	Common	Abnormal clotting[14]
	Uncommon	Blood lactate dehydrogenase increased
		Blood triglyceride increased
		Gamma-glutamyltransferase increased
		Blood cholesterol increased
		Blood creatine phosphokinase increased
		Blood potassium decreased
		Low density lipoprotein increased
		Neutrophil count increased
		PSA increased
		Weight decreased
		White blood cell count increased
Injury, poisoning and procedural complications	Common	Perineal injury[15]
	Uncommon	Surgical procedure repeated
		Contusion
		Post-procedural urine leak
		Procedural pain
		Post-procedural discharge
		Fall

The following terms represent a group of related events that describes a medical condition rather than a single event.

1 Genito-urinary tract infection (urinary tract infection, orchitis, epididymitis, cystitis).

2 Anorectal discomfort (proctalgia, rectal tenesmus).

3 Rectal haemorrhage (anal haemorrhage).

4 Hepatotoxicity (alanine aminotransferase increased, aspartate aminotransferase increased).

5 Back pain (intervertebral disc protrusion).

6 Dysuria (bladder pain, bladder spasm, hypertonic bladder, urethral spasm, urinary tract pain).

7 Micturition disorders (micturition urgency, pollakiuria, nocturia, urine flow decreased, urinary straining).

8 Urinary incontinence (urge incontinence, incontinence, stress urinary incontinence).

9 Perineal pain (pelvic pain).

10 Male sexual dysfunction (erectile dysfunction, ejaculation failure, dyspareunia, ejaculation disorder, hypospermia, painful ejaculation, retrograde ejaculation, sexual dysfunction, semen volume decreased).

11 Genital pain (penile pain, testicular pain, scrotal pain, non-infective orchitis, spermatic cord inflammation, genital contusion).

12 Prostatic pain (prostatism, prostatic disorders, prostatic fibrosis).

13 Penile swelling (balanoposthitis).

14 Abnormal clotting (fibrin D dimer increased, aPTT prolonged, INR increased).

15 Perineal injury (post-procedural haematoma, necrosis, perineal haematoma, pelvic haematoma).

Description of selected adverse reactions

Erectile dysfunction

In the Phase III European study, 60 (30.5 %) of patients in the TOOKAD-VTP arm experienced erectile dysfunction and 16 (8.1 %) experienced ejaculation failure. 53 (26.9 %) patients experienced erectile dysfunction for more than 6 months, including 34 (17.3 %) patients in whom the erectile dysfunction had not resolved at the end of the study. When the analysis was restricted to patients that underwent unilateral VTP, 33 (16.8 %) patients experienced erectile dysfunction for more than 6 months, including 17 (8.6 %) patients in whom the erectile dysfunction had not resolved at the end of the study.

Urinary retention

In the Phase III European study, 30 (15.2 %) patients experienced urinary retention. The median time to onset of urinary retention was 3 days (1-417). The median duration was 10 days (1-344).

Genito-urinary infections

The most common infections are orchitis, epididymitis and urinary tract infections including cystitis. In the Phase III European study, 20 (10.2 %) patients in the TOOKAD-VTP arm experienced genito-urinary infection. In 5 (2.5 %) patients, the infection was considered serious. The median time to onset of genito-urinary infections was 22.5 days (4-360). The median duration was 21 days (4-197).

Urinary incontinence

In the Phase III European study, 25 (12.7 %) patients experienced urinary incontinence (including incontinence, stress urinary incontinence and urge incontinence). The median time to onset of urinary incontinence was 4 days (1-142). In 18 patients the adverse event resolved with a median duration of 63.5 days (1-360), and the adverse event was still ongoing at the end of the study for 7 patients. Only 1 (0.5 %) patient had a severe (Grade 3) urinary incontinence. None of these patients required an operation for incontinence.

Perineal injury, perineal pain and prostatitis

Perineal injury and perineal pain occurred in 46 (23.4 %) patients in the controlled Phase III European study. In some cases pain relief was required for perineal pain or anorectal discomfort. One patient had Grade 3 perineal pain that started 35 weeks after the VTP procedure, and lasted for about 35 weeks before resolving without sequelae.

Prostatitis occurred in 7 (3.6 %) patients in the controlled Phase III European study. One patient had Grade 3 prostatitis considered as serious that started 4 days after the VTP procedure, and lasted for 31 days before resolving without sequelae.

Urethral stenosis

In the pivotal Phase III European study, moderate or severe urethral stenosis developed in 2 (1.0 %) patients 5 to 6 months post-procedure. This required urethral dilatation (see section 4.4).

Additional adverse reactions in the Phase II prostate cancer studies and Special Authorization

Extraprostatic necrosis

Two cases of excessive extraprostatic necrosis occurred due to incorrect laser calibration without clinical sequelae. One case of external urethral fistula occurred due to fibre misplacement (see section 4.4).

Phototoxicity

In a patient treated at 2 mg/kg of TOOKAD, one case of Grade 3 ischaemic optic neuropathy was reported 33 days after the VTP procedure. This resolved with a small defect in the visual field.

Prostatic abscess

One serious adverse event of prostatic abscess which was considered severe was reported in the study performed in Latin America in a patient who had a unilateral VTP procedure. The case resolved within three days.

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

There is limited clinical information on overdose involving TOOKAD. Healthy subjects have been exposed to doses up to 15 mg/kg of padeliporfin di-potassium (corresponding to 13.73 mg/kg of padeliporfin) without light activation and 23 patients have been treated with 6 mg/kg of padeliporfin di-potassium (corresponding to 5.49 mg/kg of padeliporfin) without significant safety issues. However, a prolongation of photosensitisation is possible and precautions against light exposure should be maintained for an additional 24 hours (see section 4.4).

An overdose of the laser light may increase the risk of undesirable extraprostatic necrosis (see section 4.4).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sensitizers used in photodynamic/radiation therapy, ATC code: L01XD07

Mechanism of action
Padeliporfin is retained within the vascular system. When activated with 753 nm wavelength laser light, padeliporfin triggers a cascade of pathophysiological events resulting in focal necrosis within a few days. Activation within the illuminated tumour vasculature, generates oxygen radicals (•OH, $O_2^{\bullet -}$) causing local hypoxia that induces the release of nitric oxide (•NO) radicals. This results in transient arterial vasodilatation that triggers the release of the vasoconstrictor, endothelin-1. Rapid consumption of the •NO radicals, by oxygen radicals, leads to the formation of reactive nitrogen species (RNS) (e.g. peroxynitrite), in parallel to arterial constriction. In addition, impaired deformability is thought to enhance erythrocyte aggregability and formation of blood clots at the interface of the arterial supply (feeding arteries) and tumour microcirculation, results in occlusion of the tumour vasculature. This is enhanced by RNS-induced endothelial cell apoptosis and initiation of self-propagated tumour cells necrosis through peroxidation of their membrane.

Pharmacodynamic effects
In patients with localised prostate cancer who received TOOKAD-VTP, necrosis was observed by Magnetic Resonance Imaging (MRI) at day 7. There was a correlation between the total energy delivered and the volume of necrosis observed at day 7. The LDI corresponds to the ratio of the cumulative length of illuminated fibre tips (cm) to the volume (cc) of the targeted zone to be treated. The targeted zone corresponds to the lobe containing the positive biopsies. Its volume is measured after prostate delineation using the treatment guidance software. In Phase II studies, treatment conditions corresponding to an LDI $\geq$ 1 were associated with a mean rate of necrosis of the targeted zone at day 7 of 89 % ± 20.75 for unilateral treatment. An LDI $\geq$ 1 appeared to be associated with a greater volume of necrosis on Day 7 MRI and greater share of patients with negative biopsy at 6 months compared with an LDI < 1 (see section 4.2).

There was no significant correlation between the percentage of prostate necrosis on Day 7 MRI and the likelihood of a negative prostate biopsy at follow-up.

Clinical efficacy and safety

Phase III Study (PCM301)

The pivotal open-label Phase III study (PCM301), conducted in 10 European countries, randomised 413 patients to TOOKAD-VTP arm or AS arm.

The main inclusion criteria were low-risk prostate cancer with Gleason 3 + 3 prostate adenocarcinoma as a maximum, two to three cores positive for cancer and a maximum cancer core length of 5 mm in any core (at least 3 mm for patients with only one positive core), clinical stage up to T2a, PSA ≤ 10 ng/mL, prostate volume equal or greater than 25 cc and less than 70 cc.
The main exclusion criteria were any prior or current treatment for prostate cancer, any surgical intervention for benign prostatic hypertrophy, life expectancy less than 10 years, medical conditions which preclude the use of general anaesthesia.

The VTP procedure consisted of a 10 minutes IV injection of 4 mg/kg of TOOKAD followed by 22 minutes 15 seconds of illumination with 753 nm laser light at 200 J/cm of fibre delivered using interstitial optical fibres, inserted transperineally into the prostate gland. In case of unilateral disease, focal treatment of one lobe was to be applied. In case of bilateral disease (discovered at entry or during follow-up), bilateral treatment was to be applied, either simultaneously or consecutively. Retreatment of lobes found positive for cancer at 12-months follow-up was allowed.

AS involved serial absolute PSA measurements and ultrasound-guided prostatic biospy at 12 and 24 months.

The study had two co-primary endpoints for TOOKAD-VTP in comparison to AS:

- A: The rate of absence of definite cancer based on histology at 24 months,
- B: The difference in rate of treatment failure associated with observed progression of disease from low to moderate or higher risk prostate cancer. Moderate/higher risk prostate cancer was defined as any of the following: > 3 cores definitively positive for cancer; Gleason primary or secondary pattern ≥ 4; at least 1 cancer core length > 5 mm; PSA > 10 ng/mL in 3 consecutive measures; T3 prostate cancer; metastasis; prostate cancer-related death.

All patients had Gleason score ≤ 3 + 3 at baseline.

In each table are also presented the results of patients meeting the indication criteria (patients with unilateral low-risk localised prostate cancer excluded the very low-risk)

Table 2 gives baseline characteristics by arm.

Table 2: PCM301 – Baseline characteristics by arm for the Intention-To-Treat (ITT) population and patients meeting the indication criteria

Characteristic	ITT population		Patients meeting indication criteria	
	TOOKAD-VTP arm N = 206	AS arm N = 207	TOOKAD-VTP arm N = 80	AS arm N = 78
Age (years)				
Mean (SD)	64.2 (6.70)	62.9 (6.68)	63.9 (6.27)	62.3 (6.32)
Range: min, max	45, 85	44, 79	48, 74	46, 73
Patients aged > 75 year old, n (%)	6 (2.9)	6 (2.9)	0	0
Unilateral disease, n (%)	157 (76.2)	163 (78.7)	80 (100)	78 (100)
Bilateral disease, n (%)	49 (23.8)	44 (21.3)	Not applicable	Not applicable
Clinical stages				
T1, n (%)	178 (86.4)	180 (87.0)	66 (82.5)	71 (91.0)
T2a, n (%)	28 (13.6)	27 (13.0)	14 (17.5)	7 (9.0)
Total number of positive cores				
Mean (SD)	2.1 (0.68)	2.0 (0.72)	2.2 (0.74)	2.1 (0.76)
Range: min, max	1, 3	1, 3	1, 3	1, 3
Estimated prostate volume (cc)				
Mean (SD)	42.5 (12.49)	42.5 (11.76)	37.2 (9.67)	37.6 (9.63)
Range: min, max	25, 70	25, 70	25, 68	25, 66
PSA (ng/mL)				
Mean (SD)	6.19 (2.114)	5.91 (2.049)	6.98 (1.796)	7.12 (1.704)
Range: min, max	0.1, 10.0	0.5, 10.0	1.0, 10.0	3.1, 10.0

Of the 206 subjects randomised TOOKAD-VTP, 10 did not receive treatment for various reasons including study withdrawal, meeting exclusion criteria, non-compliance and other medical events.

Table 3 describes the co-primary efficacy endpoints in the whole prostate gland and in the treated lobe (ITT population and patients meeting the indication criteria).

Table 3: PCM301 – Co-primary efficacy endpoints – Whole prostate gland and treated lobe(s)* – ITT population and patients meeting the indication criteria

Number of subjects with	ITT population		Patients meeting indication criteria	
	TOOKAD-VTP arm N = 206	**AS arm N = 207**	**TOOKAD-VTP arm N = 80**	**AS arm N = 78**
A: Rate of absence of definite cancer based on histology at 24 months				
Negative biopsy, n (%)	101 (49.0)[a]	28 (13.5)[a]	36 (45.0)[e]	8 (10.3)[e]
Negative biopsy in the treated lobe*, n (%)	129 (62.6)[b]	40 (19.3)[b]	52 (65.0)[f]	11 (14.1)[f]
No biopsy result, n (%)	38 (18.4)	86 (41.5)	11 (13.8)	34 (43.6)
Subjects who had radical therapy leading to missing biopsy, n (%)	12 (5.8)	55 (26.6)[c]	6 (7.5)	27 (34.6)
Other reasons[d], n (%)	26 (12.6)	31 (15.0)	5 (6.3)	7 (9.0)
Positive biopsy, n (%)	67 (32.5)	93 (44.9)	33 (41.3)	36 (46.2)
Positive biopsy in the treated lobe*, n (%)	39 (18.9)	81 (39.1)	17 (21.3)	33 (42.3)
[a]Risk Ratio (95% CI) = 3.62 (2.50 ; 5.26) ; p value < 0.001 [b]Risk Ratio (95% CI) = 3.24 (2.41 ; 4.36) ; p value < 0.001 [c]Among the 60 patients who had radical therapy, 5 patients had a Month 24 biopsy [d]For example: study withdrawal, medical reason, subject refusal [e]Risk Ratio (95% CI) = 4.39 (2.18 ; 8.83) ; p value < 0.001 [f]Risk Ratio (95% CI) = 4.61 (2.60 ; 8.16) ; p value < 0.001				
B: Difference in rate of treatment failure associated with observed progression of disease				
Number of subjects progressed at Month 24, n (%)	58 (28.2)[g]	121 (58.5)[g]	27 (33.8)[h]	53 (67.9)[h]
Progression to Gleason ≥ 4	49 (23.8)	91 (44.0)	19 (23.8)	40 (51.3)
Number of subjects progressed in the treated lobe* at Month 24, n (%)	24 (11.7)[i]	90 (43.5)[i]	7 (8.8)[j]	39 (50.0)[j]
[g]Adjusted Hazard Ratio (95% CI) = 0.34 (0.24 ; 0.46) ; p value ≤ 0.001 [h]Adjusted Hazard Ratio (95% CI) = 0.31 (0.20 ; 0.50) ; p value ≤ 0.001 [i]Adjusted Hazard Ratio (95% CI) = 0.17 (0.12 ; 0.27) ; p value ≤ 0.001 [j]Adjusted Hazard Ratio (95% CI) = 0.11 (0.05 ; 0.25) ; p value ≤ 0.001				

* The treated lobe(s) in the AS arm was defined as the lobe(s) with disease at baseline.

A secondary objective was to determine the difference between the two arms with regard to the rate of subsequent radical therapy for prostate cancer. Of 58 patients that progressed in the TOOKAD-VTP arm, only 11 underwent radical therapy, 18 patients underwent a second VTP procedure and 29 had not received further treatment at the end of the study. Of 121 patients that progressed in the AS arm, 54 underwent radical therapy and 67 had not received any active treatment at the end of the study. Patients in the AS arm were not offered subsequent VTP. In assessing overall tolerability by Month 24, post enrolment patients who underwent a radical therapy were also counted in the scoring of prostate symptoms and erectile function.

Table 4: PCM301 – Number of subjects with radical treatment at 24 months – ITT population and patients meeting the indication criteria

Characteristic	ITT population		Patients meeting indication criteria	
	TOOKAD-VTP arm N = 206	AS arm N = 207	TOOKAD-VTP arm N = 80	AS arm N = 78
Number of subjects who initiated a radical treatment, n (%)	12 (5.8)	62 (29.9)	6 (7.5)	28 (35.9)
Number of subjects who initiated a radical treatment after progression, n (%)	11 (5.3)	54 (26.1)	5 (6.3)	25 (32.1)

Effect on urinary morbidity (IPSS) and erectile function (IIEF) following TOOKAD-VTP
As shown in Table 5, in PCM301 study, the International Prostate Symptoms Score (IPSS) showed, a moderate increase 7 days after the VTP procedure, in both the ITT population and in patients meeting the indication criteria. Those results were improved at Month 3 and back to baseline values at Month 6, with further improvement until Month 24. In the Active Surveillance arm, the IPSS score slightly worsened over time until Month 24.

Table 5: PCM301 – Effect on urinary morbidity (IPSS) – ITT population and patients meeting the indication criteria

	ITT population				Patients meeting indication criteria			
	TOOKAD-VTP arm		AS arm		TOOKAD-VTP arm		AS arm	
	n	Mean score (SD)	n	Mean score (SD)	n	Mean score (SD)	n	Mean score (SD)
Baseline	179	7.6 (6.09)	185	6.6 (5.30)	71	6.7 (5.69)	73	6.0 (4.34)
Day 7	180	14.8 (8.64)	Not applicable		72	14.2 (8.89)	Not applicable	
Month 3	179	9.6 (6.86)	190	7.2 (5.75)	71	8.7 (5.72)	72	6.6 (5.11)
Month 6	182	7.5 (6.06)	189	6.8 (5.84)	74	6.4 (5.33)	73	6.3 (5.36)
Month 12	177	7.2 (5.85)	173	7.3 (5.95)	71	5.7 (5.01)	68	7.1 (5.75)
Month 24*	165	6.6 (5.47)	154	8.2 (6.47)	66	5.5 (5.34)	55	8.6 (6.56)

*Scores at Month 24 include patients who underwent radical therapy

As shown in Table 6, in the VTP arm of PCM301 study, erectile function domain scores of the 15-question International Index of Erectile Function (IIEF-15) questionnaire showed a marked decrease, 7 days after the VTP procedure followed by a subsequent improvement in the following months up to Month 24, in the ITT population and in patients meeting the indication criteria.

Table 6: PCM301 – Effect on erectile function (IIEF) – ITT population and patients meeting the indication criteria

	ITT population				Patients meeting indication criteria			
	TOOKAD-VTP arm		AS arm		TOOKAD-VTP arm		AS arm	
	n	Mean score (SD)	n	Mean score (SD)	n	Mean score (SD)	n	Mean score (SD)
Baseline	184	18.6 (10.22)	188	20.6 (9.92)	74	18.4 (10.31)	74	20.8 (10.02)
Day 7	165	11.5 (10.96)	Not applicable		68	10.1 (10.82)	Not applicable	
Month 3	171	14.7 (10.48)	182	21.0 (9.84)	69	14.3 (10.81)	70	21.7 (9.95)
Month 6	176	16.1 (9.98)	185	20.4 (9.83)	68	16.9 (9.78)	72	20.6 (9.85)
Month 12	170	15.1 (10.28)	167	19.9 (10.29)	70	16.7 (10.18)	65	20.4 (10.44)
Month 24*	159	15.0 (10.70)	152	16.8 (11.17)	62	15.4 (11.11)	54	16.4 (11.10)

*Scores at Month 24 include patients who underwent radical therapy

5.2 Pharmacokinetic properties

The pharmacokinetic properties of TOOKAD were studied in 42 healthy human male subjects (without photoactivation) and in 70 patients with localised prostate cancer (after photoactivation).

Distribution
In healthy human male subjects, the mean volume of distribution ranged from 0.064-0.279 L/kg, for posologies from 1.25 to 15 mg/kg of padeliporfin di-potassium indicating distribution into extracellular fluid. A similar mean distribution volume was seen in patients with localised prostate cancer treated with 2 and 4 mg/kg of padeliporfin di-potassium (0.09-0.10 L/kg respectively). Padeliporfin di-potassium is highly bound to human plasma proteins (99 %).

In vitro studies indicate that TOOKAD is unlikely to be a substrate of OATP1B1, OATP1B3, OCT1, OATP2B1, P-gp, BCRP, MRP2 or BSEP hepatic uptake transporters.

Biotransformation
Minimal metabolism of padeliporfin was observed in *in vitro* metabolism studies in human liver microsomes and S9 fractions. No metabolites of padeliporfin were observed in these studies.

No *in vitro* or *in vivo* studies have been conducted with radiolabelled padeliporfin. Therefore, the possibility for some *in vivo* metabolism of padeliporfin cannot be fully excluded.

In vitro studies indicate that TOOKAD is unlikely to be an inhibitor of CYP450 enzymes.

In vitro studies indicate that TOOKAD does not inhibit P-gp, OAT1, OAT3, OCT2, OCT1, BCRP and BSEP but it could inhibit both OATP1B1 and OATP1B3 transporters (see section 4.5).

Elimination
Clearance of padeliporfin di-potassium in healthy male subjects treated from 1.25 mg/kg up to 15 mg/kg of padeliporfin di-potassium ranged from 0.0245 to 0.088 L/h/kg. Based on popPK analysis the estimated half-life is 1.19 h ± 0.08 at 4 mg/kg of padeliporfin di-potassium. A similar mean clearance range was seen in patients with localised prostate cancer treated with 4 mg/kg and 2 mg/kg of padeliporfin di-potassium (0.04-0.06 L/h/kg respectively). Urinary excretion of padeliporfin in healthy human subjects was very low (< 0.2 % of the dose). Taking into account its molecular mass and the very low urinary excretion of the molecule, faecal elimination is the most probable route of elimination in human.

Elderly population
Very few patients aged over 75 years were enrolled into studies where pharmacokinetic measurements were taken so it is not known if there is a difference in these older patients compared to patients less than 75 years of age (see sections 4.2 and 5.1).

Linearity/non-linearity
In healthy human male subjects, the C_{max} was shown to be linear from 1.25 mg/kg to 15 mg/kg of padeliporfin di-potassium, covering the therapeutic range.

Effects of covariates on pharmacokinetic properties
The effects of age, weight and race were investigated in healthy volunteers and patients.
The results of the population PK study showed that age, race, health status and markers of hepatic function were unlikely to have a substantial and biologically significant impact on the pharmacokinetics of TOOKAD.
The body weight of patients (range 60-120 kg) presented a minor impact on the TOOKAD pharmacokinetic parameters for doses up to 5 mg/kg of padeliporfin di-potassium.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology and repeated dose toxicity.

In vitro genotoxicity testing identified padeliporfin as having weak potential to induce clastogenicity when illuminated by ultraviolet (UV); this correlates with the mechanism of action (formation of reactive oxygen species).

Padeliporfin was shown to be cytotoxic in the presence of UVA irradiation (*in vitro*) and considered phototoxic in the guinea pig (*in vivo*).

Carcinogenicity and reproductive toxicity studies have not been conducted with padeliporfin.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421)

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial
5 years

After reconstitution
The chemical and physical stability of TOOKAD after reconstitution with 5 % glucose solution, in its vial, has been demonstrated for 8 hours at 15°C-25°C and at 5°C ± 3°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C).
Keep the vial in the outer carton in order to protect from light.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

TOOKAD 183 mg powder for solution for injection
Amber type I glass vial, sealed with a rubber stopper crimped with an aluminium seal and covered with a blue plastic flip-off cap, containing 183 mg padeliporfin.

Pack size: 1 vial

TOOKAD 366 mg powder for solution for injection
Amber type I glass vial, sealed with a rubber stopper crimped with an aluminium seal and covered with a white plastic flip-off cap, containing 366 mg padeliporfin.

Pack size: 1 vial

6.6 Special precautions for disposal and other handling

The preparation of the solution should take place in a dimmed-light environment.

TOOKAD is prepared by reconstituting the powder for solution for injection with:
- 20 mL of 5 % glucose solution for TOOKAD 183 mg,
- 40 mL of 5 % glucose solution for TOOKAD 366 mg.

The vial should then be swirled gently for 2 minutes. Each mL of the resulting solution will contain 9.15 mg of padeliporfin. The vial should rest in an upright position for 3 minutes without further shaking or moving. Due to the photosensitising properties of TOOKAD, the content of the vial should then be transferred into an opaque syringe that should be held in an upright position for 3 minutes to ensure any foam disappears. An injection filter of 0.22 µm and an opaque tubing should be used to administer the medicinal product to the patient. Standard handling of syringes should follow.

The reconstituted solution is dark. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

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

7. MARKETING AUTHORISATION HOLDER

Steba Biotech S.A.
7 Place du Théâtre
L-2613 Luxembourg
Luxembourg

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1228/001
EU/1/17/1228/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE
B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE
C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION
D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

PRAXIS PHARMACEUTICAL S.A.
C/ Hermanos Lumiere 5
Parque Tecnologico de Alava (Miñano)
Vitoria-Gasteiz
Alava 01510
Spain

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- Periodic safety update reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to launch of TOOKAD in each Member State the marketing authorisation holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at increasing awareness and providing information concerning the signs and symptoms of certain important identified risks of padeliporfin, including photosensitivity, and also information on the existing therapeutic approaches (including VTP with

TOOKAD) for the treatment of the type of prostate cancer, potential benefits, risks and uncertainties of VTP with TOOKAD.

The MAH shall ensure that in each Member State where TOOKAD is marketed, all healthcare professionals and patients/carers who are expected to prescribe and use TOOKAD have access to/are provided with the following educational package:

- Patient information guide
- Physician guideline

The Patient information guide about TOOKAD should contain the following key elements:

- Information on the existing therapeutic approaches (including VTP with TOOKAD) for the treatment of the type of prostate cancer
- Information on the potential benefits, risks and uncertainties of VTP with TOOKAD, including: uncertainties on long-lasting benefit of TOOKAD; uncertainties on long-term safety of TOOKAD and efficacy/safety of any further treatments required such as radical prostatectomy
- Information on adverse drug reactions and the likelihood of them getting them, including: erectile dysfunction, urinary incontinence, urinary retention/urethral stricture, and photosensitivity and the need to follow the rules to protect themselves against the light after the procedure for 48 hours.

The Physician guideline about TOOKAD should contain the following key elements:

- The approaches (including VTP with TOOKAD) for the treatment of his prostate cancer and the potential benefits, risks and uncertainties of VTP with TOOKAD:
    - To state that information beyond two years after the TOOKAD -VTP procedure is limited and consequently, data on the long-term efficacy and safety of TOOKAD-VTP are currently not available
    - Information on the efficacy/safety of any subsequent treatments required, such as radical prostatectomy, is currently lacking
- Explain what the VTP procedure involves, including the need to follow the rules to protect the Patient against light after the procedure for 48 hours, due to the photosensitising effect of TOOKAD and provide a copy of the TOOKAD Package Leaflet to the Patient ahead of the VTP procedure
- Explain what side effects the Patient might expect and the likelihood of him getting them
- Explain the procedure as well as relevant efficacy and safety results of TOOKAD with simple graphics included in the Patient Information Guide.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Post-authorisation efficacy study (PAES): In order to further investigate long-term efficacy of TOOKAD and its impact on disease progression including potential impact on the efficacy of subsequent radical therapy in patients with low risk prostate cancer as well as further characterise the long term safety of TOOKAD, the MAH should submit the results of a randomised phase 3 study in patients with localised prostate cancer compared to active surveillance (7-year follow-up study including in an depth biopsy study) (PCM301 FU5).	Submission of final study results: 31/12/2020
Post-authorisation efficacy study (PAES): In order to further investigate long-term efficacy of TOOKAD and its impact on disease progression including potential impact on the efficacy of subsequent radical therapy in patients with low risk prostate cancer (excluding very low risk) as well as further characterise the long term safety of TOOKAD, the MAH should conduct and submit the results of a long-term observational cohort study of patients with unilateral low risk localised prostate cancer treated with TOOKAD VTP (CLIN1501 PCM401).	Submission of final study results: 31/12/2025

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

TOOKAD 183 mg powder for solution for injection
padeliporfin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 183 mg of padeliporfin (as di-potassium salt).
1 mL of reconstituted solution contains 9.15 mg of padeliporfin.

3. LIST OF EXCIPIENTS

Excipient: Mannitol

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Steba Biotech S.A.
7 Place du Théâtre
L-2613 Luxembourg
Luxembourg

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1228/001

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

VIAL

1. NAME OF THE MEDICINAL PRODUCT

TOOKAD 183 mg powder for solution for injection
padeliporfin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 183 mg of padeliporfin (as di-potassium salt).
1 mL of reconstituted solution contains 9.15 mg of padeliporfin.

3. LIST OF EXCIPIENTS

Excipient: Mannitol

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Steba Biotech S.A.
7 Place du Théâtre
L-2613 Luxembourg
Luxembourg

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1228/001

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

TOOKAD 366 mg powder for solution for injection
padeliporfin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 366 mg of padeliporfin (as di-potassium salt).
1 mL of reconstituted solution contains 9.15 mg of padeliporfin.

3. LIST OF EXCIPIENTS

Excipient: Mannitol

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Steba Biotech S.A.
7 Place du Théâtre
L-2613 Luxembourg
Luxembourg

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1228/002

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

VIAL

1. NAME OF THE MEDICINAL PRODUCT

TOOKAD 366 mg powder for solution for injection
padeliporfin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 366 mg of padeliporfin (as di-potassium salt).
1 mL of reconstituted solution contains 9.15 mg of padeliporfin.

3. LIST OF EXCIPIENTS

Excipient: Mannitol

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Steba Biotech S.A.
7 Place du Théâtre
L-2613 Luxembourg
Luxembourg

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1228/002

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable.

B. PACKAGE LEAFLET

Package leaflet: Information for the user

TOOKAD 183 mg powder for solution for injection
TOOKAD 366 mg powder for solution for injection
padeliporfin

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What TOOKAD is and what it is used for

TOOKAD is a medicine that contains padeliporfin (as potassium salt). It is used to treat adult men who have low-risk, localised prostate cancer in only one lobe, using a technique called Vascular-Targeted Photodynamic (VTP) therapy. The treatment is carried out under general anaesthetic (medicines that send you to sleep to prevent pain and discomfort).

Hollow needles are used to insert the fibres into the right place in the prostate. Once it has been given, TOOKAD has to be activated by laser light shone along a fibre that targets the light onto the cancer. The activated medicine then causes the death of the cancer cells.

2. What you need to know before TOOKAD is used

TOOKAD must not be used if:
- You are allergic to padeliporfin or any of the other ingredients of this medicine (listed in section 6).
- You have undergone a procedure for treating benign prostatic hypertrophy including Trans-Urethral Resection of the Prostate (TURP).
- You are having or have previously had any treatment for prostate cancer.
- You have been diagnosed with a problem with the liver called cholestasis.
- You are having an exacerbation of rectal inflammatory bowel disease.
- You are not able to have general anaesthesia or invasive procedures.

Warnings and precautions
TOOKAD should only be used by personnel trained in the VTP procedure.

Talk to your doctor or nurse if:
- You feel any irritation of the skin or problems with vision or eye irritation after the VTP procedure.
- You experience difficulties in getting or maintaining an erection.
- You feel any abnormal pain after the VTP procedure.
- You have a history of a narrowing of the urethra or urinary flow problems.
- You experience involuntary passing of urine after the VTP procedure.
- You have had an active inflammatory bowel disease or any condition that may increase the risk of causing abnormal connection between the rectum and the urethra (recto-urethral fistula).
- You have abnormal blood clotting.
- You have a reduced kidney function or if you follow a potassium restricted diet.

To date information beyond two years after VTP procedure is limited and so, at this time, data are currently not available to know whether the benefit of TOOKAD-VTP is long-lasting.

If you do require further treatment, at the moment, there is limited information on whether TOOKAD-VTP affects the efficacy and safety results of other treatments (such as surgery to remove the prostate or radiotherapy).

Photosensitivity
Strong light may cause skin reactions and eye discomfort while TOOKAD is in the blood stream.

For the 48 hours after the procedure you should avoid exposure to direct sunlight (including through windows) and all bright light sources, both indoors and outdoors. This includes sunbeds, bright computer monitor screens (see precautions below), and examination lights from medical equipment.

Sunscreen creams do not protect you against the type of light (near infra-red) that can cause problems after the procedure.

If you feel skin or eye discomfort while in hospital, you must tell your doctor or nurse so the level of lighting can be reduced and extra care can be taken to protect you from artificial and natural light.

First 12 hours after VTP procedure
After the procedure, you should wear protective goggles and will be kept under medical surveillance for at least 6 hours in a room with reduced light.
Your medical team will decide if you can leave hospital on the evening of your treatment. You may need to stay overnight if you have not fully recovered from the general anaesthetic and depending on your condition.
You must remain under reduced light conditions, without exposing your skin and your eyes to daylight. Only use light bulbs with a maximum power of 60 watts (for an incandescent light bulb) or 6 watts (for LED lights), or 12 watts (for fluorescent low-energy lights). You may watch television at a distance of 2 metres and, from 6 hours after the procedure, you may use electronic devices such as smartphones, tablets and computers. In case you need to go out during the day, you must wear protective clothing and high-protection goggles to shield your skin and eyes.

12-48 hours after VTP procedure
You may go outdoors during daylight hours but only in shaded areas or when it is overcast. You should wear dark clothes and take care to protect your hands and face from the sun.

When 48 hours have passed after the procedure, you can resume your normal activities and you can be exposed to direct sunlight.

No patients with light-sensitive conditions such as porphyria, a history of sensitivity to sunlight or a history of photosensitive dermatitis have received TOOKAD in clinical studies. However, the short duration of action of TOOKAD means that the risk of enhanced phototoxicity is expected to be low provided the precautions against light exposure are stricly followed.

There could be an additional risk of eye photosensitivity in patients who have received intra-occular anti-VEGF (medicines used to prevent new blood vessel growth) therapy. If you have received prior VEGF therapy, you should take particular care to protect your eyes from light for 48 hours post TOOKAD injection. Concomitant use of systemic VEGF inhibitors is not recommended with TOOKAD.

See also under "Other medicines and TOOKAD" for photosensitizing medicines.

Difficulties in getting or maintaining an erection
Some difficulties in getting or maintaining an erection is possible soon after the procedure and may last for more than 6 months.

Risk of damage near the prostate gland
Because the fibres that carry the light have to be inserted in such a way that the whole of the lobe of the prostate gland gets exposed, it is possible that some damage may occur outside of the prostate. Normally this is just the fat around the prostate and is not important but nearby organs such as the bladder and rectum may potentially be affected. This is normally avoidable by careful planning but should it occur there is a risk of an abnormal connection forming between the rectum and the bladder or skin. This is very rare.

Problem associated with the urethra
If you have a history of a narrowing of the urethra or urinary flow problems, treatment may increase the risk of poor flow and urinary retention.

Urinary incontinence
Short-term urinary incontinence has been observed and may result from urinary tract infection or from urgency caused by irritation to the urethra from the procedure. The condition gets better on its own or with treatment of the infection.

Active inflammatory bowel disease
If you have had an active inflammatory bowel disease or any condition that may increase the risk of causing abnormal connection between the rectum and the urethra (recto-urethral fistula), the treatment should be given only after careful evaluation.

Abnormal clotting
Patients with abnormal clotting may bleed excessively from the insertion of the needles required to position the fibres that guide the laser light. This may also cause bruising, blood in the urine and/or local pain. Abnormal clotting is not expected to affect how well the treatment works ; however, it is recommended that drugs that affect clotting are stopped prior to and for the immediate period following the VTP procedure.

See also under "Other medicines and TOOKAD" for the effects of anticoagulants and antiplatelet medicines.

Patients on a controlled potassium diet
This medicine contains potassium. In general, the dose of TOOKAD contains less than 1 mmol (39 mg) potassium, i.e. essentially 'potassium free'. However, patients weighing more than 115 kg will receive more than 1 mmol potassium. This should be taken into consideration by patients with reduced kidney function or patients on a controlled potassium diet where a rise in serum potassium would be considered detrimental.

Children and adolescents
This medicine should not be given to children and adolescents less than 18 years of age.

Other medicines and TOOKAD
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription. Some medicines (in particular any

medicines that are photosensitising or that affect blood clotting) may interact with TOOKAD and should be stopped before using TOOKAD. You may also be required to not take certain medicines for several days after the VTP procedure. Your doctor will also advise what medicines may be substituted where appropriate and when these medicines can be re-started after the VTP procedure.

The following types of medicines may be ones that your doctor will advise you to stop temporarily:

Medicines with a potentially photosensitising effect:
- Certain antibiotics used to treat infection (tetracyclines, sulphonamides, quinolones).
- Certain medicines used to treat psychiatric conditions (phenothiazines).
- Certain medicines used in type II diabetes (hypoglycaemic sulphonamides).
- Certain medicines used for hypertension, oedema, heart failure or renal failure (thiazide diuretics).
- A medicine used to treat fungal infections (griseofulvin).
- A medicine used to treat cardiac arrhythmia (amiodarone).

These medicines should be stopped at least 10 days before the procedure with TOOKAD, and for at least 3 days after the procedure, or replaced by other treatments without photosensitising properties. If it is not possible to stop a photosensitising medicine (such as amiodarone), increased sensitivity may occur, you may need to protect yourself from direct light exposure for a longer period.

Anticoagulants (medicines that prevent the blood from clotting)
These medicines (e.g. acenocoumarol, warfarin) should be stopped at least 10 days before the VTP procedure with TOOKAD.

Antiplatelet agents (medicines that decrease platelet aggregation (stickiness) in the blood and reduce clotting)
These medicines (e.g. acetylsalicylic acid) should be stopped at least 10 days before the VTP procedure with TOOKAD and re-started at least 3 days after the procedure.

Other medicines that may interact with TOOKAD
The use of medicines such as repaglinide, atorvastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin, bosentan, glyburide should be avoided on the day of TOOKAD administration and for at least 24 hours after administration.

Contraception
You or your partner or both should use an effective form of birth control to prevent your partner getting pregnant for 90 days after the VTP procedure. Check with your doctor about the birth control methods to use and how long to use them for. If your partner becomes pregnant within three months of your treatment, you must immediately tell your doctor.

Pregnancy and breast-feeding
TOOKAD is not indicated for the treatment of women.

Driving and using machines
TOOKAD has no influence on the ability to drive or use machines. However, as the procedure includes general anaesthesia, you should not perform complex tasks like driving or using machines until 24 hours after a general anaesthetic is used.

3. How TOOKAD is used

TOOKAD is restricted to hospital use only. It should only be used by personnel trained in the VTP procedure.

Dose
The recommended dose of TOOKAD is one single dose of 3.66 mg per kg of body weight, injected into a vein. The injection lasts 10 minutes.
For instructions to healthcare professionals on reconstitution of TOOKAD before injection, see "Reconstitution of the TOOKAD powder for solution for injection".

Only the lobe that contains the cancer will be treated. Additional VTP procedures of the prostate are not recommended.

VTP procedure
The day before and at the beginning of the VTP procedure, a rectal preparation is performed in order to clean the rectum. Your doctor may prescribe antibiotics to prevent infection and alpha-blockers (medicines given to prevent difficulties in urinating). You will be given a general anaesthetic to send you to sleep before the VTP procedure. Fibres to carry the laser light are inserted into the prostate gland by using hollow needles. TOOKAD is activated immediately after injection by shining light through the fibres from a connected laser device.

If you have any questions on the use of this medicine, ask your doctor, your pharmacist or your nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.
In addition, inserting needles into the prostate gland and inserting a urinary catheter for the procedure may be associated with further side effects.

Possible side effects can occur with TOOKAD and VTP procedure.

If you get any of the side effects below, **tell your doctor immediately**:
- Urinary retention (not able to pass urine). In the few days after the VTP procedure some patients may have difficulties (poor stream due to urethral narrowing) or inability to pass urine. This may necessitate inserting a catheter inside your bladder through the penis and the catheter will remain in place for a few days or weeks to drain the urine.
- Fever, pain and swelling in the area of the operation might occur after the procedure. These may be signs of infection in the urinary tract, the prostate or the genital system. In this case, you should contact your doctor as you may need further blood or urine analysis and antibiotics treatment. These infections are usually easily treated.

In addition to the side effects listed previously, other side effects can occur.

Very common side effects (may affect more than 1 in 10 people)
- Problems with or pain on passing urine (including pain or discomfort on passing urine, bladder pain, the need to pass urine urgently or more frequently or at night; involuntary passing of urine),
- Sexual problems (including difficulty in getting or maintaining an erection, ejaculation failure, loss of desire or pain on intercourse),
- Blood in the urine (haematuria),
- Perineal injury including bruising in the skin, bruising near where the needles are put into the prostate, pain and tenderness,
- Genital pain and discomfort (inflammation of the testicles or the epididymis, pain due to inflammation or fibrosis of the prostate).

Common side effects (may affect up to 1 in 10 people)
- Anorectal discomfort (discomfort near the anus and just inside the anus), haemorrhoids (piles), proctalgia (pain in the anal region),
- Problems with bowels (including diarrhoea or occasional soiling),

- General and musculoskeletal pain (muscle/bony pain, pain in the end of the limbs, back pain or bleeding into the joints),
- Haematospermia (presence of blood in the ejaculate),
- High blood pressure,
- Increases in blood lipids, lactate dehydrogenase increased, white blood cell increased, creatine phosphokinase increased, potassium decreased, prostatic specific antigen (PSA) increased,
- Skin reaction, erythema (reddening), rash, dryness, pruritus, depigmentation,
- Abnormal blood tests related to coagulation,
- Discomfort in the abdominal region,
- Fatigue (tiredness).

Uncommon side effects (may affect up to 1 in 100 people)
- Dizziness, fall,
- Headache,
- Sensory disturbance, formication (sensation like crawling insects on or under the skin),
- Eye irritation, photophobia (intolerance to light),
- Dyspnoea exertional (excessive shortness of breath during or after exercise),
- Mood disorder,
- Weight decreased.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How TOOKAD is stored

You will not have to store this medicine. This medicine is stored under the responsibility of the specialist.

The following information is intended for the specialist only.

Keep this medicine out of the sight and reach of children.

Do not use after the expiry date which is stated on the shield label after “EXP”. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C-8°C).
Store in the outer carton in order to protect it from light.

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

6. Contents of the pack and other information

What TOOKAD contains
- The active substance is padeliporfin.
  Each vial of TOOKAD 183 mg contains 183 mg of padeliporfin (as potassium salt).
  Each vial of TOOKAD 366 mg contains 366 mg of padeliporfin (as potassium salt).
  1 mL of reconstituted solution contains 9.15 mg of padeliporfin.

- The other ingredient is mannitol.

What TOOKAD looks like and contents of the pack
TOOKAD is a dark powder.

Each carton of TOOKAD 183 mg powder for solution for injection contains an amber glass vial with a blue cap.
Each carton of TOOKAD 366 mg powder for solution for injection contains an amber glass vial with a white cap.

Marketing Authorisation Holder
Steba Biotech S.A.
7 Place du Théâtre
L-2613 Luxembourg
Luxembourg

Manufacturer
Praxis Pharmaceutical S.A.
C/ Hermanos Lumiere 5
Parque Tecnologico de Álava (Miñano)
Vitoria-Gasteiz
01510 Alava
Spain

This leaflet was last revised in <{MM/YYYY}>.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

Reconstitution of the TOOKAD powder for solution for injection
The solution must be prepared in a dimmed-light environment due to the photosensitizing properties of the medicine.
1. Reconstitute the solution by adding:
   - for TOOKAD 183 mg: **20 mL** of a 5 % glucose solution in the vial containing the powder;
   - for TOOKAD 366 mg: **40 mL** of a 5 % glucose solution in the vial containing the powder.
2. Swirl the vial gently for 2 minutes. The final solution concentration is 9.15 mg/mL.
3. Allow the vial to rest in a vertical position for 3 minutes without further shaking or moving.
4. Transfer the contents of the vial into an opaque syringe.
5. Allow the opaque syringe to rest in a vertical position for 3 minutes to ensure any foam disappears.
6. Place a 0.22 µm injection filter on the syringe.
7. Connect an opaque tube to the filter.

The reconstituted solution for infusion is dark.

Illumination for photoactivation of TOOKAD
TOOKAD is locally activated immediately after injection by laser light at 753 nm delivered via interstitial optical fibres from a laser device at a power of 150 mW/cm of fibre, delivering an energy of 200 J/cm over 22 minutes 15 seconds.
Planning of optical fibre positioning should be performed at the beginning of the procedure using the treatment guidance software. During the procedure, the optical fibres are selected and positioned transperineally into the prostate gland under ultrasound guidance to achieve a Light Density Index (LDI) ≥ 1 in the targeted tissue.

Storage conditions
Store in a refrigerator (2°C-8°C).
Keep the vial in the outer carton in order to protect from light.

After reconstitution with a 5 % glucose solution in its vial, the chemical and physical stability of TOOKAD has been demonstrated for 8 hours at 15°C-25°C and at 5°C ± 3°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.