PRESCRIBING INFORMATION

1. NAME OF THE MEDICINAL PRODUCT

TOOKAD Soluble 200 mg
TOOKAD Soluble 400 mg
Powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TOOKAD Soluble 200 mg powder for solution for injection
Each vial contains 200 mg of padeliporfin di-potassium (183 mg padeliporfin).

TOOKAD Soluble 400 mg powder for solution for injection
Each vial contains 400 mg of padeliporfin di-potassium (366 mg padeliporfin).

1 mL of reconstituted solution contains 10 mg of padeliporfin di-potassium.

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 Soluble is indicated for adult patients with unilateral low-risk localised prostate cancer and with a life expectancy ≥ 10 years and:
- Clinical stage up to T2a,
- Gleason Score ≤ 6, based on high-resolution biopsy strategies,
- PSA ≤ 10 ng/mL,
- Up to 3 independent positive cores
- mpMRI by 3T without endo-rectal coil showing normal MRI or unilateral tumour without evidence of capsular or seminal vesicle involvement or metastatic tumour to lymph nodes.

TOOKAD Soluble is administered as part of focal Vascular-Targeted Photodynamic therapy (VTP).

** Cores are considered independent one from another if taken in different prostate sextants.*

PATIENT REGISTRY
A patient registry exists for VTP-treatment by TOOKAD Soluble to which only Certified Healthcare Physicians (Urologists who have received a Certificate of Training from Steba) will have access and into which each and every patient undergoing the VTP procedure must be registered. Healthcare personnel involved in the procedure should be trained to use the relevant forms and to fill out the pertinent tables associated with the registry.

PATIENT INFORMATION GUIDE
A Patient Information Guide must be handed over to the patient and discussed with him in order to explain the possible benefits, risks and uncertainties associated with TOOKAD Soluble VTP.

4.2 Posology and method of administration

TOOKAD Soluble is restricted to hospital use only. It should only be used by personnel trained in the VTP procedure, i.e. Urologists who have received a Certificate of Training from Steba and, for laser device operation, Laser Technicians who have received a Certificate of Laser Training from Steba.
MpMRI by 3T without a need for endo-rectal coil must be used for diagnosis and staging prior to procedure.

Posology
TOOKAD Soluble is administered as part of focal Vascular-Targeted Photodynamic therapy (VTP). The VTP procedure is performed under general anaesthetic after rectal preparation. Prophylactic antibiotics may be prescribed at the physician's discretion. Alpha-blockers may be started approximately one month before the procedure to reduce prostate swelling and thus reduce the risk of urinary symptoms for the immediate post-operative period.
The recommended posology of TOOKAD Soluble is one single dose of 4 mg/kg, equivalent to 3.66 mg/kg of padeliporfin.

Retreatment of the same lobe or sequential treatment of the contralateral lobe of the prostate are not recommended (see section 4.4).

Patients with 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 Soluble should be used with caution in patients with severe hepatic impairment.

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

Patients with renal impairment
There is minimal renal excretion of TOOKAD Soluble 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 population
No specific posology adjustment is necessary in this population.

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

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

Illumination for photoactivation of TOOKAD Soluble
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).

Follow-up post TOOKAD Soluble VTP
There is limited biopsy data beyond 2 years after TOOKAD Soluble 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.

The follow-up regimen after TOOKAD Soluble VTP is:
- PSA dynamics (PSA Doubling Time (DT), PSA velocity) every 3 months during the first year after treatment and then every 6 months;
- mpMRI by 3T without a need for endo-rectal coil 8 weeks and 24 months after therapy;
- biopsy of the treated area and in other suspicious areas that were not treated by TOOKAD-Soluble at 2-4 and at 7 years post TOOKAD Soluble VTP with additional biopsies based on clinical/PSA assessment;
- IPSS and IIEF-5 before therapy and, post therapy, once within the first six months and again after one year.
- Digital Rectal Examination (DRE) not more often than once a year unless clinically indicated.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Prior surgical intervention for benign prostatic hypertrophy including Trans-Urethral Resection of the Prostate (TURP).
- 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 conditions which preclude the use of general anaesthesia 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 mpMRI.

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 Soluble VTP procedure.

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 Soluble 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 Soluble VTP.

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

Day 1 (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.

Day 2 (12-48 hours after VTP procedure)
The patient may go outdoors during daylight hours but in shaded areas or only 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 Soluble in clinical studies. However, the short duration of action of TOOKAD Soluble means that the risk of enhanced phototoxicity is expected to be low provided these patients strictly follow the precautions against light exposure.

There is believed to 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 Soluble injection.
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.

Carefully calibrate the equipment 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 Soluble 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 Soluble VTP induced necrosis.
Although they were excluded from the clinical trials, patients with pre-existing stenosis should understand that there is a potential risk of increased stenosis post the TOOKAD Soluble VTP procedure (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 Soluble VTP procedure is contraindicated in patients with any previous prostatic interventions where the internal urinary sphincter may have been damaged (see section 4.3).

Inflammatory bowel disease
Only administer TOOKAD Soluble VTP, 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 Soluble 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 padeliporfin) 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 Soluble at therapeutic concentrations is unlikely to inhibit cytochrome P450 enzymes but does 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 Soluble infusion and for at least 24 hours after administration. Otherwise, co-administer with caution and close monitoring is recommended.

Photosensitisers
Medicinal products such as tetracyclines, sulphonamides, quinolones, phenothiazines, sulfonylurea hypoglycaemic agents, thiazide diuretics, griseofulvin or amiodarone have potential photosensitising effects. When possible, photosensitising medicines should be stopped at least 10 days before the procedure with TOOKAD Soluble 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
Anticoagulants and medicinal products that decrease platelet aggregation (e.g. acetylsalicylic acid) should be stopped prior to VTP procedure with TOOKAD Soluble and restarted post the procedure according to the instructions or recommendation provided by the manufacturer of each product.

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
Not applicable. TOOKAD Soluble 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 Soluble 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 Soluble 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]
		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 Soluble 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 Soluble 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 Soluble, 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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il/

4.9 Overdose

There is limited clinical information on overdose involving TOOKAD Soluble; healthy subjects have been exposed to doses up to 15 mg/kg of padeliporfin di-potassium without light activation and 23 patients have been treated with 6 mg/kg of padeliporfin di-potassium 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-}) 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 Soluble 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 ≥ 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 ≥ 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 Soluble 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 Soluble 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 biopsy at 12 and 24 months.

The study had two co-primary endpoints for TOOKAD Soluble 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. Table 2 gives baseline characteristics by arm.

Table 2: PCM301 – Baseline characteristics by arm for the Intention-To-Treat (ITT) population

Characteristic	TOOKAD Soluble VTP arm N = 206	AS arm N = 207
Age (years)		
Mean (SD)	64.2 (6.70)	62.9 (6.68)
Range: min, max	45, 85	44, 79
Patients aged > 75 years old, n (%)	6 (2.9)	6 (2.9)
Unilateral disease, n (%)	157 (76.2)	163 (78.7)
Bilateral disease, n (%)	49 (23.8)	44 (21.3)
Clinical stages		
T1, n (%)	178 (86.4)	180 (87.0)
T2a, n (%)	28 (13.6)	27 (13.0)
Total number of positive cores		
Mean (SD)	2.1 (0.68)	2.0 (0.72)
Range: min, max	1, 3	1, 3
Estimated prostate volume (cc)		
Mean (SD)	42.5 (12.49)	42.5 (11.76)
Range: min, max	25, 70	25, 70
PSA (ng/mL)		
Mean (SD)	6.19 (2.114)	5.91 (2.049)
Range: min, max	0.1, 10.0	0.5, 10.0

Of the 206 subjects randomised TOOKAD Soluble VTP, 10 did not receive treatment: 3 withdrew consent, 3 were excluded because of exclusion criteria (bladder cancer discovered on pretreatment MRI, Gleason 3 + 4 score on previous biopsy, history of transurethral prostate resection), 1 was withdrawn by the investigator because of non-compliance, 1 had a myocardial infarction, 1 was claustrophobic so unable to undergo the pretreatment MRI, and 1 had an anaesthesia reaction before receipt of any padeliporfin or laser treatment.

Tables 3 and 4 describe the co-primary efficacy endpoints in the whole prostate gland and in the treated lobe (ITT population).

Table 3: PCM301 – Co-primary efficacy endpoints – Whole prostate gland - ITT population

Number of subjects with	TOOKAD Soluble VTP arm N = 206	AS arm N = 207
A: Rate of absence of definite cancer based on histology at 24 months		
Negative biopsy, n (%)	101 (49.0)[a]	28 (13.5)[a]
No biopsy result, n (%)	38 (18.4)	86 (41.5)
Subjects who had radical therapy leading to missing biopsy, n (%)	12 (5.8)	55 (26.6)[b]
Other reasons[c], n (%)	26 (12.6)	31 (15.0)
Positive biopsy, n (%)	67 (32.5)	93 (44.9)
[a]Risk Ratio (95% CI) = 3.62 (2.50, 5.26); p value < 0.001 [b]Among the 60 patients who had radical therapy, 5 patients had a Month 24 biopsy [c]For example: study withdrawal, medical reason, subject refusal		
B: Difference in rate of treatment failure associated with observed progression of disease		
Number of subjects progressed at Month 24, n (%)	58 (28.2)[d]	120 (58.0)[d]
Progression to Gleason ≥ 4	49 (23.8)[e]	91 (44.0)[e]
[d]Crude HR (95% CI) = 0.34 (0.25, 0.47) [e]p value ≤ 0.001		

Table 4: PCM301 - Co-primary efficacy endpoints - Treated lobe/lobe with disease at baseline – ITT population

Number of subjects with	*TOOKAD Soluble VTP* arm N = 206	AS arm N = 207
A: Rate of absence of definite cancer based on histology at 24 months		
Negative biopsy, n (%)	129 (62.6)	40 (19.3)
No biopsy result, n (%)	38 (18.4)	86 (41.5)
Subjects who had radical therapy leading to missing biopsy, n (%)	12 (5.8)	55 (26.6)[a]
Other reasons[b], n (%)	26 (12.6)	31 (15.0)
Positive biopsy, n (%)	39 (18.9)	81 (39.1)
[a]Among the 60 patients who had radical therapy, 5 patients had a Month 24 biopsy [b]For example: study withdrawal, medical reason, subject refusal		
B: Difference in rate of treatment failure associated with observed progression of disease		
Number of subjects progressed at end of follow-up, n (%)	30 (14.6)[c]	105 (50.7)
[c]Hazard ratio relative to active surveillance (95% two-sided CI) = 0.17 (0.12 ; 0.27) based on a Cox proportional hazards model		

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 Soluble 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 5: PCM301 - Number of subjects with radical treatment at 24 months – ITT population

Characteristic	TOOKAD Soluble VTP arm N = 206	AS arm N = 207
Number of subjects who initiated a radical treatment, n (%)	12 (5.8)	62 (29.9)
Number of subjects who initiated a radical treatment after progression, n (%)	11 (5.3)	54 (26.1)

Effect on urinary morbidity (IPSS) and erectile function (IIEF) following TOOKAD Soluble VTP
As shown in Table 6, in PCM301 study, the International Prostate Symptoms Score (IPSS) showed, 7 days after the VTP procedure, a mean increase of 7.2 points (from 7.6 to 14.8) on a 35-point scale in comparison to baseline values. Those results were improved at Month 3 (9.6) and back to baseline values at Month 6 (7.5) with further improvement until Month 24 (6.6). In the Active Surveillance arm, the IPSS score slightly worsened over time until Month 24.

Table 6: PCM301 – Effect on urinary morbidity (IPSS) – ITT population

	TOOKAD Soluble VTP arm		AS arm	
	n	Mean score (SD)	n	Mean score (SD)
Baseline	179	7.6 (6.09)	185	6.6 (5.30)
Day 7	180	14.8 (8.64)	Not applicable	
Month 3	179	9.6 (6.86)	190	7.2 (5.75)
Month 6	182	7.5 (6.06)	189	6.8 (5.84)
Month 12	177	7.2 (5.85)	173	7.3 (5.95)
Month 24*	165	6.6 (5.47)	154	8.2 (6.47)

*Scores at Month 24 include patients who underwent radical therapy.

As shown in Table 7, erectile function domain scores of the 15-question International Index of Erectile Function (IIEF-15) questionnaire showed a marked decrease of 7.1 points (from 18.6 to 11.5) on a 30-point scale 7 days after the VTP procedure in comparison to baseline values. There is a subsequent improvement of the erectile function in the following months and, at Month 24, the IIEF-15 score was 15.0 in the VTP arm.

Table 7: PCM301 – Effect on erectile function (IIEF) – ITT population

	TOOKAD Soluble VTP arm		AS arm	
	n	Mean score (SD)	n	Mean score (SD)
Baseline	184	18.6 (10.22)	188	20.6 (9.92)
Day 7	165	11.5 (10.96)	Not applicable	
Month 3	171	14.7 (10.48)	182	21.0 (9.84)
Month 6	176	16.1 (9.98)	185	20.4 (9.83)
Month 12	170	15.1 (10.28)	167	19.9 (10.29)
Month 24*	159	15.0 (10.70)	152	16.8 (11.17)

*Scores at Month 24 include patients who underwent radical therapy.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of TOOKAD Soluble 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 Soluble 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 Soluble is unlikely to be an inhibitor of CYP450 enzymes.

In vitro studies indicate that TOOKAD Soluble 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 both healthy volunteers and patients.
The results of the population PK study showed that age, race, health status and hepatic function were unlikely to have a substantial and biologically significant impact on the pharmacokinetics of TOOKAD Soluble.
The body weight of patients (range 60-120 kg) presented a minor impact on the TOOKAD Soluble 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, 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
The expiry date of the product is indicated on the packaging materials.
After reconstitution
The chemical and physical stability of TOOKAD Soluble after reconstitution with 5 % glucose solution, in its vial, has been demonstrated for 8 hours at room temperature (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 Soluble 200 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 padeliporfin di-potassium 200 mg powder.

Pack size: 1 vial

TOOKAD Soluble 400 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 padeliporfin di-potassium 400 mg powder.

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 Soluble is prepared by reconstituting the powder for solution for injection with:
- 20 mL of 5 % glucose solution for TOOKAD Soluble 200 mg,
- 40 mL of 5 % glucose solution for TOOKAD Soluble 400 mg.

The vial should then be swirled gently for 2 minutes. Each mL of the resulting solution will contain 10 mg of padeliporfin di-potassium. The vial should rest in an upright position for 3 minutes without further shaking or moving. Due to the photosensitising properties of TOOKAD Soluble, 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. MANUFACTURER AND LICENSE HOLDER

Steba Laboratories Ltd.
16-18 Einstein St. Kiryat Weizmann, Science Park, Ness Ziona, Israel

8. MARKETING AUTHORISATION NUMBER(S)

TOOKAD 200 mg: 159 01 34862
TOOKAD 400 mg: 158 99 34863

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