Informed Consent form for obtaining medical treatment
VTP procedure with TOOKAD soluble®. An information sheet for a patient in Israel

Confidential

You were invited by your physician to undergo a new prostate cancer treatment called VTP (Vascular Targeted Photodynamic treatment) by TOOKAD soluble®. This preparation is supplied by Steba Laboratories LTD in Israel and is approved by the Israeli Ministry of Health.

Before you consent to this treatment, you must be informed of the risks and potential benefits of the procedure. This process is called an informed consent and is intended to provide you with all the relevant information about the treatment, so that you can adopt a rational choice.

Please read carefully the following information. If after reading the information sheet you have further questions, please don't hesitate to ask your physician.

I hereby declare that I got an explanation by _____ (name of the explaining physician).

1. To whom the VTP treatment with TOOKAD soluble® is intended.

The treatment is intended for patients with low-risk localized prostate cancer:
• Tumor on one side of the prostate
• Without spread to the capsule of the prostate, semen tubes or lymph nodes
• No more than 3 positive biopsy samples
• Clinical stage up to T2a
• Gleason staging $\leq$ 6
• Blood PSA level $\leq$ 10

2. General background and the importance of the treatment

VTP therapy with TOOKAD soluble® is intended to treat prostate cancer without preventing possible other treatments in the future. The treatment destroys the tumor within the prostate by a procedure which is minimally invasive. During clinical trials which included more than five hundred patients, that treatment demonstrated a good safety profile with less complications that occur after surgery, irradiations, heating treatments (HIFU) or freezing. During the trials, it was shown that the treatment reduced the probability of disease progression by more than 50 percent.
To date, VTP treatment with TOOKAD soluble® has been approved for use in the following countries: EU, Israel and Mexico.

3. How is VTP treatment with TOOKAD soluble® done?

- VTP with TOOKAD soluble® uses a drug that causes the body to be sensitive to light (photosensitizer). The drug is inserted into the blood by infusion into the vein and disperses throughout the body. In order for the drug to act it needs to be activated by laser light which is activated simultaneously with the photosensitizer. The light penetrates the prostate gland by means of optical fibers, which are inserted into the prostate by thin needles that are inserted through the skin between the scrotum and anus. The light activates the drug to destroy of prostate tissues. The entire procedure is performed under general anesthesia and can last up to 3 hours.

- **On the day before or in the morning of the procedure:** you will be admitted to the hospital.

- **On the day of the procedure:** you will be given general anesthesia. Thin fiber optics will be inserted into your prostate, under ultrasound control. This procedure is done by a small number of needles through the skin between the scrotum and the anus.

- TOOKAD soluble® will be given by infusion into a vein in the arm during approximately 10 minutes. You will receive a dose of 4 mg of TOOKAD soluble® per kilogram of body weight (mg / kg) with an energy of 200 J / cm. The TOOKAD soluble® dose is less than one third of the highest dose (15 mg / Kg) which was given to healthy volunteers and is well tolerated.

- Low intensity light, produced by a laser, is transmitted through optical fibers to activate the drug inside your prostate.

- At the end of the procedure, a thin plastic tube (catheter) is inserted into the bladder to ensure a comfortable drainage of your urine.
  You may get antibiotics to reduce the risk of infection and a painkiller will be given to you if required.

Discharge from hospital

After the VTP procedure: you will stay at the hospital for at least 6 hours.
The drug can sesitize the entire body to light but examinations demonstrated that TOOKAD soluble®
affects the skin for up to 6 hours. Other patients and healthy subjects receiving this drug did not experience skin symptoms. However, in order to avoid the possibility of skin reactions, during the first 6 hours after treatment, you will remain in a partially lit area. You should be protected from strong light for 24 hours and avoid sun exposure for the first 48 hours after treatment. If you need to go out before the end of 48 hours, the skin should be protected by long, dark clothing and the eyes by dark goggles.
6 hours after treatment you can use a phone or a computer and watch TV from a distance of at least 2 meters.
After 48 hours there are no limitations on exposure to light.

Additional visits

After discharge, you will be given a new appointment to remove the catheter from the urinary tract. Follow-up will then be proceeded by the attending physician. Follow-up will include:
- PSA – blood PSA levels and rate of change every 3 months in the first year after treatment and thereafter every 6 months.
- MRI - 8 weeks and 24 months after treatment.
- Biopsies - Between two and four years, and seven years after treatment. Biopsies will be taken from the treated area and from other areas if a tumor in these areas is suspected. Additional biopsies may be taken according to clinical assessment by the physician.
- Assessment of the urinary system functioning and sexual functioning before treatment, as well as once during 6 months and again a year after the treatment.
- Rectal examination of the prostate no more than once a year unless there is a clinical necessity.

4. You should inform the attending physician if you are taking any medication that belongs to one of the following therapeutic groups:

Interactions with other medications are possible but are unlikely to occur due to the short time during which TOOKAD soluble® is in the body.
Report to a doctor or a pharmacist if you take, has taken recently or may take any other medication, including Non-prescription medications. There are drugs (especially drugs that induce sensitivity to light or affect blood clotting) that may react with TOOKAD soluble® thus it will be necessary to stop their use before treatment. It may also be necessary not to take certain medications for several days after the procedure. Your physician will also recommend which drugs may be replaced by others, and when these medications can be re-started after treatment with TOOKAD soluble®.

Your physician may advise you to temporarily stop taking the following types of medication:
Medications that may cause light sensitivity:
- Certain antibiotics which are being used to treat infection (tetracycline, quinolones, sulfonamides).
- Certain psychiatric drugs (phenothiazines).
- Certain medications for adult diabetes (sulfonamides).
- Certain medications for the treatment of hypertension, fluid retention, heart failure or renal insufficiency (diuretic thiazides).
- a drug used to treat fungal infections (griseofulvin).
- a drug used to treat heart rate disorders (amiodarone).

These medications should be stopped for at least 10 days before treatment and at least 3 days after treatment or be replaced by other treatments that do not cause light sensitivity. If drugs that cause light sensitivity (such as amiodarone) cannot be stopped, increased sensitivity may occur and you may need to protect yourself from direct exposure to light for a longer period of time.

Blood thinners (anticoagulants):
Anticoagulants which are intended to reduce aggregation of platelets (such as acetylsalicylic acid) should be stopped prior treatment with TOOKAD soluble® and restart taking them after the procedure, according to the instructions or recommendations provided by the manufacturer of each product.

Other medicines that may respond with TOOKAD soluble®:
Use of medications such as repaglinide, atorvastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin, bosentan and glyburide should be avoided on the day of treatment with TOOKAD soluble® and at least 24 hours thereafter.

5. Are there risks associated with the procedure?
Risks associated with general anesthesia are identical with those of any such procedure. They may include nausea, vomiting, a temporary sore throat (from the tube used for ventilation), and loss of concentration during the first few hours after awakening. Serious complications associated with anesthesia for this type of procedure are extremely rare. There are some other risks that are associated with the drug itself, which are described below.

6. What are the expected side effects of this treatment?

Possible side effects in patients treated by vascular targeted photodynamic therapy (VTP) TOOKAD soluble®are:

A) **Skin reaction** – a risk of skin response similar to sunburn if you are exposed to strong lights during the first hours after administration of the medicine. While you are in the operating room and for 6 hours after surgery, your eyes and skin will be protected from light, however, this risk will disappear the next day.

B) **Bleeding and Infections** - rarely, when needles are inserted into the prostate, bleeding and infection may occur. We will take measures to prevent that, such as antibiotics that may be given to you before the procedure.

C) **Urination and sexual functioning** –all treatments for prostate cancer bear a certain risk of causing urinary tract and sexual functioning problems.

There may be temporary difficulty with urination (urgency, frequency, slight sensation of "burning") or to control urination (difficulty in starting urination or dripping control). We expect those to subside without treatment, but if not, appropriate treatment will be provided. The urine catheter will be inserted before the procedure. It is likely to be removed 24 hours after the procedure if you can urinate freely. If not, the catheter will be left for a longer time and removed once the prostate swelling, due to the procedure, will abate.

Many patients with prostate cancer experience a decrease in sexual functioning. We cannot guarantee that VTP will not exacerbate such problems.

Important information for sexually active men: If your partner falls pregnant within three months of your treatment, you should notify your physician immediately. The fetus may be exposed to risks, which are currently unknown. During the first three months after treatment, it is recommended to use contraceptives such as a condom for men or birth control pills or an intrauterine device for women.

D) **Rectal injury** - there is a risk that the anus may be injured by this treatment. In order to limit it, a light detector is placed inside the rectum during the procedure. If the rectum is injured, an opening called fistula may develop between the rectum and the urethra. That can also be a detrimental side effect of another active prostate cancer treatment (for example surgery, irradiation, brachytherapy, etc.).

E) **Pain** - symptoms of discomfort or pain may occur after treatment. If necessary, we will provide you with painkillers. You may experience urgency or tingling while you urinate after VTP, but that is likely to disappear within a week or two.

F) **Cardiovascular problems** - In previous studies with TOOKAD soluble®, no significant problems were observed. However, the procedure involves general anesthesia which can cause, in rare cases, complications such as heart attack, thrombosis (a formation of blood clot in blood vessels), pulmonary embolism (blockage of blood vessels caused by a blood clot). Therefore, your cardiovascular status will be examined very carefully and appropriate tests will be carried out to determine your suitability to undergo this treatment. However, we cannot guarantee that such events will not occur.

G) If a medical problem requiring immediate treatment occurs during the course of the procedure, the physician will provide appropriate treatment.

Your physician should be informed about any case of a side effect.
Additionally, side effects can be reported to the Ministry of Health via the link
"דיווח על תופעת לוואי עקב טיפול תרופתי" that can be found on the home page of the Ministry of Health website (www.health.gov.il) directing to the portal for reporting side effects or via the following link:
https://sideeffects.health.gov.il

7. Alternative treatments

Possible alternative treatments include:
• Active monitoring
• Heating in ultrasound (HIFU)
• Freezing of the tumor (cryotherapy)
• Cooling
• Local irradiation by radioactive "seeds" (brachytherapy)
• A complete dissection of the prostate (Radical prostatectomy)

8. What if new information accumulates?

If new information about the treatment becomes available, your physician will inform you and discuss it with you. If you decide to withdraw your consent, your physician will carry on your routine treatment.

9. What are my options if treatment is not successful?

It is expected that all the treatment options that are available for you today (see Section 7 - Alternative Treatments) will still be available if you need further treatment after treatment with a TOOKAD soluble®.
If you will need additional treatment for prostate cancer after treatment with a TOOKAD soluble ® (such as surgery for prostate removal or irradiations), it is not yet known whether such treatment will be as successful as it could have been in the first place. Namely, treatment with TOOKAD soluble® may make it difficult to perform additional treatments for your prostate cancer, reduce the likelihood that they succeed, or lead to more side effects.

10. What if something goes wrong?

If you have concerns about any aspect of this treatment, you should talk to your physician [phone number of the attending physician] and he will do his best to answer your questions. In any problem related to the treatment, I can contact Prof / Dr. _____ by phone / mobile: _____ I must report immediately to the physician of the above details about any medical problem, injury or other health occurrence that may be related to the treatment. If I am injured as a result of the treatment, I need to approach the physician in order to receive an appropriate medical treatment, as well as additional details about my right in this regard. Signing this form does not diminish my rights under the Law.

Compensation for any injury caused by the treatment will be in accordance with the requirements of Israeli law.

11. Documentation of medical information?

Each patient undergoing a procedure with TOOKAD soluble® is registered in a database available to the attending physicians and the Ministry of Health.
The database includes:
- Medical condition prior to treatment.
- Report on the course of the treatment
- Side effects, if any.
- Information collected during follow-up after the treatment.

12. Will my personal data be kept secret?

All the information collected about you during this special authorization will remain confidential. The following steps are taken to ensure the protection of your personal information:

• Your name will remain confidential to parties other than the attending physician and the hospital.
• Your medical information will be stored on a secure server in a separate computer than the one which contains your personal information.

All your medical records which were collected in the course of this treatment (blood test, biopsy results, urinary tract function, surgical interventions ...) will be available anonymously for review by the registration holder or persons on his behalf for the purpose of documentation and analysis of the results. The information will be forwarded anonymously to the health authorities in Israel. Access to the medical information will be carried out with confidentiality, in accordance with confidentiality laws and procedures.

13. Further information

For more information on the TOOKAD soluble® VTP procedure, you can contact your physician (please add here the contact details of your attending physician)

The decision of whether or not you are suitable for treatment with TOOKAD soluble® is taken by the attending physician

Thank you for reading this information sheet and for your willingness to consider the VTP procedure by TOOKAD soluble®.

If you decide to undergo the procedure, you will get a copy of this information sheet, a copy of a signed consent form, and an information card for the patient.

An informed consent form
VTP procedure with TOOKAD soluble®

The name of the attending physician: _____

Please sign with initials in each square

1. I hereby confirm that I read and understood the information sheet, about the above treatment, and had the opportunity to ask the physician questions. ☐

2. I am assured of willingness to answer questions raised by me, as well as the possibility of consulting with another entity (e.g. family physician, family members, etc.), as for the decision to undergo the medical and / or continue to continue it. ☐

3. I understand that I am free to choose not to receive the treatment and that I am free at any time, to terminate my consent to have the treatment without prejudice of my right to receive conventional medical treatment. ☐

4. Since the treatment is harmful to fetuses, in the event of pregnancy of a partner of a participant who received the treatment (three months since treatment), she has the right to be consulted concerning the risks for the pregnancy and the fate of the pregnancy. ☐

5. I understand that the information about my medical condition and the treatment I get will be documented in the patient registry which is part of the treatment program and will include the following information: The information will be forwarded anonymously to the Steba Company and to the Israeli Ministry of Health. I am assured that my identity will be kept confidential by all those who are involved in the treatment and that it will not be revealed in any publication including scientific publications. ☐

6. I understand that the Steba Labs staff can participate in the treatment procedure, I grant them permission to be present in the operating room during treatment. ☐

7. I agree to undergo the VTP procedure using TOOKAD soluble®. ☐

8. I hereby declare that I have given this consent of my own free will and that I understood all of the above and received a copy of this informed consent form, dated and duly signed. ☐

After you've initialed all of the above sections, please fill in the details below, including the date.

_____	_____	_____
Name of the patient	Date	Signature

_____	_____	_____
Name of the attending physician	Date	Signature

In case of problems contact the physician at (_____)
Or the urology staff through the hospital switchboard (_____)

This document format and content were checked and approved by the Ministry Of Health in September 2019