

**USEFUL INFORMATION FOR PATIENTS
THAT HAVE BEEN DIAGNOSED WITH
PROSTATE CANCER AND ARE ELIGIBLE
FOR VASCULAR-TARGETED
PHOTODYNAMIC (VTP) THERAPY WITH
TOOKAD®**

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Dear Patient,

After a careful evaluation of your case, you have been deemed eligible for vascular-targeted photodynamic (VTP) therapy with **TOOKAD®**

In this document, we would like to summarize some information that is fundamental in order to fully understand the treatment you have been offered and to help you take an informed decision.

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1. What are the purposes of this guide?

You have been diagnosed with low grade cancer located in one lobe of the prostate. Your disease is considered low risk and you are eligible to receive vascular-targeted photodynamic (VTP) with **TOOKAD®**. This is a form of focal therapy, which is a treatment aimed at a specific portion of the prostate.

The possible benefits, risks, and uncertainties associated with VTP with **TOOKAD®** are outlined here to help you make an informed decision. This guide does not replace the **TOOKAD®** package information, which you will receive later if you decide to undergo the procedure for targeted vascular photodynamic therapy (VTP) with **TOOKAD®**.

2. What is the treatment of low-risk prostate cancer?

There are several options for managing low-risk prostate cancer. For example:

- Active surveillance

which includes regular checkups, cyclical prostate biopsy and treatment only if the disease gets worse

- Radical prostatectomy

surgical removal of the prostate

- External beam radiotherapy

or radiotherapy which involves applying an external source of ionizing radiation to the prostate

- Brachytherapy

or insertion of radioactive implants into the prostate

- Other focal therapies including

to. cryoablation (destruction of tissue through the use of extreme cold)

b. High-Intensity Focused Ultrasound (HIFU)

c. VTP with **TOOKAD®** (intravenous injection of **TOOKAD®** followed by illumination with fibers, inserted only in the lobe of the prostate where the carcinoma is located).

Active surveillance, radical prostatectomy, external beam radiotherapy and brachytherapy have been the subject of long-term studies, which have shown a median long-term survival of 95% over 10 years.

TOOKAD[®] therapy has been investigated in clinical trials comparing its efficacy and safety with active surveillance.

Your doctor will explain these treatment options to you.

3. What is TOOKAD[®]?

➤ TOOKAD[®] is a medicine containing a substance called padeliporfin, capable of making the organs and tissues sensitive to light.

➤ The medicine is injected intravenously (IV) and then activated by laser light emanated through the fibers that have been inserted into the prostate.

➤ The location of the fibers is determined using the treatment guide software based on the volume and location of the tumor.

➤ The treatment is carried out under general anesthesia.

4. What are the potential benefits of TOOKAD[®] ?

In the main clinical study comparing TOOKAD[®] with active surveillance 197 patients were treated with TOOKAD[®] -VTP and 207 patients were under active surveillance.

After two years, 52 of the 80 patients (65.0%) with initial disease in only one lobe of the prostate had a negative biopsy (i.e., no signs of cancer) in the lobe treated with TOOKAD[®] -VTP, compared to 11 of 78 patients (14.1%) in the active surveillance group.

More than two years after TOOKAD[®] -VTP therapy, the percentage of patients who progressed to a larger or more aggressive form of cancer was half of that seen with active surveillance (27 of 80 patients [33.8 %] compared to 53 of 78 patients [67.9%]).

5. What are the risks and side effects associated with TOOKAD® therapy ?

Like all medications, TOOKAD® can cause side effects. Many of these, if they occur, are short-lived but some may last longer and may be persistent.

The following information on the most frequently observed undesirable effects is based on data from the clinical study, in which 197 patients were treated with TOOKAD®-VTP and 207 patients were under active surveillance (monitoring at regular intervals).

➤ Erectile dysfunction (difficulty getting or maintaining an erection)

- Patients with prostate cancer can have problems related to sexual function.
- TOOKAD®-VTP therapy may make these problems worse.
- If erectile dysfunction occurs, it begins soon after the TOOKAD®-VTP procedure and tends to gradually improve. However, some degree of erectile dysfunction may persist after 6 months.
- 60 patients (30.5%) in the TOOKAD®-VTP arm experienced erectile dysfunction:
 - 7 patients (3.6%) experienced erectile dysfunction for less than 6 months
 - In one of these seven patients, erectile dysfunction was moderate (need for medical therapy or devices to achieve an erection). This patient recovered while maintaining some degree of residual dysfunction.
 - Six of these patients experienced mild erectile dysfunction (some difficulties and potential need for drug therapy to achieve or maintain an erection) and recovered completely.
 - 19 patients (9.6%) experienced erectile dysfunction for more than 6 months
 - All recovered during the two years of the study.

- Among these 19 patients, erectile dysfunction was severe in one patient (impotence), moderate in 10 patients and mild in 8 patients.
- o 34 patients (17.3%) experienced erectile dysfunction which did not resolve after two years
 - Among these 34 patients, erectile dysfunction was moderate in 14 patients and mild in 20 patients.
- Urinary incontinence (loss of urine from coughing, exertion or before reaching the bathroom)
 - 25 patients (12.7%) in the TOOKAD[®]-VTP arm experienced urinary incontinence:
 - o 13 patients (6.6%) in the TOOKAD[®]-VTP arm experienced urinary incontinence for less than 6 months
 - Among these 13 patients, 12 cases occurred two months after the procedure and one case started about four months after the procedure.
 - 7 cases were moderate (needing to use sanitary pads) and 6 cases were mild (unnecessary sanitary pads).
 - Incontinence can be linked, in some cases, to infection that may arise following the procedure or to the need to use a bladder catheter.
 - o 5 patients (2.5%) in the TOOKAD[®]-VTP arm experienced urinary incontinence for more than 6 months
 - All recovered during the two years of the study.
 - Among these 5 patients, urinary incontinence was moderate in 1 patient and mild in 4 patients.
 - o 7 patients (3.6%) in the TOOKAD[®]-VTP arm experienced urinary incontinence which did not resolve after two years
 - A patient has experienced severe urinary incontinence (large urine leakage) due to previous prostate surgery which is currently not allowed prior to TOOKAD[®]-VTP therapy .
 - Urinary incontinence was moderate in one patient and mild in 5 patients.

➤ Urinary retention / urethral stricture

- Urinary retention can occur as a result of swelling of the prostate after the TOOKAD®-VTP procedure.
- In the pivotal clinical study, 15 patients (7.6%) experienced urinary retention
 - 2 cases were severe (indication for surgery) and 12 were moderate (indication for drug therapy)
 - patients in both groups needed a temporary bladder catheter.
 - 1 case was mild (possible urination / unnecessary drug therapy).
 - All patients recovered after 43 days.
- In addition, 2 patients (1.0%) developed urethral stricture (an abnormal narrowing of the channel that carries urine from the bladder to the outside of the body).
 - For these patients, urethral dilation (surgery aimed at expanding the channel that carries urine from the bladder to the outside of the body) was required.

➤ Photosensitivity (redness of the skin and eye damage)

- TOOKAD® has a photosensitizing effect, meaning it makes skin and eyes sensitive to light.
- Therefore, you will need to protect yourself from light for 48 hours after the TOOKAD®-VTP procedure .
- To date, photosensitivity has not been a problem, as patients have carefully followed the instructions for light protection.

6. What are the uncertainties regarding the risks and benefits of TOOKAD® therapy ?

What is the current knowledge on the long-term effects of TOOKAD®-VTP therapy ?

- At present, little information exists regarding the period beyond two years after the TOOKAD®-VTP.

- Patients in the study generally did not have a prostate biopsy beyond two years, so it is not known whether the benefit of TOOKAD®-VTP therapy continues over time. It is certain that the therapy delays the need for another treatment for prostate cancer but it is not known whether it can eliminate the prostate cancer for a long time.
- It is too early to know whether TOOKAD®-VTP may be the only therapy needed for your prostate cancer.
- It is not known whether other undesirable effects may subsequently arise from tissue damage (necrosis and fibrosis) caused by TOOKAD®-VTP.
- It is not known whether TOOKAD®-VTP therapy can make any prostate cancer cells remain alive after the procedure more aggressive.

What if further treatment is required after TOOKAD® -VTP therapy?

In the event that further treatment for prostate cancer is required after TOOKAD® -VTP therapy (for example, surgery to remove the prostate or radiation therapy), it is not known whether such treatment will be as successful as it would without the treatment. In other words, TOOKAD® -VTP therapy could make additional prostate cancer treatments more difficult to perform properly, less effective, or lead to more side effects.

Is there more information on potential risks and potential uncertainties?

Information is currently being collected from patients undergoing the TOOKAD® -VTP procedure to better understand the long-term risks and benefits, but no firm conclusions exist yet.

7. How you will be followed-up after TOOKAD®

If you are undergoing TOOKAD®-VTP therapy, you will be followed up to verify that the treatment was successful, as follows:

- Prostate Specific Antigen (PSA) measurement every 3 months for the first two years after VTP and every 6 months thereafter;
- Digital Rectal Examination (DRE) at least annually or more frequently based on the doctor's advice;
- prostate biopsy from the 2nd year to the 4th year and the 7th year. Other biopsies may be needed outside of these time frames if your doctor thinks the cancer may have returned, based on PSA and DRE;
- magnetic resonance imaging (MRI) to check for the absence of the tumor and to assess whether a biopsy is needed.

Where can you find more information on targeted vascular photodynamic therapy?

Your doctor will tell you what additional information is available on the efficacy and safety of TOOKAD®-VTP therapy.

This guide is intended to provide accurate information; however, the contents reported here may be different, on some occasions, from the advice offered by the doctor.

Reporting of side effects

If any side effects occur, please tell your doctor, pharmacist or nurse. You can also report side effects via the national reporting system. By reporting side effects you will help provide more information on the safety of this medicine.

As for future check-ups, we recommend that you carefully follow all that has been written in the discharge letter.

It is a great pleasure for me to have the chance to treat you. I hope you will always consider our entire medical staff as both doctors and friends.

While remaining at your complete disposal for any further clarification, I take this opportunity to offer you my best regards.

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