VASCULAR-TARGETED PHOTODYNAMIC THERAPY (VTP) WITH TOOKAD® SOLUBLE

GUIDELINE FOR THE PHYSICIAN

THIS MATERIAL IS ADDITIONAL TO THE INFORMATION INCLUDED IN THE PROTOCOL OF TRAINING FOR VTP WITH TOOKAD® SOLUBLE

1 OBJECTIVES

The objectives of this document are to provide to the physician:
- The information to be communicated to the Patient during the visit at which the existing therapeutic options for the treatment of their prostate cancer, including TOOKAD® Soluble VTP, are discussed;
- The information to be communicated to the Patient after they have decided to accept the procedure.

2 INFORMATION FOR PHYSICIANS

2.1 Physicians performing the VTP with TOOKAD® Soluble procedure should be trained and certified prior to the procedure.

2.2 A patient registry exists for VTP-treatment by TOOKAD® Soluble to which only Certified Physicians 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.
In short the registry is divided into four sections; (i) Patient/treatment (ii) VTP Procedure (iii) Pharmacovigilance (iv) Follow-up

- Prior to providing treatment the Physician will fill out the pertinent **Rx-FORM** which will automatically load the patient-information into the **PATIENT/TREATMENT section** of the REGISTRY.
- In the **VTP section** of the REGISTRY a link to the TOOGUIDE TRUS-REPORT generated during the procedure will be uploaded by the Steba administrator
- Any adverse events will be filled out by the healthcare personnel in the **PHARMACOVIGILANCE section** of the REGISTRY and in addition be reported to Steba's QPPV who will be responsible for reporting them to the Ministry of Health.
- Finally, the treating physician will be responsible for uploading information generated during periodic follow-ups into the **FOLLOW-UP section** of the REGISTRY.

3 INFORMATION TO BE PROVIDED TO THE PATIENT

In order that the patient can make an informed decision on their therapeutic options, the physician should discuss with them:

- The existing approaches (including VTP with TOOKAD® Soluble) for the treatment of their type of prostate cancer;

- Outline the potential benefits, risks and uncertainties of VTP with TOOKAD® Soluble, in particular:
    - That, 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® Soluble-VTP is long-lasting;
    - The lack of information on long term safety and efficacy/safety of any further treatments required such as radical prostatectomy;

- Explain what the VTP procedure involves, in particular, the need to follow the rules to protect the patient against the light after the procedure for 48 hours, due to the photosensitising effect of TOOKAD® Soluble:

  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.

- Explain important drug interactions:

  Photosensitisers

  Medicinal products which have potential photosensitising effects 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.

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.

- Explain what side effects the patients might expect and the likelihood of them getting them.

  The most common side effects are listed below.

  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.

  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 has been 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 patients with pre-existing stenosis were excluded from the clinical trials, there is a potential risk of increased stenosis post the TOOKAD® Soluble -VTP procedure in those patients.

  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, including transurethral resection of the prostate (TURP) for benign prostatic hypertrophy.

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.

For additional information please refer to SmPC.

The physician should provide a copy of the TOOKAD Soluble Patient Information Guide to the patient **ahead of the VTP procedure**, explain him clearly the instructions to avoid light after the procedure and remind him of the importance to follow them.

4 POST-OPERATIVE MANAGEMENT OF THE PATIENT

- **Information to the patient regarding 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

- **Follow-up**

  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 questionnaires are to be filled out once within the first six months post treatment and again after one year.
- Digital Rectal Examination (DRE) not more often than once a year unless clinically indicated.

- **Registry documentation follow-up**

  For information about the Patient Registry see section 2.2.

  In particular note that the Healthcare personnel are responsible for uploading the follow-up info in to the Registry.

- **Reporting adverse reactions**

  Reporting suspected adverse reactions after authorization 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 the portal for reporting side effects https://sideeffects.health.gov.il/

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