Part VI: Summary of the risk management plan

Summary of risk management plan for TOOKAD® (Padeliporfin)

This is a summary of the risk management plan (RMP) for TOOKAD®. The RMP details important risks of TOOKAD®, how these risks can be minimised, and how more information will be obtained about TOOKAD®'s risks and uncertainties (missing information).

TOOKAD®'s summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how TOOKAD® should be used.

This summary of the RMP for TOOKAD® should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of TOOKAD®'s RMP.

I. The medicine and what it is used for

TOOKAD® is authorised for treatment of adult men who have low-risk, localised prostate cancer in only one lobe, using a technique called Vascular-Targeted Photodynamic (VTP) therapy (see SmPC for the full indication).

It contains padeliporfin as the active substance and it is given by the intravenous route of administration.

Further information about the evaluation of TOOKAD®'s benefits can be found in TOOKAD®'s EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage

https://www.ema.europa.eu/en/documents/overview/tookad-epar-summary-public_en.pdf

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of TOOKAD®, together with measures to minimise such risks and the proposed studies for learning more about TOOKAD®'s risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of TOOKAD®, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of TOOKAD® is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of TOOKAD® are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of TOOKAD®. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	• Photosensitivity • Urethral stenosis
Important potential risks	• Complications of extra-prostatic necrosis • Procedural related injuries and complications • Long-term erectile dysfunction (>6 months) • Long-term urinary incontinence (>6 months) • Procedural related injuries and complications due to non-compliance with the device manufacturers' instructions and recommended guidance for the VTP procedure • Induction of more aggressive tumour histology by TOOKAD VTP • Difficulty of subsequent radical therapy due to reduced size and fibrosis of the VTP-treated prostate
Missing information	• Use in patients with inflammatory bowel disease • Use in patients with hepatic impairment • Use in patients with clotting disorders and concomitant use of anticoagulants or anti-platelet therapy • Long term safety

II.B Summary of important risks

Important identified risk: Photosensitivity	
Evidence for linking the risk to the medicine	Due to the mechanism of action whereby TOOKAD is activated by a specific wavelength of light, there is the possibility that whilst the drug remains in the blood stream, exposed areas of the body including the eyes may become photosensitive to bright light, in particular sunlight, within 48 hours of treatment if the recommended controls such as protection from light are not followed.

Important identified risk: Photosensitivity	
Risk factors and risk groups	The key groups at risk are those patients with known porphyria or photodermatoses. Patients exposed to bright light within the first 24-48 hours are at risk of potential eye photosensitivity injury. Patients who have had recent anti-angiogenic treatment for AMD are also at additional risk.
Risk minimisation measures	Routine risk minimisation measures • SmPC sections 4.4 provides guidance on light protection during and for 48 hours after the procedure; Section 4.8 where undesirable effects are listed; Section 5.3 information on preclinical phototoxicity is provided. • PL sections 2 and 4. • Prescription-only medicine • Restricted to hospital use • Use by personnel trained in the Vascular-Targeted Photodynamic therapy procedure Additional risk minimisation measures • Guideline for the Physician • Patient Information Guide
Additional pharmacovigilance activities	Additional pharmacovigilance activities: CLIN1501 PCM401 See section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk: Urethral stenosis	
Evidence for linking the risk to the medicine	Although relatively uncommon, stenosis can occur due to the combination of having a urinary catheter in place and inflammation due to the procedure itself. Although this can be treated usually by urethral dilation and occasionally with a urethroplasty, it is considered an identified risk due to the unpredictable nature of occurrence and the severity.
Risk factors and risk groups	All patients require catheterisation but it is those that may require longer term catheterisation that may be at higher risk as well as those with a history of urethritis or previous transurethral resection.

Important identified risk: Urethral stenosis	
Risk minimisation measures	Routine risk minimisation measures • SmPC section 4.4 to advise that a history of urethral stricture may exacerbate urinary flow problems and urinary retention; Section 4.8 where undesirable effects are listed. • PL sections 2 and 4 • Prescription-only medicine • Restricted to hospital use • Use by personnel trained in the Vascular-Targeted Photodynamic therapy procedure Additional risk minimisation measures • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: CLIN1501 PCM401 See section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Complications of extra-prostatic necrosis	
Evidence for linking the risk to the medicine	The procedure is designed to cause controlled necrosis of the prostate gland but if this is excessive it may extend into the rectum and it is possible that a fistula may occur between the rectum and the urethra. This is considered an important potential risk due to the serious nature of the event.
Risk factors and risk groups	The key risk factors for VTP are inappropriate placement of light fibres and/or excessive light exposure. However, patients with inflammatory bowel disease affecting the lower rectum may be at increased risk due to the added inflammation expected from the VTP procedure.
Risk minimisation measures	Routine risk minimisation measures • SmPC section 4.4 to provide guidance on the treatment procedure and risks to patients with a history of active rectal inflammatory bowel disease or any condition that may increase the risk of recto-urethral fistula formation; Section 4.8 where undesirable effects are listed. • PL sections 2 and 4 • Prescription-only medicine • Restricted to hospital use

Important potential risk: Complications of extra-prostatic necrosis	
	• Use by personnel trained in the Vascular-Targeted Photodynamic therapy procedure • Measurement of intrarectal fluence prior to drug injection to avoid excess light in the rectum that could result in rectal wall injury Additional risk minimisation measures • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: CLIN1501 PCM401 See section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Procedural related injuries and complications	
Evidence for linking the risk to the medicine	The procedure requires trans-perineal insertion of needles so that laser fibres can be positioned correctly into the prostate. Inevitably this can cause an inflammatory process that causes pain and discomfort in the prostate as well as some bleeding. The use of a urinary catheter during and after the operation for a short period of time may cause other urinary symptoms including the possibility of infection. Such events may cause hospitalisation hence are considered an important potential risk. These effects are usually short lived and resolve completely. Similarly, some erectile dysfunction is possible as a common finding directly after prostate surgery improving over time.
Risk factors and risk groups	All patients undergoing the procedure are at risk of transient urinary symptoms principally because of the manipulations of the prostate including the insertion of needles and the need for a urinary catheter which can also be a cause of infection or bleeding. The bleeding risk is increased if they are taking anticoagulants or anti-platelet therapy or have a bleeding diathesis and possibly in larger prostates. Additionally, the effect of the treatment which is to cause necrosis initially will cause oedema and swelling of the prostatic tissue which can increase the risk of difficulties with urination as well as pain; as the tissue shrinks, these signs and symptoms tend to regress.
Risk minimisation measures	Routine risk minimisation measures • SmPC section 4.4 to advise of risks to patients with abnormal clotting; Section 4.5 to describe management of anticoagulant medicinal products and those that decrease platelet aggregation; Section 4.8 where undesirable effects are listed. • PL sections 2 and 4

Important potential risk: Procedural related injuries and complications	
	• Prescription-only medicine • Restricted to hospital use • Use by personnel trained in the Vascular-Targeted Photodynamic therapy procedure Additional risk minimisation measures • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: CLIN1501 PCM401 See section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Long-term erectile dysfunction (>6 months))	
Evidence for linking the risk to the medicine	The TOOKAD VTP procedure involves the surgical insertion of needles into the prostate gland so the laser fibres can be positioned correctly. Erectile dysfunction is a common finding after prostate surgery and is more likely to occur soon after the operation improving over time; however, a number of patients have experienced long-term erectile dysfunction for more than 6 months.
Risk factors and risk groups	From the data, so far, the greatest risk appears to be when both lobes are treated simultaneously so where only unilateral disease is treated once (as in the approved indication), this risk would appear to be reduced.
Risk minimisation measures	Routine risk minimisation measures • SmPC section 4.4; SmPC section 4.8 where undesirable effects are listed. • PL sections 2 and 4 • Prescription-only medicine • Restricted to hospital use • Use by personnel trained in the Vascular-Targeted Photodynamic therapy procedure Additional risk minimisation measures • None

Important potential risk: Long-term erectile dysfunction (>6 months))	
Additional pharmacovigilance activities	Additional pharmacovigilance activities: CLIN1501 PCM401 See section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Long-term urinary incontinence (>6 months)	
Evidence for linking the risk to the medicine	Permanent or long-term incontinence (lasting more than 6 months) is a potential problem if both the internal and external sphincter (muscle controlling the urethra) are damaged during the surgical procedure. It is a potential risk as usually the procedure is planned to avoid this complication. It happened only in a patient who had a previous prostate tissue resection via the urethra for an enlarged gland with damage at that time to the urinary sphincter and the VTP procedure is now not recommended in patients who have previously had such an operation.
Risk factors and risk groups	The main risk factor is previous transurethral resection of the prostate that damages the urinary sphincter.
Risk minimisation measures	Routine risk minimisation measures • SmPC section 4.3 to advise of contraindication for patients having prior surgical intervention for benign prostatic hypertrophy; Section 4.4; Section 4.8 where undesirable effects are listed. • PL sections 2 and 4 • Prescription-only medicine • Restricted to hospital use • Use by personnel trained in the Vascular-Targeted Photodynamic therapy procedure Additional risk minimisation measures • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: CLIN1501 PCM401 See section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Procedural related injuries and complications due to non-compliance with the device manufacturers' instructions and recommended guidance for the VTP Procedure	
Evidence for linking the risk to the medicine	If the treating Physician does not closely follow the detailed instructions provided for use of this procedure, this could potentially result in an over-treatment of the prostate resulting in some of the treatment risks highlighted above. All the doctors performing this procedure will have been trained in its use but the circumstance of your own disease may mean that they believe that the treatment should deviate from the pre-operative planning. There is a potential risk that this may result in more treatment than is required being given to the area around the prostate.
Risk factors and risk groups	Not applicable
Risk minimisation measures	Routine risk minimisation measures • SmPC section 4.2 giving details of the use of the Treatment Guidance software; Section 4.4 where the importance of using the Treatment Guidance software is stated. • Prescription-only medicine • Restricted to hospital use • Use by personnel trained in the Vascular-Targeted Photodynamic therapy procedure Additional risk minimisation measures • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: CLIN1501 PCM401 See section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Induction of more aggressive tumour histology by TOOKAD VTP	
Evidence for linking the risk to the medicine	When the original biopsy was taken the type of cancer cells along with its location would have been of a sufficiently low grade to mean that the VTP surgery was applicable to the patient. Sometimes, because the biopsy does not sample all of the cancer tissue, it is possible that, on follow-up biopsy, if there are residual cancer cells, that more aggressive tumour cells may be discovered. It is possible that these were there prior to surgery and just missed on the biopsy or that these residual cells have become more aggressive. However, there is no evidence at present that the procedure itself influences the cells to become more aggressive.

Important potential risk: Induction of more aggressive tumour histology by TOOKAD VTP	
Risk factors and risk groups	Currently, there is no current evidence that the finding of a higher Gleason grade represents more aggressive tumour as a result of the focal therapy. The possibility that following focal therapy, the reduced area of prostate with multiple core biopsies allows a better chance to pick up tumour cells which could have been missed when the prostate was larger prior to treatment. Therefore, any focal procedure that leaves behind prostate tissue may carry the risk that previously undiagnosed aggressive cells may become apparent or progress to a more aggressive histology.
Risk minimisation measures	Routine risk minimisation measures • Restricted to hospital use • Use by personnel trained in the Vascular-Targeted Photodynamic therapy procedure • Biopsies reviewed by trained pathology personnel Additional risk minimisation measures • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: CLIN1501 PCM401 See section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Difficulty of subsequent radical therapy due to reduced size and fibrosis of the VTP-treated prostate	
Evidence for linking the risk to the medicine	The VTP procedure causes necrosis of the prostate gland and causes it to shrink in size and become firmer. Also, in order to make sure that as much of the cancer is killed as possible, some necrosis just outside the prostate gland is normal and this may cause the prostate to adhere to adjacent tissues. While there is no current evidence to suggest that this makes the surgery more difficult it is potentially possible that, in some cases, the fact that the prostate is stuck to local structures makes the surgery, should it require removal, to take longer or have more bleeding than usual. In addition, it is possible that, if other radical therapy is required such as radiotherapy (either from externally or by the insertion of radioactive seeds in the prostate), this might not be as easy as if the VTP procedure had not been performed.
Risk factors and risk groups	No particular risk factors or groups have been identified.
Risk minimisation measures	Routine risk minimisation measures • Restricted to hospital use

Important potential risk: Difficulty of subsequent radical therapy due to reduced size and fibrosis of the VTP-treated prostate	
	• Use by personnel trained in the Vascular-Targeted Photodynamic therapy procedure Additional risk minimisation measures • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: CLIN1501 PCM401 See section II.C of this summary for an overview of the post-authorisation development plan.

Missing information: Use in patients with inflammatory bowel disease	
Risk minimisation measures	Routine risk minimisation measures • SmPC section 4.3 as contraindication • SmPC section 4.4 to provide guidance on the treatment procedure and risks to patients with a history of active rectal inflammatory bowel disease • PL sections 2 and 4 • Prescription-only medicine • Restricted to hospital use • Use by personnel trained in the Vascular-Targeted Photodynamic therapy procedure Additional risk minimisation measures • None

Missing information: Use in patients with hepatic impairment	
Risk minimisation measures	Routine risk minimisation measures • SmPC section 4.2 provides information on expected impact and caution of use in patients with severe hepatic impairment. • Prescription-only medicine • Restricted to hospital use • Use by personnel trained in the Vascular-Targeted Photodynamic therapy procedure Additional risk minimisation measures • None

Missing information: Use in patients with clotting disorders and concomitant use of anticoagulants or anti-platelet	
Risk minimisation measures	• Routine risk minimisation measures • SmPC section 4.4 and 4.5 to provide guidance on the treatment procedure and risks to patients with abnormal clotting; Section 4.8 where undesirable effects are listed • PL sections 2 and 4 • Prescription-only medicine • Restricted to hospital use • Use by personnel trained in the Vascular-Targeted Photodynamic therapy procedure Additional risk minimisation measures • None

Missing information: Long term safety	
Risk minimisation measures	No risk minimisation measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: CLIN1501 PCM401 See section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

The following studies are conditions of the marketing authorisation:

CLIN1501 PCM401 - A long-term observational cohort study of patients with unilateral low risk localised prostate cancer treated with TOOKAD® Vascular Targeted Photodynamic therapy in current clinical practice.

Purpose of the study: The study aims at verifying whether the assumptions made from a 2-year clinical trial (PCM301) and preliminary results from a 7-year follow-up (PCM301 FU5) are confirmed in the real life and also at providing information that can only be gathered in the mid-long term.

Primary Objective: The co-primary objectives of the study are to assess the long term (7 years) safety and effectiveness of TOOKAD® VTP in the real-life clinical practice.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for TOOKAD®.