EUnetHTA 21

Consolidated PICO

PICO EXERCISE I - PLUVICTO

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DOCUMENT HISTORY AND CONTRIBUTORS

Version	Date	Description
V1.0	14/09/2023	Publication final consolidated PICOs

Disclaimer

This document was produced under the Third EU Health Programme through a service contract with the European Health and Digital Executive Agency (HaDEA) acting under the mandate from the European Commission. The information and views set out in this document are those of the author(s) and do not necessarily reflect the official opinion of the Commission/ Executive Agency. The Commission/Executive Agency do not guarantee the accuracy of the data included in this study. Neither the Commission /Executive Agency nor any person acting on the Commission's / Executive Agency's behalf may be held responsible for the use which may be made of the information contained therein.

This document describes a test run for the definition of PICOs for an assessment of a medicinal product. This exercise aimed at testing and improving the process developed within EUnetHTA21. As such, it has no relevance and no consequences for national assessments of medicinal products.

Furthermore, heterogeneity in terms of wording and presentation between the 3 exercises was expected.

Members of the EUnetHTA 21 consortium

Agencia Española de Medicamentos y Productos Sanitarios [AEMPS], Spain
Austrian Institute for Health Technology Assessment [AIHTA], Austria
Belgian Health Care Knowledge Centre, [KCE], Belgium
Gemeinsamer Bundesausschuss, [G-BA], Germany
Haute Autorité de Santé, [HAS], France
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, [IQWiG], Germany
Italian Medicines Agency, [AIFA], Italy
National Authority of Medicines and Health Products, I.P., [INFARMED], Portugal
National Centre for Pharmacoeconomics, St. James Hospital, [NCPE], Ireland
National Institute of Pharmacy and Nutrition, [NIPN], Hungary
Norwegian Medicines Agency, [NOMA], Norway
The Dental and Pharmaceutical Benefits Agency, [TLV], Sweden
Zorginstituut Nederland, [ZIN], The Netherlands

The work in EUnetHTA 21 is a collaborative effort. While the agencies in the Hands-on Group actively wrote the deliverable, the entire EUnetHTA 21 consortium was involved in its production throughout various stages. This means that the Committee for Scientific Consistency and Quality (CSCQ) reviewed and discussed several drafts of the deliverable prior to validation. Afterwards the Consortium Executive Board (CEB) endorsed the final deliverable prior to publication.

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
BICR	Blinded Independent Central Review
BSC	Best Supportive Care
CEB	Consortium Executive Board
CSCQ	Committee for Scientific Consistency and Quality
DoR	Duration Of Response
EUnetHTA	European Network of Health Technology Assessment
GL	Guideline
HOG	Hands-on Group
HTA	Health Technology Assessment
HTAb	Health Technology Assessment Body
JCA	Joint Clinical Assessment
JSC	Joint Scientific Consultation
MD	Medical Devices
MP	Medicinal Products
ORR	Objective Response Rate
PICO	Population, Intervention, Comparators and Outcomes
PFS	Progression Free Survival
PROM	Patient Reported Outcome Measures
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction

1 INTRODUCTION

On 17 September 2021, the European Health and Digital Executive Agency (HaDEA) signed the Service Contract for the Provision of Joint Health Technology Assessment (HTA) Work Supporting the Continuation of EU Cooperation on HTA. The contract will run for 24 months, and until 16 September 2023. EUnetHTA 21 work will build on the achievements and lessons learned from the EUnetHTA Joint Actions and focus on supporting a future EU HTA system under the HTA Regulation. For all EUnetHTA 21 deliverables the future EU HTA Regulation will serve as a basis.

As part of this work the consortium have taken part in project work on developing PICO questions, based on methods developed during the service contract.

2 METHODOLOGICAL APPROACH

> "*The starting point for every assessment of a health technology is the scoping phase. During the scoping phase, an important goal is the definition of a concise research question that should be answered by the assessment. The PICO framework provides a standard format for the definition of a research question. Within the PICO framework, research questions are defined using (at minimum) the following components: Population (P), Intervention (I), Comparators (C) and Outcomes (O). Countries may differ in the exact PICO question they need to be answered. Therefore, during the scoping phase of EUnetHTA 21 agreement on the PICO questions should be reached.*"[1]

Despite multiple acquisition efforts by EUnetHTA 21, no medicinal product was submitted for the Joint Clinical Assessment work under EUnetHTA 21 contract. Regardless, EUnetHTA 21 has as one of its objectives to test the guidelines developed. To allow testing of procedures and gaining experience on JCA for medicinal products, EUnetHTA has conducted three PICO exercises. These exercises were very important as the D4.2 scoping guideline was one of the guidelines which would require the most capacity building. Furthermore, after these exercises the D4.2 scoping guideline went under revision to implement the relevant learnings.

The PICO exercises were conducted on medicinal products which already obtained a positive CHMP opinion. Therefore, no confidential data was used.

The production was done with the focus on the scoping phase, i.e. to perform three JCA without a HTD submission. A JCA without submission still allowed to apply lessons learned within the development of the templates and methodological deliverables developed under the EUnetHTA 21 service contract. Within the given timeframe three scoping procedures without submission were conducted.

The below section provides a brief summary of the conducted scoping procedures.

3 PICO 1 – PLUVICTO (LUTETIUM (177LU) VIPIVOTIDE TETRAXETAN)

Name of Product: Pluvicto (lutetium (177Lu) vipivotide tetraxetan)
Company: Novartis Europharm Limited
Date of CHMP & MA: 13.10.2022, more information here.
Indication: Pluvicto in combination with androgen deprivation therapy (ADT) with or without androgen receptor (AR) pathway inhibition is indicated for the treatment of adult patients with progressive prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with AR pathway inhibition and taxane based chemotherapy.

[1] EUnetHTA 21 D4.2 Deliverable https://www.eunethta.eu/d4-2/

Date of PICO survey: 16-30 November 2022
Date of CSCQ validation: 14 March 2023
Number of MS participated: eight member states
Number of associated HTAb participated: n/a
Consolidated PICOs: 6 PICOs (2 in the full licenced population and 4 in subpopulations)

4 CONSOLIDATED PICOS

Below you can find the six consolidated PICOs, which were validated by the EUnetHTA 21 CSCQ.

PICO 1 (subpopulation)

P	Adult patients with progressive prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) with symptomatic bone metastases and no known visceral metastasis who have been treated with AR pathway inhibition and taxane based chemotherapy
I	PLUVICTO
C	Radium-223*
O	*See outcomes table*

* Androgen deprivation therapy (ADT) is the standard in the treatment of prostate cancer relapse or metastatic disease as it aims to reduce levels of circulating androgens, which induce prostate cancer growth and survival. The association of ADT with other agents is often indicated in the context of castration-sensitive metastatic prostate cancer.

PICO 2 (subpopulation)

P	Adult patients with progressive prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with AR pathway inhibition and one previous line of taxane based chemotherapy and who are suitable for cabazitaxel
I	PLUVICTO
C	Cabazitaxel*
O	*See outcomes table*

* Androgen deprivation therapy (ADT) is the standard in the treatment of prostate cancer relapse or metastatic disease as it aims to reduce levels of circulating androgens, which induce prostate cancer growth and survival. The association of ADT with other agents is often indicated in the context of castration-sensitive metastatic prostate cancer.

PICO 3 (subpopulation)

P	Adult patients with BRCA 1/2-mutated progressive prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with AR pathway inhibition and taxane based chemotherapy
I	PLUVICTO
C	Olaparib*
O	*See outcomes table*

* Androgen deprivation therapy (ADT) is the standard in the treatment of prostate cancer relapse or metastatic disease as it aims to reduce levels of circulating androgens, which induce prostate cancer growth and survival. The association of ADT with other agents is often indicated in the context of castration-sensitive metastatic prostate cancer.

PICO 4 (subpopulation)

P	Adult patients with progressive prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who are not suitable for chemotherapy or have been treated with docetaxel as 1st line and cabazitaxel as 2nd line or patients who have taken all available treatments to their own clinical condition (patient may be eligible for best supportive care or PLUVICTO)
I	PLUVICTO
C	Best supportive care
O	*See outcomes table*

PICO 5 (full population)

P	Adult patients with progressive prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with AR pathway inhibition and taxane based chemotherapy
I	PLUVICTO
C	Physician choice for control arm, with at least: Cabazitaxel*, or Abiraterone* + prednisolone, or Enzalutamide*, or Apalutamide*, or Olaparib*, or Radium -223*, or BSC
O	*See outcomes table*

* Androgen deprivation therapy (ADT) is the standard in the treatment of prostate cancer relapse or metastatic disease as it aims to reduce levels of circulating androgens, which induce prostate cancer growth and survival. The association of ADT with other agents is often indicated in the context of castration-sensitive metastatic prostate cancer.

PICO 6 (full population)

P	Adult patients with progressive prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with AR pathway inhibition and taxane based chemotherapy
I	PLUVICTO
C	Individualized treatment, taking into account previous therapies, with selection of - abiraterone +prednisone /prednisolone* - enzalutamide* - cabazitaxel*
O	*See outcomes table*

* Androgen deprivation therapy (ADT) is the standard in the treatment of prostate cancer relapse or metastatic disease as it aims to reduce levels of circulating androgens, which induce prostate cancer growth and survival. The association of ADT with other agents is often indicated in the context of castration-sensitive metastatic prostate cancer.

Outcomes table

Overall survival
Radiological tumor assessment, including overall response rate and duration of response
Progression free survival (radiological, clinical or PSA) by investigator and blinded independent committee review
Symptomatic skeletal event, including time to first skeletal event
Prostate specific antigen levels
Pain measured by a patient-reported outcome measure such as a numeric rating scale or a visual analogue scale
Fatigue
Health-related quality of life, measured preferably by generic and disease specific questionnaires, ie EORTC QLQ C30 plus, if possible, EORTC PR25 or FACT-P, FACT-G
Health status measured preferably by EQ-5D-5L
Any other patient centred outcome measured by patient-reported outcomes measures
Adverse events (total)
Serious adverse events
Severe adverse events (Grade ≥ 3)
Discontinuation and interruption due to adverse events
Adverse events of special interest (AESI)
Suspected unexpected serious adverse reaction (SUSAR)