EUnetHTA Joint Action 3 WP5 Strand B:

Post-launch evidence generation (PLEG) and registries

EUnetHTA WP5B PLEG Pilot on Palbociclib (Ibrance ®)

Common Evidence Gaps report

May 2021

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Conflict of interest
All participants involved in the production of this pilot have declared they have no conflicts of interest in relation to the technology assessed according to the EUnetHTA declaration of interest and confidentiality undertaking form.

Stakeholder involvement

The company in charge of the development of the product has been contacted at the beginning of the pilot and kept informed about different pilot steps and outputs.

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List of abbreviations

ABC	Advanced Breast Cancer
ECOG	Eastern Cooperative Oncology Group
EPAR	European Public Assessment Report
EUnetHTA	European Network of Health Technology Assessment
HAS	Haute Autorité de Santé, France
HER2-negative	Human Epidermal Growth Factor Receptor 2-negative
HR	Hormone Receptor
HTA	Health Technology Assessment
INFARMED	National Authority of Medicines and Health Products, Portugal
LHRH-agonist	Luteinizing Hormone-Releasing Hormone agonist
NOMA	Norwegian Medicines Agency
OS	Overall Survival
PFS	Progression Free Survival
PICO	Population, Intervention, Control, Outcome
RWD	Real World Data
STA	Single Technology Assessment
TLV	Dental and Pharmaceutical Benefits Agency, Sweden

1 BACKGROUND

1.1 Aim and rationale of the pilot

This pilot was conducted within EUnetHTA Joint Action 3 Work Package 5, for which the aim is to help in generating optimal and robust evidence for health technologies (pharmaceuticals or others) throughout the technology lifecycle, bringing benefits for patient access and public health.

Work Package 5 consists of two strands: strand A focuses on initial evidence generation and the activity of Early Dialogues, while strand B focuses on Post-Launch Evidence Generation. More information on the specific WP5B activities can be found at https://eunethta.eu/pleg/.

This document is an output of a WP5B PLEG product-specific pilot on Palbociclib (Ibrance ®). The main WP5B pilot steps are presented in Figure 1.

This pilot was proposed by the Swedish Dental and Pharmaceutical Benefits Agency (TLV), considering the uncertainties identified during the national HTA process. The proposal was supported by the following considerations:

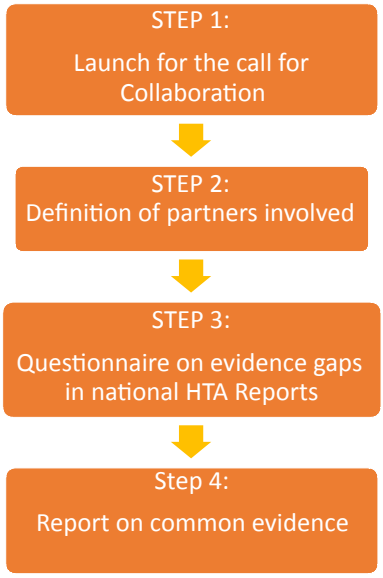
- Collecting data on the use of Ibrance® in routine clinical practice may allow to reduce some of the uncertainties identified during HTA-assessment to support its optimal uptake. The collection of data aim to support HTA agencies to follow up previous decisions, and if needed for re-assessments. The interesting data elements would for instance be the number of patients, patient characteristics, treatment duration, and main outcome measures.
- As the number of treated patients in each country is limited, a multinational approach, increasing the number of patients, enables us to study the effect in clinical practice with less delay.
- To be able to collaborate on data gathering, it is important that there is a commonly agreed definition of a minimum dataset.
- Since the product has been available on the market for some time and a number of patients have been treated, the practical conditions for collecting enough data are expected to be fulfilled.

The main objectives of this pilot are therefore as follows:

- To build a common and agreed data set for collection (which will serve as a basis for common analysis afterwards);
- To gather locally generated data (when possible) from different sources (databases, registries, health care records); and
- To assess possible levels of cross-border collaboration on the generation and exchange of real world data (RWD).

The present report corresponds to step 4 of the pilot and its aim is to synthesize the main evidence gaps and research needs identified by pilot team members in their national HTA (performed at different time points after centralized marketing authorization approval).

Figure 1. Main steps of the pilot.


STEP 1:
Launch for the call for Collaboration
STEP 2:
Definition of partners involved
STEP 3:
Questionnaire on evidence gaps in national HTA Reports
Step 4:
Report on common evidence

1.2 Overview of the disease or health condition

Advanced Breast Cancer

Breast cancer is the most common cancer in women. Advanced Breast Cancer (ABC) comprises both locally advanced and metastatic breast cancer. Although treatable, ABC remains an incurable disease with a median overall survival of 2–3 years and a 5-year survival of only 25%. For patients with hormone receptor-positive and HER2-negative advanced breast cancer, clinical guidelines recommend sequential treatment with endocrine therapy [1]. As first line therapy, aromatase inhibitors are common options in postmenopausal patients and tamoxifen in premenopausal women. Fulvestrant comprises a common alternative in second line treatment. The addition of the CDK4/6 inhibitor palbociclib (Ibrance®) to an aromatase inhibitor or to Fulvestrant provides a significant improvement in PFS, with an acceptable toxicity profile.

1.3 Palbociclib (Ibrance®): main characteristics

The pharmaceutical product palbociclib (Ibrance®) is used for treating patients with advanced breast cancer in both pre and post-menopausal women.

Regulatory status of Palbociclib (Ibrance®)

The full indication authorized in the EU is: “IBRANCE is indicated for the treatment of hormone receptor positive (HR +), human epidermal growth factor receptor 2 negative (HER2 -) locally advanced or metastatic breast cancer;

• in combination with an aromatase inhibitor.

• in combination with fulvestrant for women who have previously received endocrine therapy (see section Pharmacodynamics).

For pre- or perimenopausal women, endocrine therapy should be combined with an LHRH agonist (luteinizing hormone-releasing hormone agonist).”

HTA status of Palbociclib (Ibrance®)

During 2017 several HTA EU Member States discussed the reimbursement status of Ibrance®.

In Sweden, Ibrance® has been fully reimbursed since February 2018. It is reimbursed for both pre- and post-menopausal women with advanced breast cancer without further restriction. This gives immediate access to the national reimbursement system. TLV has published two HTA reports on Ibrance® on TLV’ s website. The reports are in Swedish with no English translation.

[1] Bröstcancer Nationellt vårdprogram. Swedish Breast Cancer Group (SweBCG), Regionala cancercentrum i samverkan. 2014 http://www.cancercentrum.se/globalassets/cancerdiagnoser/brost/vardprogram/vp-brostcancer.pdf

In Norway, all new pharmaceutical products have to be assessed as Single Technology Assessment (STA) before the decision about reimbursement/ public funding can be made. Often after completion of STA the Procurement services for Health Enterprises Ltd conducts negotiations. Subsequently a Decision Forum comprised of the four CEOs (one for each regional health authority) make decisions whether to introduce the method or not. The National System for Managed Introduction of New Health Technologies within the Specialist Health Service in Norway is responsible for the process. In Norway, Ibrance (palbociclib) is publicly funded by hospital trusts for following indications:

1. Palbociclib in combination with aromatase inhibitors for treatment of local advanced/ metastatic breast cancer Decision was made on **27.08.2018** (www.nyemetoder.no 0914-2018).
2. Palbociclib in combination with fulvestrant for treatment of HR+/HER2 negative women with locally advanced metastatic breast cancer with progression after previous endocrine treatment. The decision was made 21.10.2019 (www.nyemetoder.no 156-18).

This funding decision was based on an assumption of maximum price level for Ibrance to remain equal to or even lower than the current price to ensure that the treatment will remain cost-effective in Norway. Additionally, a requirement was made that Ibrance shall be included in a national procurement for oncology drugs from April 2020 in order to be publicly funded. Ibrance is now a part of this tender competition in Norway

n Portugal Ibrance® has been reimbursed since March 2019. The reimbursement is restricted to the following sub-populations:

- peri or pre-menopausal women submitted to previous treatment with an aromatase inhibitor, and with progression during the treatment or up to 12 months after the end of the treatment;
- post-menopausal women without previous hormonal treatment of the advanced disease;
- post-menopausal women submitted to previous treatment of the advanced disease and progression during the treatment or up to 12 months after the end of treatment.

Table 1 presents the HTA status of Ibrance among pilot team members.

Table 1. HTA status among pilot team members

HTA body	HTA status	Date of assessment finalisation
TLV	Finalised	The HTA assessment for the first indication was published in June 2017, https://www.tlv.se/download/18.43aebaef160df16da8cef39d/1516358833644/Underlag_beslut_ibrance.pdf In the following, this is referred to as HTA 1. As extra information can be said that a HTA assessment for a second indication was published in February 2018, https://www.tlv.se/download/18.1e7d91e3161bbcd37bcc62e5/1519745328488/bes_underlag_ibrance.pdf In the following, this is referred to as HTA 2.

NOMA	Finalised	*HTA assessement for indication: Ibrance in combination with aromatase inhibitors was published in 2018* https://nyemetoder.no/Documents/Forslag/Notat%20-%20Palbociklib%20-%20oppdatert%20med%20LIS-pris.pdf https://legemiddelverket.no/Documents/Offentlig%20finansiering%20og%20pris/Metodevurderinger/I/Ibrance_brystkreft_2018.pdf HTA assessment for the second indication: Ibrance in combination with fulvestrant was published in 2019 https://legemiddelverket.no/Documents/Offentlig%20finansiering%20og%20pris/Metodevurderinger/I/Ibrance_brystkreft_2019.pdf
INFARMED	Finalised	The HTA assessment was published in March 2019 (available at Ibrance file at INFOMED database https://extranet.infarmed.pt/INFOMED-fo/)

Updated in March 2021

Reimbursement status of Palbociclib (Ibrance®)

Table 2 shows the reimbursement status of Palbociclib (Ibrance®)by country for the pilot team.

Table 2. Reimbursement status across countries

Country	Reimbursement status	Decision date
Sweden	*Reimbursed*	*February 2018*
Norway	*Fully reimbursed for both indications* *Palbociclib in combination with aromatase inhibitors for treatment of local advanced/ metastatic breast cancer (www.nyemetoder.no 0914-2018)* *https://nyemetoder.no/metoder/palbociklib-ibrance-indikasjon-ii-revurdering* *Palbociclib in combination with fulvestrant for treatment of HR+/HER2 negative women with locally advanced metastatic breast cancer with progression after previous endocrine treatment. (www.nyemetoder.no 156-18).*	*Decision was made on 27.08.2018.* *The decision was made 21.10.2019*
Portugal	*Hospital inpatient setting (total cost supported by the national health care system)*	*7 March 2019*

Updated in March 2021

2 MAIN ASSESSMENT RESULTS AND COMMON EVIDENCE GAPS FROM NATIONAL HTAS

A questionnaire (Appendix 1) to collect evidence gaps and research needs identified by the pilot team members in their national HTA was elaborated on the basis of the EUnetHTA position paper on how to best formulate research recommendations for primary research arising from HTA. The questionnaire was filled out by the pilot team members. The questionnaire comprised two main sections:

1. Assessment results; and
2. Recommendations for research.

On the basis of the responses received, the pilot team identified and highlighted commonalities, which are presented in the Sections 2.1–2.3.

2.1 Main body of evidence assessed in the national HTAs

Two phase III studies were considered in the HTA:

The PALOMA-2 study was a multicentre, double-blind, randomised phase 3 study, which evaluated the effect of letrozole-associated palbociclib vs letrozole in postmenopausal women with HR-positive and HER2-negative advanced and/or metastatic breast cancer, with Eastern Cooperative Oncology Group (ECOG) performance status 0-2, and without previous endocrine treatment for advanced disease. The PFS in the study was 24.8 months (95% CI 22,1-not estimated) in the letrozole-associated palbociclib group, and 14.5 months (95% CI 12,9-17,1 months) in the letrozole group, with a hazard ratio 0,58 (95% CI 0,46–0,72, p<0,0001).

The PALOMA-2 study was followed by the PALOMA-3 study. This was a multicentre, double-blind, randomised phase 3 study, which evaluated the effect of fulvestrant-associated Palbociclib vs fulvestrant in women with HR-positive and HER2-negative advanced and/or metastatic breast cancer, with ECOG performance status 0–1, with previous endocrine treatment for advanced disease, *and with progression to 12 months after therapy*. PFS was 9.5 months (95% CI 9,2 - 11,0) in the fulvestrant-associated palbociclib group, and 4.6 months (95% CI 3,5 - 5,6 months) in the fulvestrant group, with a hazard ratio 0,46 (95% CI 0,36–0,59, p<0,0001).

There is evidence of added therapeutic value of letrozole-associated palbociclib, and fulvestrant-associated palbociclib, for the treatment of locally advanced and/or metastatic HR-positive and HER2-negative breast cancer, in ECOG performance status 0-2 post-menopausal women without previous treatment for advanced disease, and in ECOG performance status 0-1 women with progression under previous endocrine therapy or within 12 months after treatment for advanced disease, respectively. The use of palbociclib in the treatment of locally advanced and/or metastatic HR-positive and HER2-negative breast cancer, is restricted in the following subpopulations: pre- or perimenopausal women without previous hormonal treatment in the context of advanced disease; pre- or perimenopausal women with previous aromatase inhibitor treatment and progression only 12 months after the treatment; women with previous treatment for advanced disease and progression only 12 months after the treatment.

This conclusion is based on the PALOMA-2 study providing evidence of a significant improvement in PFS with letrozole-associated palbociclib, being no benefit or advantage evidence from the use of palbociclib in OS, objective response rate, median response time or QoL outcomes. Also, the PALOMA-3 study provided evidence of a significant improvement in PFS, objective response rate and QoL with fulvestrant-associated

palbociclib, not existing benefit or advantage evidence from the use of palbociclib in OS and median response time outcomes.

Survival data (OS) are uncertain at present and no safe conclusions can therefore be drawn regarding survival gains with the intervention.

2.2 Assessment results and common evidence gaps

In clinical trials, palbociclib has shown a significant improvement of progression free survival (PFS) and delayed the need for chemotherapy. However, uncertainties on drug use patterns and long-term outcomes in real world settings (including the treatment length) remain at its launch. Progression free survival is certainly the most important outcome, but here treatment length will be a proxy for that, since there is most probably a strong correlation between the two. The health economic analysis is very sensitive to changes in treatment length.

These uncertainties contributed to a mixed situation in reimbursement status, on one hand, reimbursement for palbociclib was rejected in some countries because its cost was considered too high in relation to its clinical effectiveness. On the other hand, in countries where palbociclib was and still is reimbursed, uncertainties regarding treatment length and long-term treatment outcome might have been part of the reason for uneven and delayed uptake.

One of the main uncertainties identified in the HTA processes relates to the treatment effectiveness, especially the overall survival.

Given the price for Ibrance®, the uncertainties regarding the selection of the study population and treatment duration results in substantial uncertainties regarding the price for treating a patient and thus uncertainties about the cost effectiveness of Ibrance® treatment.

The summary of common evidence gaps presented above come from feedback from pilot members see appendix 1).

2.3 Common research recommendations

Present here the common research recommendations arising from the common evidence gaps.

The pilot members reported all research recommendations as raised in their national assessment regardless the setting of the collection of data (real world setting or clinical studies).

The common concern of the project members has been to have a better understanding of over-all survival of the patients, as this is a major uncertainty at the time of reimbursement decision given short clinical studies. In an attempt to generate data on a surrogate for progression free survival, treatment length is recorded. However, the reason for discontinuation of the treatment could be of different reasons where progression could be one. In addition, the outcomes to be followed will include information about patient characteristics (e.g. age, sex and unique identifier of the patient) and drug specific information (e.g. dose, number of capsules dispensed, date of dispensing). This will allow monitoring of number of treated patients, treatment length and dosing regimens. Eventually, additional cross linking of data will have the potential of giving information on further treatment outcomes.

Further, the treatment length is of importance for the total cost of the treatment when evaluating the health economics. A potential difference in survival when comparing clinical studies and clinical practice might be that the populations differ. If patients are less sick or younger, the probability of survival might be higher although the product is as effective. In order to calibrate for this, as much information of the patients as possible is desired. The more information, the better the results of survival and treatment length can be understood. Information of disease burden, co-treatment with fulvestrant (yes/no) and age is therefore of interest. This information is of course of interest when comparing data from different countries as each country might have differences in what population is treated.

This collaboration between HTA agencies using cross-nationwide RWD data in order to improve HTA assessment is important as it aims to alleviate uncertainties regarding treatment length and any dose adjustments which in turn are related to treatment effectiveness. The collection of data and the analysis may be used to support the decision-making process for pricing and reimbursement and for subsequent re-assessments in several settings/countries.

2.4.Data Collection

Data will be gathered both retrospectively and prospectively.

The Swedish National Prescribed Drug Register is one example where data that is relevant for this pilot can be found. In Sweden, Ibrance® is dispensed at pharmacies and registered in the Swedish Prescribed Drug Register (a national health database covering all filled prescriptions of all Swedish residents). Since 2005, this register holds information about the prescriber's profession and practice, the patient (e.g. age, sex and unique identifier of the patient), and drug specific information (e.g. dose, number of capsules, date of dispensing). In addition, information about all other dispensed drugs with prescription at pharmacies, including aromatase inhibitors (letrozole or anastrozole) and fulvestrant are registered in the same registry.

There are potentially several other national databases and drug registries in the Member States that can potentially be used for data collection.

In Portugal, a project is in place to collect data retrospectively and prospectively from the National Oncology Register.

APPENDIX 1. QUESTIONNAIRE ON EVIDENCE GAPS_TEMPLATE

Agency	
Country	
Contacts	
HTA assessment status	Finalised Ongoing Further comments: free text
Evidence gaps identified in the HT assessment	Please indicate the domain in which evidence gaps have been identified during HTA (Multiple answers are possible if needed): Clinical effectiveness Safety Cost effectiveness Budget impact Condition of use Personnel recruitment and training Others (please specify)
Research question	Please provide the details on the evidence gaps and the research question(s) according to the following template:

Evidence gaps

Assessment results

For each outcome, specify the main assessment results in terms of the quality and quantity of available evidence (number of studies, type of studies), and, if applicable, the estimate of the effect size and the level of confidence in the estimate. ***Please clarify the evidence gaps for each outcome of your assessment, sorted by the level of importance:***

Outcome- level of importance 1	Outcome- level of importance 2	Outcome- level of importance 3	Outcome- level of importance 4	Outcome- level of importance 5

Recommendations for research

Question with clear rationale: potential relationship between intervention and important outcomes.

Please report the research question, for each evidence gap reported here above, according to the PICO.

Additional questions should be presented in the column "Other questions".

Population	Intervention	Comparator	Outcomes	Time Stamp	Other questions

Population or sub population of interest. *Example: to collect data patients with a mild, adult onset course (previously categorized as type IV SMA)*	The technology/ intervention and setting of use *Example: To collect data on the most appropriate dose to be used for the different patients*	Relevant comparator and setting of use	Outcomes of interest (1-5) *Example: To collect long term efficacy data*	Date when the recommendation was issued, alternatively the date of the HTA assessment finalization or the date when this form has been filled out	E.g. number of patients, duration of treatment

APPENDIX 2. QUESTIONNAIRE ON EVIDENCE GAPS

TLV

Evidence gaps

Assessment results

HTA background:
Following subpopulations with hormonal-receptor (HR)-positive and human epidermal growth factor receptor 2 (HER2)-negative locally advanced and/or metastatic breast cancer were considered: 1, in combination with aromatase inhibitors (evaluated in HTA 1), 2, in combination with fulvestrant in women who had previously received endocrine treatment (evaluated in HTA 2)

For these subpopulations, following interventions (PICO) were identified: HTA 1, palbociclib + aromatase inhibitor (anastrozol or letrozol); HTA 2, palbociclib + fulvestrant
The defined comparators (PICO) were: the most relevant comparator was considered to be treatment with aromatase inhibitor (anastrozol or letrozol) in mono therapy, in HTA 2 also treatment with everolimus och exemestane are possible comparators but TLV found fulvestrant in monotherapy was a more relevant comparator also here.
Following outcomes (PICO) were studied: **primary endpoint** in both PALOMA 1, 2 and 3 was progression free survival (PFS) in PALOMA 1 and 2, it was evaluated after RECIST v1.1, in PALOMA 3 it was evaluated with established images technique.
Secondary endpoints were: 1) Overall survival (OS) ; 2) Objective response rate (defined as full response or part response); 3) clinical benefit; 4) Median response time ; 5) Quality of life (QoL) ; 6) Adverse events rate ; 7) Serious adverse events rate ; 8) Discontinuation of treatment for serious adverse events or death ;
Less important in HTA 1 and 2 but still considered were: 9) Hospital admissions for adverse events ; 10) Toxicity or intolerance with alteration of the therapeutic regimen ; 11) Medicines interactions requiring discontinuation of other medicinal products.

Two phase III studies were considered in the HTA:
- PALOMA-2:
- PALOMA-3

The open, phase II study PALOMA-1 was also used as reference, especially in respect to the estimated effectiveness on overall survival (OS).

For HTA 1 the company performed a partitioned survival model 27 to evaluate the cost effectiveness of Ibrance in combination with letrozole compared to treatment with letrozole in monotherapy.
For HTA 2, the company also performed a cost comparison between Ibrance in combination with fulvestrant and everolimus in combination with exemastan.

These two parts of the dossiers did not introduce new critical data gaps but contained the gaps identified in the clinical data sets.

Table 2: Presentation of assessment results:

Outcomes	Number of studies (considered in which the outcome is present)	Quality of the evidence	Level of importance of the outcome
Overall survival (OS)	1, in lack of any blinded mature phase III data, PALOMA-1 was used to estimate OS	Very large	critical
Progression-free survival (PFS)	2	large	critical
Objective response rate	2	Not specified	
Median response time	2	Not specified	critical
Quality of life (QoL)	2	Not specified	
Adverse events rate	2	Large	Not neglectable
Serious adverse events rate	2	Not specified	
Discontinuation of treatment for serious adverse events or death	2	Not considerd to be crucial	critical
Hospital admissions for adverse events	0	Not specified	
Toxicity or intolerance with alteration of the therapeutic regimen	2	Not specified	
Medicines interactions requiring discontinuation of other medicinal products	0	Not specified	

Table 3: Recommendations for research

Question with clear rationale: potential relationship between intervention and important outcomes.					
Population	**Intervention**	**Comparator**	**Outcomes**	**Time Stamp**	**Other ques-tions**
Following subpopulations with hormonal-receptor (HR)-positive and human epidermal growth factor receptor 2 (HER2)-negative locally advanced and/or metastatic breast cancer were considered: 1, in combination with aromatase inhibitors (evaluated in HTA 1), 2, in combination with fulvestrant in women who had previously received endocrine treatment (evaluated in HTA 2)	HTA 1, palbociclib + aromatase inhibitor (anastrozol or letrozol); HTA 2, palbociclib + fulvestrant	HTA 1, Aromatase inhibitor (anastrozol or letrozol) in mono therapy HTA 2,fulvestrant In mono therapy	Overall survival (OS) Progression free survival (PFS) Median response time (as a proxy for treatment length) Discontinuation of treatment for serious adverse events or death (especially the discontinuation itself is important)	At the time of finalization and publication of HTA report (2017 + 2018).	

NOMA

Evidence gaps

Assessment results

HTA background:
Following subpopulations with hormonal-receptor (HR)-positive and human epidermal growth factor receptor 2 (HER2)-negative locally advanced and/or metastatic breast cancer were considered:
For these subpopulations, following interventions (PICO) were identified: palbociclib + aromatase inhibitor; palbociclib + fulvestrant
The defined comparators (PICO) were: aromatase inhibitor ; fulvestrant ; kisqali ; everolimus
Following outcomes (PICO) were studies : 1) Overall survival (OS) ; 2) Progression-free survival (PFS) ; 3) Objective response rate ; 4) Median response time ; 5) Quality of life (QoL) ; 6) Adverse events rate ; 7) Serious adverse events rate ; 8) Discontinuation of treatment for serious adverse events or death ; 9) Hospital admissions for adverse events ; 10) Toxicity or intolerance
Two phase III studies were considered in the HTA:

- PALOMA-2
- PALOMA-3

A cost-minimization analysis against Kisqali was performed based on a MAIC between palbociklib and riobociclib for one part of the indication, no information gaps in this part of the indication.
Second line: No robust information in submission file. **Evidence gaps between Ibrance and Everolimus (comparator in Norway) in all outcomes.**

Table 2: Presentation of assessment results

Outcomes	Number of studies (considered in which the outcome is present)	Quality of the evidence	Level of importance of the outcome
Overall survival (OS)	0	NA	critical
Progression-free survival (PFS)	2		critical
Objective response rate	2		critical
Median response time	2		Important
Quality of life (QoL)	2		Critical
Adverse events rate	2		Important
Serious adverse events rate	2		Critical
Discontinuation of treatment for serious adverse events or death	2		Critical
Hospital admissions for adverse events	0	NA	Important
Toxicity or intolerance with alteration of the therapeutic regimen	2	Not specified	Important
Medicines interactions requiring discontinuation of other medicinal products	0	Not specified	Important

Table 3: Recommendations for research

Question with clear rationale: potential relationship between intervention and important outcomes.

Population	Intervention	Comparator	Outcomes	Time Stamp	Other questions

Following subpopulations with hormonal-receptor (HR)-positive and human epidermal growth factor receptor 2 (HER2)-negative locally advanced and/ or metastatic breast cancer were considered: 1, in combination with aromatase inhibitors (evaluated in HTA 1), 2, in combination with fulvestrant in women who had previously received endocrine treatment (evaluated in HTA 2)	Palbociclib + aromatase inhibitor Palbociclib + fulvestrant	Aromatase inhibitor Fulvestrant Everolimus	Overall survival (OS)	At the time of finalizatio n and publicatio n of HTA report (2018 + 2019).	

INFARMED

Evidence gaps
Assessment results

HTA background:
Nine subpopulations with hormonal-receptor (HR)-positive and human epidermal growth factor receptor 2 (HER2)-negative locally advanced and/or metastatic breast cancer were defined (PICO): I) Postmenopausal women without previous hormonal treatment; II) Pre- or perimenopausal women without previous hormonal treatment; III) Pre- or perimenopausal women with previous hormonal treatment, treated with aromatase inhibitor and interval greater than 12 months or if treated with tamoxifen; IV) Pre- or perimenopausal women with previous hormonal treatment, treated with aromatase inhibitor and interval less than 12 months; V) Postmenopausal women with previous hormonal treatment, treated with aromatase inhibitor and interval less than 12 months; VI) Pre- or perimenopausal women with previous hormonal treatment in metastatic context, treated with aromatase inhibitor and goserelin; VII) Pre- or perimenopausal women with previous hormonal treatment in metastatic context, treated without aromatase inhibitor; VIII) Postmenopausal women with previous hormonal treatment in metastatic context, treated with aromatase inhibitor; IX) Postmenopausal women with previous hormonal treatment in metastatic context, treated with tamoxifen.
For these subpopulations, four interventions (PICO) were identified: palbociclib + aromatase inhibitor (subpopulations I, IX); palbociclib + aromatase inhibitor and luteinising-hormone-releasing-hormone agonist (LH-RH agonist) (subpopulations II, III, VII); palbociclib + fulvestrant (subpopulations V, VIII); palbociclib + fulvestrant and LH-RH agonist (subpopulations IV, VI).
The defined comparators (PICO) were: aromatase inhibitor (subpopulations I, IX); aromatase inhibitor and LH-RH agonist (subpopulations II, III, VII); fulvestrant (subpopulations V, VIII); fulvestrant and LH-RH agonist (subpopulations IV, VI).
Eleven outcomes (PICO) were identified: 1) Overall survival (OS) (critical); 2) Progression-free survival (PFS) (critical); 3) Objective response rate (important); 4) Median response time (important); 5) Quality of life (QoL) (critical); 6) Adverse events rate (important); 7) Serious adverse events rate (critical); 8) Discontinuation of treatment for serious adverse events or death (critical); 9) Hospital admissions for adverse events (critical); 10) Toxicity or intolerance with alteration of the therapeutic regimen (important); 11) Medicines interactions requiring discontinuation of other medicinal products (important).

Two phase III studies were considered in the HTA:

- PALOMA-2: multicentre, double-blind, randomised phase 3 study, which evaluated the effect of letrozole-associated palbociclib in postmenopausal women with HR-positive and HER2-negative advanced and/or metastatic breast cancer, with Eastern Cooperative Oncology Group (ECOG) performance status 0-2, and without previous endocrine treatment for advanced disease. PFS was 24,8 months (95% CI 22,1-not estimated) in the letrozole-associated palbociclib group and 14,5months (95% CI 12,9-17,1 months) in the letrozole group, with a hazard ratio 0,58 (95% CI 0,46–0,72, p<0,0001.
- PALOMA-3: multicentre, double-blind, randomised phase 3 study, which evaluated the effect of fulvestrant-associated palbociclib in women with HR-positive and HER2-negative advanced and/or metastatic breast cancer, with ECOG performance status 0–1, with previous endocrine treatment for advanced disease, and with progression to 12 months after therapy. PFS was 9,5 months (95% CI 9,2 - 11,0) in the fulvestrant-associated palbociclib group and 4,6 months (95% CI 3,5 - 5,6 months) in the fulvestrant group, with a hazard ratio 0,46 (95% CI 0,36–0,59, p<0,0001.

The available evidence (2 phase 3 studies) was then evaluated for each defined outcome (evidence profile per outcome):

Outcomes	Risk of bias: Allocation concealment	Adequate blinding	Incomplete inclusion	Selective reporting	Other	Indirect comparison	Inaccuracy	Quality	Outcomes classification	Number of studies
Overall survival (OS)									critical	0
Progression-free survival (PFS)	No	No	No	No	No	No	Yes*	Moderate	critical	2
Objective response rate	No	No	No	No	No	No	Yes*	Moderate	important	2
Median response time	No	No	No	No	No	No	Yes*	Moderate	important	2
Quality of life (QoL)	No	No	No	Yes**	No	No	No	Moderate	critical	2
Adverse events rate	No	No	No	No	No	No	Yes*	Moderate	important	2
Serious adverse events rate	No	No	No	No	No	No	Yes*	Moderate	critical	2
Discontinuation of treatment for serious adverse events or death	No	No	No	No	No					

Outcome- level of importance 1	Outcome- level of importance 2	Outcome- level of importance 3	Outcome- level of importance 4	Outcome- level of importance 5
Overall survival (OS) (no studies)	Hospital admissions for adverse events (no studies)	Medicines interactions requiring discontinuation of other medicinal products (no studies)		

Recommendations for research					
Question with clear rationale: potential relationship between intervention and important outcomes. ***Please report the research question, for each evidence gap reported here above, according to the PICO.*** ***Additional questions should be presented in the column "Other questions".***					
Population	**Intervention**	**Comparator**	**Outcomes**	**Time Stamp**	**Other questions**

I) Postmenopausal women without previous hormonal treatment ~~II) Pre- or perimenopausal women without previous hormonal treatment~~ ~~III) Pre- or perimenopausal women with previous hormonal treatment, treated with aromatase inhibitor and interval greater than 12 months or if treated with tamoxifen~~ IV) Pre- or perimenopausal women with previous hormonal treatment, treated with aromatase inhibitor and interval less than 12 months V) Postmenopausal women with previous hormonal treatment, treated with aromatase inhibitor and interval less than 12 months VI) Pre- or perimenopausal women with previous hormonal treatment in metastatic context, treated with aromatase inhibitor and goserelin VII) Pre- or perimenopausal women with previous hormonal treatment in metastatic context, treated without aromatase inhibitor VIII) Postmenopausal women with previous hormonal treatment in metastatic context, treated with aromatase inhibitor IX) Postmenopausal women with previous hormonal treatment in metastatic context, treated with tamoxifen	Palbociclib + aromatase inhibitor Palbociclib + aromatase inhibitor and LH-RH agonist Palbociclib + fulvestrant Palbociclib + fulvestrant and LH-RH agonist	Aromatase inhibitor Aromatase inhibitor and LH-RH agonist Fulvestrant Fulvestrant and LH-RH agonist	Overall survival (OS) Hospital admissions for adverse events Medicines interactions requiring discontinuation of other medicinal products	August 2018	

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[2] For reports in other countries, see for instance the following references:

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