Palbociclib

REJECTED

The Expert Committee, after evaluation, declines to list the medicine proposed in the application.
The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.

Section: 8. Immunomodulators and antineoplastics > 8.2. Antineoplastics and supportive medicines > 8.2.2. Targeted therapies

ATC codes: L01EF01

Indication	Other specified malignant neoplasms of breast ICD11 code: 2C6Y
INN	Palbociclib
Medicine type	Chemical agent
List type	Complementary
Formulations	**Oral > Solid:** 75 mg ; 100 mg ; 125 mg
EML status history	Application rejected in 2021 (TRS 1035) Application rejected in 2023 (TRS 1049)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	abemaciclib (ATC codes: L01EF03) ribociclib (ATC codes: L01EF02)
Patent information	Main patent is active in several jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org Read more about patents.
Tags	Cancer
Wikipedia	Palbociclib
DrugBank	Palbociclib

Expert Committee recommendation

The Expert Committee noted that breast cancer continues to be the leading cause of cancer death in women, and that more than half of women diagnosed with breast cancer have HR+/HER2– disease, making effective treatments for this disease a high priority. The Committee noted that in several high-income settings, CDK 4/6 inhibitors were emerging as first-line treatment for HR+/HER2– metastatic breast cancer. However, in low- and middle- income countries CDK 4/6 inhibitors are generally not available and aromatase inhibitors, tamoxifen and cytotoxic agents are still the main treatment options, with a relevant overall survival gain (4+ years). The Committee noted that, overall, the updated results of clinical trials on CDK 4/6 inhibitors for first-line and second-line treatment suggested a meaningful survival benefit when added to endocrine therapy (aromatase inhibitors, tamoxifen or fulvestrant) compared with endocrine therapy alone. In addition to overall survival gains, secondary benefits have been reported in trials, such as delayed time to use of chemotherapy (by about a year) and delayed deterioration in quality of life. However, the Committee noted that the pivotal trials did not include patients with low baseline neutrophil count who may be at greater risk of haematological adverse events, or patients from certain ethnic or age groups, which may influence the generalizability of the findings to the wider population. The Committee also considered that uncertainties still existed about the optimal, most active and best tolerated dose,

noting that many patients had to reduce the dose in the pivotal trials. The Committee also considered that there were uncertainties about the duration of treatment, positioning as first or second line in the metastatic setting, and whether clinically significant differences existed between agents within the pharmacological class. As was the case when these medicines were considered by the Expert Committee in 2021, the Committee noted the continuing high prices of these medicines, which pose serious affordability challenges, especially in low- and middle-income countries. The Expert Committee therefore did not recommend the inclusion of abemaciclib, palbociclib, and ribociclib on the EML for the treatment of patients with HR+/HER2– advanced breast cancer. The Committee requested that data for these medicines continue to be evaluated as they evolve, including data on price. The Committee also reiterated the recommendation of the 2021 Expert Committee that this class of medicines be flagged to the Medicines Patent Pool as potential candidates for voluntary licensing agreements.

Background

CDK 4/6 inhibitors were considered for inclusion on the EML in 2021. At the time, the Expert Committee noted that the results of the clinical trials in first- and second-line treatment settings suggested a potentially meaningful survival benefit. However, the medicines were not recommended for inclusion given that the survival data were immature, and there was uncertainty whether promising progression-free survival gains would translate to an increase in overall survival. Other areas of uncertainty identified by the Committee included questions on the optimal dose and duration of treatment, use in early-stage disease, and whether meaningful clinical differences existed between individual medicines within the pharmacological class. The Committee also noted that CDK 4/6 inhibitors are unlikely to be cost-effective in most settings due to their high prices which would pose serious affordability challenges for most countries (1).

Public health relevance

Breast cancer is the leading cause of morbidity, disability and mortality in women worldwide. In 2020, 2.3 million new cases of breast cancer were diagnosed, which accounted for 25% of all malignancies in women. Breast cancer is the most diagnosed malignancy in women worldwide, and the main cause of death in women in 110 countries. Almost 20% of cancer deaths in 2018 were from breast cancer (2), and 60% of incident breast cancer cases and two thirds of the related mortality occurred in low- and middle-income countries. The HR+/HER2– breast cancer subtype is the most common type of breast cancer, reported in more than two thirds of all cases (3). In high-income countries, the incidence of breast cancer is high and mortality rates are low, while in low- and middle-income countries, the incidence is lower, but mortality rates are high. The overall 5-year survival rates for high-income countries are estimated to be more than 85%. In comparison, in low- and middle-income countries, 5-year survival rates range between 38% and 60% (4). Impaired timely access to cancer services is a barrier for the curative management of the early disease, with most of the patients presenting with locally advanced and/or non-resectable diseases or metastatic cancer (2).

Benefits

Meta-analysis of randomized trials A systematic review and meta-analysis of six studies (3421 participants, treated with: fulvestrant plus ribociclib, palbociclib or abemaciclib; letrozole plus palbociclib or ribociclib or a non-steroidal aromatase inhibitor; or tamoxifen plus ribociclib) evaluated the efficacy of CDK 4/6 inhibitors for the treatment of metastatic breast cancer (5). For overall survival, the pooled analysis showed a significant reduction in the risk of dying in patients receiving CDK 4/6 inhibitors (hazard ratio (HR) 0.76, 95% confidence interval (CI) 0.68 to 0.85). Randomized trials The application presented evidence from seven randomized, placebo-controlled, double-blind, phase III clinical trials: MONARCH 2 and 3; PALOMA 2 and 3; and MONALEESA 2, 3, and 7. The schedules for the treatment within the clinical trials were the same as those approved for the clinical use by regulatory authorities. All the studies were designed for patients with HR+/HER2– advanced breast cancer. All the studies had safety and objective response rates as secondary endpoints. Overall survival was a protocol-specified secondary endpoint in all the trials. First-line therapy Abemaciclib The MONARCH 3 trial evaluated abemaciclib in combination with aromatase inhibitors as initial therapy in 493 postmenopausal women with advanced breast cancer (6). Participants were randomized 2:1 to receive abemaciclib in combination with anastrozole or letrozole,

or placebo in combination with anastrozole or letrozole. The absolute progression-free survival gain for the abemaciclib arm was 13.4 months (HR 0.54, 95% CI 0.42 to 0.70). Interim analysis after median follow-up of 70 months showed a median overall survival gain for abemaciclib of 12.6 months (HR 0.75, 95% CI 0.58 to 0.97) (7). Based on this trial, abemaciclib received a score of 3 on the European Society for Medical Oncology magnitude of clinical benefit scale (8). Palbociclib The PALOMA 2 trial evaluated palbociclib in combination with letrozole as first-line therapy in 666 postmenopausal women with advanced breast cancer (9). Participants were randomized 2:1 to palbociclib plus letrozole or placebo plus letrozole. The absolute progression-free survival gain for the palbociclib arm was 10.3 months (HR 0.58, 95% CI 0.46 to 0.72). Interim analysis showed no difference between the intervention and comparator arms in median overall survival. Based on this trial, palbociclib received a score of 3 on the European Society for Medical Oncology magnitude of clinical benefit scale (8). Ribociclib The MONALEESA 2 trial evaluated ribociclib in combination with letrozole as first-line therapy in 668 postmenopausal women with advanced breast cancer (10). Participants were randomized 1:1 to receive either ribociclib plus letrozole or placebo plus letrozole. After median follow-up of 26.4 months, the absolute progression-free survival gain for the ribociclib arm was 9.3 months (HR 0.57, 95% CI 0.46 to 0.70). After a median follow-up of 6.6 years, ribociclib showed an absolute survival gain compared to placebo of 12.5 months (HR for death 0.76, 95% CI 0.63 to 0.93). Based on updated results from MONALEESA 2, ribociclib received a score of 4 on the European Society for Medical Oncology magnitude of clinical benefit scale (8). The MONALEESA 7 trial evaluated ribociclib plus endocrine therapy (anastrozole, letrozole or tamoxifen, each combined with goserelin) as first-line therapy for advanced breast cancer in 672 premenopausal women (11). Participants were randomized 1:1 to either endocrine therapy with ribociclib or endocrine therapy with placebo. Median progression-free survival was 23.8 months versus 13.0 months in the ribociclib and placebo arms, respectively, with an absolute progression-free survival gain of 10.8 months (HR 0.55, 95% CI 0.44 to 0.69). An absolute gain in overall survival of 10.7 months (HR 0.76, 95% CI 0.61 to 0.96) was demonstrated for ribociclib. Based on this trial, ribociclib received a score of 5 on the on the European Society for Medical Oncology magnitude of clinical benefit scale (8). Second-line therapy Abemaciclib The MONARCH 2 trial evaluated abemaciclib in combination with fulvestrant as second-line therapy for advanced breast cancer in 669 women of any menopausal status (12). Participants were randomized 2:1 to receive abemaciclib or placebo each combined with fulvestrant. After median follow-up of 19.5 months, median progression-free survival was 16.4 months in the abemaciclib arm versus 9.3 months in the placebo arm, an absolute progression-free survival gain of 7.1 months (HR 0.55, 95% CI 0.45 to 0.68). After median follow-up of 47.7 months, median overall survival was 46.7 months in the abemaciclib arm versus 37.3 months in the placebo arm, an absolute overall survival gain of 9.4 months (HR 0.76, 95% CI 0.61 to 0.95) (13). Based on this trial, abemaciclib received a score of 4 on the European Society for Medical Oncology magnitude of clinical benefit scale (8). Palbociclib The PALOMA 3 trial evaluated palbociclib in combination with fulvestrant as second-line therapy for advanced breast cancer in 521 women of any menopausal status (14). Participants were randomized 2:1 to either palbociclib or placebo, each combined with fulvestrant. After median follow-up of 8.9 months, median progression-free survival was 9.5 months in the palbociclib arm versus 4.6 months in the placebo arm, an absolute progression-free survival gain of 4.9 months (HR 0.46, 95% CI 0.36 to 0.59). After a median follow-up of 44.8 months, median overall survival was 34.9 months in the palbociclib arm versus 28.0 months in the placebo arm, an absolute gain in overall survival of 6.9 months (HR 0.81, 95% CI 0.64 to 1.03). Based on this trial, palbociclib received a score of 4 on the European Society for Medical Oncology magnitude of clinical benefit scale (8). Ribociclib The MONALEESA 3 trial evaluated ribociclib plus fulvestrant as first- and second-line therapy for advanced breast cancer in 726 postmenopausal women (15). Participants were randomized 2:1 to either ribociclib or placebo, each combined with fulvestrant. Median progression-free survival was 20.5 months in the ribociclib arm versus 12.8 months in the placebo arm, an absolute progression-free survival gain of 7.7 months (HR 0.59, 95% CI 0.48 to 0.73). The estimated overall survival at 42 months was 57.8% in the ribociclib arm versus 45.9% in the placebo arm (HR 0.72, 95% CI 0.57 to 0.92). An absolute gain in overall survival of 12.2 months (HR 0.59, 95% CI 0.59 to 0.90) for ribociclib was calculated. Based on this trial, ribociclib received a score of 4 on the European Society for Medical Oncology magnitude of clinical benefit scale (8). Real-world studies A real-world study from five European countries (1017 participants) evaluating treatment patterns and clinical outcomes associated with palbociclib combination therapy showed progression-free survival rates at 12 and 24 months of 88.2% and 62.2%

in the first-line setting and 81.1% and 55.2% in the second-line setting, respectively (16). Overall survival rates at 12 and 24 months were 97.7% and 93.2% in the first-line setting and 96.8% and 85.2% in the second-line setting, respectively. Dose reductions were observed with palbociclib in 11% and 17% of the patients from Europe in the first- and second-line settings, respectively, mostly related to the neutropenia. The phase IIIb study CompLEEment1 (3246 participants; 38 countries) assessed the benefit of ribociclib and letrozole as first-line treatment in the subgroup of patients less likely to be included in the pivotal trials (17). Patients with a poorer performance status, namely the Eastern Cooperative Oncology Group (ECOG) 2, largely under-represented in clinical trials, showed a comparative benefit to patients with better performance status (e.g. ECOG 0 or 1). In particular, the median time to disease progression was 19.5 months (95% CI 13.5 months to not reached) in the ECOG 2 patients. Safety results were consistent with those in the overall CompLEEment1 population. Neutropenia was the most common side-effect in the ECOG 2 patient subgroup, reported in 63.4% of patients. Treatment discontinuation due to adverse events was reported in 11.6% of patients in the ECOG 2 subgroup, mostly because of neutropenia. The RENATA study presented a prospective analysis of real-world use of palbociclib with endocrine therapy in 128 patients with ER+/HER2– advanced breast cancer between October 2015 and August 2019 in Buenos Aires, Argentina (18). Overall progression-free survival was 36.7 months in the first-line setting and 24.2 months in the second-line setting. Treatment was interrupted in 2% of participants due to drug-related toxicity. Neutropenia was the main moderate-to-severe adverse event, of which 7% was febrile neutropenia (higher than in the pivotal trials). Overall, the data on survival were consistent with the pivotal PALOMA trials (18). A study in the Republic of Korea analysed the outcomes of 169 patients with breast cancer receiving letrozole or fulvestrant plus palbociclib (19). The median progression-free survival rates with letrozole plus palbociclib and fulvestrant plus palbociclib were 25.6 months (95% CI 19.1 months to not reached) and 6.37 months (95% CI 5.33 months to not reached) in the first- and second-line, respectively. Neutropenia was observed in 88.3% of the patients, most commonly grade 3 and 4. In Japan, a phase II single-arm, open-label clinical trial investigated the efficacy and safety of palbociclib plus letrozole as first-line treatment in 42 postmenopausal patients with advanced breast cancer (20). After median duration of treatment of 33 months, the probability of progression-free survival at 1 year was 75.6% (90% CI 62.4% to 84.7%), with a median progression-free survival of 35.7 months (95% CI 21.7 to 46.7 months). The safety profile in the Japanese population was consistent with the profile reported in non-Asian patients; neutropenia was the most common adverse effect, with grade 3 and 4 neutropenia occurring in 93% of patients; however, only one patient experienced febrile neutropenia.

Harms

The main adverse effect of the pharmacological class of CDK 4/6 inhibitors is haematological toxicity. Their use is associated with a predictable, reversible and generally non-infection-prone neutropenia – related to cell cycle effects on the haematopoiesis of the cell cycle blockade (21). A systematic review and meta-analysis of the efficacy and safety of CDK 4/6 inhibitors from the phase III clinical trials reported an onset of grade 3 and 4 neutropenia in 65%, 58% and 26% of patients using palbociclib, ribociclib and abemaciclib, respectively (22). However, febrile neutropenia occurred in < 1% of the trial population with all of these compounds. In general, the onset of moderate-to-severe neutropenia leads to a delay, temporary interruption or dose reduction in administration of the CDK 4/6 inhibitor but is less likely to require other interventions. For example, the use of the granulocyte-stimulating factors and/or antibiotic prophylaxis is not usually required, as febrile neutropenia occurs quite rarely (23). The only precaution recommended with the use of CDK 4/6 inhibitors is a complete blood count at the beginning of each cycle and after 2 weeks for the first two cycles to check the bone marrow reserve. Moreover, CDK 4/6 inhibitors are associated with molecule-specific safety profiles that inform the clinician’s decision to use one compound over another, along with patient preference. The different safety profiles are currently the most important factor considered in the treatment decision for patients with HR+/HER2– advanced breast cancer in first- or second-line therapy, in the absence of direct comparisons. The main differences in the safety profiles of abemaciclib, palbociclib and ribociclib from the phase III trials are summarized in Table 17 (refer TRS 1049).

Cost / cost effectiveness

Most cost–effectiveness analyses have found CDK 4/6 inhibitors unlikely to be cost-effective at current prices and usual willingness-to-pay thresholds. The average cost for 1 month of treatment with CDK 4/6 inhibitors in Europe was estimated in the application as between US$ 2000 and US$ 7000 for palbociclib, US$ 8900 for ribociclib and between US$ 3500 and US$ 12 000 for abemaciclib (24). In comparison, while the total costs per year for letrozole and palbociclib have been estimated at around US$ 52 400, letrozole alone is US$ 252. Findings from cost–effectiveness studies of CDK 4/6 inhibitors were previously reported in 2021 (1). Incremental cost–effectiveness ratios range from US$ 147 000 per quality-adjusted life year gained in Singapore (25) to US$ 634 000 per quality-adjusted life year gained in the United States (26).

WHO guidelines

WHO guidelines for the treatment of breast cancer are not available.

Availability

Abemaciclib, palbociclib and ribociclib all have regulatory approval in multiple countries globally. Abemaciclib has primary patent protection until 2029. Palbociclib has primary patent protection until 2023 in both the United States (at the US Securities and Exchange Commission) and Europe (at the European Patent Office); however, in both regions the patents may be extended up to 5 years (in 2028) under the statutes that provide for patent term extensions. Ribociclib has primary patent protection until 2027–2029. Generic products are not currently available for any of the three medicines.

Other considerations

While the pivotal clinical trials did not exclude patients of African ancestry, the definition of restrictive enrolment criteria (e.g. an absolute neutrophil count of 1500/mm3 or more) in these trials may have affected the likelihood of eligibility and screening success of women of African ancestry, who have, on average, lower neutrophil counts than Caucasian women (27). This represents a structural barrier as a result of a less inclusive conceptualization and design of the studies. No study has been conducted specifically in women of African ancestry and this gap is a priority area for research. The PALINA study is a phase II clinical trial investigating palbociclib in combination with letrozole or fulvestrant in African–American women with HR+/HER2– advanced breast cancer (28). The technical team in cancer in the WHO Department of Noncommunicable Diseases reviewed and provided comments on the application. The technical department highlighted that there was clinical evidence showing CDK 4/6 inhibitors to be associated with overall survival gains compared with older treatment regimens, but long-term or real-world data were limited. The technical department expressed its preference to focus on the established first-line therapy (e.g. hormone therapies) that was more feasible in settings with weaker health systems.

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