Labeling Supplement – Clinical Review

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Division/Office	CDER/OOD/DO1
Clinical Reviewer	Mahta Mahmoudieh
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Product: Established Name (Trade name)	Palbociclib (IBRANCE)
Formulation	Tablets and capsules, for oral use
Established Pharmacologic Class (EPC)	Tyrosine kinase inhibitor
Applicant	Pfizer Inc.
Recommended Regulatory Action	Approval

1. Executive Summary:

Palbociclib is a tyrosine kinase inhibitor (TKI) of cyclin-dependent kinases (CDK) 4 and 6 which was initially granted accelerated approval in the United States on February 3, 2015. Since this initial approval the indication has been converted to traditional approval and palbociclib currently is indicated for the following indications:

- in adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with:
    - an aromatase inhibitor as initial endocrine-based therapy;
    - or fulvestrant in patients with disease progression following endocrine therapy.
- In combination with inavolisib and fulvestrant for the treatment of adult patients with endocrine-resistant, PIK3CA-mutated, HR-positive, HER2-negative, locally advanced or metastatic breast cancer, as detected by an FDA-approved test, following recurrence on or after completing adjuvant endocrine therapy.

The current submission consists of a request for additional marketing exclusivity: Pediatric Exclusivity, based on the pediatric information as provided under Section 505A of the Federal Food, Drug, and Cosmetic Act. Additionally, the submission contains proposed labeling revisions to Section 8.4, "Pediatric Use," of the U.S. Prescribing Information (USPI) to include the results of pediatric studies conducted with palbociclib.

The request for pediatric exclusivity is based on the fulfillment of the terms of the agreed pediatric Written Request (WR) Amendment 3, dated February 04, 2025. The WR required the completion of the following three studies:

- A5481092: an open-label Phase 1/2 study to evaluate palbociclib in combination with irinotecan and temozolomide and palbociclib in combination with topotecan and cyclophosphamide in 98 pediatric patients, aged 2 to <17 years, with recurrent or refractory solid tumors including neuroblastoma and Ewing sarcoma.
- PBTC-042: a Phase 1 study of palbociclib in 27 pediatric patients, aged 4 to <17 years, with Rb1-positive recurrent, progressive or refractory primary CNS tumors.
- APEC1621I: a single arm Phase 2 study of palbociclib in 15 pediatric patients, aged 9 to <17 years, with recurrent/refractory solid tumors harboring activating alterations in cell cycle genes.

All three studies were completed and submitted to fulfill the WR without pursuing an indication in the pediatric population, as the available data do not conclusively support a favorable benefit/risk profile for palbociclib in the treatment of pediatric patients. However, the results of the studies provided descriptive information to inform labeling for palbociclib in the treatment of pediatric patients. The review team recommends that pediatric exclusivity be granted which was agreed to by the pediatric exclusivity board and the following revisions be made to the language to Section 8.4, Pediatric Use:

> *The safety and effectiveness of IBRANCE in pediatric patients have not been established.*
>
> *The safety and effectiveness of IBRANCE were assessed but not established in three trials: one open-label trial [A5481092, (NCT03709680)] that included 98 pediatric patients 2 to <17 years of age who received IBRANCE in combination with chemotherapy for recurrent or refractory solid tumors and two open-label trials that included 42 pediatric patients 4 to <17 years of age who received IBRANCE as a single agent for recurrent or refractory solid tumors [APEC1621I, (NCT03526250)] or primary central nervous system (CNS) tumors [PBTC-042, (NCT02255461)].*
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> *No new safety signals were observed in these trials. Palbociclib exposures in pediatric patients who received IBRANCE as a single agent or in combination were within range of those observed in adults given a similar dose based on body surface area.*

2. Regulatory Background

During the initial approval for palbociclib in February of 2015, the requirement for pediatric studies was waved because the disease at that time pediatric studies could be waived based solely on the indication being studies in adults. Breast cancer rarely occurs in pediatric patients and therefore studies were considered impossible or highly impracticable in pediatric patients.

Despite being granted a full waiver for pediatric investigations at the time of initial approval, the Applicant submitted a Proposed Pediatric Study Request (PPSR) for palbociclib and requested the issuance of a Written Request (WR) for the evaluation of palbociclib in refractory or recurrent rhabdomyosarcoma (RMS) and Ewing sarcoma (EWS) on May 3, 2017. On November 6, 2017, the FDA issued an Inadequate Study Request letter stating that although the clinical trial proposed in the PPSR is acceptable; the results from only this trial, which evaluates palbociclib exclusively as part of a combination regimen, will not isolate the effect of palbociclib (safety or potential efficacy) for use in children with cancer. After multiple communications between the Applicant and FDA, the FDA issued a WR for palbociclib on July 3, 2018, for the evaluation of palbociclib in recurrent/refractory pediatric solid tumors, including EWS. The initial WR included the following studies:

- Study 1 (Study A5481092): An open-label, dose-escalation and cohort expansion study to evaluate the safety, pharmacokinetics (PK) and antitumor activity of palbociclib in combination with temozolomide (TMZ) and irinotecan (IRN) in pediatric patients with recurrent or refractory (r/r) solid tumors.
- Study 2 (rEECur Study, conducted by the EURO EWING Consortium): A randomized, open-label, activity-estimating trial, comparing treatment arms of TMZ and IRN with palbociclib plus TMZ and IRN, in the treatment of patients with recurrent and/or refractory EWS.
- Study 3 (Study PBTC-042): An ongoing, open-label, Phase 1, dose escalation study to evaluate the safety and pharmacokinetics of palbociclib in pediatric patients with retinoblastoma protein 1 (Rb1)-positive recurrent, progressive, or refractory central nervous system (CNS) tumors.
- Study 4 Study (APEC1621I): An ongoing, open-label, Phase 2 trial to evaluate single-agent palbociclib in pediatric patients with tumors harboring activating alterations in cell cycle genes.

The WR was amended on February 2, 2021 (Amendment #1) and on September 23, 2021 (Amendment #2) and again on February 4, 2025 (Amendment #3).

Amendment #1 of the WR was to revise Study 1 (Study A5481092) to include topotecan (TOPO) + cyclophosphamide (CTX) as an additional backbone for combination dose escalation with palbociclib based on the results from Study 2, to specify a minimum number of patients to be enrolled in each age group, and to state that tumor-specific cohorts (TSCs) may be opened as warranted based on signals of antitumor activity observed in Part 1 of Study 1; additionally changes were made to Study 2 to specify collection of sparse PK samples for palbociclib, TOPO, and CTX in all pediatric patients (ages >2 to <18 years).

Amendment #2 was to remove Study 2 and to add a randomized component with a primary EFS efficacy endpoint to Study 1 comparing palbociclib in combination with IRN+TMZ to IRN+TMZ alone in lieu of conducting a separate randomized trial for feasibility. The revision to Study 1 was designed in conjunction with advice and support from the Children's Oncology Group (COG). COG agreed that IRN+TMZ is standard of care for this population in the United States and may have less toxicity than TOPO/+CTX or high-dose IFOS.

The WR (Amendment #3) included edits for clarity and brevity, minor revisions related to categorization of race and ethnicity, updates based on Study 1 completion following conduct of planned IA which indicated that palbociclib in combination with TOPO and CTX is ineffective for patients with recurrent or refractory neuroblastoma (NB); therefore, additional enrollment of the NB tumor specific will not occur and Study 1 will not proceed to Stage 2. The final WR (Amendment #3) contained the following studies:

- Study 1(A5481092): A Phase 1/2 study to evaluate palbociclib in combination with IRN and TMZ or in combination with TOPO and CTX in children, adolescent, and young adult patients with relapsed/refractory (r/r) solid tumors. The study consisted of a nonrandomized Phase 1 portion for patients with r/r solid tumors, followed by potential nonrandomized TSCs, and a randomized Phase 2 portion for patients with r/r EWS.
- Study 3(PBTC-042: A Phase 1 study of palbociclib in children with Rb1-positive recurrent, progressive or refractory primary CNS tumors. The study consisted of 2 cohorts: Stratum 1 (children who had been less-heavily pretreated) and Stratum 2 (children who have been heavily

pretreated (i.e., received intensive cytotoxic therapy including myeloablative chemotherapy ± craniospinal irradiation)).

- Study 4 (APEC1621I): A single arm, Phase 2 study of palbociclib in children with r/r advanced solid tumors harboring activating alterations in cell cycle genes.

3. Background and Review of Clinical Data

Study 1: A5481092

Study Design

A5481092 was a Phase 1/2 open-label study to evaluate palbociclib in combination with TMZ and IRN and palbociclib in combination with TOPO and CTX in children, adolescent, and young adult patients with relapsed or refractory solid tumors. The non-randomized Phase 1 portion of the study evaluated the safety, PK, pharmacodynamics (PD), and antitumor activity of palbociclib in combination with TMZ and IRN and palbociclib in combination with TOPO and CTX in patients with relapsed or refractory solid tumors. The randomized Phase 2 portion of the study further evaluated the efficacy, safety, and PK of palbociclib in combination with IRN and TMZ in children, adolescents, and young adults with recurrent or refractory EWS.

A dose escalation part using a rolling 6 dose escalation design was to estimate the MTD for palbociclib in combination with IRN and TMZ. A dose determination part was to evaluate the safety and tolerability of the potential RP2D for palbociclib in combination with TOPO and CTX. No primary efficacy endpoints were evaluated, and secondary efficacy endpoints included overall response rate (ORR) and duration of response (DOR). Dose expansion cohorts were to confirm the RP2D and to evaluate the preliminary antitumor activity of the combination of palbociclib with IRN and TMZ and the combination of palbociclib with TOPO and CTX. The primary efficacy endpoint was ORR and secondary efficacy endpoints included DOR, progression free survival (PFS), and overall survival (OS). Using a Simon 2 stage design, tumor specific cohorts would be opened if 2 or more patients from the Phase 1 dose escalation part/dose determination part and/or dose expansion cohorts showed a confirmed response.

Phase 1 dose escalation: As of the data cutoff date of 31 July 2023, a total of 70 patients were screened, of which 60 were enrolled and 59 were treated. Of the 33 patients treated in the palbociclib + IRN + TMZ treatment combination, 21 (63.6%) were male, the median age was 14.0 years (range: 2, 20 years), and of the 26 patients treated in the palbociclib + TOPO + CTX treatment combination, 12 (46.2%) were male, the median age was 11.0 years (range: 2, 20 years).

Phase 2 part: As of data cutoff date of 26 Aug 2024, a total of 81 patients were screened, of which 63 were enrolled (42 to the palbociclib + IRN +TMZ arm and 21 to the IRN + TMZ arm) and 62 (98.4%) were treated (41 in the palbociclib + IRN + TMZ arm and 21 in the IRN + TMZ arm). Among the 63 patients randomized, the median age (range) was 13.5 (5, 19) years in the palbociclib + IRN + TMZ arm and 15.0 (6, 20) years in the IRN + TMZ arm, with most patients aged <18 years old in both arms (36 [85.7%] in the palbociclib + IRN + TMZ arm and 18 [85.7%] in the IRN + TMZ arm).

Efficacy Findings

In the Phase 1 dose determination and dose expansion cohorts of Study A5481092, 2 patients with r/r NB, who received palbociclib plus TOPO and CTX, had a confirmed response (1 PR and 1 CR). Therefore, as per protocol, a nonrandomized tumor specific cohort was opened which enrolled an additional 5 patients with r/r NB. None of the additional 5 patients with NB had a confirmed response. Therefore, it was determined that NB should not proceed to Stage 2. No other tumor types had a response in the dose determination phase and therefore no other tumor specific cohorts were opened.

In the randomized Phase 2 portion of Study A5481092, efficacy was evaluated for futility at the prespecified time point of 33 EFS events. This analysis occurred with a data cut of July 31, 2023. At this time, the median EFS was 1.5 months (95% CI: 1.4, 4.2) in the palbociclib + IRN + TMZ arm and 4.4 months (95% CI: 2.6, NE) for the IRN + TMZ arm with an observed HR of 2.03 (95% CI: 0.90, 4.57; p-value=0.9621) which met criteria for futility and the study was stopped. The confirmed ORR was 14% (95% CI: 6%, 29%) in the palbociclib + IRN + TMZ arm and 16% (95% CI: 6%, 38%) in the IRN + TMZ arm. The median OS was 10.6 months (95% CI: 8.4, 20.8) in the palbociclib + IRN + TMZ arm and 11.4 months (95% CI: 7.5, 19.0) in the IRN + TMZ arm with a HR of 0.98 (95% CI: 0.50, 1.96).

Safety Findings

Overall, the safety profile for the palbociclib monotherapy and palbociclib + IRN + TMZ or palbociclib + TOPO + CTX treatment combinations was similar to the anticipated AEs already known for each drug as monotherapy. The most common treatment emergent adverse events (TEAEs) were related to myelosuppression (anemia, leukopenia including neutropenia, thrombocytopenia, and lymphopenia,) and GI toxicity (nausea/vomiting/diarrhea). No new safety concerns were identified in the pediatric population as compared to the known safety profiles of palbociclib single agent and the backbone chemotherapy combinations of IRN + TMZ or TOPO + CTX.

Study 3: PBTC-042

Study Design

PBTC-042 was a Phase 1 study of palbociclib in children with Rb1 positive recurrent, progressive or refractory primary CNS tumors consisting of 2 cohorts: Stratum 1 (children who had not been heavily pretreated) and Stratum 2 (children who have received intensive cytotoxic therapy including myeloablative chemotherapy with or without craniospinal irradiation). The study was designed to determine the MTD/RP2D and to evaluate the safety, PK, and efficacy of palbociclib in pediatric patients with Rb1-positive recurrent, progressive, or refractory primary CNS tumors. Secondary endpoints for efficacy included ORR, DOR, OS, and PFS.

Study PBTC-042 enrolled 35 patients of whom 34 were treated (21 in Stratum 1 and 13 in Stratum 2). Of the 34 patients treated, the median (range) age was 12.0 (4, 21) years (11.0 [4, 21] years in Stratum 1 and 12.0 [6, 21] years in Stratum 2).

Efficacy Findings

No confirmed responses (CR or PR) were achieved in any patients with Rb1 positive recurrent, progressive, or refractory CNS tumors who treated with palbociclib. In Stratum 1, the median PFS was 1.7 months (95% CI: 1.2, 1.8). In Stratum 2, the median PFS was 1.7 months (95% CI: 1.1, 2.2). OS analysis was not performed due to limited data.

Safety Findings

In both stratums of study PBTC-042 the most common TEAEs related to myelosuppression and included leukopenia, neutropenia, anemia, and lymphopenia. These safety results as well as SAEs, treatment discontinuation, treatment interruptions and fatal AEs were consistent with the expected safety profile of palbociclib in the adult population. No new safety signals were identified.

Study 4: APEC1621I

APEC1621I was a single arm, Phase 2 study of palbociclib in children with r/r advanced solid tumors harboring activating alterations in cell cycle genes, including CNS tumors, non-Hodgkin lymphomas, or histiocytic disorders. The primary efficacy objective was to determine the ORR (CR + PR) and the secondary efficacy objectives included OS and PFS.

A total of 23 patients were enrolled, of which 20 (87.0%) received treatment. The median (range) age was 15.0 (9, 21) years with most patients (10 [50%]) between the age of 12 to 16 years old.

Efficacy Findings

No confirmed responses were observed in any biomarker-selected patients with r/r solid tumors treated with palbociclib. The median OS was 7.6 months (95% CI: NE, NE). The median duration of follow-up for OS based on the reverse Kaplan- Meier method was 2.6 months (95% CI: 1.8, 2.9). Kaplan-Meier estimated median PFS was 1.6 months [95% CI (1.0, 2.1)].

Safety Findings

The most common TEAEs (≥15%) were leukopenia, neutropenia, thrombocytopenia, anemia, headache, and lymphopenia. These safety results as well as SAEs, treatment discontinuation, treatment interruptions and fatal AEs were consistent with the expected safety profile of palbociclib in the adult population. No new safety signals were identified.

Clinical Pharmacology Results:

Please see clinical pharmacology review dated September 8, 2025, in DARRTs for more detailed review of clinical pharmacology results.

4. Labeling changes

Table 1 summarizes revisions proposed by the Applicant for all sections of the Prescribing Information containing or referencing clinical data and relevant justification and recommendation from the FDA clinical review team. New text is underlined and deleted text is ~~struck through~~.

Table 1. Proposed Revisions to US Prescribing Information

Label Section	Applicant's Proposed Revision	FDA's Proposed Revision
8.4 Pediatric Use	The safety and ~~efficacy~~ effectiveness of IBRANCE in pediatric patients have not been ~~studied~~ established. The safety and effectiveness were assessed in three studies: an open-label (b) (4) (A5481092, NCT03709680) (b) (4) (b) (4) 98 pediatric patients, aged 2 to <17 years, (b) (4) recurrent or refractory solid tumors (b) (4) (b) (4), pediatric patients, aged 4 to <17 years, (b) (4) recurrent, (b) (4) or refractory (b) (4) (b) (4) tumors, (b) (4) (b) (4) (APEC1621I, NCT03526250) (b) (4) (b) (4) No new safety signals were observed in these (b) (4). Palbociclib (b) (4) exposures in pediatric patients as (b) (4) adult (b) (4)	The safety and ~~efficacy~~ effectiveness of IBRANCE in pediatric patients have not been ~~studied~~ established. The safety and effectiveness of IBRANCE were assessed but not established in three (b) (4) trials: an open-label (b) (4) (A5481092, NCT03709680) (b) (4) that included 98 pediatric patients, aged 2 to <17 years of age who received IBRANCE in combination with chemotherapy for (b) (4) recurrent or refractory solid tumors (b) (4) two open-label trials that included (b) (4) 42 pediatric patients, aged 4 to <17 years of age who received IBRANCE as a single agent for (b) (4) recurrent, (b) (4) or refractory (b) (4) solid tumors, (b) (4) {[APEC1621I, (NCT03526250)] or primary central nervous system (CNS) tumors [PBTC-042, (NCT02255461)]. (b) (4) No new safety signals were observed in these (b) (4) trials. (b) (4) Palbociclib exposures in pediatric

		patients who received IBRANCE as a single agent or in combination were within range of those observed in ~~as~~ (b) (4) adults given a similar dose based on body surface area. (b) (4)

5. Recommended Regulatory Action

The FDA review team found the Applicant to have met the terms of the PWR Amendment 3 and recommends granting additional marketing exclusivity: Pediatric Exclusivity, based on the pediatric information as provided under Section 505A of the Federal Food, Drug, and Cosmetic Act This recommendation was supported by the pediatric exclusivity review board and was granted on September 9, 2025. Additionally, the pediatric information has been updated in Section 8.4 of labeling and agreed to be the Applicant and FDA.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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