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Draft Guidance on Palbociclib

May 2022

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This guidance, which interprets the Agency’s regulations on bioequivalence at 21 CFR part 320, provides product-specific recommendations on, among other things, the design of bioequivalence studies to support abbreviated new drug applications (ANDAs) for the referenced drug product. FDA is publishing this guidance to further facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval for generic versions of this product.

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This is a new draft product-specific guidance for industry on generic palbociclib.

Active Ingredient: Palbociclib

Dosage Form; Route: Tablet; oral

Recommended Studies: Three in vivo bioequivalence studies with pharmacokinetic endpoints

1. Type of study: Fasting
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 125 mg
Subjects: Healthy males and non-pregnant, non-lactating females
Additional comments: Female subjects of reproductive potential should use non-hormonal contraception during the study and continue to use effective contraceptives for three weeks after the last dose. Male subjects with female partners of reproductive potential should use effective contraception during the study and for three months after the last dose. Applicants may consider using a reference-scaled average bioequivalence approach. If using this approach, provide evidence in the studies of high variability in the

bioequivalence parameters of area under the plasma concentration time curve and/or peak concentration (i.e., within-subject variability $\geq 30\%$). For detailed information on this approach, refer to the most recent version of the FDA guidance for industry on *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*.^a

2. Type of study: Fed
Design: Single-dose, two-treatment, two-period, crossover in vivo
Strength: 125 mg
Subjects: Healthy males and non-pregnant, non-lactating females
Additional comments: See comments above.

3. Type of study: Fasting, in presence of an acid-reducing agent
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 125 mg
Subjects: Healthy males and non-pregnant, non-lactating females
Additional comments: A proton pump inhibitor (e.g., rabeprazole) is recommended for the selection of acid-reducing agents to compare gastric pH-dependent pharmacokinetics between the test and reference palbociclib products. The elevating effect of a proton pump inhibitor on gastric pH (e.g., mean pH over 24 hours, percentage of the time when the pH ≥ 4.0 in a 24-hour interval) is dependent on the individual proton pump inhibitor and its dose. Select a proton pump inhibitor that has minimal effect on pharmacokinetics of palbociclib via other interacting mechanisms and a dose that is expected to provide a near maximum effect on gastric acid suppression (i.e., pH elevation). Subjects should be pre-treated with a proton pump inhibitor for several days (e.g., 4 to 5 days) to reach its pharmacodynamic steady-state before administering the test or reference products. Other additional comments are the same as the fasting study above.

Analyte to measure: Palbociclib in plasma

Bioequivalence based on (90% CI): Palbociclib

Waiver request of in vivo testing: 75 mg and 100 mg strengths based on (i) acceptable bioequivalence studies on the 125 mg strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all strengths

Dissolution test method and sampling times: The dissolution information for this drug product can be found in the FDA's Dissolution Methods database, <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. Conduct comparative dissolution testing on 12 dosage units for each of all strengths of the test and reference products. Specifications will be determined upon review of the ANDA.

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^a For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.