Alpelisib

Piqray®

Mechanism of Action

According to the FDA NDA 212526, "alpelisib is an inhibitor of phosphatidylinositol-3-kinase (PI3K) with inhibitory activity predominantly against PI3Kα. Gain-of-function mutations in the gene encoding the catalytic α-subunit of PI3K (PIK3CA) lead to activation of PI3Kα and Akt-signaling, cellular transformation and the generation of tumors in in vitro and in vivo models.

In breast cancer cell lines, alpelisib inhibited the phosphorylation of PI3K downstream targets, including Akt and showed activity in cell lines harboring a PIK3CA mutation. In vivo, alpelisib inhibited the PI3K/Akt signaling pathway and reduced tumor growth in xenograft models, including models of breast cancer.

PI3K inhibition by alpelisib treatment has been shown to induce an increase in estrogen receptor (ER) transcription in breast cancer cells. The combination of alpelisib and fulvestrant demonstrated increased antitumor activity compared to either treatment alone in xenograft models derived from ER-positive, PIK3CA mutated breast cancer cell lines."

Toxicology

According to the FDA NDA 212526:
In a 4-week study in Beagles given alpelisib 2, 5, 15 mg/kg/day, daily dosing via oral gavage, the major findings included

- Body weight loss started from the lowest dose of 2 mg/kg/day.
- Test item-related changes in insulin and glucose levels indicative of altered glucose metabolism at ≥ 2 mg/kg/day, and morphologically mainly atrophic changes in the epithelium of the oral mucosa, tongue, esophagus, larynx or skin partly at all dose levels as well as in the mucosa of the gastrointestinal tract and in the lymphoid system at the highest dose of 15 mg/kg/day.
- All changes were fully or partially reversible after 4 weeks of treatment-free recovery.
- Mortality: 1 Female dog at 15 mg/kg/day (HD) was euthanized on day 31 due to moribund condition. The cause of death was acute intestinal intussusception at the ileocolonic junction. Although no mortalities occurred during the 30-day treatment period, two of the high dose females were unable to be dosed on day 30 due to severe body weight loss and poor health.
- Clinical Chemistry: There was a significant dose-dependent increase in insulin levels in MD (5 mg/kg) animals (↑41% in males, 62% in females) and HD (15 mg/kg) animals (↑62% in males, 139% in females). This increase was accompanied by variable glucose levels and increased triglyceride and cholesterol values.
- Organ Weights: A decrease in pituitary gland (~35%), spleen (~30%), and thymic weights (~30%) was observed in HD animals. There was also a dose-dependent decrease in ovary

(up to ~35%), uterus (up to ~50%), and prostate weights (up to ~40%). These changes were reversible or trending towards reversible in recovery animals.
- Histological Findings: uterine atrophy at HD.

In a 13-week study, Beagles given alpelisib 0.2, 1.0, 5.0 mg/kg/day, daily dosing, followed by a 4-week treatment-free was generally well tolerated with no mortality or toxicologically significant test article-related clinical or post dosing observations, or adverse effects on the ECG or at ophthalmoscopic examination.

- Reduced body weight gain mainly at 5 mg/kg/day was associated with a reduced food intake in males of this group.
- Clinical pathology findings indicative of interference with the glucose and insulin homeostasis at all doses and minor post-mortem findings in tongue and lymphatic system of individual high-dose animals suggest a relationship to the pharmacological activity of the test article.
- All findings were fully or partially reversed after a 4-week treatment-free recovery period (in the mesenteric lymph nodes, minimal lymphoid depletion was seen in two males and one female after recovery).

In humans, the major concerning risks of alpelisib are severe hypersensitivity, severe cutaneous reactions, hyperglycemia, pneumonitis, diarrhea, and embryo-fetal toxicity.

FDA Labeled Use

Piqray® is not labeled for dogs; therefore, use of this drug in the dog is off-label.

According to the FDA's Highlights of Prescribing Information (revised 07/2021):
Piqray® is a kinase inhibitor indicated in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR)- positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, advanced or metastatic breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen.

Selected Canine Publications

:: Preclinical
None currently

:: Safety/dosing
None currently

:: Efficacy
None currently

Pharmacokinetics

According to the FDA NDA 2125260:
In a 13-week repeated dose study in dogs given 0.2, 1, 5 mg/kg/day, the major findings were as follows:

- C_{max} was dose proportional increase
- AUC > dose proportional increase
- On Day 72
    - AUC: 442-15,100 ng*hr/mL
    - C_{max}: 95-1,860 ng/mL
- No gender differences
- No accumulation
- $T_{1/2}$: not defined
- T_{max}: 0.5 - 1 hour

In male dogs given oral radio-labeled [^{14}C] alpelisib 5 mg/kg, T_{max} was reached 2 hours after oral administration, and $T_{1/2}$ was 6.2 h for the parent drug. Absolute oral bioavailability was high.

Sources

- Best Pet Rx (https://bestpetrx.com/contact-us/): (as of September 21, 2021): Unavailable

- Stokes Pharmacy (https://www.stokespharmacy.com/veterinary-rx/for-veterinarians/): (as of September 21, 2021) Unavailable

- Wedgewood Pharmacy (https://www.wedgewoodpharmacy.com/veterinary-practices/): (as of September 21, 2021) Unavailable

Anecdotal Information from Veterinary Oncologists

None currently

References

Piqray® (Alpelisib); Pharmacology Review. Center for Drug Evaluation and Research, U.S. Food and Drug Administration, NDA 212526, May 2019.

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