Lapatinib

Tykerb®

Mechanism of Action

According to the FDA NDA 22-059, lapatinib is is a 4-anilinoquinazoline kinase inhibitor of the intracellular tyrosine kinase domains of both Epidermal Growth Factor Receptor (EGFR [ErbB1]) and of Human Epidermal Receptor Type 2 (HER-2 [ErbB2]) receptors. Lapatinib inhibits ErbB-driven tumor cell growth *in vitro* and in various animal models.

Toxicology

According to the FDA NDA 22-059:

SINGLE dose

- In Beagles given a single oral dose of 50, 150, or 500 mg/kg and monitored over 7 days, there were no noted changes in behavior, skeletal muscle tone, reflexes, and overt autonomic, gastrointestinal and neurological effects.
- In 4 Beagles, increases in mean systolic, diastolic and arterial pressure were seen with 150 mg/kg at 10-14 hr timeframe, and with 500 mg/kg at 6-14 hr timeframe. One dog had 3 ventricular extrasystoles at 5 hrs after 50 mg/kg administration.

MULTIPLE doses

- Key findings in Beagles administered a **13-week** once daily oral dosing of 10, 40, and 160 mg/kg/day:
    - Two dogs were euthanized moribund (160 mg/kg/day dose, on day 31 and 86).
    - Clinical signs included decreased activity, dehydration, salivation, loose feces, ulcerations (paw, mouth), scabs, vomiting.
    - Body weights and food consumption decreased in dogs receiving 160 mg/kg/day.
    - Hematology: increased WBCs, neutrophils, monocytes; decreased basophils
    - Chemistry: increased bilirubin, total bile acids, ALP, and ALT
    - Pathology: most notable gross treatment-related pathology findings included red discoloration, primarily of the GI tract, scabs on the skin, and several gall bladder findings (distended, viscous or granular contents, flocculent bile). Histological changes in lymphoid tissue, liver, GI, spleen, thymus, muscle, pancreas, skin, mammary glands, bone marrow as well as increased pigment deposition in numerous tissues.
    - During the recovery period, body weight, food consumption increased; hematologic and chemistry values were returning to normal.

- Key findings in Beales administered a **39-week** once daily oral dosing of 10, 40, and 100 mg/kg/day:
    - 2 dogs euthanized moribund (100 mg/kg/day, on day 212 and 228)
    - Decreased body weights in the high dose dogs, and decreased food consumption
    - Hematology parameter changes seen in high dose female dogs, decreased RBC parameters and increased platelets
    - Clinical chemistry changes include increases in ALT, ALP, bilirubin, bile acids (mostly in high dose dogs)
    - Large levels of bilirubin in urine since in some high dose dogs
- Microscopic and macroscopic effects of drug seen in the GI, liver, skin, lymphoid tissue and adrenals, most resolved during recovery

FDA Labeled Use

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

According to the Highlights of Prescribing Information, updated 12/2008:
Tykerb® is a kinase inhibitor indicated in combination with:

- capecitabine for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress human epidermal growth factor receptor 2 (HER2) and who have received prior therapy including an anthracycline, a taxane, and trastuzumab. Limitations of Use: Patients should have disease progression on trastuzumab prior to initiation of treatment with TYKERB in combination with capecitabine.
- letrozole for the treatment of postmenopausal women with hormone receptor-positive metastatic breast cancer that overexpresses the HER2 receptor for whom hormonal therapy is indicated.

Tykerb® in combination with an aromatase inhibitor has not been compared to a trastuzumab-containing chemotherapy regimen for the treatment of metastatic breast cancer.

Selected Canine Publications

:: Preclinical

- In a study aiming to verify the effects of lapatinib on 4 canine primary mammary gland carcinoma cell cultures and 2 paired metastatic cell cultures (Fernando Leis-Filho A et al.),
    - Lapatinib was able to inhibit cell proliferation in all six canine primary mammary gland carcinoma cell cultures.
    - The IC_{50} values of the six cell cultures were between 14.06 nM and 584.8 nM.
    - Cell lines exhibited dose-dependent cell viability.
    - The higher the HER2 expression of a sample was, the lower the IC_{50} of lapatinib for that culture.

- In a study charting the genomic landscape of canine lung cancer (Lorch et al.),
    - HER2 point-mutated ($HER2^{V659E}$) canine pulmonary adenocarcinoma cell lines displayed constitutive phosphorylation of AKT and significantly higher sensitivity to the HER2 inhibitors lapatinib and neratinib relative to HER2-wild-type cell lines (IC_{50} < 200 nmol/L in $HER2^{V659E}$ vs. IC_{50} > 2,500 nmol/L in $HER2^{WT}$).

- In a study investigating the anti-tumour effect of lapatinib on canine TCC cell lines in vitro and in vivo (Sakai K et al.),
    - Western blotting showed that HER2 protein expression was observed in all of the [5] canine TCC cell lines. Lapatinib inhibited phosphorylation of HER2 and cell growth in a dose-dependent manner.
    - In nude mice injected with canine TCC cells and treated with intraperitoneal lapatinib for 14 days, tumor volume was significantly smaller in the lapatinib group compared with the vehicle control group.

Safety/dosing

- In a study evaluating the tolerated dosage and side effects of lapatinib in 6 healthy 18-month old Beagles (Tanaka Y et al.),
    - the MTD of lapatinib was found to be 35 mg/kg/day within 8 weeks
    - 1 dog developed grade 3 toxicity when lapatinib was administered at a dose of 40 mg/kg/day. The dose-limiting toxicity was a grade 3 adverse effect, which was defined as a weight loss of >15%.
    - After lapatinib administration for 8 weeks at 35 mg/kg/day, 3/6 dogs showed grade 3 ALP elevation.

Efficacy

- In a prospective, non-randomized clinical trial comparing 44 dogs with naturally occurring urothelial carcinoma who received lapatinib+piroxicam with 42 age-, sex-, and tumor stage-matched dogs that received piroxicam alone (Maeda et al.), those administered lapatinib+piroxicam had more favorable response rates improved survival:
    - Doses:
        - Lapatinib 20-30 mg/kg/day PO
        - Piroxicam 0.3 mg/kg/day PO
    - Response rates:
        - Lapatinib+piroxicam: CR 2%, PR 52%, SD 34%, PD 12%
        - Piroxicam: PR 9%, SD 67%, PD 24%
    - Progression-free survival:
        - Lapatinib+piroxicam: 193 days (28-560)
        - Piroxicam: 90 days (21-318)
        - Hazard ratio 0.29; 95% CI 0.18–0.47; P < 0.0001
    - Overall survival:
        - Lapatinib+piroxicam: 435 days (65-1023)
        - Piroxicam: 216 days (41-725)
        - Hazard ratio 0.41; 95% CI 0.26–0.65; P = 0.0001
    - Biomarker assessments:
        - HER2 positivity (via ICC of urine sediment) was observed in 29/44 (66%) of cases and was associated with a favorable response in dogs treated with

lapatinib/piroxicam (n.b. phospho-HER2 expression was not measured, and HER2 status was not evaluated in the piroxicam-only group).
    - The PFS and OS for HER2+ cases were longer than those for HER2- cases.
    - The OS for cases with HER2 gene amplification (via digital PCR) was longer than that for cases without HER2 amplification.
    - There was no association between $BRAF^{V595E}$ mutation and clinical response in dogs treated with lapatinib/piroxicam. PFS and OS were not related to the $BRAF^{V595E}$ mutation.
- Treatment *prior* to this clinical trial enrollment:
    - Lapatinib+piroxicam: 32/44 (73%) received NSAIDs including firocoxib, carprofen, piroxicam for a median of 112 days.
    - Piroxicam: 27/42 (64%) received NSAIDs including firocoxib, carprofen, meloxicam, or piroxicam for a median of 98 days.
- Adverse events:
    - Lapatinib+piroxicam: most grade 1 or 2, transient, no treatment discontinuation, dose-reduction in 9%; overall incidence of increase ALT and ALP were significantly higher in this group compared to piroxicam alone; dermatologic adverse events (hyperpigmentation, pruritus, skin ulceration, and alopecia) were noted in 11% of cases (intervention not required in most cases).
    - Piroxicam: leading adverse events were increased creatinine, anorexia, increased ALP, and vomiting.

Pharmacokinetics

In halothane-anesthetized dogs (Ando K et al.),

- lapatinib was intravenously administered in doses of 0.3 and 3 mg/kg over 10 min, providing the peak plasma concentrations of 696 ± 73 (1.2 μmol/L) for the low dose and 2,358 ± 424 ng/mL (4.1 μmol/L) for the high dose, with peak plasma concentrations observed 10 min after the start of either infusion. This suggests a therapeutic dose in light of previous reports showing lapatinib inhibits the ErbB1 and ErbB2 receptors, the IC_{50} of which values were 9.2 and 10.8 nmol/L.
  - The therapeutic concentration of lapatinib significantly increased total peripheral vascular resistance, CT, CTc, monophasic action potential $(MAP)_{90(sinus)}$, $MAP_{90(CL400)}$, effective refractory period, and plasma concentration of cardiac troponin I (cTnI), suggesting that lapatinib prolonged the ventricular repolarization without inducing lethal ventricular arrhythmia.
  - Limitations: the effects of repeated lapatinib administration on the cardiovascular systems were not assessed; the effect of lapatinib combined with anthracyclines, paclitaxel or trastuzumab, which are well known to possess cardiotoxicities were not assessed; and plasma concentration of cTnI, NT-proBNP, CK, AST, or LDH after our experiment were not assessed.

According to the FDA NDA 22-059,
- Lapatinib is primarily metabolized by O-dealkylation to a phenol and is predominantly CYP3A4/5 mediated.

- Bioavailability of a single dose of 10 mg/kg PO is 41.9 ± 6.06%, with less bioavailability seen at 2 mg/kg dose.

Pharmacokinetic parameters of GW572016X in Male beagle Dogs (mean ± SD)							
Route/ Dose (mg/kg)	AUC_∞ (ng hr/mL)	C_{max} (ng/mL)	T_{max} (h)	$t_{½}$ (h)	CL (mL/min/kg)	V_{ss} (L/kg)	F
IV/10	14087 ± 3094	3793 ± 167	0.08	5.85 ± 0.17	12.2 ± 2.83	5.70 ± 1.03	–
PO/10	5916 ± 852	555 ± 15.1	4.00	3.27 ± 1.18	-	-	41.9 ± 6.06
PO/2	197 ± 127	24.9 ± 13.2	4.00	3.61 ± 0.95	-	-	6.97 ± 4.50

- Excretion is primarily through biliary excretion into the GI tract and >82-99% of the drug is accounted for in the feces.

Sources

- Best Pet Rx (https://bestpetrx.com/contact-us/): (as of July 15, 2021): Available in dose range of 0.1 mg to 250 mg capsules.
    Dose 0.1 mg, quantity 30, $134
    Dose 250 mg, quantity 30, $352

- Stokes Pharmacy (https://www.stokespharmacy.com/veterinary-rx/for-veterinarians/): (as of July 14, 2021) Available in a range of sizes. Examples include the following:
    Dose 100 mg, quantity 30, $395
    Dose 300 mg, quantity 30, $600

- Wedgewood Pharmacy (https://www.wedgewoodpharmacy.com/items/lapatinib-capsule.html): (as of July 14, 2021) Available in dose range of 10.5 mg – 430 mg capsules
    Dose 10.5 mg, quantity 60, $105
    Dose 430 mg, quantity 30, $375

Anecdotal Information from Veterinary Oncologists

None currently

References

Ando K et al. Precise safety pharmacology studies of lapatinib for onco-cardiology assessed using *in vivo* canine models. *Sci Rep*. 2020 Jan 20;10(1):738. Doi: 10.1038/s41598-020-57601-x.

Fernando Leis-Filho A et al. Effects of lapatinib on HER2-positive and HER2-negative canine mammary carcinoma cells cultured in vitro. *Pharmaceutics*. 2021 Jun 17;13(6):897. doi: 10.3390/pharmaceutics13060897.

Lorch et al. Identification of recurrent activating HER2 mutations in primary canine pulmonary adenocarcinoma. *Clin Cancer Res*. 2019 Oct 1;25(19):5866-5877. doi:10.1158/1078-0432.CCR-19-1145.

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Tanaka Y et al. Evaluation of the proper dosage of lapatinib and its safety in dogs. *Translat Regulat Sci.* 2020;2(3):68-71. doi: 10.33611/trs.2020-013.

Tykerb® (Lapatinib); Pharmacology Review. Center for Drug Evaluation and Research, U.S. Food and Drug Administration, (NDA 22-059), March 13, 2007.

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