Sotorasib

Lumakras™

Mechanism of Action

According to the FDA NDA 214665, "sotorasib is an inhibitor of $KRAS^{G12C}$, a tumor-restricted, mutant-oncogenic form of the RAS GTPase, KRAS. Sotorasib forms an irreversible, covalent bond with the unique cysteine of $KRAS^{G12C}$, locking the protein in an inactive state that prevents downstream signaling without affecting wild-type KRAS. Sotorasib blocked KRAS signaling, inhibited cell growth, and promoted apoptosis only in *KRAS G12C* tumor cell lines. Sotorasib inhibited $KRAS^{G12C}$ in vitro and in vivo with minimal detectable off-target activity. In mouse tumor xenograft models, sotorasib-treatment led to tumor regressions and prolonged survival and was associated with anti-tumor immunity in *KRAS G12C* models."

Toxicology

According to the FDA NDA 214665 and Ishida et al.:
In a 28-day toxicology study in Beagles (n=3/sex/group) given 0, 30, 100, or 300 mg/kg day (once daily dosing) oral sotorasib via oral gavage, noteworthy findings included the following:

- Clinical signs: Salivation and wet fur (lower jaw and muzzle areas) in 1 dog throughout the study at 300 mg/kg.
- Hematology: Minimal to mild decrease in RBC mass in males at 300 mg/kg and in females at 100 mg/kg associated with decreased reticulocyte counts in males at 100 mg/kg and females at 300 mg/kg. There were no light microscopic correlates.
- Clinical chemistry: Mild increase in urea nitrogen in females at 100 mg/kg without noteworthy changes in creatinine (with no light microscopic correlates in the kidney).
- Conclusion: The highest non-severely toxic dose (HNSTD): 300 mg/kg.

In a 3-month toxicology study in Beagles (n=3/sex/group) given 0, 100 (low dose, LD), and 500 mg/kg (high dose, HD) twice daily (i.e. 0, 200, and 1000 mg/kg/day) oral sotorasib via oral gavage, key findings included the following:

- No mortality was noted
- Clinical signs included the following:
  - 200 mg/kg/day: eye discharge (n=4), wet fur (n=3)
  - 1000 mg/kg/day: increased activity (n=1), labored breathing (n=1), food partly digested (n=3), swollen forepaw (n=1), thin (n=1), vocalization (n=1)
  - Oily fur and salivation were observed at dose levels ≥200 mg/kg/day
- Hematology: Minimal to mild decrease in RBC mass, generally associated with a mild decrease in reticulocyte counts, no microscopic correlates in the bone marrow.
- Clinical chemistry: Minimal to mild increase in total bilirubin, alkaline phosphatase (1,000 mg/kg males only), cholesterol, and triglycerides. Minimal to mild increase in urea nitrogen and creatinine at 200 mg/kg with no light microscopic correlate in the kidney.

- Target organs included the thyroid gland (marked follicular cell atrophy), pituitary gland (hypertrophy), liver (hypertrophy), gallbladder (bile sludge), and thymus (decreased cellularity).
- Conclusion: The highest non-severely toxic dose (HNSTD): 1,000 mg/kg/day.

FDA Labeled Use

Lumakras™ 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 (Reference ID 4803215): Lumakras™ is an inhibitor of the RAS GTPase family indicated for the treatment of adult patients with *KRAS G12C*-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC), as determined by an FDA-approved test, who have received at least one prior systemic therapy. This indication is approved under accelerated approval based on overall response rate (ORR) and duration of response (DOR). Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

Selected Canine Publications

:: Preclinical

None currently

:: Safety/dosing

See Toxicology section

:: Efficacy

None currently

Pharmacokinetics

According to the FDA NDA 214665:

- $T_{1/2}$: not calculated
- Dose proportionality: C_{max} and AUC_{last} increased much less than dose proportionally.
- Accumulation: none
- Sex differences: None except C_{max} and AUC_{last} were ≤2.8-fold higher in HD males compared to HD females on Day 1
- The metabolism and excretion of [^{14}C]-sotorasib after a single oral (500 mg/kg) dose of sotorasib revealed [^{14}C]-sotorasib-derived radioactivity was minimally absorbed and was eliminated predominantly as unchanged sotorasib in feces (corroborated by Dahal et al.).
- Mean T_{max} was 3-4 hours post-dose (500 mg/kg, ^{14}C-sotorasib).

Excerpted from the FDA NDA 214665:

Summary of Toxicokinetics (3-Month Study; Dogs)

Day	Dose (mg/kg/day)	C_{max} (µg/mL)		AUC_{last} (µg·hr/mL)		T_{max} (hr)	
		M	F	M	F	M	F
1	200	2.98	3.17	8.23	12.8	0.5	1.0
	1000	6.11	2.19	26.9	10.3	13	14
90	200	4.05	4.17	12.7	12.6	13	13
	1000	4.63	4.62	13.9	14.4	13	14

Hr = hours; NA = Not applicable; AUC_{last} = AUC from time zero to the time of last quantifiable concentration (up to 24 hr)

According to a study evaluating absorption, distribution, metabolism, and excretion of radioactively labeled sotorasib ([^{14}C]-sotorasib at 500 mg/kg orally as a suspension using a 5 ml/kg dose volume via oral gavage) by Dahal et al.:

- Excretion was predominately by the fecal route, accounting for a mean of approximately 89.6 and 92.7% (male and female) of the administered dose. Urinary excretion was minor and accounted for a mean of 3.1 and 2.2% (male and female) of the administered radioactive dose. The majority of the radioactivity was recovered in the first 48 hours.
- Sotorasib underwent metabolism to 11 identified metabolites. Biotransformation was primarily through glutathione conjugation. Secondary metabolism proceeded through oxidation, glucuronidation, adn cleavage of the cysteine conjugate. Unchanged sotorasib in excreta accounted for the majority of dose in male and female dogs.
- C_{max} was reached 3-4 hours after dosing. After reaching C_{max}, blood and plasma concentration in dogs decreased quickly and radioactivity was not quantifiable after 8 hours.
- [^{14}C]-sotorasib was minimally absorbed by dogs. The low absorption of sotorasib in dogs may be explained by solubility-limited absorption.

Sources

- Best Pet Rx (https://bestpetrx.com/contact-us/): (as of February 10, 2022): Unavailable

- Stokes Pharmacy (https://www.stokespharmacy.com/veterinary-rx/for-veterinarians/): (as of February 10, 2022) Unavailable

- Wedgewood Pharmacy (https://www.wedgewoodpharmacy.com/veterinary-practices/): (as of February 10, 2022) Unavailable

Anecdotal Information from Veterinary Oncologists

None currently.

References

Dahal et al. Absorption, distribution, metabolism and excretion of [^{14}C]-sotorasib in rats and dogs: interspecies differences in absorption, protein conjugation and metabolism. *Drug Metab Dispos*. 2022 Feb 13;DMD-AR-2021-000798. doi: 10.1124/dmd.121.000798.

Ishida et al. Nonclinical safety profile of sotorasib, a $KRAS^{G12C}$-specific covalent inhibitor for the treatment of *KRAS p.G12C*-mutated cancer. *Int J Toxicol*. 2021 Oct;40(5):427-441. doi: 10.1177/10915818211022965.

Lumakras™ (Sotorasib); Pharmacology Review. Center for Drug Evaluation and Research, U.S. Food and Drug Administration, NDA 214665, May 2021.

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