Dabrafenib

Tafinlar®

Mechanism of Action

According to the FDA NDA 202806, "Dabrafenib is an inhibitor of some mutated forms of BRAF kinases with in vitro IC_{50} values of 0.65, 0.5, and 1.84 nM for BRAF V600E, BRAF V600K, and BRAF V600D enzymes, respectively. Dabrafenib also inhibits wild-type BRAF and CRAF kinases with IC_{50} values of 3.2 and 5.0 nM, respectively, and other kinases, such as SIK1, NEK11, and LIMK1 at higher concentrations. Some mutations in the BRAF gene, including those that result in BRAF V600E, can result in constitutively activated BRAF kinases that may stimulate tumor cell growth. Dabrafenib inhibits cell growth of various BRAF V600 mutation-positive tumors in vitro and in vivo.

Dabrafenib and trametinib target two different kinases in the RAS/RAF/MEK/ERK pathway. Use of dabrafenib and trametinib in combination resulted in greater growth inhibition of BRAF V600 mutation-positive tumor cell lines *in vitro* and prolonged inhibition of tumor growth in BRAF V600 mutation positive tumor xenografts compared with either drug alone."

Toxicology

According to the FDA NDA 202806, the main target organs of toxicity in dogs were the skin, male reproductive organs, and heart.

In the 4-week toxicity study with doses of 0, 1, 5, or 50 mg/kg/day with a 2-week recovery period, clinical signs, body weights, food consumption, ophthalmoscopy, electrocardiography, hematology, coagulation, clinical chemistry, and urinalysis were unremarkable.

- Macroscopic gross pathology changes in the skin (raised areas around muzzle, pedunculated areas along chin, thickening and nodular appearance of external ear) were noted predominantly in the 50 mg/kg/day group and were reversible by the end of the recovery period. In 1 of 6 dogs administered 50 mg/kg/day for 4 weeks, heart toxicity consisted of marked hypertrophy of the right atrioventricular (tricuspid) valve. (When monitored for up to 24 hours post-dose after a single dose of 1, 5, or 50 mg/kg/day, no toxicologically significant effects were seen on arterial pressure, heart rate, body temperature, or electrocardiographic intervals.)
- Microscopic histopathologic findings of the heart (focal and mild hemorrhage and fibrin deposition in the tricuspid valve; marked hypertrophy of the tricuspid valve) and skin (benign squamous papilloma, mild acanthosis, and ulceration of the chin and external ear; minimal hyperkeratosis of the external ear; minimal inflammatory cell infiltrate of the chin) were noted predominantly in the 50 mg/kg/day group and were reversible by the end of the recovery period.

In the 13-week toxicity study, dogs were orally administered 0, 5, 20, or 60 (males)/100 (females) mg/kg/day of dabrafenib (split over 2 doses/day).

- The 60 and 100 mg/kg/day doses were not tolerated, and these doses were discontinued after 2 weeks due to severity of clinical signs, including thin body condition, inappetence,

weight loss, prominent back bone, dehydration, liquid feces, red cums/gingivitis (for 1 animal, bilateral gingival erosion and ulceration including exposed bone), occasional/transient emesis, and eye discharge.
- Plasma exposure levels (AUC_{0-24}) in this study were equivalent to approximately 0, 2, and 11 times (exposure levels for 60/100 mg/kg/day animals were not obtained) the exposure level in humans receiving the recommended dose of dabrafenib, respectively.
- Dogs tolerated up to 20 mg/kg/day of dabrafenib. Skin lesions and papules were observed at all doses on various areas including the muzzle, pinna, lower jaw, inguinal, scrotum, and ventral thorax. Histopathological correlates included acanthosis, infiltration, and erosions/crusts.
- Additional toxicities included dose-responsive lymphoid depletion in the thymus and inflammation in the lungs. Degeneration/depletion in the testis and aspermia in the epididymis was noted in 100% of male dogs, irrespective of dose. Partial granular development was also noted in the prostate in dogs administered 20 mg/kg/day of dabrafenib.
- Hemorrhage of the atrioventricular value of the heart was noted in 1 of 8 dogs at 20 mg/kg/day and 3 of 8 dogs at 60 (males) and 100 (females) mg/kg/day. Toxicities seen in the heart occurred at plasma levels (AUC_{0-24}) ≥ 5 times human exposure following the recommended dose of dabrafenib.

In dogs given a combination of dabrafenib (Tafinlar®) at 0, 5 (2.5 BID), and 20 (10 BID) mg/kg with trametinib (Mekinist®) at 0, 0.0075, and 0.0225 mg/kg/day. Key findings included the following:
- One 0.0225/20 mg/kg/day male was sacrificed in moribund condition on Day 11 due to body weight loss, decreased food consumption, dark red/black liquid feces, and increased body temperature.
- Target organs of toxicity were stomach, thymus, and male reproductive organs.
- Stomach toxicity was observed at all doses and consisted of inflammation, associated with increases in white blood cells, neutrophils, and monocyte counts, and decreased cellularity in the thymus.
- Male reproductive toxicity was seen predominantly in 0.0225/20 mg/kg/day animals and consisted of germ cell degeneration/oligospermia in epididymis and germinal epithelium degeneration in the testes.
- Accumulation of trametinib was noted at the end of the dosing period.

FDA Labeled Use

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

According to the FDA' Highlights of Prescribing Information (Reference ID 4929103):
Tafinlar® is is a kinase inhibitor indicated as a single agent for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test.

Tafinlar® is indicated in combination with trametinib, for:
- the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test.

- the adjuvant treatment of patients with melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test, and involvement of lymph node(s), following complete resection.
- the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with BRAF V600E mutation as detected by an FDA-approved test.
- the treatment of patients with locally advanced or metastatic anaplastic thyroid cancer (ATC) with BRAF V600E mutation and with no satisfactory locoregional treatment options.

Selected Canine Publications

Preclinical

- In an *in vitro* study, dabrafenib decreased the production of CCL17 (a chemokine involved in regulatory T cell recruitment) a canine urothelial carcinoma cell line with $BRAF^{V595E}$ mutation (Maeda et al.).

Safety/dosing

None currently.

Efficacy

None currently.

Pharmacokinetics

According to the FDA NDA 202806, exposure levels (C_{max} and AUC) were less than dose-proportional between all doses in males and females; no drug accumulation was noted; and no sex differences were seen.

Excerpted from the FDA NDA 202806 (GSK2118436 = dabrafenib):

Mean Toxicokinetic Parameters on Day 1 and 28 Following Daily Oral Administration of GSK2118436 to Dogs

Parameter [a]	Period	Male		
		Dose of GSK2118436 (mg/kg/day)		
		1 [b]	5 [b]	50 [c,d]
AUC_{0t} (µg.h/mL)	Day 1	4.47 [3.62-5.07]	19.2 [15.2-23.6]	48.9 [23.5-72.4]
	Day 28	4.10 [3.34-4.68]	10.5 [8.32-14.4]	40.2 [26.4-46.8]
C_{max} (µg/mL)	Day 1	1.13 [0.754-1.55]	3.69 [2.00-5.36]	8.87 [3.53-15.0]
	Day 28	0.893 [0.599-1.04]	2.73 [1.49-3.87]	8.41 [4.88-11.4]
Median T_{max} (h)	Day 1	1.00 [1.00-1.00]	2.00 [1.00-2.00]	1.00 [0.50-4.00]
	Day 28	1.00 [1.00-1.00]	1.00 [1.00-1.00]	1.00 [1.00-4.00]

Parameter [a]	Period	Female		
		Dose of GSK2118436 (mg/kg/day)		
		1 [b]	5 [b]	50 [c]
AUC_{0t} (µg.h/mL)	Day 1	5.83 [1.60-11.2]	17.3 [8.68-31.7]	35.7 [17.2-51.3]
	Day 28	4.48 [2.86-7.44]	14.0 [7.35-21.4]	45.2 [21.0-74.5]
C_{max} (µg/mL)	Day 1	1.21 [0.593-2.09]	3.23 [1.57-5.53]	6.58 [4.45-9.11]
	Day 28	0.841 [0.727-0.904]	2.62 [1.51-3.21]	6.85 [4.28-9.06]
Median T_{max} (h)	Day 1	1.00 [1.00-2.00]	1.00 [1.00-1.00]	1.00 [1.00-2.00]
	Day 28	1.00 [1.00-1.00]	1.00 [1.00-2.00]	1.00 [1.00-1.00]

a. Results are reported as mean unless stated otherwise and [range].
b. n=3.
c. n=5.
d. One of the 5 male animals at 50 mg/kg/day had an episode of emesis on Day 2 (prior to the 24-hour timepoint).

Sources

- Best Pet Rx (https://bestpetrx.com/): (as of 12.3.21) Unavailable.

- Stokes Pharmacy (https://www.stokespharmacy.com/veterinary-rx/for-veterinarians/): (as of 12.3.21) Unavailable.

- Wedgewood Pharmacy (https://www.wedgewoodpharmacy.com/veterinary-practices/): (as of 12.3.21) Unavailable.

Anecdotal Information from Veterinary Oncologists

None currently.

References

Maeda S et al. $BRAF^{V595E}$ mutation associates CCl17 expression and regulatory T cell recruitment in urothelial carcinoma of dogs. *Vet Pathol*. 2021 Sep;58(5):971-980. doi: 10.1177/0300985820967449.

Tafinlar® (Dabrafenib); Pharmacology Review. Center for Drug Evaluation and Research, U.S. Food and Drug Administration, NDA 202806, April 2013.

Disclaimer: Any information regarding therapy does not promise or guarantee that a particular drug or treatment regimen will be safe, effective, or helpful in the treatment of disease in any patient. The selection of any drug or drugs for patient treatment is done at the discretion of the treating veterinarian. Use caution when combining multiple drugs and be aware of potential drug interactions. Drug costs were provided by the respective pharmacies on the dates indicated, and drug costs and availability are subject to change at the discretion of the providing pharmacy. The treating veterinarian is encouraged to refer to drug labeling, published literature, and safety data for warnings, precautions, and dosing guidelines. Referenced articles, if any, were manually selected and do not necessarily reflect the entirety of literature on the drug or drugs. Vidium Animal Health®'s services, including but not limited to the information contained herein, are governed by Vidium's Terms & Conditions, which are available via email by requesting them at vidiuminfo@tgen.org.

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v26APR2022
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