Trametinib

Mekinist®

Mechanism of Action

Trametinib is a reversible inhibitor of mitogen-activated extracellular signal-regulated kinase 1 (MEK1) and MEK2 activation and of MEK1 and MEK2 kinase activity. MEK proteins are upstream regulators of the extracellular signal-related kinase (ERK) pathway, which promotes cellular proliferation. BRAF V600E mutations result in constitutive activation of the BRAF pathway which includes MEK1 and MEK2. Trametinib inhibits cell growth of various BRAF V600 mutation-positive tumors *in vitro* and *in vivo*.

Toxicology

According to the FDA, NDA 204114:

MULTIPLE doses: In Beagles given **13 consecutive weeks** of daily trametinib orally (via gavage) at either **0.15, 0.3, 0.6 mg/m^2** (0.6 mg/m^2 was dropped down to 0.45 mg/m^2 due to signs of toxicity and 1 dog euthanized early at the highest dose), the major organs of toxicity included the skin (lesions, scabs, discharge from and swelling of prepuce or vulva), GI tract (salivation), lungs (pale, raised, or dark areas with histological findings of minimal hemorrhage, mononuclear infiltration, pleural fibrosis, and macrophage accumulation - all classified as minimal to mild), and lymph nodes. For all dogs that survived until the scheduled euthanasia, histopathologic findings were minimal or mild except in the lymph nodes where sinusal erythrocytosis/hemorrhage was classified as moderate. There were no significant effects on ECG parameters.

- CBC: reticulocyte count increased in a dose-related manner in week 13
- Chemistry: minimal and not dose-related
- Urinalysis: no significant treatment-related changes

SINGLE dose: There were "no changes in cardiovascular parameters, arterial blood pressure, heart rate, ECG intervals, or body temperature following oral administration of [single dose of] 0.5, 0.75 or 1.5 mg/m^2 to conscious dogs."

FDA Labeled Use

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

In human patients, trametinib is a kinase inhibitor indicated as a single agent for the treatment of BRAF-inhibitor treatment-naïve patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test.

Selected Canine Publications

:: Preclinical

In an *in vitro* study, drug sensitivity was evaluated in a panel of genomically characterized canine cancer cell lines. Whole exome sequencing was performed for 33 canine cancer cell lines, spanning 10 different tumor types. Twelve of the 33 cell lines were sensitive to the MEK inhibitor, trametinib. Seventy-five percent (75%; 8/12) of the trametinib-sensitive canine cancer cell lines contained mutations in MAPK pathway members: BRAF, NRAS, KRAS, or NF1 (Das S et al).

In a series of *in vitro* experiments, 3 cell lines established from histiocytic sarcoma of dogs showed sensitivity to trametinib in cell viability assays (IC_{50} of 0.18, 0.033, 0.015), blocking of cell-cycle progression at all ranges of trametinib concentrations (significant increase in G1 and decrease in S and G2 phases), and increased level of apoptosis with trametinib treatment. In an *in vivo* xenograft mouse model, administration of trametinib inhibited tumor growth and prolonged survival time, decreased tumor growth in the liver and minimized tumor-associated liver injury, and MAPK signaling was inhibited in histiocytic sarcomas of mice treated with trametinib (Takada et al).

Pharmacokinetics

- Mean toxicokinetic parameters in male dogs (excerpted from NDA 204114):

Parameter [a]	Period	Male			
		Dose of GSK1120212 (mg/m²/day)			
		0.15 (n = 4)	0.3 (n = 6)	0.6 (n = 6)	0.45 (n = 5)
AUC_{0-t} (ng.h/mL)	Day 1	NC	2.96 [1.99 – 3.78]	28.9 [26.1 – 31.6]	NA
	Week 4	46.0 [34.7 – 62.4]	94.5 [82.1 – 115]	NA	131 [112 – 150]
	Week 13	45.6 [32.8 – 59.4]	95.5 [67.1 – 146]	NA	128 [118 – 140]
C_{max} (ng/mL)	Day 1	0.838 [0.803 – 0.907]	1.57 [1.09 – 2.13]	4.63 [3.72 – 6.05]	NA
	Week 4	2.55 [2.09 – 3.21]	5.45 [4.73 – 6.44]	NA	8.91 [7.85 – 10.2]
	Week 13	2.32 [1.54 – 2.84]	5.15 [3.45 – 6.41]	NA	8.42 [6.73 – 9.76]
Median T_{max} (h)	Day 1	0.50 [0.50 – 0.50]	0.50 [0.50 – 1.00]	0.50 [0.50 – 1.00]	NA
	Week 4	0.50 [0.50 – 1.00]	2.00 [0.50 – 2.00]	NA	1.00 [0.50 – 2.00]
	Week 13	1.00 [0.50 – 2.00]	1.00 [0.50 – 4.00]	NA	1.00 [0.50 – 2.00]

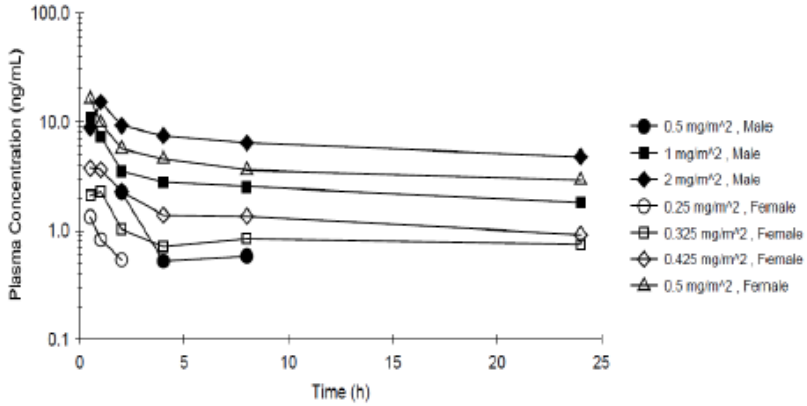
NC = Not calculated. There were insufficient plasma concentration data to calculate AUC.
NA = Not applicable. Dosing of 0.6 mg/m²/day was stopped on Day 11 for the main study female animals (451-454) and on Day 12 for the main study (401-404) and recovery (405-406) male animals and recovery female animals (455-456). Dosing resumed at a lower dose of 0.45 mg/m²/day on Day 21 for the main study female animals (451-454) and on Day 22 for the main study (401-403) and recovery (405-406) male animals and recovery female animals (455-456)..
a. Results are reported as mean unless stated otherwise and [range].

- Mean toxicokinetic parameters in female dogs (excerpted from NDA 204114):

Parameter [a]	Period	Female			
		Dose of GSK1120212 (mg/m²/day)			
		0.15 (n = 4)	0.3 (n = 6)	0.6 (n = 6)	0.45 (n = 6)
AUC_{0-t} (ng.h/mL)	Day 1	NC	5.98 [2.22 – 17.3]	33.3 [24.2 – 49.6]	NA
	Week 4	60.7 [52.3 – 82.4]	116 [95.1 – 158]	NA	177 [115 – 245]
	Week 13	51.8 [41.8 – 69.2]	107 [89.7 – 130]	NA	150 [113 – 197]
C_{max} (ng/mL)	Day 1	0.870 [0.710 – 1.15]	2.44 [1.63 – 3.06]	5.42 [2.09 – 9.02]	NA
	Week 4	3.56 [2.65 – 4.80]	7.73 [6.27 – 9.10]	NA	12.0 [9.10 – 16.9]
	Week 13	2.71 [2.17 – 3.68]	7.24 [6.21 – 8.34]	NA	9.78 [8.64 – 11.7]
Median T_{max} (h)	Day 1	0.50 [0.50 – 1.00]	0.50 [0.50 – 0.50]	0.50 [0.50 – 2.00]	NA
	Week 4	0.50 [0.50 – 0.50]	0.50 [0.50 – 1.00]	NA	1.00 [0.50 – 2.00]
	Week 13	0.75 [0.50 – 1.00]	0.50 [0.50 – 1.00]	NA	0.50 [0.50 – 1.00]

NC = Not calculated. There were insufficient plasma concentration data to calculate AUC.
NA = Not applicable. Dosing of 0.6 mg/m²/day was stopped on Day 11 for the main study female animals (451-454) and on Day 12 for the main study (401-404) and recovery (405-406) male animals and recovery female animals (455-456). Dosing resumed at a lower dose of 0.45 mg/m²/day on Day 21 for the main study female animals (451-454) and on Day 22 for the main study (401-403) and recovery (405-406) male animals and recovery female animals (455-456).
a. Results are reported as mean unless stated otherwise and [range].

- Individual single-dose concentration-time profiles for trametinib in Beagle dogs. Trametinib exhibited a long half-life as indicated by slow rate of clearance (excerpted from NDA 204114):



- High (97%) plasma protein binding
- Metabolized primarily by deacylation, demethylation, ketone formation, mono-oxygenation, and glucuronidation.
- Predominant route of elimination is via the feces; urinary excretion was <1% of the administered dose

Sources

- Best Pet Rx (https://bestpetrx.com/contact-us/): (as of October 18, 2021) Available in many doses; prices vary by dose ranges. Please refer to pharmacy website to see states served (22 states as of November 16, 2021).
    Dose range 0.1 mg – 1 mg capsules, quantity 30, ~$130.
    Dose range 1.1 - 2 mg capsules, quantity 30, ~$140.

- Stokes Pharmacy (https://www.stokespharmacy.com/veterinary-rx/for-veterinarians/): (as of August 31, 2021) Available dose range 0.09 mg – 0.8 mg capsules.
    Dose 0.09 mg capsules, quantity 30, ~$450.
    Dose 0.8 mg capsules, quantity 30, ~$495.

- Wedgewood Pharmacy (https://www.wedgewoodpharmacy.com/): (as of September 7, 2021) Available dose range of 0.04 mg – 1.5 mg capsules.
    Dose 0.04 mg capsules, quantity 30, ~$84.
    Dose 1.5 mg capsules, quantity 30, ~$97.25.

    Oil oral suspension available in 3 concentrations
        0.1 mg/mL, 36 mL bottle, $84.75.
        0.2 mg/mL, 30 mL bottle, $85.50.
        3 mg/mL, 7.5 mL bottle, $90.25.

Anecdotal Information from Veterinary Oncologists

"Doses have ranged from 0.01 mg/**kg**/day to 0.03 mg/**kg**/day."
Others have used "0.5 mg/$\mathbf{m^2}$/day" dose.
"Most common side effects are lethargy and decreased appetite."
"If side effects occur, change to every-other-day dosing or stop."
"There have not been many hematologic abnormalities, with CBCs monitored once/month."
"Proteinuria and hypertension were also noted side effects."

References

Mekinist® (Trametinib); Pharmacology Review. Center for Drug Evaluation and Research, U.S. Food and Drug Administration, (NDA 204114), April 2013.

Das S et al. Identifying candidate druggable targets in canine cancer cell lines using whole-exome sequencing. *Mol Cancer Ther*. 2019 Aug;18(8):1460-1471.doi: 10.1158/1535-7163.MCT-18-1346.

Takada M et al. Targeting MEK in a translational model of histiocytic sarcoma. *Mol Cancer Ther*. 2018 Nov;17(11):2439-2450.doi: 10.1158/1535-7163.MCT-17-1273.

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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