Trametinib

Mekinist®

Mechanism of Action

According to the FDA NDA 204114, 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 [with 7 days between each dose] to conscious dogs."

FDA Labeled Use

Mekinist® 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 4929004):
Mekinist® 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.

Mekinist® is indicated, *in combination with dabrafenib*, 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

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.).

- In canine bladder cancer (BC) organoids, epidermal growth factor receptor (EGFR)/ERK signaling was upregulated (evaluated by Western blot) compared with normal bladder cells. Trametinib even at a low concentration inhibited the cell viability of BC organoids and the activation of ERK through decreasing expression of c-Myc, ELK1, SIK1, and PLA2G4A (evaluated by qPCR). Trametinib arrested cell cycle of BC (evaluated by flow cytometry) and induced basal to luminal differentiation of BC organoids by upregulating luminal markers and downregulating basal ones (evaluated by qPCR). In vivo, trametinib decreased the tumor growth of BC organoids in mice. The xenograft-derived organoids from trametinib-administered mice showed enhanced sensitivity to carboplatin due to MSH2 upregulation, suggesting a new strategy of trametinib-carboplatin combination as a promising treatment of BC (Elbadawy et al.).

- BRAF mutant canine TCC cell lines were insensitive to vemurafenib (BRAF inhibitor) but had IC_{50} values less than 7 nM to trametinib, independent of their BRAF mutation status (Cronise KE et al.).

:: Safety/dosing

None currently

:: Efficacy

None currently

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]

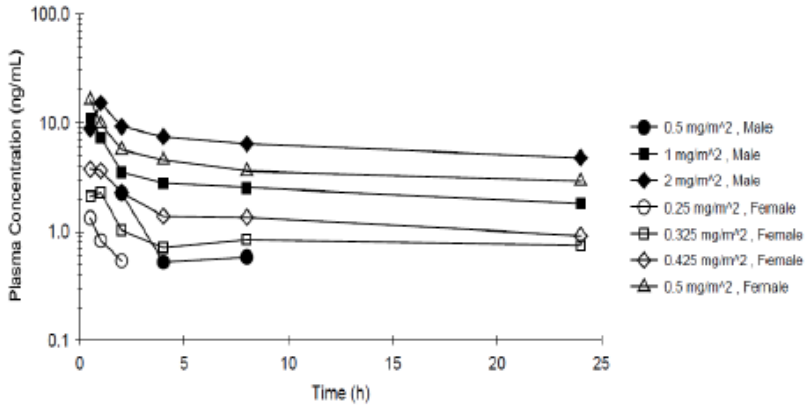
NC = Not calculated. There were insufficient plasma concentration data to calculate AUC.
NA = Not applicable. Dosing of 0.6 mg/m²/day was stopped on Day 11 for the main study female animals (451-454) and on Day 12 for the main study (401-404) and recovery (405-406) male animals and recovery female animals (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	6.98 [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:

Dose range 0.1 mg – 1 mg capsules, quantity 30, ~$130.
Dose range 1.1 - 2 mg capsules, quantity 30, ~$140.
+Please check their website to confirm that they can serve your state.

- 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.

**This dose range/concentrations may not appear on your online portal. If so, please call Wedgewood Pharmacy (call center 877.357.6613) to prescribe this drug.*

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

Cronise KE et al. Identifying the ErbB/MAPK signaling cascade as a therapeutic target in canine bladder cancer. *Mol Pharmacol*. 2019 Jul;96(1):36-46. doi: 10.1124/mol.119.115808.

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.

Elbadawy M et al. Anti-tumor effect of trametinib in bladder cancer organoid and the underlying mechanism. *Cancer Biol Ther*. 2021 Jun 3;22(5-6):357-371. doi: 10.1080/15384047.2021.1919004.

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

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.

Questions? Call Vidium Customer Support at (833) 794-0318, email VidiumInfo@tgen.org, or visit www.vidiumah.com

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