# Imatinib

Gleevec®

## Mechanism of Action

According to the FDA NDA 021588, "imatinib mesylate is a protein-tyrosine kinase inhibitor that inhibits the Bcr-Abl tyrosine kinase, the constitutive abnormal tyrosine kinase created by the Philadelphia chromosome abnormality in CML. Imatinib inhibits proliferation and induces apoptosis in Bcr-Abl positive cell lines as well as fresh leukemic cells from Philadelphia chromosome positive chronic myeloid leukemia. Imatinib inhibits colony formation in assays using *ex vivo* peripheral blood and bone marrow samples from CML patients.

*In vivo*, it inhibits tumor growth of Bcr-Abl transfected murine myeloid cells as well as Bcr-Abl positive leukemia lines derived from CML patients in blast crisis.

Imatinib is also an inhibitor of the receptor tyrosine kinases for platelet-derived growth factor (PDGF) and stem cell factor (SCF), c-kit, and inhibits PDGF- and SCF-mediated cellular events. *In vitro*, imatinib inhibits proliferation and induces apoptosis in GIST cells, which express an activating c-kit mutation."

## Toxicology

According to the FDA NDA 021335, repeated daily oral dosing for 13 weeks of imatinib was tolerated well in dogs.

- Doses of 600 mg/m$^2$/day (30 mg/kg/day) in the dog were not severely toxic when administered daily for 13 weeks. Target organs were epithelial and glandular tissues. Reduced spermatogenesis and testis weights were noted. The liver changes were more severe in the dog than in other species: clinical chemistry changes (elevated transaminases) were seen at doses ≥ 600 mg/m$^2$ day. Histological changes included mild multifocal hepatocellular necrosis, single cell necrosis in the bile duct, and bile duct hyperplasia and were seen most frequently at doses ≥ 2000 mg/m$^2$/day. The bile duct hyperplasia was still present following the 4-week recovery period and was associated with peribiliary fibrosis.
- Emesis was seen at doses ≥ 600 mg/m$^2$/day (30 mg/kg/day) administered for 2 weeks. Since emesis was seen only following oral administration (not i.v.), it is most likely a local irritation effect of imatinib that causes emesis.
- In dogs given 13 weeks of daily oral imatinib, the highest dose level that does not produce evidence of lethality (HNSTD) was 30 mg/kg, and the dose with no observed adverse effect level (NOAEL) was 3 mg/kg.
- The hematopoietic system was affected by imatinib doses ≥ 200 mg/m$^2$/day in the dog; the major hematological effect involved decreases in red cell parameters and white blood cells. At this dose, lymphoid tissues were also affected, demonstrated by lymphoid atrophy and lymphoid depletion.
- Toxicity on the gastrointestinal tract was evident at ≥ 60 mg/m$^2$/day (3 mg/kg/day) for 13 weeks, manifested as significant diarrhea.

- At 2000 mg/m$^2$/day (100 mg/kg/day), transitional cell hyperplasia (in the kidneys) were seen in the dog after 2 weeks.

Imatinib is known to induce hepatotoxicity in a proportion of dogs; this hepatotoxicity appears to be idiosyncratic in nature, resulting in elevations in ALT and ALP that necessitate discontinuation of therapy (London C).

## FDA Labeled Use

Gleevec® 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 4654232):
Gleevec® is a kinase inhibitor indicated for the treatment of

- Newly diagnosed adult and pediatric patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase.
- Patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in blast crisis (BC), accelerated phase (AP), or in chronic phase (CP) after failure of interferon-alpha therapy.
- Adult patients with relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL).
- Pediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) in combination with chemotherapy.
- Adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene rearrangements.
- Adult patients with aggressive systemic mastocytosis (ASM) without the D816V c-Kit mutation or with c-Kit mutational status unknown.
- Adult patients with hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) who have the FIP1L1-PDGFRα fusion kinase (mutational analysis or fluorescence in situ hybridization [FISH] demonstration of CHIC2 allele deletion) and for patients with HES and/or CEL who are FIP1L1-PDGFRα fusion kinase negative or unknown.
- Adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP).
- Patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST).
- Adjuvant treatment of adult patients following resection of Kit (CD117) positive GIST.

## Selected Canine Publications

### :: Preclinical

- In dogs, the mean fraction of imatinib in plasma ($f_p$) was low at 45%, and ($f_p$) for CGP74588 (the active metabolite of imatinib) was similarly low (30%). The unbound fraction of imatinib and CGP74588 in plasma was 19%, which was higher compared to humans, rats, and mice. (Kretz et al.).

Canine mast cell tumor cells:

- Ex vivo evaluation of imatinib mesylate on a canine grade II mast cell tumor with c-Kit exon 11 mutations revealed caspase-dependent apoptosis, concurrent reduced Ki67 and BCL-2 expression, and marked reduction of Kit expression (Rossi et al.).
- In canine mast cell tumor xenografted SCID mice receiving oral imatinib at 100 mg/kg/day and 200 mg/kg/day, significant tumor regression (including complete remission) occurred (Kobie et al.).
- Imatinib caused dose-dependent inhibition of proliferation in C2 canine mastocytoma cells with $IC_{50}$ of 269+/- 180 nM, and growth-inhibitory effects were associated with cell-cycle arrest and apoptosis (Gleixner et al.).
- Cell lines harboring wild-type *KIT* had lower sensitivity to TKIs. The growth of one cell line was seemingly reduced by TKIs through the inhibition of other tyrosine kinases than c-Kit receptor (Takeuchi et al.).

Canine oral fibrosarcoma cells: PDGFR-α and PDGFR-β were detected in 5/6 and 6/6 canine oral fibrosarcoma (COF) tumor biopsies and were present in 2 COF cell lines. KIT and KDR were not detected in any sample. Imatinib $IC_{50}$ values ranged from 7.9–33.4 μM. The addition of doxorubicin resulted in synergistic cytotoxicity. Anti-PDGFR-β siRNA transfection reduced PDGFR-β protein expression by 77 % and 67 % and reduced cell viability by 24% and 28% in the two cell lines, respectively (Milovancev et al.).

Canine mammary carcinoma cells: Imatinib could effectively inhibit cell proliferation of B-CMT, a novel canine mammary cancer cell line (Li et al.).

Canine hemangiosarcoma cells: Cell viability was inhibited by increasing concentrations of imatinib, with an $IC_{50}$ of 50-79 μM among 3 hemangiosarcoma cell lines. Increasing concentrations of imatinib induced apoptosis in a dose-dependent manner in one cell line (SB-HSA), with an $IC_{50}$ of 11 μM for this effect. Imatinib blocked tyrosine phosphorylation in a dose-dependent manner with a substantial decrease in phosphorylation occurring at 10 μM and near-complete inhibition of phosphorylation occurring at 50 μM. Imatinib (50 mg/kg/day, intraperitoneal) inhibited hemangiosarcoma tumor growth in a macroscopic tumor xenograft model which suggests that imatinib may be useful for improving the management of hemangiosarcoma (Dickerson et al.).

## Safety/dosing and Efficacy

- In 21 dogs with gross MCT receiving imatinib mesylate at 10 mg/kg/day PO for 1-9 weeks (Isotani et al.):
  - 10 dogs (48%) had some beneficial response (CR or PR) to imatinib mesylate within 14 days of treatment initiation. Among these 10 responders, 5 received concurrent prednisolone. All 5 dogs that had a demonstrable c-kit ITD mutation in exon 11 responded to the drug (1 CR, 4 PR).
  - The response could not be predicted based on presence or absence of a mutation in exon 11 of c-kit.
  - 11 dogs had received prior treatment, including surgery, prednisolone, vinblastine, lomustine, or combinations of these therapies
  - 10 dogs received imatinib as an initial treatment.
  - No abnormalities were noted in the CBC and serum biochemistry.

- In 3 dogs with mast cell tumor and bone marrow involvement, aberrant KIT IHC expression (intensity and localization), and receiving imatinib (4.4 mg/kg/day) with prednisone (20 mg/m$^2$ PO q12h), all had a complete remission with no toxicities (Marconato et al.)
    - 1 dog received imatinib/prednisone alone (DFI 78 days, survival 159 days).
    - 2 dogs received concurrent lomustine (60 mg/m$^2$ q28 days or monthly)
        - 1 dog had lomustine added after 2 months of imatinib/pred (upon demonstration of increased bone marrow mast cells) and continued with the imatinib-lomustine combination for 3 months until disease progression (DFI 150 days, survival 159 days)
    - 1 dog started with the imatinib-lomustine combination and was continued on with no sign of tumor relapse by the end of study (75 days).

- In a randomized prospective clinical trial comparing response and adverse events between imatinib mesylate (at 10 mg/kg/day PO) vs. vinblastine (4 weekly, then 4 biweekly, at 2 mg/m$^2$ IV) + prednisone (2 mg/kg/day, then tapered and discontinued over the course of 12 weeks) therapy in 24 dogs with cutaneous mast cell tumors, the objective response rate was significantly higher (30.79%) in the imatinib group compared to the vinblastine/prednisone group (9.09%). Adverse events in the imatinib group were all grade 1, significantly different from the vinblastine/prednisone group (Macedo et al.).

Case reports:

**Mast cell tumor**

- Partial response sustained for 7 weeks in a 15-yr-old male mixed breed dog treated with imatinib (10 mg/kg/day) with concomitant prednisolone for the first 3 weeks for MCT (carrying a *c-kit* c.1523A>T mutation) in right foot (sole), lymph node metastasis, and mastocytemia (Yamada et al.).
- Complete response sustained for 66 and 255 days in 2 dogs treated with imatinib (10 mg/kg/day) with concomitant prednisolone for mast cell tumors (carrying 2 novel c-KIT mutations in exon 11: a 9-base pair deletion [c.1663-1671del] and a point mutation [c.1676T>A] and with metastatic lymph node progression (Nakano et al.).
- Partial response sustained for 44 days in a 4-yr-old female Bernese Mountain dog receiving imatinib (10 mg/kg/day) for an intestinal mast cell tumor with an in-frame ITD mutation (c.1250_1261dup) in the region corresponding to genomic exon 8 and splenic metastasis (Kobayashi et al.).

**Gastrointestinal stromal tumor (GIST)**:

- Partial response was sustained for at least 140 days in a 10-yr-old female miniature Dachshund receiving imatinib (10 mg/kg/day, then reduced to 7 mg/kg/day, then EOD due to increased ALT) for a non-resectable ileocaecocolic GIST harboring a *c-kit* exon 11 deletion mutation (Kobayashi et al.).
- Complete response was achieved after 2 months of receiving imatinib (10 mg/kg/day) and sustained for 4 years and 5 months (died of pneumonia with no GIST recurrence) in a 13-yr-old spayed mixed-breed dog with a recurrent and disseminated GIST carrying a mutation (1523A>T, Asn508Ile) within exon 9 of the c-kit gene (Irie at el.).

**Meningioma**:

- Partial response sustained for ~9 weeks with imatinib (8 mg/kg PO q 24 hours) added to hydroxyurea (50 mg/kg/day PO) with prednisolone (1 mg/kg PO q 12 hours) in

an 8-yr-old male Belgian Malinois with transitional cerebellar meningioma with positive PDGFR-α IHC staining (Jung et al.).

**Glioma (astrocytoma)**:

- Partial response sustained for ~ 3 years with imatinib (8 mg/kg/day, then tapered to 5 mg/kg/day) in addition to hydroxyurea (50 mg/kg EOD, then tapered to 30 mg/kg EOD), and prednisolone (0.5 mg/kg q12h) in a 8-year-old neutered male Yorkshire Terrier with a low-grade glioma(astrocytoma) in the pons (Yun et al.).

**Soft tissue sarcoma**:

- Partial response sustained for 5 months with imatinib (10 mg/kg/day) for a twice recurrent soft tissue sarcoma in the gluteal muscle in a 14 yr-old female spayed Yorkshire Terrier (Kim GH and Kim JH).

## Pharmacokinetics

Excerpted from Ishizuka et al.:

Table I. Pharmacokinetic parameters of imatinib in male and female dogs.

| Dog sex | | Dose (mg/kg) | $T_{max}$ (h) | C(0) or $C_{max}$ (μM) | AUC (μM min) | MRT (h) | CL or CL/F (ml/min/kg) | $V_{dss}$ (L/kg) | $V_{dz}$ or $V_{dz}/F$ (L/kg) | t1/2 (min) | Bioavailability (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Female | i.v. (n=4) | 20 | | 21.9±4.7 | 1155±254 | 3.8±0.9 | 31±6 | 6.7±1.4 | 8.3±1.8 | 194±47 | 107±55 |
| | p.o. (n=3) | 30 | 4–9 | 2.0±1.0 | 1647±856 | 16.6±7.4 | 54±45 | | 34.3±21.6 | 217±150 | |
| Male | i.v. (n=4) | 20 | | 53.5±63.9 | 896±420 | 4±2.3 | 47±22 | 9.2±3.1 | 11.5±3.8 | 541±306 | 76±55 |
| | p.o. (n=4) | 30 | 6–9 | 0.8±0.2 | 964±630 | 20.1±10.1 | 56±34 | | 57.9±30.4 | 683±397 | |

Pharmacokinetic parameters in plasma are given as mean ± SD. Abbreviations used are: $T_{max}$, time to maximum concentration; C0, plasma concentration at time 0; $C_{max}$, maximum concentration; CL or CL/F, clearance; $V_{dss}$, volume of distribution at steady state; $V_{dz}$ or $V_{dz}/F$, apparent terminal volume of distribution; MRT, mean residence time; AUC, are under the plasma concentration-time curve from 0 to the last measurement point; t1/2, elimination half-life; i.v., intravenous injection; p.o., oral administration.

Table III. Imatinib metabolism in liver microsomes of rat and dog, and metabolism by recombinant CYP forms.

| | Activities (nmol/mg/min[a] or nmol/min/nmol P450[b]) |
|---|---|
| Male rat liver microsomes | 0.064 ± 0.009[a] |
| Male dog liver microsomes | 0.081 ± 0.008[a] |
| Dog CYP3A12 | 0.480 ± 0.010 [b] |
| Dog CYP2C21 | nd |

The reaction mixture (total volume, 0.2 ml) contained 2 μM imatinib, 10 mM $MgCl_2$, 10 mM G-6-P, and 0.4 mg $ml^{-1}$ microsomes or 5–10 pmol for recombinant P450. The reaction was started by adding 1 mM NADPH and 1 enzyme unit of G-6-PDH after pre-incubation at 37°C for 5 min. Incubation was carried out at 37°C for 10 min. Imatinib metabolism was measured using high-performance liquid chromatography (HPLC). Data were represented as mean ± SD (n = 3). nd, not detected.

## Sources

- Best Pet Rx+ (https://bestpetrx.com/): (as of September 7, 2021) Available in dose range 0.1 mg - 550 mg capsules

Dose 0.1 mg capsules, quantity 30, $140.50
Dose 400 mg capsules, quantity 30, $498.10
Dose 550 mg capsules, quantity 30, $594.50

*+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 in dose range 17 mg (could go lower if needed) - 440 mg capsules

Dose 17 mg capsules, quantity 30, $150.00
Dose 440 mg, quantity 30, $325.00

- Wedgewood Pharmacy (https://www.wedgewoodpharmacy.com/veterinary-practices/): (as of September 7, 2021) Available in dose range* 5 mg - 500 mg capsules

Dose 5 mg capsules, quantity 30, $83.00
Dose 500 mg, quantity 30, $140.25

**This dose range 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 as high as 10 mg/kg/day seems generally well-tolerated."

## References


Dickerson et al. Imatinib and dasatinib inhibit hemangiosarcoma and implicate PDGFR-β and Src in tumor growth. *Transl Oncol.* 2013 Apr;6(2):158-68. doi: 10.1593/tlo.12307.

Gleevec® (Imatinib); Pharmacology Review. Center for Drug Evaluation and Research, U.S. Food and Drug Administration, NDA 021335 (capsule), May 2001.

Gleevec® (Imatinib); Pharmacology Review. Center for Drug Evaluation and Research, U.S. Food and Drug Administration, NDA 021588 (tablet), April 2003.

Gleixner KV et al. Synergistic antiproliferative effects of KIT tyrosine kinase inhibitors on neoplastic canine mast cells. *Exp Hematol*. 2007 Oct;35(10):1510-21. doi: 10.1016/j.exphem.2007.06.005.

Irie M et al. Imatinib mesylate treatment in a dog with gastrointestinal stromal tumors with a c-kit mutation. *J Vet Med Sci*. 2015 Nov;77(11):1535-9. doi: 10.1292/jvms.15-0096.

Ishizuka M et al. Plasma pharmacokinetics and CYP3A12-dependent metabolism of c-kit inhibitor imatinib in dogs. *Xenobiotica*. 2007 May;37(5):503-13. doi: 10.1080/00498250600962849.

Isotani M et al. Effect of tyrosine kinase inhibition by imatinib mesylate on mast cell tumors in dogs. *J Vet Intern Med* 2008;22:985-988. doi: 10.1111/j.1939-1676.2008.00132.x.

Jung HW et al. Imatinib mesylate plus hydroxyurea chemotherapy for cerebellar meningioma in a Belgian Malinois dog. *J Vet Med Sci*. 2014 Nov;76(11):1545-8. doi: 10.1292/jvms.14-0001.

Kim GH and Kim JH. Effective palliative treatment of recurrent soft tissue sarcoma in a dog using imatinib mesylate (Gleevec®). *Veterinarni Medicina* 2018;63(11):532-536. doi.org/10.17221/34/2018-VETMED.

Kobayashi M et al. Canine intestinal mast cell tumor with c-kit exon 8 mutation responsive to imatinib therapy. *Vet J*. 2012 Jul;193(1):264-7. doi: 10.1016/j.tvjl.2011.10.027.

Kobayashi M et al. Imatinib-associated tumour response in a dog with a non-resectable gastrointestinal stromal tumour harbouring a c-kit exon 11 deletion mutation. *Vet J*. 2013 Oct;198(1):271-4. doi: 10.1016/j.tvjl.2013.05.035.

Kobie et al. The tyrosine kinase inhibitor imatinib [STI571] induces regression of xenografted canine mast cell tumors in SCID mice. *Res Vet Sci*. 2007 Apr;82(2):239-41. doi:10.1016/j.rvsc.2006.06.006.

Kretz O et al. In vitro blood distribution and plasma protein binding of the tyrosine kinase inhibitor imatinib and its active metabolite, CGP74588, in rat, mouse, dog, monkey, healthy humans and patients with acute lymphatic leukaemia. *Br J Clin Pharmacol*. 2004 Aug;58(2):212-6. doi:10.1111/j.1365-2125.2004.02117.x

Li R et al. A novel canine mammary cancer cell line: preliminary identification and utilization for drug screening studies. *Front Vet Sci*. 2021 May 27;8:665906. doi: 10.3389/fvets.2021.665906.

London C. Tyrosine kinase inhibitors in veterinary medicine. *Top Companion Anim Med*. 2009 Aug;24(3):106-12. doi: 10.1053/j.tcam.2009.02.002.

Macedo et al. Imatinib mesylate for the treatment of canine mast cell tumors: assessment of the response and adverse events in comparison with the conventional therapy with vinblastine and prednisone. *Cells*. 2022 Feb 7;11(3): 571. doi: 10.3390/cells11030571.

Marconato L et al. Clinicopathological features and outcome for dogs with mast cell tumors and bone marrow involvement. *J Vet Intern Med* 2008;22:1001-1007. doi: 10.1111/j.1939-1676.2008.0128.x.

Milovancev M et al. Antiproliferative effects of masitinib and imatinib against canine oral fibrosarcoma in vitro. *BMC Vet Res*. 2016 Jun 4;12:85. doi: 10.1186/s12917-016-0712-x.

Nakano Y et al. Imatinib responsiveness in canine mast cell tumors carrying novel mutations of c-KIT exon 11. *J Vet Med Sci*. 2014 Apr;76(4):545-8. doi: 10.1292/jvms.13-0156.

Rossi G et al. Ex vivo evaluation of imatinib mesylate for induction of cell death on canine neoplastic mast cells with mutations in c-Kit exon 11 via apoptosis. *Vet Res Commun*. 2013 Jun;37(2):101-8. doi: 10.1007/s11259-013-9550-5.

Takeuchi Y et al. Biological effect of tyrosine kinase inhibitors on three canine mast cell tumor cell lines with various KIT statuses. *J Vet Pharmacol Ther.* 2012 Feb;35(1):97-104. doi: 10.1111/j.1365-2885.2011.01296.x.

Yamada O et al. Imatinib elicited a favorable response in a dog with a mast cell tumor carrying a c-kit c.1523A>T mutation via suppression of constitutive KIT activation. *Vet Immunol Immunopathol*. 200 Jul 15;142(1-2):101-6. doi: 10.1016/j.vetimm.2011.04.002.

Yung T et al. Characteristics of $^{18}$F-FDG and $^{18}$F-FDOPA PET in an 8-year-old neutered male Yorkshire Terrier dog with glioma: long-term chemotherapy using hydroxyurea plus imatinib with prednisolone and immunoreactivity for PDGFR-β and LAT1. *Vet Q*. 2021 Dec;41(1):163-171. doi: 10.1080/01652176.2021.1906466.



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