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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

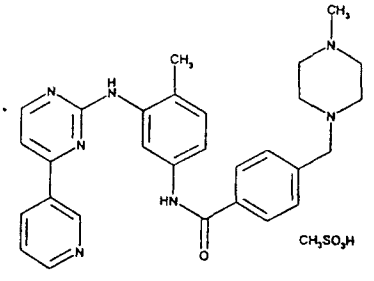
21-335/S-004

Pharmacology Review(s)

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA number:	21-335
Review number:	2
Serial number/date/type of submission:	004/28 June.2002/SNDA
Information to sponsor:	Yes () No (X)
Sponsor and/or agent:	Novartis Pharmaceuticals Corporation
Manufacturer for drug substance :	Novartis Ringaskiddy Ltd.
Reviewer name:	Kimberly A. Benson, Ph.D.
Division name:	Division of Oncological Drug Products
HFD #:	150
Review completion date:	16 December 2002

Drug:

Trade name:	Gleevec™
Generic name:	Imatinib mesylate (Pending)
Code name:	STI571; CGP 57148B
Chemical name:	4-[4-(Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-phenyl]-benzamide methanesulfonate
CAS registry number:	220127-57-1 [152459-95-5 for the free base]
Mole file number:	None
Molecular formula/ weight:	$C_{30}H_{35}N_7SO_4$/589.7
Structure:	

Relevant INDs: [redacted]

Drug class: Protein-tyrosine kinase inhibitor

Indication: For the treatment of patients with newly diagnosed Philadelphia positive chronic myeloid leukemia (CML).

Clinical formulation:

Ingredient	Amount (mg)
STI571 mesylate	
Microcrystalline cellulose	
Crospovidone	
Silica, colloidal anhydrous/ Colloidal Silicon Dioxide	
Magnesium stearate	

Route of administration: Oral tablets

Proposed use: For the treatment of patients with newly diagnosed Philadelphia positive chronic myeloid leukemia (CML). The prescribed dose (400 or 600 mg/day) should be administered orally, once daily with a meal and a large glass of water.

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

OVERALL SUMMARY AND EVALUATION:

Introduction:

Gleevec® (imatinib mesylate) is an inhibitor of protein-tyrosine kinases associated with Bcr-Abl, the platelet-derived growth factor (PDGF) receptor and c-Kit. The inhibition of Bcr-Abl kinase is important, as it is believed to play a role in the deregulated myeloid cell proliferation that is the hallmark of chronic myeloid leukemia (CML). The Philadelphia chromosome arises from a reciprocal translocation between chromosomes 9 and 22. Replacement of the first exon of c-Abl with sequences from the Bcr gene result in a Bcr-Abl fusion gene with a 210-kD protein product that exhibits enhanced protein-kinase activity and is present in 95% of CML.

Studies were conducted in the mouse, rat, dog, rabbit, monkey, and cellular assay systems to explore the pharmacology, general toxicology, genotoxicity and reproductive effects of imatinib mesylate. Where possible, the animals were administered the drug orally, the route used in the clinic. Long-term studies were conducted in the rat and monkey, for 26 and 39 weeks, respectively.

Safety evaluation:

Gleevec® has been used clinically at a maximum dose of 800 mg/day, or 471 mg/m^2/day. A pre- and postnatal developmental study utilized a high dose of 45 mg/kg in the rat, or 270 mg/m^2/day, which is approximately 57% of the maximum human dose based on body surface area. At this dose, significant fetal loss was seen in the pregnant rats. The high dose dams had a significantly higher number of stillborn pups and a significantly lower number of viable offspring. During the first 4 days of life, pup mortality was significantly higher in the litters of the dams treated with 45 mg/kg of imatinib. The offspring of the dams that were treated with the high dose from day 6 of gestation through lactation had decreased body weights from birth until terminal sacrifice, at approximately 98 days of age. The female offspring of the HD females also exhibited an increase in early resorptions and a decrease in the number of viable fetuses when they were mated with male offspring from litters of dams that received the same dose of imatinib.

No significant treatment-related effects were seen on learning behavior in the offspring of imatinib treated female rats. In the M maze test, the HD offspring had a slight but significantly higher number of errors during the memory retention phase of the study. Developmental parameters were essentially unaffected by the drug treatment also. There was a slight non-significant decrease in the males from HD litters that achieved criterion for preputial separation within the allotted timeframe, most likely a transient delay in development.

A single oral dose of imatinib to lactating rats showed that both imatinib and its metabolites are present in the rat's milk. The concentration of imatinib in the milk is three-fold higher than that in the plasma.

Safety issues relevant to clinical use:

The studies reviewed in this Supplemental NDA add additional support to the reproductive toxicity of imatinib mesylate in animal studies, and the importance of assuring that a patient is not pregnant prior to starting Gleevec® therapy, as well as advising the patient to take precautions to avoid pregnancy during therapy. Women should also be told to not breastfeed while taking Gleevec®.

Other clinically relevant issues:

None

Conclusions:

The toxicology studies submitted with this Supplemental NDA further illustrate the caution that must be exercised with Gleevec® and women of childbearing years.

Communication review:

Labeling review:

Sponsor's version:

WARNINGS

Pregnancy

Pregnancy Category D. (See WARNINGS.)

Pharmacology/Toxicology's Revised Version:

WARNINGS

Pregnancy

one-half the maximum human dose of 800 mg/day, based on body surface area) also experienced significant post-implantation loss as evidenced by either early fetal resorption or stillborn, nonviable pups and early pup mortality. At doses higher than 100 mg/kg, total fetal loss was noted in all animals. Fetal loss was not seen at doses ≤30 mg/kg (one-third the maximum human dose of 800 mg).

Male and female rats were exposed *in utero* to a maternal imatinb mesylate dose of 45 mg/kg (approximately one-half the maximum human dose of 800 mg) from day 6 of gestation and through milk during the lactation period. These animals then received no imatinib exposure for nearly 2 months. Although fertility was not affected, fetal loss was seen when these male and female animals were then mated. There are no adequate and well-controlled studies in pregnant women. If Gleevec™ (imatinib mesylate) is used during pregnancy, or if the patient becomes pregnant while taking (receiving) Gleevec, the patient should be apprised of the potential hazard to the fetus.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been performed with imatinib mesylate.

Positive genotoxic effects were obtained for imatinib in an *in vitro* mammalian cell assay (Chinese hamster ovary) for clastogenicity (chromosome aberrations) in the presence of metabolic activation. Two intermediates of the manufacturing process, which are also present in the final product, are positive for mutagenesis in the Ames assay. One of these intermediates was also positive in the mouse lymphoma assay. Imatinib was not genotoxic when tested in an *in vitro* bacterial cell assay (Ames test), an *in vitro* mammalian cell assay (mouse lymphoma) and an *in vivo* rat micronucleus assay.

In a study of fertility, in male rats dosed for 70 days prior to mating, testicular and epididymal weights and percent motile sperm were decreased at 60 mg/kg, approximately three-fourths the maximum clinical dose of 800 mg/day, based on body surface area. This was not seen at doses ≤20 mg/kg (one-fourth the maximum human dose of 800 mg). When female rats were dosed 14 days prior to mating and through to gestational day 6, there was no effect on mating or on number of pregnant females.

In female rats dosed with imatinib mesylate at 45 mg/kg (approximately one-half the maximum human dose of 800 mg, based on body surface area) from gestational day 6 until the end of lactation, red vaginal discharge was noted on either gestational day 14 or 15. .

Pregnancy

Pregnancy Category D. (See WARNINGS.)

Nursing Mothers

It is not known whether imatinib mesylate or its metabolites are excreted in human milk. However, in lactating female rats administered 100 mg/kg, a dose approximately equal to the maximum clinical dose of 800 mg/day based on body surface area, imatinib and its metabolites were extensively excreted in milk. Concentration in milk was approximately three-fold higher than in plasma. It is estimated that approximately 1.5% of a maternal dose is excreted into milk, which is equivalent to a dose to the infant of 30% the maternal dose per unit body weight. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, women should be advised against breastfeeding while taking Gleevec.

RECOMMENDATIONS:

Internal comments:
None

External recommendations (to sponsor):
See label changes incorporated in this review.

Draft letter content for sponsor (if not same as above):

Future development or issues:
Carcinogenicity studies are ongoing by the sponsor.

Reviewer signature:

Team leader signature:

cc: /Div file
/JLeighton
/AStaten

Memorandum of non-concurrence:
Not applicable

Addendum to review:
None
Studies reviewed within this submission:
Study No. 017021: An oral pre- and postnatal development study in rats. Volume 2.4, page 5-8.

DMPK(CH)R00-097: Metabolism in milk and plasma after single peroral administration of ^{14}C-labeled STI571 (100 mg/kg as the methanesulfonic salt) to lactating rats. Volume 2.5, page 5-409.

Studies previously reviewed:

Pharmacology

Report PKF-98-02342: CGP 57148B: A potent protein-tyrosine kinase which inhibits PDGF receptor and c-Kit mediated signal transduction. Volume 1.9, page 5-58.

RD-2000-01471: ST1571: an ATP-competitive inhibitor of the c-AbI protein-tyrosine kinase. Volume 1.9, page 5-75.

PKF-99-01118: Acute and maximally tolerated dose of ST1571 (CGP 5714813) in mice. Volume 1.9, page 5-89.

RD-2000-01407: Pharmacological profile of CGP 74588A: in vitro studies of the methanesulfonate salt of CGP 74588, a major metabolite of ST1571. Volume 1.9, page 5-103.

RD-2000-00329: ST1571 does not decrease the tolerability of mice to conventional cytotoxic anticancer agents. Novartis Report, 2000. Volume 1.10, page 5-1.

Pharmacokinetics/Toxicokinetics

DMPK(US) R98-1782: CGP 5714813: A 13-week oral (gavage) toxicity study in rats. Toxicokinetic report: Determination and toxicokinetics of CGP 57148 in plasma. Volume 1.31, page 5-322.

DMPK(US) R99-683: CGP 5714813: A 26-week oral (gavage) toxicity study in rats with a 4-week recovery period. Toxicokinetic report: Determination and toxicokinetics of ST1571 in plasma. Volume 1.31, page 5-341.

DMPK(US) R99-039: CGP 5714813: A 13-week oral (gavage) toxicity study in cynomolgus monkeys with a 4-week recovery period. Toxicokinetic report: Determination and toxicokinetics of CGP 57148 in monkey plasma. Volume 1.32, page 5-181.

DMPK(CH) R00-097: Galactogenic transfer, kinetics and metabolism in milk and plasma after single peroral administration of ^{14}C-labeled ST1571 (100 mg/kg as the methanesulfonic acid salt) to lactating rats. Volume 1.32, page 5-286.

DMPK(CH) R00-1004: Quantitative whole-body autoradioluminography in female normal and bearing C6 tumors BALB/c nu/nu mice following a 50 mg/kg po dose of [^{14}C]ST1571. Volume 1.33, page 5-26.

Safety Pharmacology

DP00-R07: STI571: Safety pharmacology study - Effects on acetic acid-induced stretching, convulsions, and gastrointestinal transit. Volume 1.9, page 5-304.

Toxicology

Test 007033: ST1571: 26-week oral (gavage) toxicity study in rats with a 4-week recovery period. Report DMPK (US) R99-683. Volume 1.15; page 5-1.

987003: A 13-week oral (gavage) toxicity study in cynomolgus monkeys with a 4-week recovery period. Volume 1.22, page 5-1.

Test 007048: ST1571: 39-week oral gavage (b.i.d.) toxicity study in monkeys with a 4-week recovery period. Volume 3.1, page 1.

Genetic Toxicology

NOTOX 271608: Evaluation of the mutagenic activity of ST1571 D9 in the *Salmonella typhimurium* reverse mutation assay and the *Escherichia coli* reverse mutation assay (with independent repeat). Volume 1.27, page 5-177.

NOTOX 272036: Evaluation of the mutagenic activity of ST1571 D6 in the *Salmonella typhimurium* reverse mutation assay and the *Escherichia coli* reverse mutation assay (with independent repeat). Volume 1.27, page 5-203.

001815: Mutagenicity test using S*almonella typhimurium* (Batch control). Volume 1.27, page 5-229.

001889: Oral bone marrow micronucleus test in rats. Volume 1.27, page 5-278.

001864: Mutation assay at the thymidine kinase locus of L5178Y mouse lymphoma cells. Volume 1.27, page 5-306.

Test 946215: CGP 53715: Gene mutation test with Chinese hamster cells V79. Volume 1.27, page 5-257.

Reproductive Toxicology

Test 974046: CGP 571488: An oral study for effects on fertility and early embryonic development in rats. Novartis Pharmaceuticals Corporation, Summit, New Jersey, 22 May 99. Volume 1.28; page 5-1.

Test 966086:CGP 5714813: A Study for Effects on Embryo and Fetal Development in Rats. Novartis Crop Protection, Toxicology/Experimental Toxicology, 4332 Stein, Swit. 25 Aug 97. Volume 1.29; page 5-1.

Test 966088: GP 5714813: A Study for Effects on Embryo and Fetal Development in Rabbits. Novartis Crop Protection, Toxicology/Experimental Toxicology, 4332 Stein, Switz. 25 Aug 97. Volume 1.30; page 5-1.

Special Toxicology

Test 001091: ST1571 Single-dose oral mechanistic toxicity and safety pharmacology study in dogs. Novartis Pharma AG, (Basel), Toxicology/Pathology report, 28-Dec-00. Volume 1.27; page 5-100.

Studies not previously reviewed:

Pharmacology

PKF-99-01118: Acute and maximally tolerated dose of ST1571 (CGP 5714813) in mice. Volume 1.9, page 5-89.

PKF-99-01289: Antitumor activity of the platelet-derived growth factor receptor (PDGFR) inhibitor ST1571 against BALB/c 3T3 fibroblasts rendered tumorigenic due to PDGF over expression. Volume 1.10, page 5-26.

PKF-99-00972: Inhibition of PDGF-mediated tumor cell growth by ST1571 (CGP 5714813) in vitro and in vivo. Volume 1.10, page 5-60.

PKF-99-01161: Antitumour and antimetastatic activity of ST1571 in the BN-472 rat mammary carcinoma model. Volume 1.10, page 5-81.

PKF-99-01153: The PDGF-receptor inhibitor, ST1571, shows no activity against human lung cancer transplanted into the lungs of nude mice. Volume 1.10, page 5-97.

RD-2000-00328: Evaluation of the antitumor activity of ST1571 in experimental xenograft tumor models. Volume 1.10, page 5-106.
RD-2000-00185: ST1571: Effects on human umbilical cord endothelial cell proliferation and on sprout formation from rat aortic squares grown in a fibrin gel. Volume 1.10, page 5-121.
RD-2000-00187: ST1571: Effects on angiogenesis induced by growth factor-impregnated, subcutaneous implants in mice. Volume 1.10, page 5-135.

Pharmacokinetics/Toxicokinetics

BPK(CH) 1996/145: Plasma concentrations of CGP 57148 in a range finding study for teratogenicity in rabbits, Test No. 96-6087. Volume 1.32, page 5-1.
BPK(CH) 1996/105: Plasma concentrations of CGP 57148 in a 4-week toxicity study in the unrestrained dog by 3-hour daily i.v. infusion. Test No. 96-6048. Volume 1.32, page 5-66.
DMPK(US) R00-1153: A 4-week oral exploratory toxicity study in dogs. Toxicokinetic report: Determination and toxicokinetics of ST1571 in dog plasma. Volume 1.32, page 5-123.
DMPK (US) R00-2049: CGP 5714813: Single-dose oral mechanistic toxicity and safety pharmacology study in dogs. Toxicokinetic report: Determination and toxicokinetics of ST1571 in dog plasma and method cross validation. Volume 1.32, page 5-139.
DMPK(US) R99-174: CGP 57148B: A 2-week oral (gavage) dose range-finding study in monkeys. Toxicokinetic report: Determination and toxicokinetics of CGP 57148 in plasma. Volume 1.32, page 5-155.
DMPK(US) R00-655: CGP 5714813: 2-week oral gavage (b.i.d.) dose range-finding study in monkeys. Toxicokinetic report: Determination and toxicokinetics of CGP 57148 in plasma. Appendix 6 to Test No. 007019 (A 2.14). Volume 1.32, page 5-170.
DMPK(F) 1998/035: In vitro blood distribution and binding of CGP 57148B to plasma (or serum) proteins from human, dog, rat and cynomolgus monkey. Volume 1.32, page 5-213.
DMPK(F) R99-010: In vitro blood distribution and binding of ST1571 to human plasma proteins. Volume 1.32, page 5-236.
DMPK (CH) R99-2582: In vitro binding of ^{14}C-labeled ST1571 to human alpha,-acid glycoprotein. Volume 1.32, page 5-262.
DMPK(US) R99-2667: Interspecies scaling based on a physiologically-based pharmacokinetic model. Volume 1.33, page 5-1.
DMPK(CH) R00-2167: Kinetics and metabolism in plasma of male rats after single peroral administration of ^{14}C-labeled ST1571 (10 mg/kg dosed as the methanesulfonic acid salt). Volume 1.33, page 5-124.
DMPK(CH) R00-2119: Quantification of radioactivity by autoradioluminography in sections of pigmented rats following a 10 mg/kg iv dose of [14C]ST1571. Volume 1.33, page 5-151.
DMPK(CH) R00-103: Embryofetal transfer in pregnant rats on Day 13 and Day 17 of gestation after oral administration of [^{14}C]ST1571. Volume 1.33, page 5-161.
R00-1290: Kinetics, distribution, and excretion after single peroral administration of ^{14}C-labeled ST1571 (100 mg/kg as methanesulfonic acid salt) in a bile-duct cannulated dog. Volume 1.33, page 5-176.
DMPK(CH) R00-1290-01: Metabolite patterns in the plasma and urine of a bile-duct cannulated dog after a single dose of [^{14}C] ST1571 (100 mg1kg as methanesulfonic acid salt). Volume 1.33, page 5-200.
R00-1 663: Placental transfer of radioactivity in rabbits and metabolism in plasma and urine after peroral administration of [^{14}C]ST1571. Volume 1.33, page 5-227.

DMPK(US) R99-2116: Pharmacokinetics and metabolism following a single intravenous or oral dose of [^{14}C]ST1571 in the monkey. Volume 1.33, page 5-261.
DMPK(CH) R99-1830: Mechanistic transport studies across Caco-2 cell monolayers. Volume 1.33, page 5-309.
DMPK(CH) R00-1200: ST1571: Determination of transporter binding potential of anticipated co-medications using Caco-2 cell monolayers. Volume 1.33, page 5-326.
DMPK(US) R99-015: Metabolism of ST1571 by liver slices from human and monkey. Volume 1.33, page 5-356.
DMPK(CH) R00-880: In vitro stability in artificial gastric fluid. Volume 1.33, page 5-382.
DMPK(CH) 1997/564: Identification of the human cytochrome P450 isozyme(s) involved in the biotransformation of ST1571 (CGP 57148B) in vitro. Volume 1.34, page 5-1.
DMPK(CH) R98-770: A study to assess the absorption, disposition, kinetics and biotransformation of radiolabeled ST1571 after a single oral dose of 200 mg to healthy volunteers. Volume 1.34, page 5-52.
DMPK(CH) R98-296: Evaluation of ST1571 as an inhibitor of human P450 enzymes. Volume 1.34, page 5-195.
DMPK(CH) R99-1880: Effect of ST1571 on 5-fluorouracil metabolism in human liver cytosol. Volume 1.34, page 5-245.
DMPK(CH) R00-963: Inhibition of the oxidative metabolism of ST1571 by various comedications in human liver microsomes. Volume 1.34, page 5-258.
DMPK(CH) R00-1730: Inhibition of the metabolism of [^{14}C]ST1571 by its major oxidative metabolite CGP 74588 in human liver microsomes. Volume 1.34, page 5-279.
DMPK(CH) R00-1539: Inhibition of CYP2C8-dependent paclitaxel 6a-hydroxylation by ST1571. Volume 1.34, page 5-294.
DMPK(CH) R00-1540: Effect of CGP 74588 on the metabolism of P450 isozyme-specific marker substrates in human liver microsomes. Volume 1.35, page 5-1.
BPK(CH) 1995/067: Quantitative determination of CGP 57148B in plasma by Volume 1.35, page 5-57.
BPK(CH) 1996/110: Quantitative determination of CGP 57148 in plasma by an improved Volume 1.35, page 5-76.
DMPK(US) R99-170: Quantitative determination of CGP 57148 and its CGP 74588 metabolite in human plasma by . Volume 1.35, page 5-92.
DMPK(US) R99-1709: Quantitative determination of ST1571 and its metabolite CGP74588 in human, monkey and rat plasma by
method. Volume 1.35, page 5-117.

<u>Toxicology</u>
Study 987004: CGP 5714813: A repeat 13-week oral (gavage) toxicity study in rats. (DMPK(US)R98-1782. Volume 1.14, page 5-1.
Test 001045: STI 571: 4-week oral exploratory toxicity study in dogs. Volume 1.18, page 5-1.
Test 977090: ST1571: A 2-week oral (gavage) dose range-finding study in monkeys. Volume 1.21, page 5-1.
Test 007019: ST1571: 2-week oral gavage (b.i.d.) dose range-finding toxicity study in monkeys. Volume 1.21, page 5-167.
Test 946195: CGP 5714813: Pilot 14-day intravenous toxicity study in rats. Volume 1.22, page 5-290.

MIN 954193: CGP 5714813: Pilot intravenous rising-dose tolerance study in dogs. Volume 1.24, page 5-1.
Test 966048: 4-Week toxicity study with CGP 57148B in the unrestrained dog by intermittent (3-hour daily) or continuous intravenous infusion. Volume 1.25, page 5-1.
Test 946223: CGP 5714813: Pilot 14-day intraperitoneal toxicity study in rats. Volume 1.27, page 5-1.

Studies previously reviewed within IND [redacted]

Pharmacology
Report PKF 98-00751: CGP 57148: A potent protein-tyrosine kinase inhibitor with selectivity for the Abl platelet-derived growth factor receptor and c-Kit tyrosine kinases. Volume 1.9; page 5-1.
Report BS117: Interactions of CGP 5714813, tyrosine kinase inhibitor, with neurotransmitter receptors in vitro. Volume 1.9; page 5-116.
Report BS 30: CNS-evaluation of CGP 57148B (Tyrosine kinase inhibitor). (1996). Volume 1.9; page 5-132.
Project 606205: Evaluation of the cardiovascular, respiratory and renal effects of CGP 57 148B. Volume 1.9; page 5-152.
Pharmacokinetics and Toxicokinetics
PKF-98-00125: Pharmacokinetics of CGP 57148 after oral administration of CGP 57148B to mice. (1998). Volume 1.31; page 5-207.
BPK(CH) 1995/076: Plasma concentrations of CGP 57148 in rats after i.v., p.o. and s.c. administration. Volume 1.31; page 5-214.
BPK(CH) 1996/003: Plasma concentrations of CGP 57148 in rats after p.o. administration of 100, 200 or 400 mg/kg of CGP 57148B. Volume 1.31; page 5-230.
BPK(CH) 1995/075: Plasma concentrations of CGP 57148 in dogs after p.o. and i.v. administration. Volume 1.31; page 5-248.
Report BPK(CH) 19961090: Plasma concentrations of CGP 57148 in a 2-week oral toxicity study in rats, Test No. 96-6023. Volume 1.31; page 5-265.
BPK(CH) 1996/086: Plasma concentrations of CGP 57148 in a 4-week intravenous toxicity study in rats. Test No. 95-6109 (MIN 954194). Volume 1.31; page 5-285.
BPK(CH) 1997/024: Plasma concentrations of CGP 57148 in a 13-week oral toxicity study in rats. Test No. 96-6106. Volume 1.31; page 5-303.
BPK(CH) 1996/092: Plasma concentrations of CGP 57148 in a 2-week oral toxicity study in dogs. Test No. 96-6024. Volume 1.32; page 5-191.
BPK(CH) 1996/021: Plasma concentrations of CGP 57148 in a 4-week intravenous toxicity study in dogs. Test No. 95-6111 (MIN 954195). Volume 1.32; page 5-44.
BPK(CH) 1997/023: Plasma concentrations of CGP 57148 in a 13-week oral toxicity study in dogs. Test No. 96-6105. Volume 1.32; page 5-95.
BPK(CH) 1995/116: Plasma protein binding of CGP 57148 (preliminary study). Volume 1.32; page 5-203.
DMPK(CH) 1997/232: Absorption and disposition of [14C]CGP 57148B in rats and dogs after intravenous and peroral administration. Volume 1.33; page 5-42.
DMPK(CH) 1997/038: Metabolic stability of [14C]CGP 57148B in vitro. Species comparison using S12 liver fractions from rat, dog and man. Volume 1.33; page 5-334.

DMPK(CH) 1997/355: CGP 57148713: Structure elucidation of metabolites in rat bile and dog urine. Volume 1.35; page 5-27.

Toxicology

Single Dose Studies

Report 95078: CGP 57148B. Acute intravenous toxicity study in rats, Test no. 956108, (MIN 954186). Volume 1.11; page 5-1.

Repeated Dose Studies

MIN 954194: CGP 5714813: 4-week intravenous toxicity study in rats. Volume 1.23, page 5-1.
Test 966023: CGP 57114813: 2-week oral toxicity study in rats. Volume 1.11; page 5-38.
Test 966106: CGP 5714813: 13-week oral toxicity study in rats. Volume 1.12; page 5-1.
Test 966024: CGP 5714813: 2-week oral toxicity study in dogs. Volume 1.17; page 5-1.
Test 966105: CGP 5714813: 13-week oral toxicity study in dogs. Volume 1.19; page 5-1.
T96006: CGP 5714813: 4-week intravenous toxicity study in dogs. (MIN 954195). Volume 1.24; page 5-79.

Reproductive Toxicology

Test 966085: CGP 57148B: Embryonic and fetal development dose range-finding study in rats. Volume 1.28: page 5-256.
Test 966087: CGP 5714813: Embryonic and fetal development dose range-finding study in rabbits. Volume 1.28; page 5-292.

Genetic Toxicology

In vitro studies

Test 956104: CGP 57148B: Salmonella and Escherichia/mammalian-microsome mutagenicity test. Volume 1.30; page 5-206.
Test 956105: CGP 57148B: Gene mutation test with Chinese hamster cells V79. Volume 1.30; page 5-279.
Test 956106: GP 5714813: Cytogenetic test on Chinese hamster cells in vitro. Volume 1.31; page 5-1.
Test 966052: Mouse lymphoma mutagenicity assay, in vitro. Volume 1.31; page 5-38.

In vivo studies

Test 956107: CGP 57148B: Micronucleus test, rat, in vivo study. Volume 1.31; page 5-126.

Special Toxicology

MIN 964014: CGP 57148B: 5-day intravenous irritation study in rabbits. Volume 1.31, page 5-163.

Introduction and drug history:

Gleevec® (imatinib mesylate) is an inhibitor of protein-tyrosine kinases associated with Bcr-Abl, the platelet-derived growth factor (PDGF) receptor and c-Kit. The inhibition of Bcr-Abl kinase is important, as it is believed to play a role in the deregulated myeloid cell proliferation that is the hallmark of chronic myeloid leukemia (CML). The Philadelphia chromosome arises from a reciprocal translocation between chromosomes 9 and 22. Replacement of the first exon of c-Abl with sequences from the Bcr gene result in a Bcr-Abl fusion gene with a 210-kD protein product that exhibits enhanced protein-kinase activity and is present in 95% of CML.

Imatinib has been investigated for toxicological effects in numerous studies in mice, rats, rabbits, dogs and monkeys. Target organs for drug toxicity in these animals include the liver, hematopoietic system, lymphoid tissue, gastrointestinal tract, testes and ovaries. In both the rat and rabbit, imatinib is fetotoxic when administered during gestation. In the rat the drug was also a teratogen, primarily causing malformations of the skeletal system. In genotoxicity assays, two intermediate products in the drug product manufacturing process, that are present in the final product, were positive mutagens. Imatinib was positive for clastogenicity in the Chinese hamster ovary cell assay.

Gleevec® was approved for use in chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failing interferon-alpha therapy in May of 2001. Mild to moderate nausea, periorbital edema and mild to moderate musculoskeletal symptoms were the most common adverse events reported during clinical trials, and all appeared to have a dose-response relationship with Gleevec®. During clinical trials, serious adverse fell into 5 broad categories: rash, liver function test abnormalities, myelosuppression, gastrointestinal hemorrhage, and edema and fluid retention (sometimes accompanied by renal failure).

TABLE OF CONTENTS

PHARMACOLOGY:

No new pharmacology studies submitted.

SAFETY PHARMACOLOGY:

No new safety pharmacology studies submitted.

PHARMACOKINETICS/TOXICOKINETICS:

Distribution:

Study title: DMPK(CH)R00-097: Metabolism in milk and plasma after single peroral administration of ^{14}C-labeled STI571 (100 mg/kg as the methanesulfonic salt) to lactating rats.

Key findings: This study was reviewed in the initial NDA submission. In that report, exact metabolites were not identified, only the retrieval of ^{14}C-labeled, with no differentiation between ^{14}C-STI571 and ^{14}C-STI571-metabolites. Because of this, the original report stated that the results show STI571 and/or its metabolites are transferred to the lactating rat's milk. This study clarified that by showing that both the parent compound and the metabolite are found in the milk.

Study no:	**DMPK(CH) R00-097**
Volume #, and page #:	Volume 2.5, page 5-409.
Conducting laboratory and location:	Novartis Pharma AG, Switzerland
Date of study initiation:	22 September 2000
GLP compliance:	No compliance included
QA report:	yes ( ) no (X)
Drug, lot #, radiolabel, and % purity:	STI571, batch RSE 052-9, ^{14}C label, >98% pure
Formulation/vehicle:	0.5% w/w Klucel with 0.1% w/w polysorbate 80

Dosing:

Species/strain:	Rat/HAN:WIST (WIGA) – lactating – Day 11 after parturition
#/sex/group or time point:	4/timepoint
Age:	Approximately 8-12 weeks
Weight:	240-315 g
Doses in administered units:	100 mg/kg – single dose (19.2 MBq/kg)
Route, form, volume, and infusion rate:	Oral, gavage, 10 mL/kg volume
Sampling schedule:	Milk and blood at 0.5, 2, 4, 8, 24, 48, 72, and 96 hours
Analytical method:	Liquid scintillation counting of total ^{14}C radioactivity

Results:

^{14}C-Pharmacokinetic Parameters of STI571 and Its Metabolites in Lactating Rats Following a PO dose of 100 mg/kg						
Matrix	**Parameter**	**^{14}C**	**STI571**	**74588**	**71422**	**72383**
Plasma	C_{max} [µmol/L]	29.2	22.2	0.78	0.26	ND
	t_{max} [h]	2	2	2	2	2
	$AUC_{(0-24)}$ [µmol•h/mL]	338	253	9.23	3.33	NA
Milk	C_{max} [µmol/L]	94.7	50.3	9.64	0.29	0.36
	t_{max} [h]	2	2	8	24	8
	$AUC_{(0-24)}$ [µmol•h/mL]	1994	800	174	5.18	7.32

Metabolites – CGP74588 (N-desmethyl); CGP71422 (piperazine N-oxide); CGP72383 (pyridine-N-oxide)

Data from oral administration of STI571 to lactating rats shows that the t_{max} for ^{14}C concentrations in the blood and plasma is 2 hours. High concentrations were still detected in blood and plasma at 8 hours post administration. At 24 hours, 15-20% of the concentrations at t_{max} was still detected in blood and plasma. ^{14}C transferred to the milk rapidly, as radioactivity was detected at the first time point, 30 minutes after ^{14}C-STI571 administration. Transfer from blood to milk was extensive, as the milk-to-blood ratio was >3 over the entire sampling period. This ratio was maximum toward the end of the sampling, as the ^{14}C concentration in the milk at 24, 48 and 72 hours post administration was 16, 47 and 25 times greater than the ^{14}C concentration in the blood at these same time points, respectively. These data show that metabolites normally present in plasma are all found in the milk. The pyridine-N-oxide CGP72383 was only detected in the milk. At 24 hours, 40% of the total milk ^{14}C-AUC was unchanged drug, 9% the N-desmethyl metabolite and 0.7% the N-oxide metabolites. In the plasma, 75% of the total ^{14}C-AUC was unchanged drug, 3% the N-desmethyl metabolite and 1% the piperazine N-oxide metabolite.

PK/TK summary:

Imatinib mesylate and its metabolites were detected in the plasma and milk of lactating female rats given a single oral dose of 100 mg/kg on day 11 after parturition. The levels in the milk were three-fold higher than that seen in the plasma. Mean extraction yield from the milk was 83%, though after dissolution of the evaporated extract, the recovery went down to 64%. When the evaporated milk extract was residue of the milk extract (the fat droplets) was analyzed, STI571 was the major component in the fat droplets.

PK/TK conclusions:

These results indicate that nursing infants would be exposed to imatinib mesylate and its N-desmethyl and N-oxide metabolites if a patient were to breastfeed while taking Gleevec®. This information allows for the clarification in the label of Gleevec® from the statement in the

original label that in the lactating rat "imatinib and/or its metabolites were extensively excreted in milk" to the more accurate "imatinib and its metabolites were extensively excreted in milk"

TOXICOLOGY:

No new toxicology studies submitted.

GENETIC TOXICOLOGY:

No new genetic toxicology studies submitted.

CARCINOGENICITY:

No carcinogenicity studies included in this submission.

REPRODUCTIVE TOXICOLOGY:

Study title: An oral pre-and postnatal development study in rats.

Key study findings: No maternal lethality was seen. A red vaginal discharge was seen in the HD group (45 mg/kg). The HD group also had: decreased maternal body weight gain and food consumption, increased stillbirths and pup mortality in the first four days of life, decrease in viable pups per litter. The HD offspring rats also exhibited decreased body weights. The HD offspring females had a significant increase in early resorptions and a decrease in viable fetuses when mated to HD male offspring.

Study no.:	Study 017021
Volume #, and page #:	Volume 2.4, page 5-8
Conducting laboratory and location:	Novartis Pharmaceuticals Corp., Summit, NJ
Date of study initiation:	4 March 2001
GLP compliance:	Compliance included and signed
QA reports:	yes (X) no ( )
Drug, lot #, and % purity:	STI571, lot# 9923006, 100% pure
Formulation/vehicle:	Purified water, USP

Methods:

Species/strain:	Rat/Wistar ——— Crl:WI(IGS BR
Age:	Approximately 11 weeks upon arrival
Doses employed:	0, 5, 15, and 45 mg/kg/day
Route of administration:	Oral gavage; 10 mL/kg
Study design:	**Females** –F_0 dosed daily during gestation and until the end of lactation – from gestational day (GD) 6 until postpartum day (PD) 21 **Males** – not dosed

Offspring – at weaning, PND 21, litters culled to 4, 2/sex if possible. All pups tested in open field motor activity, one of each sex in both stages of passive avoidance and one of each sex in both phases of M-maze learning and memory. The M-maze pups were then used in the F_1 mating study.

Number/sex/group: 24 ♀/group

Parameters and endpoints evaluated:

Females

Clinical observations, mortality, maternal body weights and food consumption, pregnancy/delivery observations and gross necropsy.

Offspring

Viability, mortality, clinical signs, individual weights, sex ratio, righting reflex, pinna detachment, eye opening, acoustic startle, pupillary reflex, vaginal opening, preputial separation, open field motor activity, passive avoidance (learning/acquisition and retention/memory), M-maze (learning/acquisition and retention/memory), F_1 mating parameters.

Results:

Maternal toxicity:

Mortality: No maternal mortalities

Clinical signs: HD – 21% red vaginal discharge day 14 or 15 of gestation.

Body weight: Body weight gain
HD - GD 15-18 – 22% ↓ from control
HD – GD 18-20 – 33% ↓ from control

Food consumption: HD – GD 6-9 – ↓ 9% from control
HD – GD 15-18 – ↓ 8% from control
HD – PD 4-7 – ↓ 21% from control
HD – PD 7-10 – ↓ 19% from control
HD – PD 10-14 – ↓ 16% from control

In-life observations:

Dams: No treatment effect on number of females impregnated
No treatment effect on duration of gestation
No treatment effect on number of females surviving delivery
No treatment effect on number of litters delivered
No treatment effect on sex ratio of offspring
Non-significant increase in stillborn pups in HD group
Non-significant decrease in liveborn pups in HD group
Non-significant increase in number of cannibalized/missing pups in HD litters

Offspring: HD – ↓ pup weight per litter post natal days (PND)
PND 0 – ↓ 16% from control
PND 4 – ↓ 20% from control
PND 7 – ↓ 21% from control
PND 14 – ↓ 12% from control
PND 21 – ↓ 11% from control
HD – offspring body weights from 28-98 days old, consistently lower than control rats. ♂ - average 9% ↓ and ♀ average 8% ↓
HD – ♂ ↓ litters reaching criterion for preputial separation
HD – ♀ ↓ litters righting themselves on PND 0, though successfully completed this within the PND 0-2 timeframe.
No treatment related effect on open field test
No effect on learning acquisition or memory retention with passive avoidance.
No effect on learning acquisition with M-maze.
HD- ♂ M-maze rats, ↑ errors during the retention phase.

Terminal and necroscopic evaluations:

Dams: HD – one female with a renal papilla and one female with a distended uterine horn filled with clear fluid.

Offspring: HD – pups dying/missing and/or cannibalized on PND 0 - ↑ 1000% compared to control
HD – pups dying/missing and/or cannibalized on PNDs 1-4 - ↑ 900% compared to control
HD – pups surviving 21 days – ↓ 26% from control
No gross pathological treatment related effects in the F_1 generation pups.
HD – mated F_1 females – 8%↓ in weight gain from GD 3-13 compared to control
HD – mated F_1 females – 22% ↓ in implantation sites, 67% ↑ in early resorptions and 28% ↓ in mean number of viable fetuses.

Summary of individual study findings:

The doses used in this study were chosen based on the results from the embryo-fetal development study reviewed in the initial NDA (Study 966086). Rats in that study were dosed with 10, 30 or 100 mg/kg from gestational day 6 through 15. The high dose tested in that study, 100 mg/kg, produced maternal toxicity, teratogenic effects and embryo-fetal toxicity. No maternal effects were noted with the 30-mg/kg dose, though protruding tongue and shortened 13th ribs were seen in the offspring. The high dose in the study reviewed herein, 45 mg/kg, was chosen because it was expected to produce an effect on external development and possibly survival of the offspring, but not be so embryo-fetal toxic as to allow for adequate survival to assess developmental and behavioral parameters.

No maternal lethality was seen in this study. The only clinical sign seen in the maternal rats was a red vaginal discharge seen in 21% of the rats treated with the highest dose, 270 mg/m^2. The high dose rats also had a decrease in body weight gain in the final third of gestation. These same rats had a decrease in food consumption during periods of the middle and end segments of gestation and during days 4-14 of the 21-day nursing period for the litter.

The length of gestation, the number of delivered litters and the sex ratio of the offspring pups were not significantly affected by the imatinib mesylate treatment. There were significant effects, however, on several pregnancy and lactation parameters in the HD rat group. The number of pups missing/dying or cannibalized on PND 0 and PND 4 were significantly increased over control, leading to a significantly decreased number of viable pups at the end of the lactation period. The HD dams also had an increase number of stillborn pups and decreased number of viable pups at birth, though this was not statistically significant. Pup weights per litter through lactation were decreased in the HD group, compared to control. The pup weights continued to be lower than the controls post-weaning until day 98.

To determine if the decrease in body weight gain seen in the treated dams is due to direct maternal toxicity or due to the small litters, with increased stillbirths and decreased viable pups, it is important to look at the original embryo-fetal toxicity study. In this study, similar decreases in food consumption and body weight gains were seen in the HD dams, 100 mg/kg. These animals were euthanized at GD 20 and the female rats were weighed minus the gravid uterus. When this was done, the gravid uteri of the HD animals were significantly smaller than the control, but there was no difference across dose groups in the carcass weights, the body weight minus the weight of the gravid uterus. Therefore the decrease in body weight gain seen in the HD group of the original study was due to the fetal loss and not to a direct effect on maternal toxicity, as evidenced by a decrease in body weight gain. In the present study, the F_0 females were allowed to deliver their litters, so the gravid uterus weight was not obtained. It is likely that the same situation is true with this study. The decrease in body weight gains seen in the 45 mg/kg group is due to the effect on the litter, decreased pup weights and number of viable pups and increase in stillbirths, and not due to a direct maternal toxicity.

The developmental parameters were not affected by imatinib mesylate administration during gestation, with the exception of 3 HD litters not achieving preputial separation within the timeframe. The HD litter females also did not successfully complete the righting reflex on PND 0, but they did achieve criterion within the timeframe of PND 2. No treatment related effects were seen when the rats were tested in an open field motor activity paradigm.

Learning and memory were assessed in the F_1 generation pups, one per sex from each litter when possible. A passive avoidance paradigm was used, in addition to an M-maze test. The learning tests were conducted when the pups were 63 ± 2 days old and the memory retention was tested when the same pups were 70 ± 2 days old. Upon completion of the memory tests, the M-maze rats were then used to examine the F_1 mating parameters. No effects were seen in the passive avoidance test. Learning acquisition with the M-maze was not affected by treatment, but a significant increase in errors was seen with the HD male offspring when tested for memory retention.

When the F_1 generation pups were mated, significant body weight effects persisted in the pregnant rats. The HD females body weights averaged 8% lower than control until GD 13, when the dams were sacrificed and reproductive data were obtained. In the F_1 generation females, no effect of treatment was seen on fertility. However, in the HD pregnant females, a significant decrease was seen in implantation sites and viable embryos. These rats also exhibited a significant increase in early resorptions.

Reproductive toxicology summary:

The most notable maternal occurrence in the present study was the red vaginal discharge seen in 21% of the high dose dams. The reason for this finding is not clear, as each of the affected dams delivered healthy litters and did not have a significantly higher number of post-implantation losses.

Previous reproductive toxicology studies have shown that when administered to female rats and rabbits, imatinib had a clear embryo-fetal toxic effect. When imatinib was administered to male rats, fertility was not impaired. The teratogenic potential of imatinib was investigated in both rat and rabbit studies. In the rat, there was a slight indication of teratogenicity at the MD of 180 mg/m^2/day. When imatinib was administered to pregnant rats from GD 6-15, the HD of 600 mg/m^2/day was clearly teratogenic. Evidence of teratogenicity in the rabbit, when the pregnant animal is dosed from GD7-19, has not been observed with imatinib, with doses up to 1200 mg/m^2/day.

Additional information obtained from the present study, besides reaffirming the embryo-fetal toxicity of imatinib mesylate, include the treatment-related effects seen on the body weights of the *in utero* exposed rats, which persisted from parturition until the animals were euthanized at about day 98. These decreased weights were also seen in the mated F_1 females, persisting until the animals were euthanized at GD 13. The F_1 females that were exposed *in utero* to the HD imatinib mesylate also had increased resorptions and decreases in the number of viable fetuses. This effect is seen in female rats treated during gestation with imatinib mesylate, and this study shows that this is again seen in females exposed during gestation and lactation.

Reproductive toxicology conclusions:

The reported developmental study, in addition to previously reviewed reproductive toxicology studies, show that imatinib mesylate clearly impacts the ability of rats and rabbits to carry fetuses to term, based on the significant incidence of fetal loss due to early resorptions. The teratogenic potential of imatinib to surviving fetuses was demonstrated in the rat studies. The study reviewed here again showed that imatinib mesylate is embryo-fetal toxic, as evidenced by the increase in resorptions, stillborn pups and early pup mortality. This study does show that there are no clear indications of treatment-related developmental effects in the offspring that were exposed *in utero* to imatinib mesylate. While there was a significant effect on memory in the M-maze HD animals, the lack of other learning and memory treatment-related effects diminishes the impact of this one result.

Labeling recommendations:

Women should be advised against becoming pregnant or breastfeeding while taking Gleevec®.

SPECIAL TOXICOLOGY STUDIES:

No new special toxicology studies submitted.

ADDENDUM TO REVIEW:

None

APPENDIX/ATTACHMENTS:

None

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/s/

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