Imatinib Mesilate *(BANM, rINNM)*

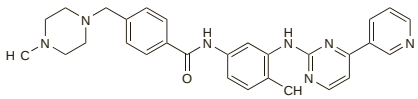
CGP-57-148B; Imatinib, Mésilate d'; Imatinib Mesylate *(USAN)*; Imatinibi Mesilas; Mesilato de imatinib; STI-571. α-(4-Methyl-1-piperazinyl)-3′-{[4-(3-pyridyl)-2-pyrimidinyl]amino}-*p*-tolu-*p*-toluidide methanesulfonate.

Иматиниба Мезилат

$C_{29}H_{31}N_7O,CH_4O_3S$ = 589.7.

CAS — 152459-95-5 (imatinib); 220127-57-1 (imatinib mesilate).

ATC — L01XE01.



(imatinib)

Adverse Effects and Precautions

For general discussions see Antineoplastics, p.635, p.639, and p.641.

The most common adverse effects of imatinib mesilate include gastrointestinal disturbances, superficial oedema, myalgia, muscle cramps, rashes, fatigue, and headache. There are reports of erythema multiforme and Stevens-Johnson syndrome. Other adverse effects include dizziness, taste disturbances, paraesthesia, insomnia, eye disorders or visual disturbances, epistaxis, dyspnoea, dry skin, alopecia, night sweats, pyrexia, weakness, and rigors. Hepatotoxicity may occur; fatal cases of hepatic necrosis have been reported. Aseptic necrosis of bone, mainly in the femoral head, has been reported rarely.

Myelosuppression, manifest as neutropenia, thrombocytopenia, or anaemia, occurs more frequently in leukaemic patients, and may be associated with the underlying disease. Gastrointestinal bleeding, however, is more frequent in those patients treated for stromal tumours. Ulceration can occur; gastrointestinal perforation, fatal in some cases, has been reported rarely.

Severe fluid retention can occur, which may result in pleural and pericardial effusion, pulmonary oedema, and ascites. Some fatalities have been reported, and treatment may need to be stopped if there is unexpected, rapid weight gain. Elderly patients and those with a history of cardiac disease may be at increased risk. Isolated cases of left ventricular dysfunction have been reported; patients with cardiac disease or risk factors for cardiac failure should be monitored. There are reports, including fatalities, of cerebral oedema, increased intracranial pressure and papilloedema.

Imatinib mesilate should be taken with food and a large glass of water to minimise gastrointestinal irritation. Complete blood counts and liver function should be monitored regularly.

Effects on the heart. Ten patients receiving imatinib developed severe congestive heart failure without obvious cause; all patients had normal left ventricular function before imatinib was started. Mitochondrial abnormalities were found after myocardial biopsy on 2 of the patients. These findings were confirmed by studies on *mice* and *in vitro*. The authors suggested that patients be closely followed for clinical manifestations of left ventricular dysfunction.[1]

Subsequent evaluation by the manufacturer (*Novartis*) established that the frequency of reported cardiac events was less than 1%. However, they recommended that patients with known cardiac disease or risk factors for cardiac failure be monitored accordingly, that those developing clinical manifestations suggestive of congestive cardiac failure be thoroughly evaluated and treated, and that elderly patients or those with underlying heart disease be evaluated for baseline left ventricular ejection fraction.[2]

1. Kerkelä R, *et al.* Cardiotoxicity of the cancer therapeutic agent imatinib mesylate. *Nat Med* 2006; **12:** 908–16.
2. Novartis, Canada. Health Canada endorsed important safety information on Gleevec (imatinib mesylate): recent safety information regarding reports of significant left ventricular ejection fraction reduction and congestive heart failure with GLEEVEC (imatinib mesylate) (issued 21st September, 2006). Available at: http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2006/gleevec_2_hpc-cps-eng.php (accessed 01/08/08)

Effects on the kidneys. Imatinib has been associated with the development of acute renal failure, requiring haemodialysis.[1-3]

1. Kitiyakara C, Atichartakarn V. Renal failure associated with a specific inhibitor of BCR-ABL tyrosine kinase, STI 571. *Nephrol Dial Transplant* 2002; **17:** 685–7.
2. Pou M, *et al.* Acute renal failure secondary to imatinib mesylate treatment in chronic myeloid leukemia. *Leuk Lymphoma* 2003; **44:** 1239–41.
3. Foringer JR, *et al.* Acute renal failure secondary to imatinib mesylate treatment in prostate cancer. *Ann Pharmacother* 2005; **39:** 2136–8.

Effects on the lungs. Interstitial pneumonitis has been reported with imatinib;[1-8] presenting symptoms included dry cough and dyspnoea. Doses of imatinib ranged from 100 mg to 600 mg daily. In most cases, the pneumonitis resolved after stopping imatinib and starting corticosteroid therapy. The mechanism was unclear, and may involve a hypersensitivity reaction. In an analysis of 27 cases of interstitial lung disease associated with imatinib therapy,[8] 30% of patients showed a hypersensitivity reaction radiological pattern. Pre-existing lung disease may be a risk factor.

1. Bergeron A, *et al.* Hypersensitivity pneumonitis related to imatinib mesylate. *J Clin Oncol* 2002; **20:** 4271–2.
2. Rosado MF, *et al.* Imatinib mesylate-induced interstitial pneumonitis. *J Clin Oncol* 2003; **21:** 3171–3.
3. Ma CX, *et al.* Imatinib mesylate-induced interstitial pneumonitis. *Mayo Clin Proc* 2003; **78:** 1578–9.
4. Yokoyama T, *et al.* Interstitial pneumonia induced by imatinib mesylate: pathologic study demonstrates alveolar destruction and fibrosis with eosinophilic infiltration. *Leukemia* 2004; **18:** 645–6.
5. Isshiki I, *et al.* Interstitial pneumonitis during imatinib therapy. *Br J Haematol* 2004; **125:** 420.
6. Rajda J, Phatak PD. Reversible drug-induced interstitial pneumonitis following imatinib mesylate therapy. *Am J Hematol* 2005; **79:** 80–1.
7. Lin J-T, *et al.* Fulminant, but reversible interstitial pneumonitis associated with imatinib mesylate. *Leuk Lymphoma* 2006; **47:** 1693–5.
8. Ohnishi K, *et al.* Twenty-seven cases of drug-induced interstitial lung disease associated with imatinib mesylate. *Leukemia* 2006; **20:** 1162–4.

Effects on reproductive potential. Oligospermia[1] and ovarian failure[2] have been reported after treatment with imatinib. Patients should be counselled before therapy about the risk of impaired fertility.

1. Seshadri T, *et al.* Oligospermia in a patient receiving imatinib therapy for the hypereosinophilic syndrome. *N Engl J Med* 2004; **351:** 2134–5.
2. Christopoulos C, *et al.* Primary ovarian insufficiency associated with imatinib therapy. *N Engl J Med* 2008; **358:** 1079–80.

Effects on the skin, hair, and nails. There are reports of acute generalised exanthematous pustulosis in patients receiving imatinib.[1,2] The authors noted that severe skin reactions had been reported in some other patients receiving the drug, and speculated that the effect might be dose-dependent and related to its pharmacological action. In subsequent reports[3-5] of cutaneous adverse effects, this dose-dependency has also been observed, with effects especially at doses of 600 mg daily and above. In a report of a livedoid pattern of rash in 3 patients taking imatinib, the authors noted that adverse skin reactions to imatinib tend to be strongly dose-dependent, are self-limiting, and do not usually affect the mucous membranes.[6] Epidermal necrolysis occurred in a patient who underwent stem cell transplantation after treatment with imatinib.[7] The authors suggested that prolonged inhibition of platelet-derived growth factor by imatinib may have impaired the repair of skin damage caused by the conditioning therapy. In a report of 19 patients exhibiting skin reactions, the authors suggested that the actions of imatinib on platelet-derived growth factor may have caused an increase in dermal interstitial fluid pressure, capable of inducing oedema and the subsequent erythema and desquamation that was observed. Rare reactions included psoriasis, hyaline cell syringoma, and malpighian epithelioma, all of which occurred after at least 1 year of therapy.[8] Follicular mucinosis[9] and panniculitis[10] have also been reported with use of imatinib, as has Stevens-Johnson syndrome.[11,12] Palmoplantar hyperkeratosis and nail dystrophy can occur.[13] Repigmentation of grey hair has also been reported.[14]

Oral corticosteroids have been used to resolve most cases of skin eruptions.[8] In other instances, re-introduction of imatinib at low doses, gradually increased to full dosage, has been successfully tolerated.[8,12,15] In one patient, who developed exfoliative dermatitis with imatinib and had recurrent reactions despite decreased doses, a once-weekly dose of imatinib was associated with a less severe rash that eventually disappeared over a period of 4 months.[16]

1. Brouard M, Saurat J-H. Cutaneous reactions to STI571. *N Engl J Med* 2001; **345:** 618–19.
2. Schwarz M, *et al.* Imatinib-induced acute generalized exanthematous pustulosis (AGEP) in two patients with chronic myeloid leukemia. *Eur J Haematol* 2002; **69:** 254–6.
3. Valeyrie L, *et al.* Adverse cutaneous reactions to imatinib (STI571) in Philadelphia chromosome-positive leukemias: a prospective study of 54 patients. *J Am Acad Dermatol* 2003; **48:** 201–6.
4. Drummond A, *et al.* A spectrum of skin reactions caused by the tyrosine kinase inhibitor imatinib mesylate (STI 571, Glivec). *Br J Haematol* 2003; **120:** 911–13.
5. Ugurel S, *et al.* Dose-dependent severe cutaneous reactions to imatinib. *Br J Cancer* 2003; **88:** 1157–9.
6. Martínez-González MC, *et al.* Livedoid skin reaction probably due to imatinib therapy. *Ann Pharmacother* 2007; **41:** 148–52.
7. Schaich M, *et al.* Severe epidermal necrolysis after treatment with imatinib and consecutive allogeneic hematopoietic stem cell transplantation. *Ann Hematol* 2003; **82:** 303–4.
8. Breccia M, *et al.* Early and tardive skin adverse events in chronic myeloid leukaemia patients treated with imatinib. *Eur J Haematol* 2005; **74:** 121–3.
9. Yanagi T, *et al.* Follicular mucinosis associated with imatinib (STI571). *Br J Dermatol* 2004; **151:** 1276–8.
10. Ugurel S, *et al.* Panniculitis in a patient with chronic myelogenous leukaemia treated with imatinib. *Br J Dermatol* 2003; **149:** 678–9.
11. Hsiao L-T, *et al.* Stevens-Johnson syndrome after treatment with STI571: a case report. *Br J Haematol* 2002; **117:** 620–2.
12. Rule SAJ, *et al.* Managing cutaneous reactions to imatinib therapy. *Blood* 2002; **100:** 3434–5.
13. Deguchi N, *et al.* Imatinib mesylate causes palmoplantar hyperkeratosis and nail dystrophy in three patients with chronic myeloid leukaemia. *Br J Dermatol* 2006; **154:** 1216–18.
14. Etienne G, *et al.* Imatinib mesylate and gray hair. *N Engl J Med* 2002; **347:** 446.
15. Park MA, *et al.* Successful progressive challenge after a cutaneous reaction to imatinib mesylate (Gleevec): a case report and review of the literature. *Allergy Asthma Proc* 2004; **25:** 345–7.
16. Tanvetyanon T, Nand S. Overcoming recurrent cutaneous reactions from imatinib using once-weekly dosing. *Ann Pharmacother* 2003; **37:** 1818–20.

Effects on the spleen. There are isolated reports of splenic rupture in patients receiving imatinib mesilate.[1]

1. Elliott MA, *et al.* Adverse events after imatinib mesylate therapy. *N Engl J Med* 2002; **346:** 712–13.

Gynaecomastia. Gynaecomastia was noted in 7 of 38 men assessed for hormone concentrations while enrolled in studies of imatinib; the authors attributed the disorder to reductions in testosterone concentrations due to imatinib.[1]

1. Gambacorti-Passerini C, *et al.* Gynaecomastia in men with chronic myeloid leukaemia after imatinib. *Lancet* 2003; **361:** 1954–56.

Hypophosphataemia. Hypophosphataemia and associated changes in bone and mineral metabolism were reported in a study of patients receiving imatinib. Patients with normal serum-phosphate concentrations also had similar changes in bone turnover. Hypophosphataemia was apparently related to patient age and imatinib dose; it was also associated with decreased serum concentrations of calcium and vitamin D.[1] In a review of data, the manufacturers (*Novartis*) noted an incidence of 50% of patients in 2 studies; overall 1.5% had grade 4 hypophosphataemia. However, the reported incidence of hypophosphataemia as an adverse effect of imatinib was only 3%. They suggested that phosphate concentrations be monitored in patients taking imatinib until further elucidation of the effect of the drug on bone is available.[2] While some have questioned the association between treatment with imatinib and hypophosphataemia,[3] others have also reported hypophosphataemia during treatment with the drug.[4] The effect, however, appears to be reversible on stopping imatinib.

1. Berman E, *et al.* Altered bone and mineral metabolism in patients receiving imatinib mesylate. *N Engl J Med* 2006; **354:** 2006–13.
2. Owen S, *et al.* Imatinib and altered bone and mineral metabolism. *N Engl J Med* 2006; **355:** 627.
3. Tournis S, Lyritis GP. Imatinib and altered bone and mineral metabolism. *N Engl J Med* 2006; **355:** 627.
4. Joensuu H, Reichardt P. Imatinib and altered bone and mineral metabolism. *N Engl J Med* 2006; **355:** 628. Correction. *ibid.*; 1627.

Pregnancy. Two of 3 pregnancies in 2 patients taking imatinib were successful; the infants were both small for weight, but healthy and without congenital abnormalities. In the third case, a first trimester miscarriage occurred. Both women continued imatinib throughout their pregnancies.[1]

In another report,[2] 10 women became pregnant while being treated with imatinib for chronic myeloid leukaemia. Imatinib therapy was stopped upon discovery of the pregnancy; exposure to imatinib ranged from 4 to 9 weeks. Two patients had a spontaneous abortion shortly after stopping imatinib, and another patient elected to have a therapeutic abortion. Seven other pregnancies went to term, resulting in 8 babies. One infant had hypospadias which was surgically corrected without complications; all other infants were healthy. The partners of 8 male patients also conceived while the men were receiving imatinib, one of them twice. All male patients continued therapy with imatinib. One spontaneous abortion occurred. Of the 8 babies born, 1 was found to have a mild rotation of the small intestine requiring surgery shortly after birth. The authors considered it possible that the brief exposure to imatinib may have slightly increased the risk of spontaneous abortion. While concluding that normal pregnancies are possible during imatinib therapy, the authors of both reports emphasised that possible teratogenic effects cannot be ruled out, and that patients should still be advised to use appropriate and effective contraception.

A similar warning was issued in a review of outcome data from 125 pregnancies involving exposure to imatinib. The authors noted that 63 pregnancies had resulted in the live birth of normal infants; a further 35 women terminated the pregnancy (in 3 cases because fetal abnormalities were found), and 18 ended in spontaneous abortion.[3] However, there were 9 infants with congenital abnormalities, several of which were strikingly similar, a fact that was considered to be of some concern.

1. AlKindi S, *et al.* Imatinib in pregnancy. *Eur J Haematol* 2005; **74:** 535–7.

2. Ault P, *et al.* Pregnancy among patients with chronic myeloid leukemia treated with imatinib. *J Clin Oncol* 2006; **24:** 1204–8.
3. Pye SM, *et al.* The effects of imatinib on pregnancy outcome. *Blood* 2008; **111:** 5505–8.

Interactions

Imatinib mesilate is metabolised by the cytochrome P450 isoenzyme CYP3A4, and drugs that inhibit this enzyme, such as azole antifungals and macrolide antibacterials, may increase blood concentrations of imatinib. Equally, inducers of CYP3A4 (such as carbamazepine, dexamethasone, St John's wort, phenobarbital, phenytoin, and rifampicin) may reduce blood concentrations of imatinib; imatinib dosage may need to be increased in these patients (see Uses and Administration, below).

In vitro studies have indicated that imatinib itself inhibits the cytochrome P450 isoenzymes CYP3A4, CYP2C9, and CYP2D6, and may increase blood concentrations of drugs that are substrates of these enzymes.

The dose of levothyroxine may need to be increased before imatinib is given to patients with hypothyroidism (see Antineoplastics under Interactions of Levothyroxine, p.2172).

Antifungals. In a small study in healthy subjects, *ketoconazole* significantly increased imatinib exposure; mean maximum plasma concentration and area under the concentration-time curve increased, and clearance of imatinib decreased. The half-life of imatinib appeared relatively unchanged. To avoid overexposure, single subtherapeutic doses of imatinib had been used (200 mg); the authors noted that clinical significance might arise with use of imatinib in daily doses of 800 mg or more.[1]

1. Dutreix C, *et al.* Pharmacokinetic interaction between ketoconazole and imatinib mesylate (Glivec) in healthy subjects. *Cancer Chemother Pharmacol* 2004; **54:** 290–4.

St John's wort. Exposure to imatinib was significantly reduced when it was given after 2 weeks of treatment with St John's wort; area under the concentration-time curve was decreased, maximum plasma concentration and half-life of imatinib were reduced, and clearance increased.[1,2]

1. Frye RF, *et al.* Effect of St John's wort on imatinib mesylate pharmacokinetics. *Clin Pharmacol Ther* 2004; **76:** 323–9.
2. Smith PF, *et al.* The influence of St. John's wort on the pharmacokinetics and protein binding of imatinib mesylate. *Pharmacotherapy* 2004; **24:** 1508–14.

Pharmacokinetics

Imatinib mesilate is well absorbed after oral doses with peak blood concentrations occurring after 2 to 4 hours. The mean bioavailability is about 98%. Imatinib is reported to be about 95% bound to plasma proteins. Plasma elimination half-lives of imatinib and its major active metabolite, the *N*-demethylated piperazine derivative, are about 18 and 40 hours respectively. The major enzyme responsible for the metabolism of imatinib is cytochrome P450 isoenzyme CYP3A4; isoenzymes CYP1A2, CYP2D6, CYP2C9, and CYP2C19 also play a minor role. About 81% of a dose is eliminated within 7 days in the faeces (68%) and urine (13%). It is excreted mostly as metabolites, with only 25% as unchanged drug.

◊ References.

1. Peng B, *et al.* Absolute bioavailability of imatinib (Glivec) orally versus intravenous infusion. *J Clin Pharmacol* 2004; **44:** 158–62.
2. Peng B, *et al.* Clinical pharmacokinetics of imatinib. *Clin Pharmacokinet* 2005; **44:** 879–94.

Uses and Administration

Imatinib mesilate is a tyrosine kinase inhibitor that inhibits the BCR-ABL tyrosine kinase created by the Philadelphia chromosome abnormality in chronic myeloid leukaemia (p.653) and acute lymphoblastic leukaemia (p.651). It also inhibits the tyrosine kinase for platelet-derived growth factor and stem cell factor, c-kit (CD117), which is overexpressed in gastrointestinal stromal tumours (see Soft-tissue Sarcoma, p.676). Imatinib is also indicated for patients with myelodysplastic syndromes (p.654), hypereosinophilic syndrome, aggressive systemic mastocytosis (p.1138), and dermatofibrosarcoma protuberans. Imatinib is given orally as the mesilate but doses are expressed as the base. Imatinib mesilate 119.5 mg is equivalent to about 100 mg of imatinib.

In the treatment of **chronic myeloid leukaemia**, patients in chronic phase may be given the equivalent of 400 mg of the base daily, increased to 600 mg daily or 400 mg twice daily if required. Patients in blast crisis or accelerated phase are given 600 mg daily, increased to 400 mg twice daily if necessary.

In the treatment of patients with newly diagnosed **acute lymphoblastic leukaemia**, imatinib 600 mg daily may be given with induction, consolidation, or maintenance chemotherapy. The same dose may be given as monotherapy for patients with relapsed or refractory disease.

In the treatment of unresectable or metastatic malignant **gastrointestinal stromal tumours**, doses of 400 or 600 mg daily are recommended.

For patients with **myelodysplastic disease**, the recommended dose of imatinib is 400 mg daily. For **mastocytosis**, 400 mg daily is given, unless there is associated eosinophilia, in which case a starting dose of 100 mg daily is recommended, increased to 400 mg if response is inadequate. Similarly, the recommended dose for **hypereosinophilic syndrome** is 400 mg daily, although a subset of patients with FIP1L1-platelet-derived growth factor receptor-α fusion kinase should be started on 100 mg daily, increased to 400 mg if response is insufficient. Patients with **dermatofibrosarcoma protuberans** may be given 400 mg twice daily.

Doses should be taken with food, and accompanied by plenty of water, to minimise gastric irritation. Dose adjustments may be necessary if myelosuppression or hepatotoxicity occurs; blood counts and liver function should be regularly monitored (see Administration in Hepatic Impairment, below).

Doses of imatinib should be increased by 50%, and clinical response should be carefully monitored, in patients given potent CYP3A4 inducers such as rifampicin or phenytoin. For children's doses, see Administration in Children, below.

Administration in children. In the UK, the licensed dose of imatinib for children with chronic myeloid leukaemia (CML) is 340 mg/m^2 daily, for those in chronic or advanced phase; a total dose of 800 mg should not be exceeded. The dose may be increased to 570 mg/m^2 daily (maximum total dose 800 mg) in children with disease progression, with unsatisfactory haematological response after at least 3 months of treatment, with no cytogenetic response after 12 months of treatment, or with loss of a previously achieved haematological or cytogenetic response.

In the USA, the recommended dose of imatinib is 340 mg/m^2 daily in children with newly diagnosed CML; the dose should not exceed 600 mg. For children with chronic phase CML recurring after stem cell transplantation or who are resistant to interferon alfa therapy, the recommended dose of imatinib is 260 mg/m^2 daily.

Treatment can be given as a once-daily dose, or split into morning and evening doses. There is no experience with the use of imatinib in children under 2 years of age.

Administration in hepatic impairment. Imatinib is metabolised in the liver. Licensed product information in the UK recommends that patients with mild, moderate, or severe liver impairment should be given the minimum recommended dose of 400 mg daily. In the USA, patients with mild and moderate impairment should be given initial doses of 400 mg daily, but in those with severe hepatic impairment, 300 mg daily is recommended. In both countries, degrees of hepatic impairment are defined as:

- mild: total bilirubin equal to 1.5 times the upper limit of normal (ULN); aspartate aminotransferase (AST/SGOT) greater than ULN. AST/SGOT can be normal or less than ULN if the total bilirubin is greater than ULN
- moderate: total bilirubin greater than 1.5 to 3 times the ULN
- severe: total bilirubin greater than 3 to 10 times the ULN

If, during treatment, elevations in bilirubin greater than 3 times the ULN or in liver transaminases greater than 5 times the ULN occur, imatinib should be withheld until bilirubin levels have returned to less than 1.5 times the ULN and transaminase levels to less than 2.5 times the ULN. Treatment may then be continued at a reduced daily dose. In adults the dose is reduced from 800 mg to 600 mg, from 600 mg to 400 mg, and from 400 mg to 300 mg. In children, the dose should be reduced from 340 mg/m^2 daily to 260 mg/m^2 daily, or from 260 mg/m^2 daily to 200 mg/m^2 daily.

Hypereosinophilic syndrome. Imatinib has been reported to produce clinical responses in patients with the hypereosinophilic syndrome (HES).[1-4] Some reports suggest that imatinib also has activity in mast-cell disease, even in the absence of associated eosinophilia.[5] However, not all patients with HES respond to imatinib.[4] Many patients with the myelodysplastic variant of HES express a novel kinase derived from an abnormal fusion of platelet-derived growth factor receptor-α gene with a neighbouring gene, FIP1L1. Almost all patients with this FIP1L1-platelet-derived growth factor receptor-α fusion kinase will respond to imatinib, but a subset of patients with HES without known imatinib targets have also been reported to respond to the drug.[6,7]

1. Gleich GJ, *et al.* Treatment of hypereosinophilic syndrome with imatinib mesilate. *Lancet* 2002; **359:** 1577–8.
2. Cools J, *et al.* A tyrosine kinase created by fusion of the PDGFRA and FIP1L1 genes as a therapeutic target of imatinib in idiopathic hypereosinophilic syndrome. *N Engl J Med* 2003; **348:** 1201–14.
3. Koury MJ, *et al.* Reversal of hypereosinophilic syndrome and lymphomatoid papulosis with mepolizumab and imatinib. *Am J Med* 2003; **115:** 587–9.
4. Payne SM, Kovacs MJ. Imatinib mesylate treatment in two patients with idiopathic hypereosinophilic syndrome. *Ann Pharmacother* 2004; **38:** 1215–18.
5. Pardanani A, *et al.* Imatinib for systemic mast-cell disease. *Lancet* 2003; **362:** 535–7.
6. Müller AMS, *et al.* Imatinib mesylate as a novel treatment option for hypereosinophilic syndrome: two case reports and a comprehensive review of the literature. *Ann Hematol* 2006; **85:** 1–16.
7. Antoniu SA. Imatinib mesylate for the treatment of hypereosinophilic syndromes. *Curr Opin Investig Drugs* 2006; **7:** 980–4.

Malignant Neoplasms. References.

1. Druker BJ, *et al.* Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. *N Engl J Med* 2001; **344:** 1031–7.
2. Druker BJ, *et al.* Activity of a specific inhibitor of the BCR-ABL tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome. *N Engl J Med* 2001; **344:** 1038–42.
3. Joensuu H, *et al.* Effect of the tyrosine kinase inhibitor STI571 in a patient with a metastatic gastrointestinal stromal tumor. *N Engl J Med* 2001; **344:** 1052–6.
4. Demetri GD, *et al.* Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N Engl J Med* 2002; **347:** 472–80.
5. Kantarjian HM, *et al.* Dose escalation of imatinib mesylate can overcome resistance to standard-dose therapy in patients with chronic myelogenous leukemia. *Blood* 2003; **101:** 473–5.
6. Peggs K, Mackinnon S. Imatinib mesylate—the new gold standard for treatment of chronic myeloid leukemia. *N Engl J Med* 2003; **348:** 1048–50.
7. Deininger MW, *et al.* Practical management of patients with chronic myeloid leukemia receiving imatinib. *J Clin Oncol* 2003; **21:** 1637–47.
8. Druker BJ. Imatinib mesylate in the treatment of chronic myeloid leukaemia. *Expert Opin Pharmacother* 2003; **4**: 963–71.
9. Borthakur G, Cortes JE. Imatinib mesylate in the treatment of chronic myelogenous leukemia. *Int J Hematol* 2004; **79:** 411–19.
10. Hochhaus A, La Rosee P. Imatinib therapy in chronic myelogenous leukemia: strategies to avoid and overcome resistance. *Leukemia* 2004; **18:** 1321–31.
11. Verweij J, *et al.* Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. *Lancet* 2004; **364:** 1127–34.
12. Deininger MWN, Druker BJ. Specific targeted therapy of chronic myelogenous leukemia with imatinib. *Pharmacol Rev* 2003; **55:** 401–23.
13. Deininger M, *et al.* The development of imatinib as a therapeutic agent for chronic myeloid leukemia. *Blood* 2005; **105:** 2640–53.
14. Kantarjian HM, *et al.* New insights into the pathophysiology of chronic myeloid leukemia and imatinib resistance. *Ann Intern Med* 2006; **145:** 913–23.
15. Moen MD, *et al.* Imatinib: a review of its use in chronic myeloid leukaemia. *Drugs* 2007; **67:** 299–320.
16. Siddiqui MAA, Scott LJ. Imatinib: a review of its use in the management of gastrointestinal stromal tumours. *Drugs* 2007; **67:** 805–20.
17. Cross SA, Lyseng-Williamson KA. Imatinib: in relapsed or refractory Philadelphia chromosome-positive acute lymphoblastic leukaemia. *Drugs* 2007; **67:** 2645–54.

Pulmonary hypertension. Imatinib has produced beneficial responses in patients with pulmonary arterial hypertension (p.1179) and may have a role, particularly in patients who fail to respond to other therapies.[1-3]

1. Ghofrani HA, *et al.* Imatinib for the treatment of pulmonary arterial hypertension. *N Engl J Med* 2005; **353:** 1412–13.
2. Patterson KC, *et al.* Imatinib mesylate in the treatment of refractory idiopathic pulmonary arterial hypertension. *Ann Intern Med* 2006; **145:** 152–3.
3. Souza R, *et al.* Long term imatinib treatment in pulmonary arterial hypertension. *Thorax* 2006; **61:** 736.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Glivec; Ziatir; ***Austral.:*** Glivec; ***Belg.:*** Glivec; ***Braz.:*** Glivec; ***Canad.:*** Gleevec; ***Chile:*** Glivec; ***Cz.:*** Glivec; ***Denm.:*** Glivec; ***Fin.:*** Glivec; ***Fr.:*** Glivec; ***Ger.:*** Glivec; ***Gr.:*** Glivec; ***Hong Kong:*** Glivec; ***Hung.:*** Glivec; ***India:*** Imatib; Zoleta; ***Indon.:*** Glivec; ***Irl.:*** Glivec; ***Israel:*** Glivec; ***Ital.:*** Glivec; ***Jpn:*** Glivec; ***Malaysia:*** Glivec; ***Mex.:*** Glivec; ***Neth.:*** Glivec; ***Norw.:*** Glivec; ***NZ:*** Glivec; ***Philipp.:*** Glivec; ***Pol.:*** Glivec; ***Port.:*** Glivec; ***Rus.:*** Glivec (Гливек); ***S.Afr.:*** Gleevec; ***Singapore:*** Glivec; ***Spain:*** Glivec; ***Swed.:*** Glivec; ***Switz.:*** Glivec; ***Thai.:*** Glivec; ***Turk.:*** Glivec; ***UK:*** Glivec; ***USA:*** Gleevec; ***Venez.:*** Glivec.

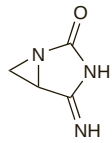
Imexon *(rINN)*

BM-06002; Imexón; Imexonum. (5*R*,*S*)-4-Amino-1,3-diazabicyclo[3.1.0]hex-3-en-2-one.

Имексон

$C_4H_5N_3O$ = 111.1.

CAS — 59643-91-3.



Profile

Imexon is a cyanoaziridine compound that appears to act as an antineoplastic in several ways, one of which is by causing mitochondrial disruption in the cancer cell, thus inducing apoptosis. It is under investigation for the treatment of malignant neoplasms, including ovarian cancer, pancreatic adenocarcinoma, multiple myeloma, and metastatic malignant melanoma.

Interleukin-2

BG-8301 (teceleukin); Epidermal Thymocyte Activating Factor; ETAF; IL-2; Interleucina 2; T-cell Growth Factor.

Description. Interleukin-2 is a naturally-occurring 133-amino-acid glycoprotein with a molecular weight of about 15 000. It is available from natural sources or as a product of recombinant DNA technology (rIL-2).

In addition to aldesleukin (below) modified forms of interleukin-2 produced by recombinant DNA technology have included celmoleukin and teceleukin.

Aldesleukin *(BAN, USAN, rINN)*

Aldesleukiini; Aldesleukina; Aldesleukine; Aldesleukinum; Aldeslökin; Des-alanyl-1, Serine-125 Human Interleukin-2; Recombinant Interleukin-2; 125-L-Serine-2–133-interleukin 2 (human reduced).

Альдеслейкин

CAS — 110942-02-4.

ATC — L03AC01.

ATC Vet — QL03AC01.

Description. Aldesleukin (modified human recombinant interleukin-2) is produced by recombinant DNA technology using an *Escherichia coli* strain containing an analogue of the human interleukin-2 gene. It differs from native interleukin-2 in that it is not glycosylated, it has no N-terminal alanine, and it has serine substituted for cysteine at position 125.

Incompatibility. Aldesleukin 33 800 units/mL in glucose 5% lost significant biological activity when mixed with other drugs including ganciclovir sodium, lorazepam, pentamidine isetionate, prochlorperazine edisilate, and promethazine hydrochloride.[1] However, the incompatibility was not detectable by spectrophotometric methods and only lorazepam was visually incompatible, suggesting that these methods may be invalid for assessing the compatibility of proteins.

1. Alex S, *et al.* Compatibility and activity of aldesleukin (recombinant interleukin-2) in presence of selected drugs during simulated Y-site administration: evaluation of three methods. *Am J Health-Syst Pharm* 1995; **52:** 2423–6.

Stability. Aldesleukin lost 75 to 100% of activity when reconstituted with glucose 5% or sodium chloride 0.9% in a plastic syringe and given over 24 hours with a syringe driver.[1,2] Loss of activity was not seen if aldesleukin was reconstituted with water alone[2] or with the addition of albumin.[1,2] It was suggested that loss of activity could be suspected because of lack of toxicity,[1,2] and that the lack of toxicity in some published studies could be due to this.[1,3] However, the authors of these studies indicated that they had reconstituted aldesleukin with albumin.[4,5] Reconstitution with low concentrations of albumin has been advocated to avoid bioavailability problems,[1,4,6] but is not recommended for currently licensed preparations. Vials of aldesleukin are reconstituted with water for injection.

However, UK licensed product information allows for further dilution of reconstituted aldesleukin with up to 500 mL of glucose 5%, containing human albumin 0.1%, when infused over a 24-hour period; the albumin should be added and mixed with the glucose before addition of the reconstituted aldesleukin.

For short intravenous infusion, the US licensed product information indicates that dilution in glucose 5% outside of a specified range (below 30 micrograms/mL and above 70 micrograms/mL) results in increased variability in drug delivery.

Reconstitution or dilution of aldesleukin preparations with sodium chloride 0.9% is not recommended because increased aggregation occurs.

1. Miles DW, *et al.* Reconstitution of interleukin 2 with albumin for infusion. *Lancet* 1990; **335:** 1602–3.
2. Vlasveld LT, *et al.* Reconstitution of interleukin-2. *Lancet* 1990; **336:** 446.
3. Miles DW, *et al.* Toxicity and reconstitution of recombinant interleukin-2 with albumin. *Lancet* 1991; **338:** 1464.
4. Franks CR. Reconstitution of interleukin-2. *Lancet* 1990; **336:** 445–6.
5. Hamblin T. Reconstitution of interleukin-2 with albumin for infusion. *Lancet* 1990; **336:** 251.
6. Lamers CHJ, *et al.* Bioavailability of interleukin-2 after reconstitution with albumin. *Lancet* 1992; **340:** 241.

Units

100 units of human interleukin-2 are contained in one ampoule of the first International Standard Preparation (1987). The activity of interleukin-2 has also been expressed in Nutley and Cetus units: 100 international units is reportedly equivalent to about 83.3 Nutley units and to about 16.7 Cetus units. US licensed product information states that 18 million international units of aldesleukin are equivalent to 1.1 mg of protein.

Adverse Effects and Treatment

Toxicity is related to dose and route and is often severe; fatalities have been recorded. Decreased vascular resistance and increased capillary permeability (the 'capillary leak syndrome') is common in patients given aldesleukin, and results in hypotension, reduced organ perfusion, and oedema. The incidence and severity of this syndrome is lower after subcutaneous than intravenous dosage. Fluid replacement may be necessary to treat the resultant hypovolaemia and dopamine or other pressor agents may be needed to help maintain organ perfusion. Capillary leak syndrome may also be associated with cardiac effects including tachycardia, angina, myocardial infarction; respiratory effects such as dyspnoea, pulmonary oedema, and respiratory failure; renal abnormalities including uraemia and oliguria or anuria; mental status changes including irritability, depression, confusion, and drowsiness. Therapy should be stopped if patients develop severe lethargy or somnolence, as continuing may result in coma. Raised liver enzymes, gastrointestinal disturbances, fever and flu-like symptoms (malaise, rigors, chills, arthralgia, and myalgia), rashes, pruritus, anaemia, leucopenia, and thrombocytopenia, are also relatively common. Paracetamol (but not NSAIDs, see Effects on the Kidneys, below) may be used prophylactically for fever. Pethidine may be used to control rigors. Antiemetics and antidiarrhoeals may also be required. Antihistamines may benefit some patients with pruritic rash. Injection site reactions are common after subcutaneous doses; necrosis has occurred. Aldesleukin therapy is associated with impaired neutrophil function, and an increased risk of bacterial infections (see below), including sepsis and bacterial endocarditis; this has been reported mainly after intravenous use, and antibacterial prophylaxis may be necessary.

◊ References.

1. Sundin DJ, Wolin MJ. Toxicity management in patients receiving low-dose aldesleukin therapy. *Ann Pharmacother* 1998; **32:** 1344–52.
2. Schwartzentruber DJ. Guidelines for the safe administration of high-dose interleukin-2. *J Immunother* 2001; **24:** 287–93.
3. Dutcher J, *et al.* Kidney cancer: the Cytokine Working Group experience (1986-2001): part II: management of IL-2 toxicity and studies with other cytokines. *Med Oncol* 2001; **18:** 209–19.
4. Schwartz RN, *et al.* Managing toxicities of high-dose interleukin-2. *Oncology (Huntingt)* 2002; **16** (suppl 13): 11–20.

Bacterial infections. The incidence of sepsis and bacteraemia is increased in patients receiving interleukin-2 via intravenous catheters,[1,2] and possibly subcutaneously,[3] although others have not found this to be the case.[4,5] The increased incidence of non-opportunistic bacterial infection may be a particular problem in patients with AIDS who are treated with interleukin-2.[6] The mechanism is uncertain, but may be related to impairment of neutrophil function by the cytokine.[7]

1. Snydman DR, *et al.* Nosocomial sepsis associated with interleukin-2. *Ann Intern Med* 1990; **112:** 102–7.
2. Shiloni E, *et al.* Interleukin-2 therapy, central venous catheters, and nosocomial sepsis. *Ann Intern Med* 1990; **112:** 882–3.
3. Jones AL, *et al.* Infectious complications of subcutaneous interleukin-2 and interferon-alpha. *Lancet* 1992; **339:** 181–2.
4. Buter J, *et al.* Infection after subcutaneous interleukin-2. *Lancet* 1992; **339:** 552.
5. Schomburg AG, *et al.* Cytokines and infection in cancer patients. *Lancet* 1992; **339:** 1061.
6. Murphy PM, *et al.* Marked disparity in incidence of bacterial infections in patients with the acquired immunodeficiency syndrome receiving interleukin-2 or interferon-γ. *Ann Intern Med* 1988; **108:** 36–41.
7. Klempner MS, *et al.* An acquired chemotactic defect in neutrophils from patients receiving interleukin-2 immunotherapy. *N Engl J Med* 1990; **322:** 959–65.

Effects on endocrine function. It has been suggested that patients with adrenal metastases may be particularly susceptible to adrenal haemorrhage and consequent failure during interleukin therapy.[1] Results also suggested that lack of endogenous steroid production may increase the risk of early severe interleukin-2 toxicity.[1]

Effects on thyroid function have also been reported, with the development of hypothyroidism[2-4] and goitre.[3]

1. VanderMolen LA, *et al.* Adrenal insufficiency and interleukin-2 therapy. *Ann Intern Med* 1989; **111:** 185.
2. Atkins MB, *et al.* Hypothyroidism after treatment with interleukin-2 and lymphokine-activated killer cells. *N Engl J Med* 1988; **318:** 1557–63.
3. van Liessum PA, *et al.* Hypothyroidism and goitre during interleukin-2 therapy without LAK cells. *Lancet* 1989; **i:** 224.
4. Sauter NP, *et al.* Transient thyrotoxicosis and persistent hypothyroidism due to acute autoimmune thyroiditis after interleukin-2 and interferon-α therapy for metastatic carcinoma: a case report. *Am J Med* 1992; **92:** 441–4.

Effects on the kidneys. Intravenous aldesleukin therapy was associated with varying degrees of acute renal dysfunction in almost all of 99 adult patients.[1] The clinical syndrome of hypotension, oliguria, fluid retention, and associated azotaemia with intense tubular avidity for filtered sodium all support prerenal acute renal failure as the cause of renal dysfunction. However, renal function values returned to baseline levels within 7 days in 62% of patients and in 95% by 30 days. Patients with elevated pretreatment serum-creatinine values, particularly those aged over 60 years, and those who had previously undergone a nephrectomy, were at risk of more severe and prolonged changes in renal function, and might be particularly vulnerable to the use of indometacin for associated fever and chills, which could potentiate renal impairment through its effects on intrarenal prostaglandin production. Similar effects were noted in a study[2] of 15 children given continuous infusion of aldesleukin. A further study[3] of the renal haemodynamic effects of aldesleukin infusion found it to have a specific renal vasoconstrictor effect; changes in renal prostaglandin synthesis contributed to the decreased renal blood flow.

1. Belldegrun A, *et al.* Effects of interleukin-2 on renal function in patients receiving immunotherapy for advanced cancer. *Ann Intern Med* 1987; **106:** 817–22.
2. Cochat P, *et al.* Renal effects of continuous infusion of recombinant interleukin-2 in children. *Pediatr Nephrol* 1991; **5:** 33–7.
3. Geertsen PF, *et al.* Renal haemodynamics, sodium and water reabsorption during continuous intravenous infusion of recombinant interleukin-2. *Clin Sci* 1998; **95:** 73–81.

Effects on the skin. Pseudosystemic sclerosis has been reported after use of aldesleukin; a reduction in skin thickening was seen after aldesleukin therapy was stopped and corticosteroids started.[1]

1. Marie I, *et al.* Pseudosystemic sclerosis as a complication of recombinant human interleukin 2 (aldesleukin) therapy. *Br J Dermatol* 2007; **156:** 182–3.

Precautions

Aldesleukin should be given with great care, if at all, to patients with pre-existing cardiac or pulmonary disease, and those with severe renal or hepatic impairment. It should be avoided in patients with CNS metastases or seizure disorders.

Risk factors for toxicity and poor response include restricted physical activity (Eastern Cooperative Oncology Group performance status of 1 or greater), 2 or more metastatic sites, and a period of less than 24 months between diagnosis of primary tumour and consideration for aldesleukin therapy. UK licensed product information states that aldesleukin should not be used to treat metastatic renal cell carcinoma in patients with all three of these risk factors.

Aldesleukin may worsen auto-immune diseases, and should be used with caution in patients with these conditions. Bacterial infections should be adequately treated before beginning therapy. Aldesleukin may increase effusions from serosal surfaces, and these should generally be treated before starting aldesleukin therapy.

Vital signs, blood counts, renal and hepatic function, serum electrolytes, and pulmonary and cardiac function should be monitored before starting treatment and then regularly during therapy.

Activity. For mention of the loss of activity when aldesleukin was given by continuous infusion without albumin, see Stability above.