otherwise interfere with the drug's therapeutic action. To be effective, tenecteplase, like the other clot busters, must be used within the first hours of a heart attack.

Tyrosine Kinase Inhibitor

The Philadelphia (Ph) chromosome, a truncated chromosome 22, was the first consistent chromosomal abnormality identified in human malignancy (27). Improved chromosome banding techniques demonstrated that this chromosome was the result of a reciprocal translocation between the long arms of chromosomes 9 and 22. The molecular consequences cause the fusion of the c-Abl oncogene (chromosome 9) and the Bcr sequence (chromosome 22) into the Bcr-Abl gene. This fusion catalyzes the phosphorylation of tyrosine residues from adenosine triphosphate (ATP). Ultimately, this activates several other multiple signaling pathways that affect cell growth, adhesion, and proliferation.

The size of the protein generated by this fusion gene depends on the breakpoint in the Bcr region. For example, 95% of patients with chronic myelogenous leukemia (CML) and up to approximately 20% of adult patients with ALL will demonstrate a 210-kDa fusion protein. Alternatively, a 185-kDa fusion protein is observed in 10% of adult patients with ALL and is the predominant Bcr-Abl fusion protein in Ph chromosome–positive children with ALL. The product of this fusion gene is a constitutively active tyrosine kinase with markedly enzymatic activity when compared to the Abl kinase. Because all of these events (cell growth, adhesion, proliferation) depend on the increased tyrosine kinase activity of the fusion protein, it is apparent that inhibition of the enzymatic activity of Bcr-Abl would be an effective treatment of CML. Bcr-Abl is present in most patients with CML, and the causative abnormality of the disease and its kinase activity are central for transformation.

Imatinib Mesylate (Gleevec)

Imatinib mesylate demonstrates potent and selective inhibitory activity in vivo against Abl tyrosine kinases, such as Bcr-Abl, through competitive inhibition at the ATP-binding site (28) (Fig. 19.17). It does so without any significant effect on normal cells or other cells affected by the tyrosine oncogenes. Phase I clinical trials of the drug (as ST1571) conducted in June 1998 demonstrated significant activity against CML even in patients who were interferon refractory. A significant finding was that the drug is most advantageous when used early in the disease, in the chronic phase. Thus, some experts have proposed a treatment algorithm that calls for all CML patients to receive imatinib while transplantation is being evaluated. In patients whose condition responded to imatinib and for whom the risk of death from transplantation is higher (all except the youngest patients with sibling donors), the procedure could be withheld or deferred.

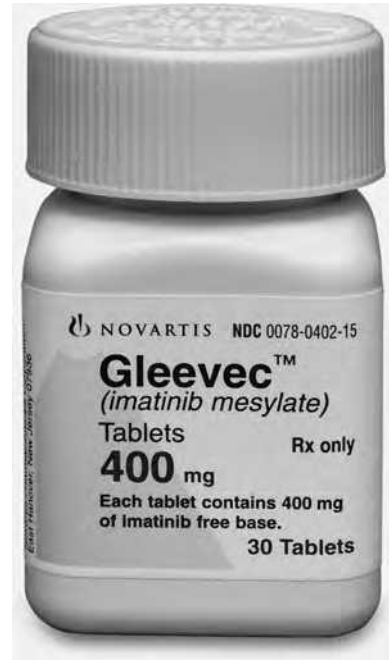

FIGURE 19.17 The product package of Gleevec. (Courtesy of Novartis, Inc.)

The chronic phase dosage is 400 to 600 mg daily. The accelerated phase or blast crisis dosage ranges from 600 to 800 mg daily. The patient should be instructed to take this medication with food and a large glass of water because of mild gastrointestinal effects. Serum concentrations of imatinib are affected by medications that inhibit or induce the CYP 3A4 enzyme. Other common adverse effects