Use in other populations

There are no reports of different clinical efficacy of generic imatinib vs. Gleevec in children with CML or patients with GIST.

Imatinib absorption is not significantly different in children.16 Once absorbed, the area under the curve (AUC) in children is within the range as in adults (29.4-34.6 mcg/h/mL vs. 24.8-39.7 mcg/h/mL).

Imatinib absorption is similar between patients with GIST vs. CML.20,21 Reduced absorption was reported in two CML forms after gastric bypass and gastrectomy.22,23 Response was maintained in one patient20 but not the other.23 Animal data suggest that absorption occurs mostly in the ileum, followed by duodenum, colon and jejunum.24

Solubility of imatinib is pH-dependent, optimally at pH 5.8.25 In clinical studies, however, imatinib absorption is not significantly affected by concurrent use of antacids22 or proton pump inhibitors.23

Role of different crystal forms

There are no reports of different clinical efficacy related to polymorphism of the imatinib. The Novartis application to the Indian Patent Office apparently did not claim any clinical difference between the crystal forms.19

Beta-crystal26 is more stable than the alpha-crystal27 at room temperature.19 This is relevant if it affects the stability, dissolution and bioavailability of a product.19 However, the European Medicines Agency found both crystal forms to be highly soluble and would not significantly influence the performance of generic imatinib.28 There are no data to suggest that the pH-dependent solubility of imatinib affects the crystal forms differently.27

Bioequivalence data

Generic imatinib approved by Health Canada and the European Medicines Agency have been shown to be bioequivalent to Gleevec with similar imatinib level and exposure (AUC) after oral ingestion.1,5 Imatinib, the most commonly used generic product in the clinical reports,7,8,10,11 was claimed to be bioequivalent to Gleevec by its manufacturer Cipla,14 although no details have been provided.14,15 No bioequivalence data were found with other generic imatinib used in these reports.

Discussion

There have been no reports of different clinical efficacy related to generic imatinib approved by Health Canada and the European Medicines Agency. These products have been shown to be bioequivalent to Gleevec. Therefore, their pharmacological effect is expected to be similar to Gleevec. Anecdotal concerns regarding these generic imatinib products appear to be unfounded.

Reduced efficacy was only seen with other versions of generic imatinib.10,25 Several of which were reported by single authors.19,25 Contradictory results with the same generic product were reported in two larger case series (90% response vs. 33% relapse).20,21 Some of these results could be due to lack of bioequivalence, given that approval of generics require only in vitro dissolution tests in some countries.12,13

Polymorphism has not been found to be a significant factor because both crystal forms are highly soluble.19,25 This is reflected by the equivalent serum imatinib levels established with generic imatinib vs. Gleevec.10,15 Hence, the pharmacologic effect is expected to be similar with either product. An analogy is the dissolution of the same amount of granulated sugar vs. sugar cube in water. Once dissolved, either product would give the same amount of glucose in solution. Hypoglycemia should respond similarly to either sugar product.

Since absorption is similar in children15 and in patients with GIST compared to adult patients with CML,20,21 similar serum level and pharmacologic effect can be expected based on bioequivalence established with generic imatinib in adult patients with CML. The impact of gastrectomy and gastric acidity in patients with GIST also appear to be limited. Any reduced absorption due to gastrectomy25,26 would apply equally to Gleevec and generic imatinib with bioequivalence established. There is no evidence that any change in gastric acidity would differentially affect dissolution of alpha- vs. beta-crystal forms, particularly since imatinib absorption seems to be independent of gastric acidity.22,23

Conclusion

There is no evidence that generic imatinib approved by Health Canada and the European Medicines Agency is less effective than Gleevec. Bioequivalence has been established and no other pharmacological differences seem likely to contribute to different pharmacological effect.

## References