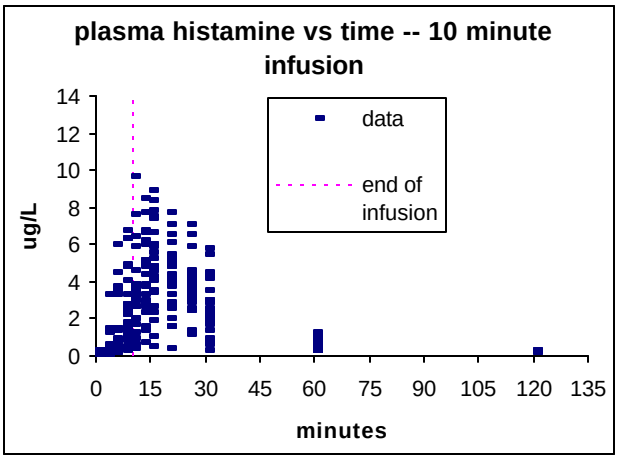
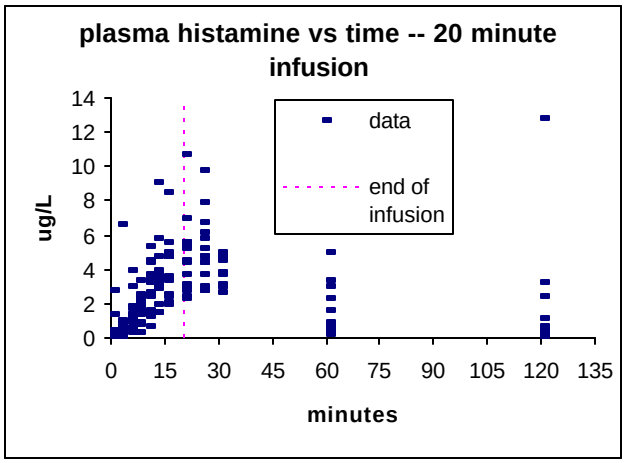
Report to the Oncologic Drugs Advisory Committee for NDA 21-240:
Pharmacokinetics of histamine following subcutaneous administration
Prepared by the Office of Clinical Pharmacology and Biopharmaceutics

Excluding studies in individuals with renal and hepatic impairment, plasma concentration-time data was collected from 37 individuals (approximately 11 samples/individual):

- Study MM-2: 3 patients received 1 mg administered subcutaneously over 10 minutes
- Study MP-MA-403: 21 healthy volunteers received 1 mg administered subcutaneously over 10 minutes
- Study MP-MA-103: 13 patients received 1 mg administered subcutaneously over 20 minutes.

Only 1 of these 37 individuals was sampled on more than one occasion: 1 of the 3 patients receiving 1 mg over 10 minutes was sampled following 2 dosing events separated by several days. The data from these 37 individuals is graphed below.





Histamine is rapidly absorbed: histamine concentrations begin to increase almost immediately after infusion is initiated. The conclusion of rapid absorption is confirmed by the time to maximal plasma concentration (Tmax): Tmax occurs very shortly after infusion is stopped:

Tmax (minutes post end-of-infusion)		
MEAN	**STDEV**	**RANGE**
5.7	8.4	-17.5 - 40

Relative to end-of-infusion, Tmax did not differ between the 2 infusion rates.

Histamine is also rapidly eliminated: as can be seen in the graphs, concentrations approached endogenous levels within 2 hours post-infusion. This rapid time course predicts that no accumulation is occurring when BID doses are reasonably well separated (6 hrs or more).