Questions to the Committee

December 13, 2000

NDA 21-240 **histamine hydrochloride injection (1 mg/ml)**
Maxim Pharmaceuticals, Inc.

Indication: adjunctive use with interleukin-2 (aldesleukin) in the treatment of adult patients with advanced metastatic melanoma that has metastasized to the liver

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Study MP-US-M01 is a randomized multi-center, open-labeled study designed to demonstrate the added benefit of histamine to IL-2 in the treatment of metastatic melanoma. 305 patients were enrolled in the study. There was no stratified randomization based on prognostic factors. The primary efficacy endpoint is survival. The applicant is seeking the following indication based on efficacy results in a subgroup of 129 patients with liver metastases in study MP-US-M01:

Histamine dihydrochloride is indicated for adjunctive use with interleukin-2 in the treatment of adult patients with advanced metastatic melanoma that has metastasized to the liver.

The following table summarizes the FDA's analysis of efficacy (based on the updated survival 9/8/00 cut-off) from study MP-US-M01:

	ITT IL-2 (N=153)	ITT H/IL-2 (N=152)	LM Subgroup* IL-2 (N=74)	LM Subgroup* IL-2 (N=55)	Non LM Subgroup** IL-2 (N=79)	Non LM Subgroup** H/IL-2 (N=97)
Survival (Months)						
Median	8.0	8.9	5.0	9.2	10.3	8.7
95% CI	(6.0, 9.2)	(6.9, 10.4)	(3.9, 6.7)	(6.4, 12.7)	(8.6, 12.3)	(6.6, 10.4)
p-value	0.0526		0.0033		0.7808	
Response Rate	3%	3%	0%	4%	5%	2%
TTP (FDA, Month)						
	2.7	2.7	2.6	2.7	2.7	2.7
95% CI	(2.6, 2.7)	(2.7, 2.8)	(2.5, 2.7)	(2.6, 2.8)	(2.6, 2.8)	(2.6, 2.8)
p-value	0.4108		0.1315		0.9075	

*Patient subgroup with liver metastases at study entry
** Patient subgroup without liver metastases at study entry

The following table summarizes the FDA's analysis of safety from study MP-US-M01:

	ITT IL-2 (N=153)	ITT H/IL-2 (N=152)	LM Subgrp* IL-2 (N=74)	LM Subgrp* H/IL-2 (N=55)
Withdrawal**	143	140	71	51
Death	3	3	0	2
Progression	109	110	56	38
AE	20	16	10	6
Death within 30 days of study med	16 (10%)	17 (11%)	10 (14%)	10 (18%)
Grade 4 toxicity	8 (5%)	10 (7%)	1 (1%)	4 (7%)
Grade 3 toxicity	90 (59%)	79 (52%)	49 (66%)	31 (56%)

**Reasons for withdrawal as per the applicant

Metastatic melanoma is known to have a variable clinical course influenced by prognostic factors. There were many imbalances in known prognostic factors and other patient characteristics between the two treatment arms in the subgroup of patients with liver metastases, perhaps because there was no stratified randomization. These included performance status, albumin, disease-free interval, and number of metastatic sites. These imbalances consistently favored the histamine/IL-2 arm. When the data are adjusted for imbalances, the result becomes less favorable, losing statistical significance. The statistically strong effect seen in the unadjusted analysis appears to be in part the result of baseline imbalances.

Questions to the Committee

1. Does the survival difference in the planned primary analysis of this single study, the ITT analysis, represent substantial evidence of the efficacy of histamine dihydrochloride as an adjunctive treatment with IL-2 for patients with metastatic melanoma?

2. Does the survival difference observed in the subgroup of patients with liver metastases in this single study represent substantial evidence of the efficacy of histamine dihydrochloride as an adjunctive treatment with IL-2 for patients with melanoma that has metastasized to the liver?

3. If you have concluded that efficacy has been shown, is the safety of the histamine/IL-2 combination acceptable for patients with metastatic melanoma?

4. In view of the efficacy and safety data presented, should histamine dihydrochloride be approved for adjunctive use with IL-2 in the treatment of patients with metastatic melanoma?

5. In view of the efficacy and safety data presented, should histamine dihydrochloride be approved for adjunctive use with IL-2 in the treatment of patients with melanoma that has metastasized to the liver?