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RESEARCH**

APPLICATION NUMBER:
50-807

MEDICAL REVIEW(S)

Division of Oncology Drug Products

NDA Efficacy and Safety Update/ Labeling Supplement
Submission Number 50807
Submission Code

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Reviewer Patricia Cortazar, M.D.
Team Leader John R Johnson, M.D.
Review Completion Date July 27, 2006

Proprietary Name: Epirubicin hydrochloride for injection
Therapeutic Class: Anthracycline cytotoxic agent
Applicant: Mayne Pharma (USA), Inc.

Dosing Regimen: 100 to 120 mg/m² by intravenous infusion

Indication: "Epirubicin hydrochloride Injection is indicated as a component of adjuvant therapy in patients with evidence of axillary node tumor involvement following resection of primary breast cancer."

1 Summary

This medical review addresses a proposal by Mayne Pharma (USA) Inc, submitted under 505(b)(2), to approve Epirubicin Hydrochloride injection (NDA 50807). The basis of this 505(b)(2) application is a formulation change to the reference listed drug (RLD) Ellence® (epirubicin hydrochloride injection), approved under NDA 50778 as a component of adjuvant therapy in patients with evidence of axillary node tumor involvement following resection of primary breast cancer.

Mayne's product is a lyophilized formulation requiring reconstitution prior to administration, whereas Ellence® is a ready to use solution. The two products share the same active ingredient (epirubicin hydrochloride), dosage strength from parenteral solution (2 mg/mL when Mayne product reconstituted), route of administration (intravenous), and dosing regimen. Mayne's product differs in inactive ingredients from the RLD; lactose monohydrate, not presented in the RLD formulation, is used as a _____ and RLD inactive ingredients water for injection, sodium chloride and _____ are not contained in the Mayne's formulation.

The differences in the two formulations will not affect bioavailability since they are both administered as intravenous solutions; however the differences in excipients are beyond those considered for a 505(j) generic application. Bioequivalence is not required since the two products are administered intravenously using the same dose regimen.

In this 505(b)(2) submission, Mayne Pharma is basing the approval of Epirubicin Hydrochloride, on the Agency's previously determination of safety and efficacy of Ellence® (epirubicin hydrochloride injection), approved September 15, 1999, under NDA 50778 as a component of adjuvant therapy in patients with evidence of axillary node tumor involvement following resection of primary breast cancer.

There were no additional clinical studies submitted to support this application. The clinical information in the labeling of Mayne's product will be the same as the Ellence® label.

Chemistry deficiencies in the area of impurity profiles and manufacturing controls were resolved satisfactorily through two amendments. All test results met specifications. It was noted that test result for individual unknown impurity is close to the specification limit (NMT _____ from stability studies, this

2 Recommendation on Regulatory Action

Recommendation on Approval: This application is recommended for approval.

Recommendation on Phase 4 Studies: No Phase 4 studies are required.

Recommendation on Risk Management: No special risk management is required.

3 Summary of clinical findings from Ellence®

MA-5

Trial MA-5 was a randomized open label, multicenter study of CEF (epirubicin at 120 mg/m²) versus CMF in node positive pre and perimenopausal breast cancer patients following definitive local surgical treatment. Patients were stratified by nodal status (1-3, 4-10, and >10 positive nodes), type of initial surgery (lumpectomy versus mastectomy), and by hormone receptor status (ER or PR > 10, both < 10, or unknown status). A total of 716 patients were randomized to receive CEF (356) or CMF (360) for a total of six 28-day cycles, in the following doses and schedule:

Arm 1: CEF Cyclophosphamide 75 mg/m² PO D 1-14

Epirubicin 60 mg/m² IV D 1, 8

5-Fluorouracil 500 mg/m² IV D 1, 8

Arm 2: CMF Cyclophosphamide 100 mg/m² PO D 1-14

Methotrexate 40 mg/m² IV D 1, 8

5-Fluorouracil 600 mg/m² IV D 1, 8

The primary endpoint was relapse-free survival (RFS). Secondary endpoints were overall survival (OS), toxicity rate, and quality of life. RFS was measured from the time of randomization to the date of first indication of relapse or disease-related death.

Progression was defined as local, regional, or distant recurrence. Contralateral breast cancer was considered a second primary, not a recurrence.

GFEA-05

Trial GFEA 05 was a randomized open label, Phase III study of FEC 50 versus FEC 100 in women with either 4 or more involved lymph nodes, or with 1-3 involved lymph nodes and tumor grade 2-3 and ER/PR negative, pre and postmenopausal breast cancer patients following definitive local surgical treatment. Patients were stratified by nodal status (1-3, 4-10, and >10 positive nodes). A total of 565 patients were randomized to receive FEC-100 (276) or FEC-50 (289) for a total of six 21-day cycles, in the following doses and schedule:

Arm 1: FEC-100: 5-Fluorouracil 500 mg/m² IV D 1

Epirubicin 100 mg/m² IV D 1

Cyclophosphamide 500 mg/m² PO D 1

Arm 2: FEC-50: 5-Fluorouracil 500 mg/m² IV D 1

Epirubicin 50 mg/m² IV D 1

Cyclophosphamide 500 mg/m² PO D 1

Patients received concomitant 30 mg daily of Tamoxifen for 3 years regardless of receptor status. The primary endpoint was disease-free survival (DFS), defined as the time from randomization to the day of a locoregional and/or distant metastasis. Secondary endpoint was overall survival (OS). Contralateral breast cancer was considered a second primary, not a recurrence. Patients with contralateral breast cancer, second primary malignancy or death from causes other than breast cancer were censored at the time of their last visit.

10 years of follow-up

Relapse Free Survival

In the MA-5 trial, at 10 years of follow-up, a total of 168 (47.2%) of the 356 randomized patients in the CEF treatment group and 201 (55.8%) of the 360 randomized patients in the CMF group relapsed or died of primary tumor related causes. The Kaplan Meier estimates of RFS at 10 years were 51% (95% CI = 45.7-56.4) and 44% (95% CI = 38.7-49.3) in the CEF and CMF groups, respectively. RFS in the ITT showed statistically significant superiority of the CEF regimen over CMF, HR: 0.78 (CI = 0.63 – 0.96) Log-rank p-value=0.017. The overall reduction in risk of relapse was 22% at 10 years. Kaplan Meier estimates of the median RFS were 10.1 (95% CI=7.8 -ne) and 6.5 years (95% 4.9-9.5) for the CEF and CMF arms, respectively, indicating a prolongation of RFS of 3.6 years in favor of CEF. The Table below presents the RFS estimates at 10 years for the ITT population and for the patients subgroups defined based on the pre-defined prognostic factors.

Table 1: Relapse Free-Survival Estimates at 10 Years and 25th Percentile

Variable	CEF			CMF		
	Randomized N (%)	10-year RFS (%)	25 th percentile (95% CI)	Randomized N (%)	10-year RFS (%)	25 th percentile (95% CI)
Total Patients	356 (100)	51	2.6 (2.0-3.5)	360 (100)	44	1.9 (1.7-2.2)
Positive Nodes						
1-3	218 (61)	58	3.9 (2.8-5.7)	218 (61)	55	2.3 (2.0-3.4)
≥4	138 (39)	38	1.8 (1.5-2.4)	142 (39)	26	1.4 (1.2-1.9)
4-10	115 (32)	43	1.9 (1.5-3.1)	118 (33)	29	1.7 (1.4-2.0)
>10	23 (7)	13 ¹	1.2 (0.7-1.9)	24 (7)	13 ¹	0.9 (0.6-1.3)
Surgery						
Partial mastectomy	175 (49)	58	3.4 (2.1-4.9)	176 (49)	51	2.1 (1.8-2.7)
Total mastectomy	181 (51)	44 ²	2.0 (1.8-3.1)	184 (51)	37	1.9 (1.5-2.1)
Receptor Status						
Negative	75 (21)	55 ³	1.5 (1.2-2.6)	70 (19)	48 ²	1.7 (1.3-2.2)
Positive	241 (68)	48	3.0 (2.1-3.8)	245 (68)	41	1.9 (1.7-2.3)
Unknown	40 (11)	45	4.0 (1.4-10.1)	45 (12)	47	3.6 (2.1-8.9)
Menopausal Status						
Perimenopausal	80 (22)	51 ⁴	2.1 (1.6-4.2)	75 (21)	49	2.4 (1.9-4.5)
Premenopausal	276 (78)	51	2.9 (2.0-3.6)	285 (79)	42	1.9 (1.6-2.1)
Tumor size						
T0-T2	311 (87)	52	2.9 (2.0-3.6)	315 (88)	45	2.0 (1.8-2.3)
T3-T4	14 (4)	21 ⁵	1.7 (1.2-3.8)	22 (6)	14	0.8 (0.4-1.9)
Tx or missing	31 (9)	51 ⁶	2.0 (1.5-6.3)	23 (6)	61 ⁶	3.5 (1.6-ne)

In the GFEA-05 trial, in the ITT population the relapse rate at 10-year follow-up was 53.3% (154/289) in the FEC 50 group and 48.6% (134/276) in the FEC 100 group. The Kaplan Meier estimates of RFS rate at 10 years were 43% (95% CI = 37%-49%) in the FEC 50 group and 49% (95% CI = 43%-56%) in the FEC 100 group. These results showed statistically significant longer RFS at 10 years of the FEC 100 regimen over FEC 50 (stratified log-rank test: p= 0.04) with a reduction of the risk of relapse by 22%, as

estimated by the log-rank test. Based on Kaplan Meier estimates, median RFS was prolonged by approximately 41 months. The RFS estimates at 10 years and the corresponding 25th and 50th percentile by the prognostic factors are summarized in Table below. The study was prospectively stratified only by the number of involved lymph nodes.

Table 2: Relapse-free Survival (RFS) Estimates at 10 Years and 25th and 50th Percentiles:ITT population (Sponsor's Table).

	FEC 50				FEC 100			
	No. (%) Pts	RFS at 10 yrs (%)	25th Percentile (95% CI)	50th Percentile (95% CI)	No. (%) Pts	RFS at 10 yrs (%)	25th Percentile (95% CI)	50th Percentile (95% CI)
Total	289 (100)	43	23.3 (20.3-28.2)	72.1 (49.2-114.8)	276 (100)	49	34.8 (26.9-51.1)	113.0 (103.0-139.2)
Positive Nodes §								
1-3	52 (18)	63	70.5 (22.3-ne)	ne	46 (17)	65	45.0 (14.6-ne)	ne
≥4	229 (79)	39	22.5 (17.4-27.1)	56.6 (41.6-87.8)	225 (82)	47	34.8 (26.7-47.8)	110.2 (85.0-125.8)
4-10	180 (62)	43	23.4 (19.1-29.5)	64.4 (46.0-124.9)	176 (64)	50	36.6 (28.7-54.3)	113.0 (96.6-ne)
>10	49 (17)	26	17.4 (5.5-29.2)	35.2 (28.0-56.6)	49 (18)	36	26.7 (16.9-36.8)	70.5 (36.5-121.2)
Surgery §								
Conservative	126 (44)	51	30.5 (24.4-47.3)	124.0 (92.0-ne)	134 (49)	49	40.3 (26.7-67.2)	111.3 (96.6-ne)
Radical	155 (54)	37	19.1 (14.1-23.8)	48.0 (33.2-70.8)	136 (49)	50	28.2 (21.4-42.5)	113.0 (83.4-139.2)
Receptor Status §								
Positive	174 (60)	43	23.8 (20.8-30.6)	72.0 (45.0-ne)	169 (61)	44	36.8 (28.7-54.3)	108.3 (85.0-121.5)
Negative	81 (28)	42	20.4 (12.8-30.9)	66.1 (37.0-ne)	85 (31)	39	26.9 (16.8-45.0)	ne
Menopausal Status §								
Premenopausal	146 (50)	45	24.4 (21.2-31.9)	72.1 (47.4-ne)	127 (46)	49	36.5 (26.7-53.9)	113.0 (74.1-139.2)
Peri-/Postmenopausal	133 (46)	40	21.4 (14.2-29.2)	70.5 (37.6-119.8)	142 (51)	50	34.0 (21.8-54.3)	111.3 (85.7-ne)
Tumor Size §								
T0 T1 T2	210 (73)	46	28.9 (23.3-35.9)	109.8 (61.6-ne)	210 (76)	50	36.5 (27.1-53.8)	121.2 (90.6-ne)
T3 T4	66 (23)	33	12.8 (10.1-21.1)	29.2 (21.2-66.1)	51 (19)	43	26.9 (17.4-42.5)	85.0 (36.6-ne)

§ Patients who were in the subgroup of "unknown" were not included in the analyses and are not reported in this table
ne=not estimable

Survival

In the MA-5 trial, a total of 134 (38%) of the 356 randomized patients in the CEF

treatment group and 153 (42%) of the 360 randomized patients in the CMF group died. The table below presents the overall survival estimates at 10 years for the ITT population and for the patients subgroups defined based on the prognostic factors present at study entry. The Kaplan Meier estimates of overall survival at 10 years were 61% (95% CI= 56.2-66.7%) for the CEF group and 57% (95% CI=51.7-62.2 %) for the CMF group with an estimated HR of 0.82 (CI= 0.65-1.04) (p=0.10) according to the logrank Test. The overall relative reduction in risk of death was 18%.

Table 3: Overall Survival Estimates at 10 Years and 25th Percentile According to Strata or Relevant Prognostic Factors, ITT Population

Variable	CEF			CMF		
	Randomized N (%)	10-year OS (%)	25 th percentile (95% CI)	Randomized N (%)	10-year OS (%)	25th percentile (95% CI)
Total Patients:	351 (100)	62	5.5 (4.4-6.6)	359 (100)	57	3.9 (3.3-5.0)
Positive Nodes						
1-3	215 (61)	68	6.9 (5.5-10.1)	218 (61)	65	5.8 (4.0-7.9)
≥4	136 (39)	49	4.3 (2.9-5.2)	141 (39)	45 ¹	2.9 (2.3-3.8)
4-10	114 (32)	36	4.3 (2.9-6.0)	117 (33)	50 ²	3.5 (2.6-4.6)
>10	22 (6)	14 ²	4.1 (1.7-5.7)	24 (7)	21 ²	1.7 (1.2-2.8)
Surgery						
Partial mastectomy	171 (49)	70 ³	6.6 (5.2-ue)	176 (49)	64 ²	5.1 (3.9-7.6)
Total mastectomy	180 (51)	54	4.6 (3.5-6.0)	183 (51)	50	3.3 (2.7-4.0)
Receptor Status						
Negative	74 (21)	34	3.1 (2.5-5.0)	70 (20)	50	3.0 (2.2-3.5)
Positive	238 (68)	64	6.6 (5.3-7.4)	244 (68)	54	4.0 (3.4-5.3)
Unknown	39 (11)	53 ⁴	4.3 (1.8-8.5)	45 (12)	68	10.9 (5.5-ue)
Menopausal Status						
Perimenopausal	78 (22)	57 ¹	5.1 (2.7-7.4)	74 (21)	58	5.3 (3.5-7.9)
Premenopausal	273 (78)	63	5.5 (4.5-6.9)	285 (79)	56	3.7 (3.1-4.6)
Tumor size						
T0-T2	307 (88)	64 ⁵	5.7 (4.6-7.0)	314 (88)	58	4.0 (3.5-5.5)
T3-T4	14 (4)	21 ⁵	3.2 (2.4-5.7)	22 (6)	27 ⁵	1.6 (1.1-2.9)
Tx or missing	30 (8)	55	5.1 (2.3-10.6)	23 (6)	48	4.8 (3.6-ue)

3 Summary of safety findings from Ellence®

Mortality:

Updated safety results indicate no additional risk for dose-intensive CEF. A total of 133 (38%) out of 354 patients treated with CEF treatment died compared to 153 (42%) of 360 patients treated with CMF during the follow-up of > 10 years. A higher percentage of patients in the CMF group died due to progression of disease after completion of chemotherapy (42% CMF group vs. 34%, in the CEF group).

Second Primary Tumors:

A total of 16 additional cases of second primaries were reported, six in patients receiving CEF and 10 in the CMF group. The most common tumor was contra lateral breast cancer (8 cases) with more cases in the CMF group (6 CMF versus 2 CEF). At 5 years of follow-up, five cases of AML (4 in the CEF group and 1 in the CMF group) and one case of ALL (CEF) were reported in this trial. No new cases of secondary leukemia were

reported with longer follow-up.

GFEA-05

Mortality:

During the 10-year follow-up the overall frequency of death from all causes was greater in the FEC-50-treated patients than in the FEC-100-treated patients: a total of 107 patients (40%) treated with FEC 100 died compared to 135 (48%) treated with FEC 50.

Second Primary Tumors

Second primary cancers were reported at similar frequencies in each treatment group. The most frequent second primary cancer was contralateral breast cancer: its frequency in the FEC 50 group was twice that observed in the FEC 100 group (6.1% versus 3.4%). Other second primary cancers reported occurred with a very low frequency. Twenty-eight of the 49 patients who developed second primaries died at the database cut-off time for this analysis (25 June 2003).

Cardiotoxicity

Cardiac function disorders occurred in each treatment group, in 19 (7.1%) of the 266 patients who were treated with FEC 100 and in 18 (6.4%) of the 280 patients who were treated with FEC 50. Similarly to what was found at 5-years of follow-up, cardiotoxicity events included abnormal ECG findings, decreases in LVEF, and CHF. ECG abnormalities, including left ventricular hypertrophy, right bundle branch block, right fascicular hemiblock, repolarization disorders and tachycardia, were reported in 3.2% (9/280) of the FEC 50-treated patients and in 3.7% (10/266) of the FEC 100-treated patients.

Epirubicin Secondary Leukemia

The occurrence of secondary acute myelogenous leukemia, with or without a preleukemic phase, has been reported in patients treated with anthracyclines. Secondary leukemia is more common when such drugs are given in combination with DNA-damaging antineoplastic agents, when patients have been heavily pretreated with cytotoxic drugs, or when doses of the anthracyclines have been escalated. These leukemias can have a short 1- to 3- year latency period. An analysis of 7110 patients who received adjuvant treatment with epirubicin in controlled clinical trials as a component of poly chemotherapy regimens for early breast cancer, showed a cumulative risk of secondary acute myelogenous leukemia or myelodysplastic syndrome (AML/MDS) of about 0.27% (approximate 95% CI, 0.14-0.40) at 3 years, 0.46% (approximate 95% CI, 0.28-0.65) at 5 years and 0.55% (approximate 95% CI, 0.33-0.78) at 8 years.

The cumulative probability of developing AML/MDS was found to be particularly increased in patients who received more than the maximum recommended cumulative dose of epirubicin (720 mg/m²) or cyclophosphamide (6,300 mg/m²), as shown in the Table below.

Cumulative probability of AML/MDS in relation to cumulative doses of epirubicin and cyclophosphamide

Years from Treatment Start	Cumulative Probability of Developing AML/MDS % (95% CI)			
	Cyclophosphamide Cumulative Dose $\leq 6,300 \text{ mg/m}^2$		Cyclophosphamide Cumulative Dose $> 6,300 \text{ mg/m}^2$	
	Epirubicin Cumulative Dose $\leq 720 \text{ mg/m}^2$ N=4760	Epirubicin Cumulative Dose $> 720 \text{ mg/m}^2$ N=111	Epirubicin Cumulative Dose $\leq 720 \text{ mg/m}^2$ N=890	Epirubicin Cumulative Dose $> 720 \text{ mg/m}^2$ N=261
3	0.12 (0.01-0.22)	0.00 (0.00-0.00)	0.12 (0.00-0.37)	4.37 (1.69-7.05)
5	0.25 (0.08-0.42)	2.38 (0.00-6.99)	0.31 (0.00-0.75)	4.97 (2.06-7.87)
8	0.37 (0.13-0.61)	2.38 (0.00-6.99)	0.31 (0.00-0.75)	4.97 (2.06-7.87)

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