

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

50-807

PHARMACOLOGY REVIEW(S)



DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	50,807
SERIAL NUMBER:	000
DATE RECEIVED BY CENTER:	7/21/2005
PRODUCT:	Epirubicin for Injection
INTENDED CLINICAL POPULATION:	Adjuvant therapy in patients with axillary node positive primary breast cancer
SPONSOR:	Mayne Pharma (USA) Inc.
DOCUMENTS REVIEWED:	Proposed labeling
REVIEW DIVISION:	Division of Drug Oncology Products
PHARM/TOX REVIEWER:	Haleh Saber-Mahloogi, Ph.D.
PHARM/TOX SUPERVISOR:	David E. Morse, Ph.D.
DIVISION DIRECTOR:	Robert Justice, M.D.
PROJECT MANAGER:	Paul Zimmerman, R.Ph.

Date of review submission to Division File System (DFS): 4/19/06

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EXECUTIVE SUMMARY

I. Recommendations

- A. Recommendation on approvability: The application is approvable for the specified indication.
- B. Recommendation for nonclinical studies: There are no outstanding issues. All studies required were previously included in NDA 50-778 for Ellence® (epirubicin hydrochloride for injection).
- C. Recommendations on labeling: The sponsor did not propose to change the Pharmacology/ Toxicology information in the labeling of Ellence®. This information will be identical to that for Ellence®.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

Safety Pharmacology

- Epirubicin had very little effect on mean blood pressure and heart rate, when tested i.v. in rats at doses of 7-14 mg/kg.
- No effect on systemic arterial pressure, heart rate, or respiratory functions was observed when epirubicin was given i.v. to dogs at 2 mg/kg.
- Epirubicin did not affect the renal excretion of water and electrolytes when given i.v. to rats (3-12 mg/kg).
- Epirubicin significantly slowed gastric emptying, when given i.v. to rats at 12 mg/kg.
- Epirubicin, when given i.v. to rats at 1 or 2.5 mg/kg, resulted in anti-anabolic, anti-estrogenic, anti-gonadotrophic, and anti-thyroid activities.

Acute Toxicology

Acute toxicity in mice, dogs, and rats consisted of anorexia, lethargy, and appeared to be dose related. GI toxicity was apparent in dogs.

Chronic Toxicology

Toxicities in the 6-week repeat dose i.v. toxicology studies in rabbits and dogs included: weight loss, bone marrow/hematopoietic depression, GI toxicities including diarrhea, vomiting, and lesions, cardiac injury, lesions in liver, spleen, and kidneys; toxicities to the reproductive organs, hyper-pigmentation, and injection site reactions.

Toxicities in the 13-week repeat dose i.v. toxicology studies in rats and dogs included: anorexia, GI toxicity, alopecia, pigmentation of the skin, hepatotoxicity, nephrotoxicity, cardiotoxicity, hematopoietic depletion, reproductive toxicity.

In general, males appeared to be more susceptible to the toxic effects of epirubicin in the general toxicology studies.

Genetic toxicology and carcinogenicity

Epirubicin was positive for mutagenicity, clastogenicity, and carcinogenicity potentials.

Reproductive toxicology

Epirubicin can reduce the fertility. In addition, epirubicin can cause embryo-fetal toxicities.

B. Pharmacologic activity: Anthracycline/ DNA intercalating/ cytotoxic agent

C. Nonclinical safety issues relevant to clinical use:

Adverse events associated with epirubicin have been well established (see labeling for Ellence®). The following nonclinical findings were also reported in humans:

Cardiac, hematopoietic, GI, and endocrine/reproductive toxicities, cutaneous reactions, injection site reactions, and carcinogenicity (e.g. secondary leukemia).

**APPEARS THIS WAY
ON ORIGINAL**

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 50807

Review number: 1

Sequence number/date/type of submission: 000/ July 21, 2005/ 505(b)2

Information to sponsor: Yes () No (X)

Sponsor and/or agent: Mayne Pharma (USA) Inc.
Mack-Cali Centre II
650 From Road, 2nd Floor
Paramus, NJ 07652

Manufacturer for drug substance

Reviewer name: Haleh Saber-Mahloogi, Ph.D.
Division name: Division of Drug Oncology Products
Review completion date: April 2006

Drug:

Trade name: None

Generic name: epirubicin hydrochloride for injection

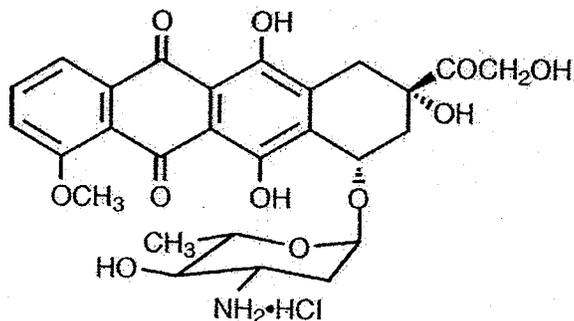
Code name: None

Chemical name: (8S-cis)-10-[(3-amino-2,3,6-trideoxy-(alpha)-L-arabino-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-5,12-naphthacenedione hydrochloride

CAS registry number: 56390-09-1

Molecular formula/molecular weight: C₂₇H₂₉NO₁₁ HCl/ 579.95

Structure:



Relevant INDs/NDAs/DMFs:

NDA # Product	Pharmacology/ Toxicology Reviewer	Date of Review
50-778 Ellence® (approved product)	Dr. Doo Y. Lee Ham	7/14/1999

Drug class: anthracycline/ DNA intercalating agent/ cytotoxic

Intended clinical population: indicated as a component of adjuvant therapy in patients with evidence of axillary node tumor involvement following resection of primary breast cancer

Clinical formulation: supplied as a sterile, orange-red, lyophilized powder in single-dose vials containing 50 mg or 200 mg of epirubicin. Each 50 or 200 mg vial contains 250 or 1000 mg lactose, respectively.

Prior to use, Epirubicin Hydrochloride for Injection 50 mg and 200 mg vials will be reconstituted with Sterile Water for Injection, USP, resulting in a solution concentration of 2 mg/mL with a pH of 4.7 to 5.0. Reconstituted solutions are stable for 24 hours when stored at 2 to 8°C (36 to 46°F) and protected from light, or 25°C (77°F) in normal lighting conditions.

Route of administration: i.v. infusion

Data reliance: Except as specifically identified, all data and information discussed below and necessary for approval of NDA 50-807 are owned by Pharmacia & Upjohn or are data for which Mayne Pharma Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 50-807 that Mayne Pharma Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Mayne Pharma Inc. does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of this NDA.

Studies reviewed within this submission: No studies submitted

Studies not reviewed within this submission: Not applicable

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

Epirubicin is an anthracycline cytotoxic agent and 4-epimer of doxorubicin. It is generally accepted that anthracyclines interfere with DNA replication within eukaryotic cells.

Epirubicin forms a complex with DNA by intercalation of its planar rings between nucleotide base pairs, with consequent inhibition of nucleic acid (DNA and RNA) and protein synthesis. Such intercalation triggers DNA cleavage by topoisomerase II, resulting in cytotoxic activity. Epirubicin also inhibits DNA helicase activity, preventing the enzymatic separation of double-stranded DNA and interfering with replication and transcription. Epirubicin is also involved in oxidation/reduction reactions by generating cytotoxic free radicals. The antiproliferative and cytotoxic activity of epirubicin is thought to result from these or other possible mechanisms.

Epirubicin is cytotoxic in vitro to a variety of established murine and human cell lines and primary cultures of human tumors. It is also active in vivo against a variety of murine tumors and human xenografts in athymic mice, including breast tumors.

2.6.2.2 Primary pharmacodynamics

The following is from Ellence® labeling:

Epirubicin is an anthracycline cytotoxic agent. Epirubicin forms a complex with DNA by intercalation of its planar rings between nucleotide base pairs, with consequent inhibition of nucleic acid (DNA and RNA) and protein synthesis. Such intercalation triggers DNA cleavage by topoisomerase II, resulting in cytotoxic activity. Epirubicin also inhibits DNA helicase activity, preventing the enzymatic separation of double-stranded DNA and interfering with replication and transcription. Epirubicin is also involved in oxidation/reduction reactions by generating cytotoxic free radicals. The antiproliferative and cytotoxic activity of epirubicin is thought to result from these or other possible mechanisms.

2.6.2.3 Secondary pharmacodynamics

Not available.

2.6.2.4 Safety pharmacology

Cardiac toxicity is a well recognized dose limiting adverse effect of the anthracyclines. Based on the labeling for Ellence®: "myocardial toxicity, manifested in its most severe form by potentially fatal congestive heart failure (CHF), may occur either during therapy with epirubicin or months to years after termination of therapy. The probability of developing clinically evident CHF is estimated as approximately 0.9% at a cumulative dose of 550 mg/m², 1.6% at 700 mg/m², and 3.3% at 900 mg/m². In the adjuvant treatment of breast cancer, the maximum cumulative dose used in clinical trials was 720 mg/m². The risk of developing CHF increases rapidly with increasing total cumulative doses of epirubicin in excess of 900 mg/m²; this cumulative dose should only be

exceeded with extreme caution. Active or dormant cardiovascular disease, prior or concomitant radiotherapy to the mediastinal/pericardial area, previous therapy with other anthracyclines or anthracenediones, or concomitant use of other cardiotoxic drugs may increase the risk of cardiac toxicity. Cardiac toxicity with Ellence® may occur at lower cumulative doses whether or not cardiac risk factors are present.”

The following summary Table was excerpted from NDA 50-778 for the RLD:

A Summary of General pharmacology effects of epirubicin

Types of Tests	Species	Route	Doses, mg/kg	Results
Cardiovascular activity	Rat	IV	7, 10, 14 for epirubicin 4, 8, 10 for doxorubicin (as reference drug)	Both compounds at the tested doses had very little effect on mean blood pressure and heart rate
Cardiovascular/ respiratory functions	Dog	IV	2 for epirubicin	No effect on systemic arterial pressure or heart rate and respiratory functions
Diuresis	Rat	IV	3, 6, 12 for epirubicin	No effect on renal excretion of water and electrolytes
Gastric emptying	Rat	IV	3, 6, 12	Epirubicin significantly slowed gastric emptying only at 12 mg/kg
Endocrine system	Rat	IV	0.4, 1.0, 2.5	Epirubicin had effects on the endocrine system from 1.0 mg/kg as antianabolic, antiestrogenic, antigonadotrophic, and antithyroid activities

2.6.2.5 Pharmacodynamic drug interactions

Based on the labeling for Ellence®:

Taxanes. Coadministration of paclitaxel or docetaxel did not affect the pharmacokinetics of epirubicin when given immediately following the taxane.

Cimetidine. Coadministration of cimetidine (400 mg twice daily for 7 days starting 5 days before chemotherapy) increased the mean AUC of epirubicin (100 mg/m²) by 50% and decreased its plasma clearance by 30%.

Drugs metabolized by cytochrome P-450 enzymes. No systematic in vitro or in vivo evaluation has been performed to examine the potential for inhibition or induction by epirubicin of oxidative cytochrome P-450 isoenzymes.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

See section 2.6.2.4, “Safety Pharmacology”.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

According to the labeling for Ellence®:

Distribution. Following intravenous administration, epirubicin is rapidly and widely distributed into the tissues. Binding of epirubicin to plasma proteins,

predominantly albumin, is about 77% and is not affected by drug concentration. Epirubicin also appears to concentrate in red blood cells; whole blood concentrations are approximately twice those of plasma.

Metabolism. Epirubicin is extensively and rapidly metabolized by the liver and is also metabolized by other organs and cells, including red blood cells. Four main metabolic routes have been identified:

(1) reduction of the C-13 keto-group with the formation of the 13(S)-dihydro derivative, epirubicinol; (2) conjugation of both the unchanged drug and epirubicinol with glucuronic acid; (3) loss of the amino sugar moiety through a hydrolytic process with the formation of the doxorubicin and doxorubicinol aglycones; and (4) loss of the amino sugar moiety through a redox process with the formation of the 7-deoxy-doxorubicin aglycone and 7-deoxy-doxorubicinol aglycone. Epirubicinol has in vitro cytotoxic activity one-tenth that of epirubicin. As plasma levels of epirubicinol are lower than those of the unchanged drug, they are unlikely to reach in vivo concentrations sufficient for cytotoxicity. No significant activity or toxicity has been reported for the other metabolites.

Excretion. Epirubicin and its major metabolites are eliminated through biliary excretion and, to a lesser extent, by urinary excretion. Mass-balance data from 1 patient found about 60% of the total radioactive dose in feces (34%) and urine (27%). These data are consistent with those from 3 patients with extrahepatic obstruction and percutaneous drainage, in whom approximately 35% and 20% of the administered dose were recovered as epirubicin or its major metabolites in bile and urine, respectively, in the 4 days after treatment.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

Not available.

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

Excerpted from review of

Excerpted from review of NDA 50-778, 7/14/1999

Toxicity studies of epirubicin were conducted in mice, rats, rabbits and dogs. In acute studies, epirubicin toxicity was evaluated in mice, rats and dogs, often in comparison with doxorubicin. Chronic toxicity studies were conducted: 6 week i.v. toxicity studies in rabbits and dogs, and 13 week i.v. toxicity studies in rats and dogs. Overall the toxicological profile of epirubicin was qualitatively similar to that of doxorubicin. When tested in comparison with doxorubicin, epirubicin appeared to be less toxic.

In special toxicity studies, when hematotoxicity of epirubicin was compared with doxorubicin in rats, both compounds induced similar dose-related decrease in WBC with nadir on day 8. Epirubicin 6 mg/kg and doxorubicin 3 mg/kg were equitoxic on leukocytes. Also, slight to marked decreases in platelets were noted in both compound at high doses. In bone marrow toxicity study, decreases in WBC, platelet, RBC, Hb, Hct values were observed in male dogs treated with epirubicin and doxorubicin both at 1 mg/kg. The immune response of epirubicin was compared with adriamycin in mice. The effect in IgG was more pronounced with epirubicin than adriamycin, irrespective of the treatment schedule used. Epirubicin had a slight immunosuppressive effect on delayed hypersensitivity reactions. The potential immunogenicity of epirubicin was evaluated in guinea pigs. No passive systemic anaphylaxis was induced by epirubicin, however, a delayed skin hypersensitivity reaction was observed.

The cardiotoxicity study of epirubicin was compared with doxorubicin after single and multiple dose regimens in rats. After single dose regimen (6 & 9 mg/kg IMI 28, 3 & 6 mg/kg doxorubicin) in rats, epirubicin induced a multifocal degenerative cardiomyopathy qualitatively similar to that observed after intravenous doxorubicin. However, its cardiotoxic effects were considerably less severe than those of doxorubicin in rats. In a multidose regimens, male rats received epirubicin and doxorubicin at equi-myelotoxic dose of 1 mg/kg/week for 7. Both compounds induced cardiomyopathy with myocardial lesions and renal impairments. The myocardial damage was moderate for epirubicin and severe for doxorubicin.

In a Segment I fertility study, epirubicin caused decreases in size/weight of testes, epididymides, and hypospermatogenesis in male rats while in females, epirubicin had no effect on pre-coital, mating performance, or fertility. In Segment II reproductive studies, pregnant rats were given i.v. doses of 0, 2 or 4 mg/kg/day on gestation days 9 and 10. Both doses of epirubicin resulted in maternal toxicities and fetal malformations. Pregnant rabbits received i.v. doses of 0, 1 or 3 mg/kg/day on days 10-12 of gestation. Both doses induced 80% and 100% abortion, maternal toxicities but no teratogenic effects. In a Segment III peri-postnatal toxicity study, i.v. doses of epirubicin ranging from 0.03 to 2 mg/kg/day were given from day 17 of pregnancy to day 7 after delivery. Two high doses of 1 and 2 mkd were lethal to dams. Epirubicin exposure caused maternal toxicities and reduced nursing ability. In another Segment III peri-postnatal study, i.v. doses of epirubicin ranging from 0.05 to 0.5 mg/kg/day were given from day 17 of pregnancy to day 21 after delivery. High dose of 0.5 mkd resulted in maternal toxicities characterized by significant decreases in body weight and food consumption, gross alterations (lymphoid organs, ovaries, uteri), and reducing nest building and nursing ability. Beside reduced litter size/weight, no noteworthy changes were observed in the offsprings. Progeny weights and viability index were lower, developmental delays and reduced physical activity was noted in the newborns whose mothers were exposed to HD epirubicin in utero. Epirubicin had no effect on reproduction parameters, progeny survival to weaning, and functional and behavioral tests.

The mutagenic potential of epirubicin was investigated using in vitro tests and in vivo experiments. Epirubicin was mutagenic in 3 strains of *S. typhimurium*, TA 1538, TA 100 and TA 98 with and without metabolic activation. Epirubicin was clastogenic without metabolic activation in vitro in the gene mutation test on V79 Chinese hamster lung cells. Epirubicin induced both chromatid and chromosome aberrations on human lymphocytes. Epirubicin induced chromosome aberrations in mouse bone marrow in vivo.

In carcinogenicity studies, s.c. doses of 0.75 and 1 mg/kg/day epirubicin given to newborn rats increased the incidence of tumors increased 21% (control) to 80-85% in the treated females and 66-81% in treated males. In long-term toxicity study, single (3 mg/kg dox; 3.6 mg/kg epi) and multidose i.v. doses ranging from 0.06 to 0.5 mg/kg epirubicin was given to 7 and 13 weeks old female rats. Mammary gland tumors and subcutaneous tumors were observed. These findings suggest that epirubicin appears to be carcinogenic.

2.6.6.2 Single-dose toxicity

Excerpted from review of

4 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

2.6.6.4 Genetic toxicology

According to the labeling for Ellence®:

Epirubicin was mutagenic in vitro to bacteria (Ames test) either in the presence or absence of metabolic activation and to mammalian cells (HGPRT assay in V79 Chinese hamster lung fibroblasts) in the absence but not in the presence of metabolic activation. Epirubicin was clastogenic in vitro (chromosome aberrations in human lymphocytes) both in the presence and absence of metabolic activation and was also clastogenic in vivo (chromosome aberration in mouse bone marrow).

2.6.6.5 Carcinogenicity

According to the labeling for Ellence®:

Treatment-related acute myelogenous leukemia has been reported in women treated with epirubicin-based adjuvant chemotherapy regimens. Conventional long-term animal studies to evaluate the carcinogenic potential of epirubicin have not been conducted, but intravenous administration of a single 3.6 mg/kg epirubicin dose to female rats (about 0.2 times the maximum recommended human dose on a body surface area basis) approximately doubled the incidence of mammary tumors (primarily fibroadenomas) observed at 1 year. Administration of 0.5 mg/kg epirubicin intravenously to rats (about 0.025 times the maximum recommended human dose on a body surface area basis) every 3 weeks for ten doses increased the incidence of subcutaneous fibromas in males over an 18-month observation period. In addition, subcutaneous administration of 0.75 or 1.0 mg/kg/day (about 0.015 times the maximum recommended human dose on a body surface area basis) to newborn rats for 4 days on both the first and tenth day after birth for

2.6.7 TOXICOLOGY TABULATED SUMMARY

Not available.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Mayne Pharma (USA) Inc. submitted this NDA as a 505(b)2. The proposed "epirubicin hydrochloride for injection" in 50 mg/vial and 200 mg/vial, is a lyophilized, sterile powder intended for i.v. administration, after being reconstituted in Water for Injection. Each 50 or 200 mg vial contains 25 or 100 mg of lactose as excipients, respectively.

The basis of the 505(b)2 application is a formulation change to the reference listed drug (RLD) Ellence® (epirubicin hydrochloride for injection), NDA 50-778. Ellence® is a ready to use (RTU) solution. The 2 products have the same active ingredient (epirubicin hydrochloride), dosage form (solution for injection), strength (2 mg/mL, after reconstitution of Mayne product), route of administration (i.v.), and dosing regimen. Mayne's product has lactose monohydrate, not present in Ellence®. Ellence® has the following excipients, which are not present in Mayne's product: NaCl and HCl.

It appears that some of the non-clinical and clinical studies conducted by Farmitalia (whose product right was later transferred to Pharmacia & Upjohn) and by Pharmacia & Upjohn, in support of NDA 50-778, used lyophilized product of 10 and 50 mg.

Conclusions: there are no outstanding pharmacology/toxicology issues which preclude approval of the application for the specified indication.

Unresolved toxicology issues: None

Recommendations: The pharmacology/toxicology information of the reference listed drug (Ellence®), supports approval of this 505(b)2 NDA

Suggested labeling: The sponsor did not propose to change the Pharmacology/ Toxicology information in the labeling. This information will be identical to that for Ellence®.

Signatures:

Reviewer Signature _____
Haleh Saber-Mahloogi, Ph.D.
Pharmacology/ Toxicology Reviewer

Supervisor Signature _____ Concurrence Yes X No _____
David E. Morse, Ph.D.
Supervisory Pharmacologist

APPENDIX/ATTACHMENTS

None.

**This is a representation of an electronic record that was signed electronically and
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/s/

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4/19/2006 03:42:03 PM
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