

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**21-371**

**Pharmacology Review(s)**

## PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA number: 21-371  
Review number: 1  
Sequence number/date/type of submission: Original NDA  
Information to sponsor: Yes ( ) No (X)  
Sponsor and/or agent: Novavax, Inc  
Manufacturer for drug substance :

Reviewer name: Alex Jordan  
Division name: DRUPD  
HFD #: 580  
Review completion date: 4/22/02

Drug:

Trade name: Estrasorb  
Generic name (list alphabetically): estradiol, micellar nanoparticles  
Code name:  
Chemical name:  
CAS registry number:  
Mole file number:  
Molecular formula/molecular weight:  
Structure:

Relevant INDs/NDAs/DMFs:

Drug class: estrogen

Indication:

Clinical formulation: estradiol, soybean oil, water, polysorbate 80 and ethanol.

Route of administration: topical

Proposed use: estrogen replacement

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.



**TABLE OF CONTENTS - PHARMACOLOGY/TOXICOLOGY REVIEW**

**I. PHARMACOLOGY:..... 1**

**II. SAFETY PHARMACOLOGY:..... 1**

**III. PHARMACOKINETICS/TOXICOKINETICS:..... 1**

**IV. GENERAL TOXICOLOGY:..... 1**

**V. GENETIC TOXICOLOGY:..... 2**

**VI. CARCINOGENICITY:..... 2**

**VII. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY:..... 2**

**VIII. SPECIAL TOXICOLOGY STUDIES:..... 2**

**IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS:..... 2**

**X. APPENDIX/ATTACHMENTS:..... 2**

**APPEARS THIS WAY  
ON ORIGINAL**

## ***PHARMACOLOGY/TOXICOLOGY REVIEW***

### **I. PHARMACOLOGY:**

Primary pharmacodynamics: estrogenic

Mechanism of action: estrogen

Drug activity related to proposed indication: estrogen

Secondary pharmacodynamics:

**Pharmacology summary: estrogen**

**Pharmacology conclusions: estrogen**

### **II. SAFETY PHARMACOLOGY**

Not done

### **III. PHARMACOKINETICS/TOXICOKINETICS:**

None reviewed

### **IV. GENERAL TOXICOLOGY:**

A 91 day rabbit dermal irritation study produced a localized mild to moderate inflammatory response at the site of application.

**Toxicology summary:** No toxicology studies were submitted. The toxicology of estrogen is well known. Polysorbate 80 is a nonionic surfactant used widely as an additive in foods, pharmaceutical preparations and cosmetics as an emulsifier, dispersant or stabilizer. Polysorbate 80 has been examined for toxicity, genetic toxicity and carcinogenicity and the data published in a National Toxicology Program Technical Report Series PG:224 p YR:1992 IP: VI:415. The report concludes that polysorbate 80 was not mutagenic in *Salmonella typhimurium* strains TA100, TA1535, TA1537 and TA98. Under the conditions of the two 2-yr feed studies, there was equivocal evidence of carcinogenic activity in male F344/N rats based on an increased incidence of pheochromocytomas of the adrenal medulla. There was no evidence of carcinogenic activity in female F344/N rats or in male or female B6C3F1 mice given 25,000ppm or 50,000ppm. Administration of polysorbate 80 was associated with inflammation and squamous hyperplasia of the forestomach in male and female mice and with ulcers of the forestomach in female mice. In a paper published in *J Toxicol Sci* 1999 24(4):353, polysorbate 80 was administered IV to rabbits during days 6 to 18 of gestation at doses of 1, 3 and 10 mg/kg. There were no effects on any parameters of reproduction.

**Toxicology conclusions:** The increase in pheochromocytomas was extremely marginal (21/50; 19/50; 29/50; C; MD; HD) and in my opinion, not biologically significant. Estrasorb has no untoward toxicity.

**V. GENETIC TOXICOLOGY:**

not done

**VI. CARCINOGENICITY:**

Not done

**VII. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY:**

not done

**VIII. SPECIAL TOXICOLOGY STUDIES:**

Not done

**IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS:**

**Conclusions: From standpoint of Pharmacology, Estrasorb is approvable**

**General Toxicology Issues: none**

**Recommendations: approval**

**Labeling with basis for findings: no issues**

**X. APPENDIX/ATTACHMENTS:**

**Addendum to review: none**

**Other relevant materials (Studies not reviewed, appended consults, etc.):**

**Any compliance issues: no**

**APPEARS THIS WAY  
ON ORIGINAL**

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
Alexander W. Jordan  
4/29/02 07:50:15 AM  
PHARMACOLOGIST

APPEARS THIS WAY  
ON ORIGINAL

NDA 21-371  
Estrasorb™ (estradiol topical emulsion)  
Novavax, Inc.

**Statistical Review(s) of Carcinogenicity Studies**

No carcinogenicity studies performed with this product.

**APPEARS THIS WAY  
ON ORIGINAL**



NDA 21-371  
Estrasorb™ (estradiol topical emulsion)  
Novavax, Inc.

**CAC/ECAC Report**

No CAC/ECAC report was needed with this product.

APPEARS THIS WAY  
ON ORIGINAL