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RESEARCH**

*APPLICATION NUMBER:*  
**022574Orig1s000**

**PHARMACOLOGY REVIEW(S)**

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

**PHARMACOLOGY/TOXICOLOGY NDA LABELING REVIEW**

Application number: 22-532 505(b)1  
Supporting document/s: none  
Applicant's letter date: 8-21-2009  
CDER stamp date: 8-21-2009  
Product: Yaz® + Metafolin® (BeYaz®)  
drospirenone 3 mg, ethinyl estradiol 0.02 mg,  
and levometafolate 0.451 mg  
Indication: Improvement in folate status in women using  
oral contraceptives.  
Applicant: Bayer Healthcare Pharmaceuticals Inc  
Review Division: Reproductive and Urologic Drugs  
Reviewer: Leslie McKinney, PhD  
Supervisor/Team Leader: Alex Jordan, PhD  
Division Director: Scott Monroe, MD  
Project Manager: Pamela Lucarelli

# 1 Executive Summary

## 1.1 Recommendations

### 1.1.3 Labeling

NDA 22-532: drospirenone 3 mg, ethinyl estradiol 0.02 mg, and levometafolate 0.451 mg

NDA 22-574: drospirenone 3 mg, ethinyl estradiol 0.03 mg, and levometafolate 0.451 mg

NDA 21-676: drospirenone 3 mg, ethinyl estradiol 0.02 mg

NDA 21-098: drospirenone 3 mg, ethinyl estradiol 0.03 mg

This review will address labeling for two related new NDAs, NDA 22-532, Yaz® plus Metafolin® (new trade name BeYaz®) and NDA 22-574, Yasmin® plus Metafolin® (trade name to be determined). This review will also address labeling for two related approved NDAs, 21-676, Yaz®, and 21-098, Yasmin®, which are being revised to conform to the Physician's Labeling Rule (PLR). The aim is to have the relevant Pharm Tox sections common to all 4 NDAs be identical and to have the sections unique to the two new NDAs also be identical. The format of this review is to show each section of the label with either the current text or the sponsor's proposed text in normal typeface, and to show the reviewer's proposed changes in italicized typeface.

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NDA 22-532: Yaz® plus Metafolin® (new trade name BeYaz®)

NDA 22-574: Yasmin® plus Metafolin® (trade name not yet assigned)

### Label section INDICATIONS AND USAGE

This section of the label contains a description of the drug. The PLR format requires the designation of the established pharmacological class in this section. Levometafolate has been designated an NME, and therefore must be assigned a pharmacological class. PharmTox proposes 'folate' as the pharmacological class.

Proposed labeling:

*TRADENAME is an estrogen/progestin COC containing folate indicated for use by women to:*  
(indications follow). COC: combined oral contraceptive

### Label section 13 NONCLINICAL TOXICOLOGY

#### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Sponsor's labeling for estradiol and drospirenone:

In a 24 month oral carcinogenicity study in mice dosed with 10 mg/kg/day drospirenone alone or 1 + 0.01, 3 + 0.03 and 10 + 0.1 mg/kg/day of drospirenone and ethinyl estradiol, 0.1 to 2 times the exposure (AUC of drospirenone) of women taking a contraceptive dose, there was an increase in carcinomas of the Harderian gland in the group that received the high dose of drospirenone alone. In a similar study in rats given 10 mg/kg/day drospirenone alone or 0.3 + 0.003, 3 + 0.03 and 10 + 0.1 mg/kg/day drospirenone and ethinyl estradiol, 0.8 to 10 times the exposure of women taking a contraceptive dose, there was an increased incidence of benign and total (benign and malignant) adrenal gland pheochromocytomas in the group receiving the high dose of

drospirenone. [REDACTED] (b) (4)  
[REDACTED]  
[REDACTED] (5.16).]

Reviewer's proposed labeling for estradiol and drospirenone (changes highlighted in boldface):

*In a 24 month oral carcinogenicity study in mice dosed with 10 mg/kg/day drospirenone alone or 1 + 0.01, 3 + 0.03 and 10 + 0.1 mg/kg/day of drospirenone and ethinyl estradiol, 0.1 to 2 times the exposure (AUC of drospirenone) of women taking a contraceptive dose, there was an increase in carcinomas of the Harderian gland in the group that received the high dose of drospirenone alone. In a similar study in rats given 10 mg/kg/day drospirenone alone or 0.3 + 0.003, 3 + 0.03 and 10 + 0.1 mg/kg/day drospirenone and ethinyl estradiol, 0.8 to 10 times the exposure of women taking a contraceptive dose, there was an increased incidence **of benign and malignant** adrenal gland pheochromocytomas in the group receiving the high dose of drospirenone. **Mutagenesis studies for drospirenone were conducted in vivo and in vitro and no evidence of mutagenic activity was observed.***

Rationale for changing the statement about mutagenicity:

Recommendations for PLR formatting are to simplify text when possible. The standard battery of mutagenicity tests were negative, as stated in the original labeling. The additional text, which

[REDACTED] (b) (4)

Sponsor's labeling for levomefolate:

[REDACTED] (b) (4)

Reviewer's proposed labeling for levomefolate:

*Long-term animal studies have not been conducted to evaluate the carcinogenic potential of levomefolate. Mutagenesis studies for levomefolate were conducted in vitro and in vivo and no evidence of mutagenic activity was observed.*

*Reviewer's note: The sponsor does not have ownership*

(b) (4)

### **13.2 Animal Toxicology and/or Pharmacology**

Sponsor's labeling:

(b) (4)

*Reviewer proposes eliminating this text. The rationale for the change is that it is not necessary and does not add support to the clinical sections.*

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22532	ORIG-1	BAYER HEALTHCARE PHARMACEUTICA LS INC	YAZ Folate
NDA-22574	ORIG-1	BAYER CORP PHARMACEUTICA L DIV	YASMIN PLUS (DEOSPIRENONE ETHINYL ESTRAD

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/s/  
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LESLIE C MCKINNEY  
08/13/2010

ALEXANDER W JORDAN  
08/13/2010  
I concur

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

**PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION**

Application number: 22-574 505(b)1  
Supporting document/s: none  
Applicant's letter date: November 16, 2009  
CDER stamp date: November 16, 2009  
Product: Yasmin® + Metabolin® (no trade name assigned)  
drospirenone 3 mg, ethinyl estradiol 0.03 mg, and  
levometafolate 0.451 mg  
Indication: Improvement in folate status in women using oral  
contraceptives.  
Applicant: Bayer Healthcare Pharmaceuticals Inc  
Review Division: Reproductive and Urologic Drugs  
Reviewer: Leslie McKinney, PhD  
Supervisor/Team Leader: Alex Jordan, PhD  
Division Director: Scott Monroe, MD  
Project Manager: Pamela Lucarelli

**Disclaimer**

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 22-574 are owned by Bayer Healthcare Pharmaceuticals Inc. or are data for which Bayer has obtained a written right of reference. Any information or data necessary for approval of NDA 22-574 that Bayer 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. Note: Levometafolate (L-methylfolate) is not a reference listed drug, but is a GRAS compound approved by CFSAN as a food additive. Any data or information described or referenced below from a previously approved application that Bayer 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 NDA 22-574.

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# 1 Executive Summary

## 1.1 Recommendations

### 1.1.1 Approvability

NDA 22-574 Yasmin® + Metafolin® (drospirenone 3 mg, ethinyl estradiol 0.03 mg, and levometafolate 0.451 mg) has been submitted by Bayer Healthcare Pharmaceuticals, Inc. for improvement in folate status in women using oral contraceptives. Yasmin® (drospirenone 3 mg, ethinyl estradiol 0.03 ug) is an FDA approved contraceptive, and levometafolate is both a naturally occurring human metabolite and an FDA approved food additive. There were no new non-clinical safety concerns for the addition of levometafolate to Yasmin® at the proposed dose. Based on previous approval for drospirenone and ethinyl estradiol as Yasmin®, as well as previous designation of levometafolate as a GRAS compound and FDA approval of levometafolate as a food additive, PharmTox recommends approval of Yasmin® plus levometafolate.

### 1.1.2 Additional Non Clinical Recommendations

There are no nonclinical recommendations.

### 1.1.3 Labeling

PharmTox recommends removing sections from the label that refer to nonclinical findings for levometafolate (Section 8.1 Pregnancy and Section 13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility). There are no safety findings to report. In addition, the sponsor cannot reference findings from the FDA docket in the label that are not owned by them.

## 1.2 Brief Discussion of Nonclinical Findings

Levometafolate (also known as L-methylfolate, L-methyltetrahydrofolate, or L-MTHF), a metabolite of folic acid, is a naturally occurring folate found in foods. L-MTHF has been accepted by CFSAN as a food additive and is generally recognized as safe (GRAS). The proposed daily dose of L-MTHF in Yasmin metafolate (0.451 mg) is below the acceptable level of L-MTHF in foods of 1 mg/day.

This NDA incorporates by reference all of the nonclinical information previously submitted on August 21, 2009 to NDA 22-574, YAZ® + Metafolin®. YAZ® + Metafolin® and Yasmin® + Metafolin® contain the same amount of levometafolate and differ only in the dose of ethinyl estradiol (0.02 vs 0.03 mg). For that reason, the review filed to NDA 22-532 will serve as the review for this NDA.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22574	ORIG-1	BAYER CORP PHARMACEUTICA L DIV	YASMIN PLUS (DEOSPIRENONE ETHINYL ESTRAD

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/s/

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LESLIE C MCKINNEY  
07/08/2010

ALEXANDER W JORDAN  
07/09/2010

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR A NEW NDA/BLA

**NDA Number: 22-574**      **NDA Type: 505(b)1**

**Drug Name: Yasmin Plus (drospirenone 3 mg, ethinyl estradiol 0.03 mg, and levometafolate 0.451 mg)**

**Applicant: Bayer Health Care Pharmaceuticals**

**Stamp Date: Nov 16-2009**      **PDUFA Date: Sept 16, 2010**

**Related IND: 51,693**      **Cross-referenced NDAs, INDs: 21-098 (Yasmin), 21-676 (Yaz), 72,287 (Yasmin plus Metafolin)**

On **initial** overview of the NDA application for RTF:

	<b>Content parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
1	On its face, is the pharmacology/toxicology section of the NDA organized (in accord with 21 CFR 314 and current guidelines for format and content) in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section of the NDA indexed and paginated in a manner allowing substantive review to begin?	X		
3	On its face, is the pharmacology/toxicology section of the NDA legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505b1 and b2 including referenced literature) completed and submitted in this NDA (carcinogenicity, mutagenicity*, teratogenicity*, effects on fertility, juvenile studies, acute and repeat dose adult animals studies*, animal ADME studies, safety pharmacology, etc)?	X		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		Yasmin® (drospirenone + ethinyl estradiol) is an approved oral contraceptive. Levometafolate (L-MTHF) is a GRAS compound that is used as a dietary supplement. No nonclinical studies were required for the combination of Yasmin + L-MTHF.
6	On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted a rationale to justify the alternative route?	X		
7	Has the sponsor submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	X		The sponsor has relied upon public domain information as well as previously conducted proprietary studies to support the NDA.
8	Has the sponsor submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor?	X		There was no preNDA meeting for this submission and there were no nonclinical requests. Nonclinical data for this submission are cross-referenced to IND 72,287 (Yaz + Metafolin) which supports NDA 22-

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR A NEW NDA/BLA

				532 (Yaz + Metformin) that is currently under review.
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m <sup>2</sup> or comparative serum/plasma levels) and in accordance with 201.57?		X	Dose multiples for Section 8.1 (Pregnancy) may have to be revised.
10	If there are any impurity – etc. issues, have these been addressed? (New toxicity studies may not be needed.)		X	Exact concentrations of impurities of L-MTHF were not available for nonclinical studies; impurities were considered qualified for the IND based on high multiples of exposure in the cited studies. The sponsor is expected to provide impurity levels for the clinical lots for the NDA.
11	Has the sponsor addressed any abuse potential issues in the submission?			N/A
12	If this NDA is to support a Rx to OTC switch, have all relevant studies been submitted?			N/A
13	From a pharmacology/toxicology perspective, is the NDA fileable? If “no”, please state below why it is not.		X	

Any Additional Comments:

The sponsor has provided a tabular listing of all the nonclinical studies for drospirenone and ethinyl estradiol cross-referenced to NDA 21-098 or NDA 21-676.

For L-MTHF, the sponsor has cross-referenced IND 72,287, which contains study reports for data that was previously referenced as ‘unpublished data’. These studies include safety pharmacology, single- and repeat-dose toxicity, genotoxicity and reproductive toxicity, local tolerance and sensitization studies for L-MTHF. No carcinogenicity studies for L-MTHF were required.

Leslie McKinney, PhD

Reviewing Pharmacologist

December 21, 2009

Date

Alex Jordan, PhD

Team Leader/Supervisor

Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22574	ORIG-1	BAYER CORP PHARMACEUTICA L DIV	YASMIN PLUS (DEOSPIRENONE ETHINYL ESTRAD

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LESLIE C MCKINNEY  
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