

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**022532Orig1s000**

**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: (b) (4)  
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, (b) (4) and NDA 22-574, (b) (4) (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: (b) (4) (b) (4)  
 NDA 22-574: (b) (4) (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:

(b) (4)

(b) (4)

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. (b) (4)

. However, this reviewer recommends an even further simplification of the text (as shown above), given the questionable relevance of the data on unscheduled DNA synthesis and adduct formation to humans.

Sponsor's labeling for levomefolate:

No carcinogenicity studies of levomefolate calcium were conducted. Levomefolate calcium was not mutagenic in vitro (Ames and mouse lymphoma gene mutation) and in vivo (mouse micronucleus) genotoxicity tests. There was no evidence of an effect on fertility in male or female rats given very large doses of a racemic mixture containing levomefolate calcium and its 'R' isomer (approximately 104 times the dose of levomefolate calcium in Calyova).

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 of the cited fertility studies.* [redacted] (b) (4)

[redacted]

[redacted] (b) (4)

[redacted]

[redacted]

[redacted]

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  
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**PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION**

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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 22-532 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 22-532 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: 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 22-532.

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# 1 Executive Summary

## 1.1 Recommendations

### 1.1.1 Approvability

NDA 22-532 (b) (4) drospirenone 3 mg, ethinyl estradiol 0.02 mg, and levometafolate 0.451 mg has been submitted by Bayer Healthcare Pharmaceuticals, Inc. for improvement in folate status in women using oral contraceptives. Yaz® (drospirenone 3 mg, ethinyl estradiol 0.02 mg) 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 Yaz® at the proposed dose. Based on previous approval for drospirenone and ethinyl estradiol as Yaz®, as well as previous designation of levometafolate as a GRAS compound and FDA approval of levometafolate as a food additive, PharmTox recommends approval of (b) (4).

### 1.1.2 Additional Non Clinical Recommendations

There are no nonclinical recommendations.

### 1.1.3 Labeling

(b) (4)

## 1.2 Brief Discussion of Nonclinical Findings

Levometafolate (L-methylfolate 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 (b) (4) (0.451 mg) is below the acceptable level of L-MTHF in foods of 1 mg/day.

The pharmacology and toxicology of L-methylfolate has been extensively researched in the open scientific literature and has also been reviewed by CFSAN and other regulatory agencies. There were no new nonclinical findings.

## 2 Drug Information

### 2.1 Drug

#### 2.1.1 CAS Registry Number

ethinyl estradiol-β-cyclodextrin clathrate: 256463-26-0

drospirenone: 67392-87-4

L-methylfolate, calcium (1:1): 151533-22-1

#### 2.1.2 Generic Name (INN/USAN)

ethinyl estradiol-β-cyclodextrin clathrate: ethinylestradiol betadex

drospirenone: drospirenone

L-methylfolate, calcium: levomefolate calcium

#### 2.1.3 Code Name

ethinyl estradiol-β-cyclodextrin clathrate: ZK 227269

drospirenone: ZK30595

L-methylfolate, calcium: ZK 270898

#### 2.1.4 Chemical Name

ethinyl estradiol-β-cyclodextrin clathrate: 19-Nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol, Bis(β-cyclodextrin clathrate)

drospirenone: 6β,7β,15β,16-dimethylene-3-oxo-17α-pregn-4-ene-21, 17-carbolactone

L-methylfolate, calcium: N-[4-[[[(2-amino-1,4,5,6,7,8-hexahydro-5-methyl-4-oxo-(6S)-pteridiny]methyl]amino]benzoyl]-L-glutamic acid, calcium salt

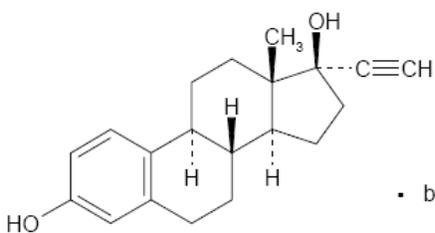
#### 2.1.5 Molecular Formula/Molecular Weight

ethinyl estradiol-β-cyclodextrin clathrate: C<sub>104</sub>H<sub>164</sub>O<sub>72</sub> / 2566.4 g/mol

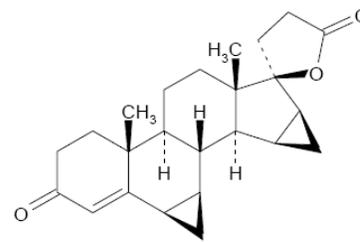
drospirenone: C<sub>24</sub>H<sub>30</sub>O<sub>3</sub> / 366.50 g/mol

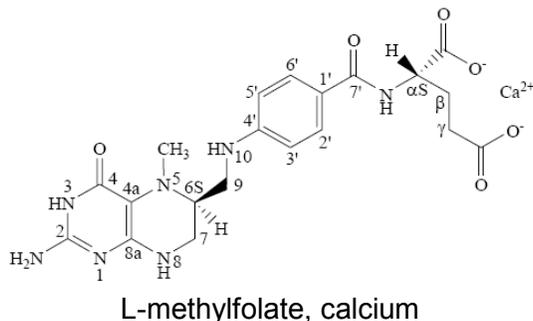
L-methylfolate: (b) (4)  
C<sub>20</sub>H<sub>23</sub>CaN<sub>7</sub>O<sub>6</sub> / 497.52 g/mol (Ca salt)

#### 2.1.6 Structures



• beta-Cyclodextrin-clathrate 1:2





### 2.1.7 Pharmacologic class

ethinyl estradiol: synthetic hormone  
 drospirenone: synthetic hormone  
 L-methylfolate: nutrient

## 2.2 Relevant IND/s, NDA/s, and DMF/s

INDs: 51,693 Yasmin® (drospirenone 3 mg/ethinyl estradiol 0.03 mg)  
 60,738 YAZ® (drospirenone 2 mg/ethinyl estradiol 0.02 mg)  
 (b) (4)  
 (b) (4)  
 72,287 (drospirenone 2 mg/ethinyl estradiol 0.02 mg plus 0.451 mg L-5 methyltetrahydrofolate (L-5-MTHF))

NDA: 21-098 Yasmin® approved 2001 for oral contraception  
 21-676 YAZ® approved 2006 for oral contraception  
 21-873 YAZ® approved 2006 for PMDD  
 22-045 YAZ® approved 2007 for acne vulgaris

DMFs: drospirenone: 12138 (Bayer Schering Pharma AG)  
 ethinyl estradiol, Betadex: 14960 (Bayer Schering Pharma AG)  
 (b) (4)

## 2.3 Clinical Formulation

The drug product is administered in tablet form.

### 2.3.1 Drug Formulation

**Sponsor's Table 1-1, 2.3P: Composition of Drospirenone 3.0 mg + Ethinylestradiol 0.02 mg + Levomefolate calcium 0.451 mg coated tablet**

Composition	Reference to Standard	Function	Amount (mg)
<b>Drug substances</b>			
Drospirenone micronized	specification	drug substance	3.000
Ethinylestradiol betadex clathrate micronized <sup>a</sup>	specification	drug substance	0.020
Levomefolate calcium micronized	specification	drug substance	0.451
<b>Excipients</b>			
Lactose monohydrate	Ph. Eur., USP/NF, Ph. Jap.	(b) (4)	
Cellulose microcrystalline	Ph. Eur., USP/NF		
Croscarmellose sodium	Ph. Eur., USP/NF, Ph. Jap.		
Hydroxypropylcellulose (b) (4)	Ph. Eur., USP/NF		
Magnesium stearate	Ph. Eur., USP/NF, Ph. Jap.		
Weight (uncoated tablet)			
Film-coating			
(b) (4)	specification	(b) (4)	
Hypromellose (b) (4)	Ph. Eur., USP/NF, Ph. Jap.		
(b) (4)	Ph. Eur., USP/NF		
Talc	Ph. Eur., USP/NF, Ph. Jap.		
Titanium dioxide	Ph. Eur., USP/NF, Ph. Jap. Directive 95/45/EC		
Ferric oxide red	USP/NF, JPE Directive 95/45/EC		
Weight (film-coating)			
Weight (coated tablet)		82.0000	

<sup>a</sup> calculated as ethinylestradiol

### 2.3.2 Comments on Novel Excipients

All excipients are compendial.

Sponsor's comment on **β-Cyclodextrin** (from Nonclinical Overview p 7):

“β-Cyclodextrin is an excipient used to stabilize the ethinyl estradiol in the drug product. A literature-based safety assessment supporting the use of this excipient was included in NDA 21-676 for YAZ® (Drospirenone 3 mg/Ethinyl Estradiol 0.020 mg Tablets) for use as an oral contraceptive and in (b) (4)

The daily intake of β-cyclodextrin via this product (ca. (b) (4) /kg/day) is approximately (b) (4) times lower than the ADI of 5 mg/kg/day recommended by the Joint FAO/WHO Expert Committee on Food Additives.”

### 2.3.3 Comments on Impurities/Degradants of Concern

Because L-MTHF undergoes a natural process of oxidation, batches of L-MTHF can contain a large number of breakdown products as well as (b) (4), none of which are of toxicological concern. These were grouped by the sponsor as:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Two of the impurities, (b) (4), were tested individually for acute oral toxicity in the rat and for genotoxicity in a standard Ames test. No oral toxicity was reported for a dose of 2000 mg/kg and no genotoxicity was reported for 5000 ug/plate. No rationale for testing these two particular impurities was given. The racemate and the (b) (4) were also tested and found negative for acute oral and genotoxicity. The studies listed below were submitted in full to this NDA.

**Sponsor’s Table 4-2 Section 2.4 Nonclinical overview: Unpublished (b) (4) KGaA GLP systemic toxicology and genotoxicity studies of impurities of levomefolate calcium (5-L-MTHF-Ca)\***

Study Type	Species/Strain	Dose Levels	Results	Reference
Acute (oral)	Rat (Wistar) HsdCpb:WU	2000 mg/kg	No deaths or clinical signs LD <sub>50</sub> > 2000 mg/kg	(b) (4)
Reverse mutation (Ames test)	<i>Salmonella typhimurium</i> TA 98, 100, 102, 1535 & 1537 <i>Escherichia coli</i> WP2 uvrA pKM101	5-5000 µg/plate + metabolic activation with S9 mix	Negative	

\* Study results were also published in The EFSA Journal (2004) 135, 1-20. Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food on a request from the Commission related to Calcium L-Methylfolate. Available at the European Food Safety Authority Press Room Web site [www.efsa.europa.eu](http://www.efsa.europa.eu).

(b) (4)



#### **2.4 Proposed Clinical Population and Dosing Regimen**

The daily dose of levomefolate calcium to be administered with YAZ® is 0.451 mg, which is equivalent to 400 mg folic acid.

## 2.5 Regulatory Background

Yasmin® and Yaz® have been approved since 2001 and 2006, respectively, for oral contraception. FDA-approval for secondary indications of premenstrual dysphoric disorder and acne vulgaris were given in 2006 and 2007, respectively.

L-methylfolate (L-5-methyl-tetrahydrofolic acid, or L-5-MTHF) is a form of folic acid that occurs naturally in the human body and in foods, and is approved as a dietary supplement. A number of reviews and monographs have been published documenting the biochemistry and toxicology of MTHF in both the levo and racemic forms. Approval history for use as a food supplement is as follows:

- 1998: 5-MTHF, an equimolar mix (racemate) of the D- and L-diastereoisomer, was permitted for use as a new dietary ingredient under Dietary Substance and Control Act (DSHEA) in the United States. (Reference FDA/OHRMS Dockets Management home page [www.fda.gov/ohrms/dockets/dockets/95s0316/rpt0023\\_01.pdf](http://www.fda.gov/ohrms/dockets/dockets/95s0316/rpt0023_01.pdf))
- 1999: An independent expert panel appointed by FDA concluded that levomefolate calcium is generally recognized as safe (GRAS) for use as source of folate in conventional foods and dietary supplements.
- 2001: The L isomer of 5-MTHF, levomefolate calcium, was permitted for use as a new dietary ingredient under the DSHEA in the United States in June 2001. The application, submitted by Merck KGaA is available at the FDA/OHRMS Dockets Management home page [www.fda.gov/ohrms/dockets/dockets/95s0316/rpt0095\\_01.pdf](http://www.fda.gov/ohrms/dockets/dockets/95s0316/rpt0095_01.pdf))
- 2004: Levomefolate calcium was approved for use as a source of folate in foods in Europe, with a tolerable upper limit of 1 mg/adult person/day. (Reference The EFSA Journal (2004) 135, 1-20. Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food on a request from the Commission related to Calcium L-Methylfolate. Available at the European Food Safety Authority Press Room Web site [www.efsa.europa.eu](http://www.efsa.europa.eu)).
- 2005: The joint FAO/WHO expert committee on Food Additives (JECFA) cited no safety concern for the use of levomefolate calcium as an alternative to folic acid in foods for special dietary uses and other foods. (Reference: JECFA/65/SC. Food and Agriculture Organization World Health of the United Nations Organization. Joint FAO/WHO Expert Committee on Food Additives. Sixty-fifth meeting. Geneva, 7-16 June 2005). [ftp://ftp.fao.org/es/esn/jecfa/jecfa65\\_summary.pdf](http://ftp.fao.org/es/esn/jecfa/jecfa65_summary.pdf)
- 2008: Levomefolate calcium was approved by Food Standards, Australia and New Zealand (FSANZ) as a permitted form of folate for the voluntary fortification of certain foods where permitted. (Reference FSANZ Final Assessment Report, Application A566, L-5-methyltetrahydrofolate, calcium as a permitted vitamin form of folate.) <http://www.foodstandards.govt.nz/srcfiles/A566%20L-Methylfolate%20FAR%20FINAL.pdf>

At the preIND meeting for (b) (4) held on Sept. 8, 2005, the Division indicated that prior nonclinical studies of L-methylfolate were adequate to support its use as an active

pharmaceutical ingredient and also agreed that no new toxicology studies of the combination were required.

### **3 Studies Submitted**

#### **3.1 Studies Reviewed**

The proposed use of L-methylfolate as an additive to a prescription oral contraceptive changes its status from a food additive to a prescription drug. On the basis of prior approval as a food additive, no new nonclinical studies were requested for this NDA. However, because prior reviews of the nonclinical toxicology cited unpublished study reports, the Division requested that the sponsor submit full study reports if they were available. The sponsor obtained the study reports for the nonclinical toxicology of L-methylfolate conducted by Merck KGaA and submitted them to this NDA. All of the submitted studies have been summarized in the EFSA Journal 135, 1-20 (2004) and will not be re-reviewed here. Instead, tabular summaries of the results will be placed under the appropriate section headers.

#### **3.2 Studies Not Reviewed**

All nonclinical studies on ethinyl estradiol and drospirenone were cross-referenced to NDA 21-098 Yasmin® or 21-676 YAZ® and were not reviewed here. Nonclinical genotoxicity studies on impurities and/or degradative products of drospirenone or ethinyl estradiol conducted after approval of Yaz were cross-referenced to IND 60,738. They were reviewed by Dr. Krishan Rajeha, with no new safety findings, and are not discussed here.

#### **3.3 Previous Reviews Referenced**

- 1998: 5-MTHF, an equimolar mix (racemate) of the D- and L-diastereoisomer, was permitted for use as a new dietary ingredient under Dietary Substance and Control Act (DSHEA) in the United States. (Reference FDA/OHRMS Dockets Management home page [www.fda.gov/ohrms/dockets/dockets/95s0316/rpt0023\\_01.pdf](http://www.fda.gov/ohrms/dockets/dockets/95s0316/rpt0023_01.pdf))

This review includes study summaries of nonclinical pharmacology (in vivo and in vitro), ADME, acute and chronic toxicity, genotoxicity, and reproductive toxicity drawn from open literature or conducted by Knoll Pharmaceuticals (see Appendix for tabular list). Clinical studies testing 5-MTHF for the treatment of depression were also summarized.

- 1999: An independent expert panel appointed by FDA concluded that levomefolate calcium is generally recognized as safe (GRAS) for use as source of folate in conventional foods and dietary supplements.

- 2001: The L isomer of 5-MTHF, levomefolate calcium, was permitted for use as a new dietary ingredient under the DSHEA in the United States in June 2001. The application, submitted by Merck KGaA, is available at the FDA/OHRMS Dockets Management home page [www.fda.gov/ohrms/dockets/dockets/95s0316/rpt0095\\_01.pdf](http://www.fda.gov/ohrms/dockets/dockets/95s0316/rpt0095_01.pdf)) Data submitted in support of this application were drawn from the open literature.
- 2004: Levomefolate calcium was approved for use as a source of folate in foods in Europe, with a tolerable upper limit of 1 mg/adult person/day. (Reference The EFSA Journal (2004) 135, 1-20. Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food on a request from the Commission related to Calcium L-Methylfolate. Available at the European Food Safety Authority Press Room Web site [www.efsa.europa.eu](http://www.efsa.europa.eu))

This review contains study summaries of nonclinical acute and chronic toxicity, genotoxicity, and developmental toxicity (Segment 2) of levomefolate as well as acute oral and mutagenicity of 2 impurities, (b) (4). Oral toxicity and mutagenicity studies of the D-isomer and the racemate, D/L mefolinate, were also reviewed in summary form. *All of the unpublished studies summarized in this document were conducted by Merck KGaA or Merck Eprova between 1998 and 2003 and have been submitted in full to this NDA by Bayer, which licenses Metafolin® from Merck KGaA.*

- Review filed under IND 60,738 by Dr. Krishan Rajeha of nonclinical genotoxicity studies on impurities and/or degradative products of drospirenone or ethinyl estradiol conducted after approval of Yaz®.

## 4 Pharmacology

### 4.1 Primary Pharmacology

The primary pharmacology of L-methylfolate is well described in the open scientific literature and can be considered general knowledge. Folic acid (vitamin B9) is naturally occurring in a wide variety of vegetables, legumes and fruits. It is converted in the liver by dihydrofolate reductase to its biologically active form, tetrahydrofolate.

Tetrahydrofolate serves as a one-carbon donor in a number of biochemical reactions, including amino acid and nucleic acid metabolism. Unlike other folates, in the absence of vitamin B12, tetrahydrofolate will *not* serve as a methyl donor, and therefore cannot mask vitamin B12 deficiency.

### 4.2 Secondary Pharmacology

No significant findings for secondary pharmacology for L-methylfolate have been reported in the open literature.

### 4.3 Safety Pharmacology

No significant findings for safety pharmacology for L-methylfolate have been reported.

## 5 Pharmacokinetics/ADME/Toxicokinetics

### 5.1 PK/ADME

PK/ADME data for L-5 methylfolate are widely available in the open literature and have been summarized in the previously cited regulatory reviews. Briefly, dietary folates are absorbed primarily in the proximal part of the small intestine. Reduced folate is transformed to L-5-methyltetrahydrofolate in the mucosae of the duodenum and upper jejunum. It is transported to tissues via active transport and can cross the blood brain barrier. An enterohepatic cycle helps maintain a constant supply of L-5-MTHF to the tissues.

### 5.2 Toxicokinetics

See 1998 document under FDA/OHRMS Dockets Management home page [www.fda.gov/ohrms/dockets/dockets/95s0316/rpt0023\\_01.pdf](http://www.fda.gov/ohrms/dockets/dockets/95s0316/rpt0023_01.pdf) for general information regarding toxicokinetics of methyltetrahydrofolate (racemate).

## 6 General Toxicology

Studies submitted to the NDA relevant to each section are listed in tabular form below. All studies have been previously summarized in The EFSA Journal (2004) 135, 1-20 available at [www.efsa.europa.eu](http://www.efsa.europa.eu). Additional supportive toxicology information available in open literature and FDA docket documents will not be summarized here.

### 6.1 Single-Dose Toxicity

#### GLP systemic toxicology and genotoxicity studies of levomefolate calcium (L-5-MTHF Ca)

Study Type	Species/Strain	Dose Levels	Results	Reference
Single-Dose (oral)	Rat (Wistar) HsdCpb:WU	2000 mg/kg	No deaths or clinical signs LD <sub>50</sub> > 2000 mg/kg	4.2.3.1 <a href="#">T14420</a>

### 6.2 Repeat-Dose Toxicity

#### GLP systemic toxicology and genotoxicity studies of levomefolate calcium (L-5-MTHF Ca)

Study Type	Species/Strain	Dose Levels	Results	Reference
Repeated-Dose (oral)	Rat HanIbm:WIST	0, 25, 100 & 400 mg/kg/d for 13 weeks	No treatment-related effects at any dose. NOEL = 400 mg/kg	4.2.3.2 <a href="#">758316</a>

## 7 Genetic Toxicology

### 7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

GLP systemic toxicology and genotoxicity studies of levomefolate calcium (L-5-MTHF Ca)

Study Type	Species/Strain	Dose Levels	Results	Reference
Reverse mutation (Ames test)	<i>Salmonella typhimurium</i> TA 98, 100, 102, 1535 & 1537 <i>Escherichia coli</i> WP2 uvrA pkM101	5-5000 µg/plate + metabolic activation with S9 mix	Negative	4.2.3.3.1 <a href="#">T14475</a>

### 7.2 *In Vitro* Chromosomal Aberration Assays in Mammalian Cells

GLP systemic toxicology and genotoxicity studies of levomefolate calcium (L-5-MTHF Ca)

Study Type	Species/Strain	Dose Levels	Results	Reference
Forward mutation	Mouse lymphoma cells L5178Y TK <sup>(+/-)</sup>	5-5000 µg/plate + metabolic activation with S9 mix	Negative	4.2.3.3.1 <a href="#">T14646</a>

### 7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)

GLP systemic toxicology and genotoxicity studies of levomefolate calcium (L-5-MTHF Ca)

Study Type	Species/Strain	Dose Levels	Results	Reference
Micronucleus test	Rats (Wistar) HsdCpd:WU	2000 mg/kg (oral)	Negative	4.2.3.3.2 <a href="#">T14803</a>

### 7.4 Other Genetic Toxicity Studies

GLP systemic toxicology and genotoxicity studies of levomefolate calcium (L-5-MTHF Ca)

Study Type	Species/Strain	Dose Levels	Results	Reference
Unscheduled DNA synthesis	Rats (Han Wistar) [CrI:WI (Glx/BRL/Han) Br]	0, 800 & 2000 µg/kg (oral)	Negative	4.2.3.3.2 <a href="#">70/099-D6173</a>

## 8 Carcinogenicity

No carcinogenicity studies were conducted for L-5-methylfolate.

## 9 Reproductive and Developmental Toxicology

Extensive reproductive and developmental toxicity studies were conducted with the racemic mixture and documented in summary form in the 1998 document under FDA/OHRMS Dockets Management home page [www.fda.gov/ohrms/dockets/dockets/95s0316/rpt0023\\_01.pdf](http://www.fda.gov/ohrms/dockets/dockets/95s0316/rpt0023_01.pdf). Studies submitted to this NDA for the L-isomer were for Segment 2 only.

## 9.1 Fertility and Early Embryonic Development

No studies submitted

## 9.2 Embryonic Fetal Development

### GLP systemic toxicology and genotoxicity studies of levomefolate calcium (L-5-MTHF Ca)

Study Type	Species/Strain	Dose Levels	Results	Reference
Developmental (oral)	Rat (Wistar) HsdCpb:WU	0, 100, 300 & 1000 mg/kg/d on Days 5-19 of gestation	No maternal toxicity, fetotoxicity, or developmental toxicity at any dose level NOEL = 1000 mg/kg	4.2.3.5 <a href="#">T9453</a>

## 9.3 Prenatal and Postnatal Development

No studies submitted

## 10 Special Toxicology Studies

### GLP systemic toxicology and genotoxicity studies of levomefolate calcium (L-5-MTHF Ca)

Study Type	Species/Strain	Dose Levels	Results	Reference
Local toxicity dermal	New Zealand white rabbit	0.5 g in solution applied to intact, shaved skin	Negative	4.2.3.6.1 <a href="#">T14490</a>
Local toxicity ocular	New Zealand white rabbit	0.1 g solid material applied to conjunctival sac	Negative	4.2.3.6.1 <a href="#">T14491</a>
Sensitization	Guinea pig	Induction stage 1: 0.1 mL of 10 g/L injected (1 mg total) Induction stage 2: 1 mL of 50 g/L applied as an 8 cm <sup>2</sup> patch (50 mg total) Challenge: 0.5 mL of 10 g/L applied as a 4 cm <sup>2</sup> patch (5 mg total)	Intradermal induction: slight irritant Topical induction: slight irritant Topical challenge: not irritant	4.2.3.7.1 <a href="#">T14492</a>

## 11 Integrated Summary and Safety Evaluation

The human metabolite L-methylfolate has no known toxicities when administered exogenously in synthetic form. As a food additive, and now as a pharmaceutical additive, it can serve to maintain plasma levels of folate. From a PharmTox perspective, there are no safety concerns related to addition of L-methylfolate (0.451 mg) to the formulation of Yaz®.

## 12 Appendix/Attachments

The studies below were reviewed by CFSAN in 1998 as part of their evaluation of racemic methyltetrahydrofolate for use as a food additive.

<b>Sponsor's Table 4-3 Section 2.4 Nonclinical Overview: Unpublished toxicology studies of 5-MTHF-Ca racemic mixture (4.3 D95S-0316-0023 1998)</b>			
<b>Study Type</b>	<b>Species/Strain</b>	<b>Dose levels</b>	<b>Results</b>
Acute (oral)	Rat	5000 mg/kg	No deaths. Transient reaction to treatment. LD <sub>50</sub> > 5000 mg/kg
4-week (oral)	Rat	0, 40, 120 &	NOEL = 360 mg/kg/d
	Dog	360 mg/kg/d	NOEL = 120 mg/kg/d, based on decreased food consumption at 360 mg/kg bw/d
26-week (oral)	Rat	0, 40, 120 & 360 mg/kg/d	Reduced bodyweight gain at 120 & 360 mg/kg/d. Elevated serum glucose at 360 mg/kg/d.
	Dog	0, 20, 60 & 180 mg/kg/d	NOEL = 180 mg/kg/d
2-generation reproduction (oral)	Rat	0, 40, 120 & 360 mg/kg/d	NOEL = 360 mg/kg/d
Developmental (oral)	Rat Rabbit	0, 50, 150 & 450 mg/kg/d	NOEL = 450 mg/kg/d Lower bodyweight gain at 450 mg/kg/d during treatment. NOEL = 450 mg/kg/d
Developmental toxicity (oral peri/postnatal)	Rat	0, 40, 120 & 360 mg/kg	Slightly lower bodyweight gain during lactation at 360 mg/kg/d
Reverse mutation (Ames test)	Bacteria (Salmonella typhimurium)	1, 10, 100 & 1000 µg/plate + metabolic activation with S9 mix	Negative
Forward mutation	Mouse lymphoma cells	10, 100, 500 & 1000 µg/plate + metabolic activation with S9 mix	Negative
Chromosomal aberration	Human lymphocytes	1, 10, 100 & 800 µg/plate	Negative
Unscheduled DNA synthesis	HeLa cells	0, 10, 100 & 2000 µg/mL plate + metabolic activation with S9 mix	Negative
Micronucleus test	Rats	700 mg/kg (ip)	Negative

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22532	ORIG-1	BAYER HEALTHCARE PHARMACEUTICALS INC	YAZ Folate

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/s/

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LESLIE C MCKINNEY  
03/24/2010

ALEXANDER W JORDAN  
04/05/2010

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR A NEW NDA/BLA

**NDA Number: 22-532**                      **NDA Type: 505(b)1**

**Drug Name:** (b) (4) (drospirenone, ethinyl estradiol, and levometafolate)

**Applicant: Bayer Health Care Pharmaceuticals**

**Stamp Date: 8-21-09**                      **PDUFA Date: June 24, 2010**

**Related IND: 72,287**                      **Cross-referenced NDAs: 21-098, 21-676**

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		Yaz® (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 Yaz + 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		For submission of the NDA, Pharm/Tox requested that the sponsor provide summaries of the nonclinical data for L-MTHF, with careful referencing as to which studies were in the public domain. Bayer has provided the requested information.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR A NEW NDA/BLA

9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?		X	Dose multiples for Section 8.1 (Pregnancy) will 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 provided study reports for data that was previously referenced as ‘unpublished data’ in the nonclinical summaries for IND 72,287. These studies include safety pharmacology, single- and repeat-dose toxicity, genotoxicity and reproductive toxicity, local tolerance and sensitization studies. No carcinogenicity studies for L-MTHF were required.

Leslie McKinney, PhD

Reviewing Pharmacologist

September 29, 2009

Date

Alex Jordan, PhD

Team Leader/Supervisor

Date

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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LESLIE C MCKINNEY  
09/30/2009

ALEXANDER W JORDAN  
10/02/2009