

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
ANDA 091328

Name: Levonorgestrel Tablets, 0.75 mg (Rx/OTC)

Sponsor: Lupin Pharmaceuticals Inc.

Approval Date: January 23, 2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 091328

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 091328

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 091328

Lupin Pharmaceuticals Inc.
U.S. Agent for: Lupin Limited
Attention: Leslie Sands
Director, Regulatory Affairs
Harborplace Tower
111 South Calvert Street, 21st floor
Baltimore, MD 21202

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated April 15, 2009, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Levonorgestrel Tablets, 0.75 mg (Rx/OTC).

Reference is also made to your amendments dated November 5 2009; September 30 and December 7, 2011; January 3, January 4, January 17, March 14, March 29, June 20, and August 22, 2012.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved, effective on the date of this letter. The Division of Bioequivalence has determined your Levonorgestrel Tablets, 0.75 mg (Rx/OTC), to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug product (RLD), Ortho Plan B[®] Tablets, 0.75 mg, of Teva Branded Pharmaceutical Products R&D, Inc. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Please note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the Act.

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Office of Prescription Drug Promotion with a completed Form FDA 2253 at the time of their initial use.

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

Sincerely yours,

{See appended electronic signature page}

Gregory P. Geba, M.D., M.P.H.
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

ROBERT L WEST

01/23/2013

Deputy Director, Office of Generic Drugs, for
Gregory P. Geba, M.D., M.P.H.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 091328

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **LEVONORGESTREL TABLETS, 0.75 mg** safely and effectively. See full prescribing information for **LEVONORGESTREL TABLETS, 0.75 mg**.

Levonorgestrel Tablets, 0.75 mg, for oral use

Initial U.S. Approval: 1982

INDICATIONS AND USAGE
Levonorgestrel tablets, 0.75 mg are progestin-only emergency contraceptive, indicated for prevention of pregnancy following unprotected intercourse or a known or suspected contraceptive failure. Levonorgestrel tablets, 0.75 mg are available only by prescription for women younger than age 17 years, and available over the counter for women 17 years and older. Levonorgestrel tablets, 0.75 mg are not intended for routine use as a contraceptive. (1)

DOSAGE AND ADMINISTRATION
The first tablet is taken orally as soon as possible within 72 hours after unprotected intercourse. The second tablet should be taken 12 hours after the first dose. Efficacy is better if levonorgestrel tablet, 0.75 mg is taken as soon as possible after unprotected intercourse. (2)

DOSAGE FORMS AND STRENGTHS
A total of two 0.75 mg tablets taken 12 hours apart as a single course of treatment. (3)

CONTRAINDICATIONS
Known or suspected pregnancy. (4)

WARNINGS AND PRECAUTIONS
• Ectopic Pregnancy: Women who become pregnant or complain of lower abdominal pain after taking levonorgestrel tablets, 0.75 mg should be evaluated for ectopic pregnancy. (5.1)

- Levonorgestrel tablets, 0.75 mg are not effective in terminating an existing pregnancy. (5.2)
- Effect on menses: Levonorgestrel tablets, 0.75 mg may alter the next expected menses. If menses is delayed beyond 1 week, pregnancy should be considered. (5.3)
- STI/HIV: Levonorgestrel tablets, 0.75 mg does not protect against STI/HIV. (5.4)

ADVERSE REACTIONS
The most common adverse reactions (≥10%) in the clinical trial included menstrual changes (26%), nausea (23%), abdominal pain (18%), fatigue (17%), headache (17%), and dizziness (11%), and breast tenderness (11%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Lupin Pharmaceuticals Inc. at 1-800-399-2561 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS
Drugs or herbal products that induce certain enzymes, such as CYP3A4, may decrease the effectiveness of progestin-only pills. (7)

- USE IN SPECIFIC POPULATIONS**
- Nursing Mothers: Small amounts of progestin pass into the breast milk of nursing women taking progestin-only pills for long-term contraception, resulting in detectable steroid levels in infant plasma. (8.3)
 - Levonorgestrel tablets, 0.75 mg are not intended for use in premenarcheal (8.4) or postmenopausal females (8.5).
 - Clinical trials demonstrated a higher pregnancy rate in the Chinese population. (8.6)

See 17 for PATIENT COUNSELING INFORMATION.

Revised 12/2011

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* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Levonorgestrel tablets, 0.75 mg are progestin only emergency contraceptive indicated for prevention of pregnancy following unprotected intercourse or a known or suspected contraceptive failure. To obtain optimal efficacy, the first tablet should be taken as soon as possible within 72 hours of intercourse. The second tablet should be taken 12 hours later.

Levonorgestrel tablets, 0.75 mg are available only by prescription for women younger than age 17 years, and available over the counter for women 17 years and older.

Levonorgestrel tablets, 0.75 mg are not indicated for routine use as a contraceptive.

2 DOSAGE AND ADMINISTRATION

Take one tablet of levonorgestrel tablet, 0.75 mg orally as soon as possible within 72 hours after unprotected intercourse or a known or suspected contraceptive failure. Efficacy is better if the tablet is taken as soon as possible after unprotected intercourse. The second tablet should be taken 12 hours after the first dose. Levonorgestrel tablets, 0.75 mg can be used at any time during the menstrual cycle.

If vomiting occurs within two hours of taking the tablet, consideration should be given to repeating the dose.

3 DOSAGE FORMS AND STRENGTHS

Each levonorgestrel tablet, 0.75 mg is supplied as a white to off white round biconvex tablets, debossed with 'LU' on one side and 'S24' on the other's side.

4 CONTRAINDICATIONS

Levonorgestrel tablets, 0.75 mg are contraindicated for use in the case of known or suspected pregnancy.

5 WARNINGS AND PRECAUTIONS

5.1 Ectopic Pregnancy

Ectopic pregnancies account for approximately 2% of all reported pregnancies. Up to 10% of pregnancies reported in clinical studies of routine use of progestin only contraceptives are ectopic. A history of ectopic pregnancy is not a contraindication to use of this emergency contraceptive method. Healthcare providers, however, should consider the possibility of an ectopic pregnancy in women who become pregnant or complain of lower abdominal pain after taking levonorgestrel tablets, 0.75 mg. A follow up physical or pelvic examination is recommended if there is any doubt concerning the general health or pregnancy status of any woman after taking levonorgestrel tablets, 0.75 mg.

5.2 Existing Pregnancy

Levonorgestrel tablets, 0.75 mg are not effective in terminating an existing pregnancy.

5.3 Effects on Menses

Some women may experience spotting a few days after taking levonorgestrel tablets, 0.75 mg. Menstrual bleed ng patterns are often irregular among women using progestin only oral contraceptives and women using levonorgestrel for postcoital and emergency contraception.

If there is a delay in the onset of expected menses beyond 1 week, consider the possibility of pregnancy.

5.4 STI/HIV

Levonorgestrel tablets, 0.75 mg do not protect against HIV infecton (AIDS) or other sexually transmitted infections (STIs).

5.5 Physical Examination and Follow up

A physical examination is not required prior to prescribing levonorgestrel tablets, 0.75 mg. A follow up physical or

pelvic examination is recommended if there is any doubt concerning the general health or pregnancy status of any woman after taking levonorgestrel tablets, 0.75 mg.

5.6 Fertility Following Discontinuation

A rapid return of fertility is likely following treatment with levonorgestrel tablets, 0.75 mg for emergency contracepton; therefore, routine contraception should be continued or initiated as soon as possible following use of levonorgestrel tablets, 0.75 mg to ensure ongoing prevention of pregnancy.

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

A double blind, controlled clinical trial in 1,955 evaluable women compared the efficacy and safety of levonorgestrel tablet, 0.75 mg (one 0.75 mg tablet of levonorgestrel taken within 72 hours of unprotected intercourse, and one tablet taken 12 hours later) to the Yuzpe regimen (two tablets each containing 0.25 mg levonorgestrel and 0.05 mg ethinyl estradiol, taken within 72 hours of intercourse, and two tablets taken 12 hours later).

The most common adverse events (>10%) in the clinical trial for women receiving levonorgestrel tablets, 0.75 mg included menstrual changes (26%), nausea (23%), abdominal pain (18%), fatigue (17%), and headache (17%), dizziness (11%), and breast tenderness (11%). Table 1 lists those adverse events that were reported in ≥5% of levonorgestrel tablets, 0.75 mg users.

Table 1. Adverse Events in ≥ 5% of Women, by % Frequency

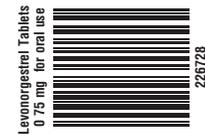
	Levonorgestrel Tablets, 0.75 mg N = 977 (%)
Nausea	23.1
Abdominal Pain	17.6
Fatigue	16.9
Headache	16.8
Heavier Menstrual Bleeding	13.8
Lighter Menstrual Bleeding	12.5
Dizziness	11.2
Breast Tenderness	10.7
Vomiting	5.6
Diarrhea	5.0

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of levonorgestrel tablets, 0.75 mg. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal Disorders

Abdominal Pain, Nausea, Vomiting



(b) (4)	
Customer: Lupin Limited	Location: Goa
Product Code & Name: 226728 Levonorgestrel Tablets, 0.75 mg for Oral Use (Insert Front)	
SAP Code: xxxxxxxxxxxx	File No: xxxx
Version No.: 4	Date: 02 12 2011
Open Size: 210 x 330 mm	
Folding Size: 53 x 57 mm	Pharma code: xxxxx
Colours: 1 (Black)	Perforation: No
Substrate: 40 gsm Bible Paper	Gluing: No
Artwork Sr. No.: xxx	
Artwork Status: in process	
Note - This approval will be considered for final printing	
Please recheck for corrections indicated earlier, in this proof also	
Prepared by (b) (6)	Checked by _____ Approved by _____
Customer Approval	
Checked by _____	Approved by _____
Packaging Dvmpmt	Production Regulatory Affairs Quality Assurance

General Disorders and Administration Site Conditions

Fatigue

Nervous System Disorders
Dizziness, Headache

Reproductive System and Breast Disorders

Dysmenorrhea, Irregular Menstruation, Oligomenorrhea, Pelvic Pain

7 DRUG INTERACTIONS

Drugs or herbal products that induce enzymes, including CYP3A4, that metabolize progestins may decrease the plasma concentrations of progestins, and may decrease the effectiveness of progestin only pills. Some drugs or herbal products that may decrease the effectiveness of progestin only pills include:

- barbiturates
- bosentan
- carbamazepine
- felbamate
- griseofulvin
- oxcarbazepine
- phenytoin
- rifampin
- St. John's wort
- topiramate

Significant changes (increase or decrease) in the plasma levels of the progestin have been noted in some cases of co-administration with HIV protease inhibitors or with non nucleoside reverse transcriptase inhibitors. Consult the labeling of a concurrently used drug to obtain further information about interactions with progestin only pills or the potential for enzyme alterations.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Many studies have found no harmful effects on fetal development associated with long term use of contraceptive doses of oral progestins. The few studies of infant growth and development that have been conducted with progestin only pills have not demonstrated significant adverse effects.

8.3 Nursing Mothers

In general, no adverse effects of progestin only pills have been found on breastfeeding performance or on the health, growth, or development of the infant. However, isolated post marketing cases of decreased milk production have been reported. Small amounts of progestin pass into the breast milk of nursing mothers taking progestin only pills for long term contraception, resulting in detectable steroidal levels in infant plasma.

8.4 Pediatric Use

Safety and efficacy of progestin only pills for long term contraception have been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents less than 17 years and for users 17 years and older. Use of levonorgestrel tablets, 0.75 mg emergency contraception before menarche is not indicated.

8.5 Geriatric Use

This product is not intended for use in postmenopausal women.

8.6 Race

No formal studies have evaluated the effect of race. However, clinical trials demonstrated a higher pregnancy rate in Chinese women with both levonorgestrel tablets, 0.75 mg and the Yuzpe regimen (another form of emergency contraception). The reason for this apparent increase in the pregnancy rate with emergency contraceptives in Chinese women is unknown.

8.7 Hepatic Impairment

No formal studies were conducted to evaluate the effect of hepatic disease on the disposition of levonorgestrel tablets, 0.75 mg.

8.8 Renal Impairment

No formal studies were conducted to evaluate the effect of renal disease on the disposition of levonorgestrel tablets, 0.75 mg.

9 DRUG ABUSE AND DEPENDENCE

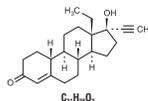
Levonorgestrel is not a controlled substance. There is no information about dependence associated with the use of levonorgestrel tablets, 0.75 mg.

10 OVERDOSAGE

There are no data on overdose of levonorgestrel tablets, 0.75 mg, although the common adverse event of nausea and associated vomiting may be anticipated.

11 DESCRIPTION

Each levonorgestrel tablet, 0.75 mg contains 0.75 mg of a single active steroid ingredient, levonorgestrel (18,19-Dihydro-4-en-20-yn-3-one-13-ethyl-17-hydroxy-17 α), a totally synthetic progestogen. The inactive ingredients present are colloidal silicon dioxide, corn starch, lactose monohydrate, magnesium stearate, and povidone. Levonorgestrel has a molecular weight of 312.45, and the following structural and molecular formulas:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Emergency contraceptive pills are not effective if a woman is already pregnant. Levonorgestrel tablets, 0.75 mg are believed to act as an emergency contraceptive principally by preventing ovulation or fertilization (by altering tubal transport of sperm and/or ova). In addition, it may inhibit implantation (by altering the endometrium). It is not effective once the process of implantation has begun.

12.3 Pharmacokinetics

Absorption

No specific investigation of the absolute bioavailability of levonorgestrel in humans has been conducted. However, literature indicates that levonorgestrel is rapidly and completely absorbed after oral administration (bioavailability about 100%) and is not subject to first pass metabolism.

After a single dose of levonorgestrel (0.75 mg) administered to 16 women under fasting conditions, the mean maximum serum concentration of levonorgestrel was 14.1 ng/mL at an average of 1.6 hours. See Table 2.

Table 2: Pharmacokinetic Parameter Values Following Single Dose Administration of Levonorgestrel Tablet, 0.75 mg to Healthy Female Volunteers under Fasting Conditions

	Mean (± SD)					
	C _{max} (ng/mL)	T _{max} (hr)	CL (L/h)	V _d (L)	t _{1/2} (h)	AUC _{0-∞} (ng hr/mL)
Levonorgestrel	14.1 (7.7)	1.6 (0.7)	7.7 (2.7)	260.0	24.4 (5.3)	123.1 (50.1)

C_{max} = maximum concentration

T_{max} = time to maximum concentration

CL = clearance

V_d = volume of distribution

t_{1/2} = elimination half life

AUC_{0-∞} = area under the drug concentration curve from time 0 to infinity

Effect of Food: The effect of food on the rate and the extent of levonorgestrel absorption following single oral administration of levonorgestrel tablets, 0.75 mg have not been evaluated.

Distribution

The apparent volume of distribution of levonorgestrel is reported to be approximately 1.8 L/kg. It is about 97.5 to 99% protein bound, principally to sex hormone binding globulin (SHBG) and, to a lesser extent, serum albumin.

Metabolism

Following absorption, levonorgestrel is conjugated at the 17 β -OH position to form sulfate conjugates and,

to a lesser extent, glucuronide conjugates in plasma. Significant amounts of conjugated and unconjugated 3 α , 5 β tetrahydrolevonorgestrel are also present in plasma, along with much smaller amounts of 3 α , 5 α tetrahydrolevonorgestrel and 16 β hydroxylevonorgestrel. Levonorgestrel and its phase I metabolites are excreted primarily as glucuronide conjugates. Metabolic clearance rates may differ among individuals by several fold, and this may account in part for the wide variation observed in levonorgestrel concentrations among users.

Excretion

About 45% of levonorgestrel and its metabolites are excreted in the urine and about 32% are excreted in feces, mostly as glucuronide conjugates.

Specific Populations

Pediatric

This product is not intended for use in the premenarcheal population, and pharmacokinetic data are not available for this population.

Geriatric

This product is not intended for use in postmenopausal women and pharmacokinetic data are not available for this population.

Race

No formal studies have evaluated the effect of race on pharmacokinetics of levonorgestrel tablets, 0.75 mg. However, clinical trials demonstrated a higher pregnancy rate in Chinese women with both levonorgestrel tablets, 0.75 mg and the Yuzpe regimen (another form of emergency contraception). The reason for this apparent increase in the pregnancy rate with emergency contraceptives in Chinese women is unknown. (See **USE IN SPECIFIC POPULATIONS (8.6)**.)

Hepatic Impairment

No formal studies were conducted to evaluate the effect of hepatic disease on the disposition of levonorgestrel tablets, 0.75 mg.

Renal Impairment

No formal studies were conducted to evaluate the effect of renal disease on the disposition of levonorgestrel tablets, 0.75 mg.

Drug-Drug Interactions

No formal drug-drug interaction studies were conducted with levonorgestrel tablets, 0.75 mg. (See **DRUG INTERACTIONS (7)**.)

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity: There is no evidence of increased risk of cancer with short term use of progestins. There was no increase in tumorigenicity following administration of levonorgestrel to rats for 2 years at approximately 5 mcg/day, to dogs for 7 years at up to 0.125 mg/kg/day, or to rhesus monkeys for 10 years at up to 250 mcg/kg/day. In another 7 year dog study, administration of levonorgestrel at 0.5 mg/kg/day did increase the number of mammary adenomas in treated dogs compared to controls. There were no malignancies.

Genotoxicity: Levonorgestrel was not found to be mutagenic or genotoxic in the Ames Assay, in vitro mammalian culture assays utilizing mouse lymphoma cells and Chinese hamster ovary cells, and in an in vivo micronucleus assay in mice.

Fertility: There are no reversible effects on fertility following cessation of exposures to levonorgestrel or progestins in general.

14 CLINICAL STUDIES

A double-blind, randomized, multinational controlled clinical trial in 1,955 evaluable women (mean age 27) compared the efficacy and safety of levonorgestrel tablets, 0.75 mg (one 0.75 mg tablet of levonorgestrel taken within 72 hours of unprotected intercourse, and one tablet taken 12 hours later) to the Yuzpe regimen (two tablets each containing 0.25 mg levonorgestrel and 0.05 mg ethinyl estradiol, taken within 72 hours of intercourse, and two additional tablets taken 12 hours later). After a single act of intercourse occurring anytime during the menstrual cycle, the expected pregnancy rate of 8% (with no contraceptive use) was reduced to approximately 1% with levonorgestrel tablets, 0.75 mg.

Emergency contraceptives are not as effective as routine hormonal contraception since their failure rate, while low based on a single use, would accumulate over time with repeated use. (See **INDICATIONS AND USAGE (1)**.)

At the time of expected menses, approximately 74% of women using levonorgestrel tablets, 0.75 mg had vaginal bleed similar to the normal menses, 14% bled more than usual, and 12% bled less than usual. The majority of women (87%) had their next menstrual period at the expected time or within + 7 days, while 13% had a delay of more than 7 days beyond the anticipated onset of menses.

16 HOW SUPPLIED/STORAGE AND HANDLING

Levonorgestrel Tablets, 0.75 mg are white to off-white round biconvex tablets, debossed with "LU" on one side and "S24" on the other side.

Levonorgestrel Tablets, 0.75 mg are available in a wallet containing 2 tablets (NDC 68180 851 11). Each wallet is packed in a carton (NDC 68180 851 13).

Store Levonorgestrel Tablets, 0.75 mg at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

17.1 Information for Patients

- Take levonorgestrel tablet, 0.75 mg as soon as possible and not more than 72 hours after unprotected intercourse or a known or suspected contraceptive failure.
- If you vomit within two hours of taking either tablet, immediately contact your healthcare provider to discuss whether to take another tablet.
- Seek medical attention if you experience severe lower abdominal pain 3 to 5 weeks after taking levonorgestrel tablet, 0.75 mg, in order to be evaluated for an ectopic pregnancy.
- After taking levonorgestrel tablet, 0.75 mg, consider the possibility of pregnancy if your period is delayed more than one week beyond the date you expected your period.
- Do not use levonorgestrel tablet, 0.75 mg as routine contraception.
- Levonorgestrel tablets, 0.75 mg are not effective in terminating an existing pregnancy.
- Levonorgestrel tablet, 0.75 mg does not protect against HIV infection (AIDS) and other sexually transmitted diseases/infections.
- For women younger than age 17 years, levonorgestrel tablets, 0.75 mg are available only by prescription.

Distributed by
Lupin Pharmaceuticals, Inc.
6511 more, Maryland 21202
United States

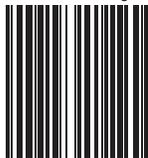
Manufactured by
Lupin Limited
Pitampur (M.P.) 454 775
INDIA

December 2011

ID# 226728

(b) (4)			
Customer: Lupin Limited		Location: Goa	
Product Code & Name: 226728 Levonorgestrel Tablets, 0.75 mg for Oral Use (Insert Back)			
SAP Code: xxxxxxxxxxxx		File No: xxxxx	
Version No.: 4		Date: 02 12 2011	
Open Size: 210 x 330 mm			
Folding Size: 53 x 57 mm		Pharma code: xxxxx	
Colours: 1 (Black)		Perforation: No	
Substrate: 40 gsm Bible Paper		Gluing: No	
Artwork Sr. No.: xxx			
Artwork Status: in process			
Note - This approval will be considered for final printing			
Please recheck for corrections indicated earlier, in this proof also			
Prepared by	Checked by	Approved by	
(b) (6)			
Customer Approval			
Checked by			Approved by
Packaging Dvmp	Production	Regulatory Affairs	Quality Assurance

Levonorgestrel
Tablets 0.75 mg



226729

**Levonorgestrel Tablets
0.75 mg**

Important information about Levonorgestrel Tablets, 0.75 mg, Birth Control and Sexually Transmitted Diseases

For additional information intended for healthcare professionals, please see accompanying prescribing information for Levonorgestrel Tablets, 0.75 mg

What are levonorgestrel tablets, 0.75 mg?

Levonorgestrel tablets, 0.75 mg are emergency contraception that helps prevent pregnancy after birth control failure or unprotected sex. It is a **backup** method of preventing pregnancy and is not to be used routinely.

Levonorgestrel tablets, 0.75 mg can reduce your chance of pregnancy after unprotected sex (if your regular birth control was used incorrectly or fails, or if you have had sex without birth control). For example, if you were using a condom and it broke or slipped, if you did not use your regular birth control as you should have, or if you did not use any birth control, levonorgestrel tablets, 0.75 mg may work for you.

What levonorgestrel tablets, 0.75 mg is not.

Levonorgestrel tablets, 0.75 mg will not work if you are already pregnant and will not affect an existing pregnancy. Levonorgestrel tablets, 0.75 mg should not be used as regular birth control. It is important to have another reliable source of birth control that is right for you. Levonorgestrel tablets, 0.75 mg will not protect you from HIV infection (the virus that causes AIDS) and other sexually transmitted diseases.

When is the appropriate time to use levonorgestrel tablets, 0.75 mg?

You can use levonorgestrel tablets, 0.75 mg **after** you have had unprotected sex in the last 72 hours (3 days), and you do not want to become pregnant.

Levonorgestrel tablets, 0.75 mg can be used as a backup or emergency method to regular birth control if, for example,

- Your regular birth control method was used incorrectly or failed (your partner's condom broke or slipped)
- You made a mistake with your regular method
- You did not use any birth control method

When is it not appropriate to use levonorgestrel tablets, 0.75 mg?

- Levonorgestrel tablets, 0.75 mg should not be used as a regular birth control method. It does not work as

well as most other forms of birth control when they are used consistently and correctly. Levonorgestrel tablet, 0.75 mg is a **backup or emergency** method of contraception.

- Levonorgestrel tablets, 0.75 mg should not be used if you are already pregnant because it will not work.
- Levonorgestrel tablets, 0.75 mg should not be used if you are allergic to levonorgestrel or any other ingredients in levonorgestrel tablets, 0.75 mg.
- Levonorgestrel tablets, 0.75 mg does not protect against HIV (the virus that causes AIDS) or other sexually transmitted diseases (STDs). The best ways to protect yourself against getting HIV or other STDs are to use a latex condom correctly with every sexual act or not to have sex at all.

How does levonorgestrel tablets, 0.75 mg work?

Levonorgestrel tablets, 0.75 mg are two pills with levonorgestrel, a hormone that has been used in many birth control pills for over 35 years. Levonorgestrel tablets, 0.75 mg contain a higher dose of levonorgestrel than birth control pills, but works in a similar way to prevent pregnancy. It works mainly by stopping the release of an egg from the ovary. It is possible that levonorgestrel tablets, 0.75 mg may also work by preventing fertilization of an egg (the uniting of sperm with the egg) or by preventing attachment (implantation) to the uterus (womb).

How can I get the best results from levonorgestrel tablets, 0.75 mg?

You have only a few days to try to prevent pregnancy after unprotected sex. **The sooner you take levonorgestrel tablets, 0.75 mg, the better it works.** Take the first levonorgestrel tablet, 0.75 mg **as soon as possible within 72 hours (3 days)** after unprotected sex. Take the second tablet **12 hours** later.

How effective is levonorgestrel tablets, 0.75 mg?

The sooner you take levonorgestrel tablets, 0.75 mg, the better it will work. Take levonorgestrel tablets, 0.75 mg as soon as possible after unprotected sex. If it is taken as soon as possible within 72 hours (3 days) after unprotected sex, it will significantly decrease the chance that you will get pregnant. Seven out of every 8 women who would have gotten pregnant will not become pregnant.

How will I know if levonorgestrel tablets, 0.75 mg worked?

Most women will have their next menstrual period at the expected time or within a week of the expected time. If

your menstrual period is delayed beyond 1 week, you may be pregnant. You should get a pregnancy test and follow up with your healthcare professional.

What if I am already pregnant and use levonorgestrel tablets, 0.75 mg?

There is no medical evidence that levonorgestrel tablets, 0.75 mg would harm a developing baby. If you take levonorgestrel tablets, 0.75 mg (accidentally) after you are already pregnant or it does not work and you become pregnant, it is not likely to cause any harm to you or your pregnancy. The pregnancy will continue. Levonorgestrel tablets, 0.75 mg will not work if you are already pregnant.

What should I do if my menstrual period is delayed beyond 1 week and I have severe lower stomach (abdominal) pain?

If you have severe lower stomach (abdominal) pain about 3 to 5 weeks after taking levonorgestrel tablets, 0.75 mg, you may have a pregnancy outside the uterus, which is called a tubal pregnancy. A tubal pregnancy requires immediate medical treatment, so you should see a healthcare professional right away.

Can I use levonorgestrel tablets, 0.75 mg for regular birth control?

No. Levonorgestrel tablets, 0.75 mg should **not** be used for regular birth control. It is an emergency or backup method to be used if your regular birth control fails or is used incorrectly or if you have sex without birth control. You should protect yourself against STDs and pregnancy every time you have sex. If you have unprotected sex again after taking levonorgestrel tablets, 0.75 mg, it will not help protect you from getting pregnant.

How often can I use levonorgestrel tablets, 0.75 mg?

Levonorgestrel tablet, 0.75 mg is meant for emergency protection only, and is not designed to be used frequently. If you find that you need to use emergency contraception often, talk to your healthcare professional and learn about methods of birth control and STD prevention that are right for you.

Will I experience any side effects from levonorgestrel tablets, 0.75 mg?

When used as directed, levonorgestrel tablet, 0.75 mg is safe for women. Some women will have mild, temporary side effects, such as menstrual changes, nausea, lower stomach (abdominal) pain, tiredness, headache, dizziness, breast pain and vomiting. These are similar to the side effects that some women have when taking regular birth control pills. Some women taking levonorgestrel tablets, 0.75 mg will have menstrual changes such as spotting or

(b) (4)	
Customer: Lupin Limited	Location: Goa
Product Code & Name: Levonorgestrel Tablets, 0.75 mg Med Guide (Insert-Front)	
SAP Code: xxxxxxxxxxxx	File No: xxxx
Version No.: 4	Date: 02.12.2011
Open Size: 260 x 180 mm	
Folding Size: 53 x 45 mm	Pharma code: xxxx
Colours: 1 (Black)	Perforation: No
Substrate: 60 gsm Maplitho Paper	Gluing: No
Artwork Sr. No.: xxx	
Artwork Status: in process	
Note - This approval will be considered for final printing. Please recheck for corrections indicated earlier, in this proof also.	
Prepared by : (b) (6)	Checked by: (b) (6)
Customer Approval	
Checked by:	Approved by:
Packaging Dvmt.	Production
Regulatory Affairs	Quality Assurance

bleeding before their next period. Some women may have a heavier or lighter next period, or a period that is early or late. **If your period is more than a week late, you should get a pregnancy test.**

What warnings should I know about when using levonorgestrel tablets, 0.75 mg?

Levonorgestrel tablets, 0.75 mg does not protect against the AIDS virus (HIV) or other sexually transmitted diseases (STDs).

Do not use:

- If you are already pregnant (because it will not work)
- If you are allergic to levonorgestrel or any of the ingredients in levonorgestrel tablets, 0.75 mg
- For regular birth control

When using this product, you may have:

- Menstrual changes
- Headache
- Nausea
- Dizziness
- Lower stomach (abdominal) pain
- Breast pain
- Tiredness
- Vomiting

Keep out of reach of children.

In case of overdose, get medical help or contact a Poison Control Center right away at 1-800-222-1222.

What are the directions for using levonorgestrel tablets, 0.75 mg?

Women 17 years of age and older:

- Take the first levonorgestrel tablet, 0.75 mg as soon as possible within 72 hours (3 days) after unprotected sex.
- Take the second tablet 12 hours after you take the first tablet.
- If you vomit within 2 hours of taking either dose of medication, call a healthcare professional to find out if you should repeat the dose.

Prescription only for women younger than age 17. If you are younger than age 17, see a healthcare professional.

What should I do if I have questions about levonorgestrel tablets, 0.75 mg?

If you have questions or need more information about this product, call our toll-free number, 1-800-399-2561 from Monday-Friday, 9:00 am - 5:00 pm EST, visit our website at www.birthcontrolhealth.com, or ask a healthcare professional.

Other information

Tablets are enclosed in a wallet seal. **Do not use if the wallet seal is broken.**

Store levonorgestrel tablets, 0.75 mg at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). [see USP Controlled Room Temperature].

You may report side effects to FDA at 1-800-FDA-1088.

Active ingredient: levonorgestrel 0.75 mg in each tablet

Inactive ingredients: colloidal silicon dioxide, corn starch, lactose monohydrate, magnesium stearate, and povidone.

Protect yourself in more ways than one!

If you are sexually active, but you are not ready for a pregnancy, it is important to use regular pregnancy protection. There are many types of birth control. Whichever type you choose, it is important to use your regular birth control method as directed.

This ensures that you have effective protection against pregnancy every time you have sex.

But things do not always go as planned. For example, if you were using a condom and it broke or slipped, or if you did not use your regular birth control as you should have, or if you did not use any birth control, levonorgestrel tablet, 0.75 mg may work for you. Levonorgestrel tablet, 0.75 mg is an emergency contraceptive that helps prevent pregnancy after unprotected sex or when your birth control fails or is not used correctly.

Remember, levonorgestrel tablets, 0.75 mg are only for emergency pregnancy prevention. There are many other products that work for regular birth control that are available by prescription or over-the-counter.

There is also another form of protection to think about when you have sex: protection against sexually transmitted diseases (STDs). Some common STDs are HIV/AIDS, chlamydia, genital herpes, gonorrhea, hepatitis, human papilloma virus (HPV), genital warts, syphilis, and trichomonas. Some of these STDs can be very serious and can lead to infertility (inability to have a baby), problems during pregnancy, chronic illness, and even death.

All sexually active women are at risk of catching STDs because they may not know that their partner has an STD (the partner himself may not know). **If your partner uses a latex condom correctly each and every time you have sex with him, this will help reduce, but not eliminate, the chance that you will catch an STD.**

No other birth control methods will effectively protect you from STDs. The female condom may give you some STD protection, but it is not as effective as a male latex condom.

For more information on STDs, call the Centers for Disease Control and Prevention (CDC) AIDS/STD Hotline. The CDC phone numbers are 1-800-342-AIDS (2437) for English, 1-800-344-7432 for Spanish, or 1-800-243-7889 for hearing impaired, TDD.

Be sure to protect yourself against pregnancy and STDs by using some form of birth control plus a latex condom. Of course, not having sex is the most effective way to prevent pregnancy and stay free of STDs.

Levonorgestrel tablet, 0.75 mg is used to prevent pregnancy after unprotected sex.

Levonorgestrel tablet, 0.75 mg should not be used for regular birth control, if you are already pregnant (because it will not work), or if you are allergic to levonorgestrel or any of the ingredients in levonorgestrel tablets, 0.75 mg.

The sooner you take levonorgestrel tablets, 0.75 mg, the better it will work.

Levonorgestrel tablets, 0.75 mg does not protect against the AIDS virus (HIV) or other sexually transmitted diseases (STDs)

Common side effects associated with the use of levonorgestrel tablets, 0.75 mg include menstrual changes, nausea, lower stomach (abdominal) pain, tiredness, headache, dizziness, breast pain and vomiting.

Distributed by:

Lupin Pharmaceuticals, Inc.
Baltimore, Maryland 21202
United States

Manufactured by:

Lupin Limited
Pithampur (M.P.) - 454 775
INDIA

December 2011

ID#: 226729

(b) (4)	
Customer: Lupin Limited	Location: Goa
Product Code & Name: 226729 Levonorgestrel Tablets, 0.75 mg Med Guide (Insert-Back)	
SAP Code: xxxxxxxxxxxx	File No: xxxx
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Open Size: 260 x 180 mm	
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Prepared by : (b) (6)	Checked by: Approved by:
Customer Approval	
Checked by:	Approved by:
Packaging Dvmp.	Production
Regulatory Affairs	Quality Assurance

LUPIN PHARMACEUTICALS, INC.

MADESM

(MORNING AFTER DEPENDABLE EDECATION) PROGRAM

**THE MARKETING, EDUCATION, DISTRIBUTION,
AND MONITORING PROGRAM FOR**

LEVONORGESTREL TABLETS, 0.75 mg

Introduction

The (MORNING AFTER DEPENDABLE EDECATION) Program is carefully constructed to help ensure that levonorgestrel tablet will be used responsibly and appropriately.

Levonorgestrel Tablet, 0.75 mg is an over-the-counter (OTC) product for women age 17 or older, with a prescription-only requirement for women younger than age 17. The sales and marketing plan for levonorgestrel tablets, 0.75 mg has been designed to limit the availability of this product, to the extent practical, to pharmacies and clinics, and to educate healthcare professionals and consumers within the target age groups regarding the responsible use of levonorgestrel tablets, 0.75 mg. The need to take levonorgestrel tablets, 0.75 mg in as timely a manner as possible dictates that any responsible marketing program not only address healthcare professionals but also include extensive consumer education which includes a direct access component as a means of gaining such information. Thus, the MADESM (MORNING AFTER DEPENDABLE EDECATION) program contains elements that include an appropriate consumer education component. In addition, Lupin Pharmaceuticals will work closely with retail pharmacies and drug wholesalers to ensure that they will carry levonorgestrel tablets, 0.75 mg and that they will understand and follow the prescription age requirement for the dispensing of the product to women younger than age 17.

The MADESM program is intended to address issues affecting access to levonorgestrel tablets, 0.75 mg by providing sources of accurate and responsible information to both healthcare providers and consumers. It is also designed to provide a framework for pharmacies to ensure availability of levonorgestrel tablets, 0.75 mg as an OTC product when sought by knowledgeable



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consumers who are 17 years or older. Women younger than age 17 will require a prescription from their healthcare provider in order to obtain levonorgestrel tablets, 0.75 mg. The MADESM program is not intended to impact or change those who can lawfully prescribe or dispense levonorgestrel tablets, 0.75 mg under prevailing state laws.

Four core elements of MADESM contribute to the achievement of program objectives.

- Labeling/Packaging/Informational toll free number (to provide essential information to consumers in an accessible, easy to understand format. The levonorgestrel tablets, 0.75 mg packaging is designed to meet both prescription and OTC requirements.)
- Education (to provide information intended to educate physicians, pharmacists, pharmacy staff, nurse practitioners, and patients. Educational initiatives will focus on clearly instructing all audiences on the lower age requirement that women younger than age 17 obtain a prescription for levonorgestrel tablets, 0.75 mg.)
- Distribution (to ensure that levonorgestrel tablets, 0.75 mg will be available only to licensed drug wholesalers, retail operations with pharmacy services and clinics with licensed healthcare practitioners, and to successfully facilitate the levonorgestrel tablets, 0.75 mg prescription-only age requirement. These settings will also provide easy access by the consumer to a pharmacist or other healthcare professional should questions arise.)
- Monitoring (to evaluate the effectiveness of the program by determining if the age restriction is understood by all audiences and is properly being adhered to.)

I. Labeling/Packaging

The levonorgestrel tablets, 0.75 mg labeling was developed to provide clear and comprehensive communication of the key messages outlined above, and to make known additional sources of information. The levonorgestrel tablets, 0.75 mg packaging is designed to meet all requirements of both a prescription and over-the-counter product. The levonorgestrel tablets, 0.75 mg packaging will allow pharmacies to appropriately dispense levonorgestrel tablets, 0.75 mg as



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either a prescription or OTC product. The package also provides educational information to the consumer in a patient friendly format.

Elements of the package are as follows:

- The back of the carton includes the Drug Facts as well as a space for the pharmacy to place the required prescription labeling;
- The statement, “Rx only for women younger than age 17” appears on the Principal Display Panel and “prescription only for women younger than age 17. If you are younger than age 17, see a healthcare professional” appears on the Drug Facts panel of the carton;
- The inner portion of the carton houses the levonorgestrel tablets, 0.75 mg and clearly states the directions for when to take levonorgestrel tablets, 0.75 mg;
- The levonorgestrel tablets, 0.75 mg Package Insert and an educational booklet designed for the consumer (Consumer Information Leaflet) will be housed inside the carton;
- The toll-free number for the Information Line, which is operational from Monday to Friday, 9:00 am to 5:00 pm EST, and the levonorgestrel tablets, 0.75 mg web address are clearly displayed in the Drug Facts panel of the package should the consumer have additional questions on levonorgestrel tablets, 0.75 mg.

II. Education

The MADESM Program provides for an intensively educational approach to the introduction of levonorgestrel tablets, 0.75 mg as an OTC to those age 17 years or older. Educational programs will focus on both healthcare professionals as well as consumers. The consumer advertising is designed to stimulate discussions with healthcare providers. The program will assist healthcare providers in developing an adequate knowledge base so that they can provide responsible and accurate counseling to patients.

Efforts directed to raising consumer awareness of the product and its appropriate use will follow appropriate professional education programs. The educational materials will address not only



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levonorgestrel tablets, 0.75 mg but will encourage healthcare professionals to urge users to adopt routine forms of contraception and avoid reliance on levonorgestrel tablets, 0.75 mg as their primary form of birth control.

A. Educational Program to HealthCare Professionals.

Levonorgestrel tablets, 0.75 mg will be introduced and explained to healthcare professionals to raise awareness and knowledge levels as to this product for emergency contraception. This program is intended to ensure that healthcare professionals are prepared to support their patient populations.

Specifically, the lower prescription age requirement will be emphasized to healthcare professionals to ensure that they are knowledgeable of the prescription requirement for women younger than age 17, and that they understand how to appropriately dispense the levonorgestrel tablets, 0.75 mg package in both prescription and OTC scenarios.

B. Educational Campaign(s) to Consumers

Call center support for calls and inquiries resulting from Lupin Pharmaceutical's campaigns designed to convey critical awareness and educational messages as well as information about product availability, the time sensitivity of use, and the age requirements to obtain levonorgestrel tablets, 0.75 mg as a prescription or OTC product will be provided.

1. The intent will be to make consumers aware of the availability of emergency contraception, its appropriate use and the need to use it as soon as possible. Women younger than age 17 will be encouraged to contact their healthcare professional to learn about emergency contraception, routine forms of birth control, and sexually transmitted infection (STI)/human immunodeficiency virus (HIV).
2. The direct to consumer campaign will be designed to target those ages 17 to 44.
 - i) The language and visuals used will be appropriate and of interest to this targeted age group.



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III. Distribution

Lupin Pharmaceuticals believes that in the interest of responsible usage (and in recognition of the circumstances of the need for emergency contraception), levonorgestrel tablets, 0.75 mg should be available in those retail pharmacy outlets that typically sell a broad range of OTC medications and that have pharmacy services staffed with pharmacists (or, in the case of clinics, other healthcare professionals) during normal business hours to answer questions. Since levonorgestrel tablets, 0.75 mg will have a prescription only requirement for women younger than age 17, Lupin Pharmaceuticals and the third party distributors, wholesaler distribution and chain drug companies, will only be allowed to distribute levonorgestrel tablets, 0.75 mg to licensed pharmacies or other licensed healthcare clinics, as it would be unlawful to distribute a prescription product to any business that does not have a valid pharmacy license and/or physician license. Since levonorgestrel tablets, 0.75 mg has both Rx and OTC labeling, it will be treated as any other Rx product for distribution purposes; specifically, it would only be distributed to licensed pharmacies or healthcare clinics. Therefore, levonorgestrel tablets, 0.75 mg will not be available at gas stations or convenience stores. Additionally, since levonorgestrel tablets, 0.75 mg has both Rx and OTC labeling, the pharmacies will keep the product behind the counter and control it as an Rx product. The pharmacy and clinic settings will also allow pharmacists and other healthcare providers to properly restrict OTC access to those age 17 years or older.

IV. Monitoring

Lupin Pharmaceuticals intends to monitor trends in the use of emergency contraception to evaluate the effectiveness of the MADESM program and will make adjustments as appropriate. Monitoring will be accomplished in several ways, with information gathered from both healthcare professionals and consumers.

Monitoring actual use of levonorgestrel tablets, 0.75 mg is complex due to the difficulties inherent in identifying those who have purchased the product and in gathering useful,



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generalizable information. Consequently, the monitoring component will rely on a variety of sources intended to provide trend data, observational data, and signals of program effectiveness and potential problems. Monitoring components may include the following:

1. A market research survey or surveys of a subset of healthcare professionals (e.g. OB/GYN, family practice, pharmacists, nurses, family planning and health clinic personnel) to determine:
 - Whether the prescription requirement for women younger than age 17 is understood and is being adhered to at the point of purchase
 - Attitudes toward and experience with patients' usage of levonorgestrel tablets, 0.75 mg
 - Trends among emergency contraception users within their patient population (especially source of awareness, repeat use, use instead of more effective forms of contraception, incidence of STIs, etc.)
 - Nature of interactions with levonorgestrel tablets, 0.75 mg users (Does the contact with the healthcare professional occur prior to product usage? after usage? Are the women in search of contraceptive counseling? What types of side effects are being seen in use?)
 - Areas where additional information is needed in the marketplace, as identified by the questions raised by the users
2. Gathering data from actual users of levonorgestrel tablets, 0.75 mg is difficult because the number of users will be relatively small and because the decision to use emergency contraception is a private and emotional one. Women choosing to use the product are expected to wish to remain anonymous and are entitled to maintain their privacy. Nevertheless, Lupin Pharmaceuticals may work with a variety of sources in an effort to obtain and analyze consumer data in accordance with HIPAA regulations to assess the effectiveness of the MADESM program elements.



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MADESM Program

3. Monitoring compliance of the levonorgestrel tablets, 0.75 mg prescription age requirement can be somewhat complex because there will be no documented information on the purchasers of levonorgestrel tablets, 0.75 mg who were old enough to obtain it as an OTC product. Lupin Pharmaceuticals intends to monitor the level of comprehension of the prescription age requirement particularly at the pharmacy level, where the age of consumers must be assessed at the point of purchase. The following program will provide accurate information directly related to accessing compliance:

- **Point of Purchase Monitoring Program:**

Lupin Pharmaceuticals will continue to conduct a “Point-of-Purchase Monitoring Program”, which intends to track how levonorgestrel tablets, 0.75 mg is being sold at the time of purchase. Due to the challenges of obtaining specific purchase data on an OTC product and respecting consumer privacy, this program will include anonymous shoppers who will be directed to visit locations where levonorgestrel tablets, 0.75 mg is available and purchase the product. These transactions will be documented and analyzed to determine the level of comprehension of the levonorgestrel tablets, 0.75 mg prescription age requirement and how it is handled at the point of purchase. The shoppers in this program will be 15 to 16 years old. Parental consent will be obtained for the shoppers as they will be under the age of 18 years. Locations for this program will be selected based on areas where levonorgestrel tablets, 0.75 mg use is high, and will be in different regions of the US to provide a national representation of the findings. These findings would provide concrete information on how the prescription age requirement for levonorgestrel tablets, 0.75 mg is being addressed at the pharmacy and if it is properly being followed. Lupin Pharmaceuticals will use these findings to identify areas where more education on the prescription age restriction is needed and will focus their efforts on improving the level of understanding among pharmacists and the pharmacy staff. Findings from the study will be communicated to the pharmacy, and the corporate office, if appropriate, since education and retraining will be the first course of remedial action. In the case of



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repeat violators, the violator's State Board of Pharmacy will be notified. The Point-of-Purchase Monitoring Program will be conducted annually.

V. Reporting

Lupin Pharmaceuticals will provide FDA a monitoring report with the available results from the above monitoring activities, including the point of purchase monitoring, on an annual basis, with submission of the report within 60 calendar days after the interval date. Any change in reporting period will be requested by Lupin and agreed to by FDA.

Prepared by:

Lupin Pharmaceuticals, Inc.

Baltimore, Maryland 21202

United States

August 2012

Drug Facts
Active ingredient (in each tablet)
 Levonorgestrel USP 0.75 mg.....Emergency contraceptive

Use
 reduces chance of pregnancy after unprotected sex (if a contraceptive failed or if you did not use birth control)

Warnings
Allergy alert: Do not use if you have ever had an allergic reaction to levonorgestrel

Sexually transmitted diseases (STDs) alert: This product does not protect against HIV/AIDS or other STDs

Do not use
 if you are already pregnant (because it will not work)
 for regular birth control

When using this product you may have
 ■ dizziness ■ tiredness ■ headache ■ breast pain ■ nausea ■ lower stomach (abdominal) pain ■ vomiting

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control center right away.

Directions
 ■ women 17 years of age or older:
 ■ take the first tablet as soon as possible within 72 hours (3 days) after unprotected sex. The sooner you take the first tablet, the better it will work.
 ■ take the second tablet 12 hours after you take the first tablet
 ■ if you vomit within 2 hours of taking the medication, call a healthcare professional to find out if you should repeat the dose

Other information
 ■ before using this product read the enclosed consumer information leaflet for complete directions and information.
 ■ this product is not recommended for regular birth control. It does not work as well as most other birth control methods used correctly.
 ■ this product works mainly preventing ovulation (egg release). It may also prevent fertilization of a released egg (joining of sperm and egg) or attachment of a fertilized egg to the uterus (implantation).
 ■ when used correctly every time you have sex, latex condoms greatly reduce, but do not eliminate, the risk of pregnancy and the risk of catching or spreading HIV, the virus that causes AIDS. See condom labeling for additional STD information.
 ■ tablets are enclosed in a wallet seal. Do not use if the wallet seal is broken.
 ■ store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Inactive ingredients
 colloidal silicon dioxide, corn starch, lactose monohydrate, magnesium stearate, povidone.

Questions or comments?
 For more information or to speak to a healthcare professional, call 855-327-1136 from Monday-Friday, 9:00 am - 5:00 pm EST or visit website at: www.birthcontrolhealth.com

LOT NO.
EXP.

NDC 68180-851-13

Levonorgestrel Tablets,
0.75 mg

Each tablet contains:
levonorgestrel USP 0.75 mg
Usual Dosage: Take the first tablet as soon as possible but not later than 72 hours (3 days) after unprotected sex.
The sooner you take the first tablet, the more effective Levonorgestrel Tablets will be.
Take second tablet 12 hours later.
Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

218354

NDC 68180-851-13

Levonorgestrel Tablets,
0.75 mg

Emergency Contraceptive

This product is a **backup** method of preventing pregnancy and not for routine use. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

Rx only for women younger than age 17

Reduces the chance of pregnancy after unprotected sex (i.e., if a regular birth control method fails or after sex without birth control). Not Intended To Replace Regular Birth Control.
Levonorgestrel Tablets Should Be Used Only In Emergencies.

2 Tablets

www.birthcontrolhealth.com

NDC 68180-851-13
Levonorgestrel
Tablets, 0.75 mg

Distributed by:
Lupin Pharmaceuticals, Inc.
Baltimore, Maryland 21202
United States

Manufactured by:
Lupin Limited
Pithampur (M.P.) - 454775, INDIA
M.L.: 28/6/2010



120 mm

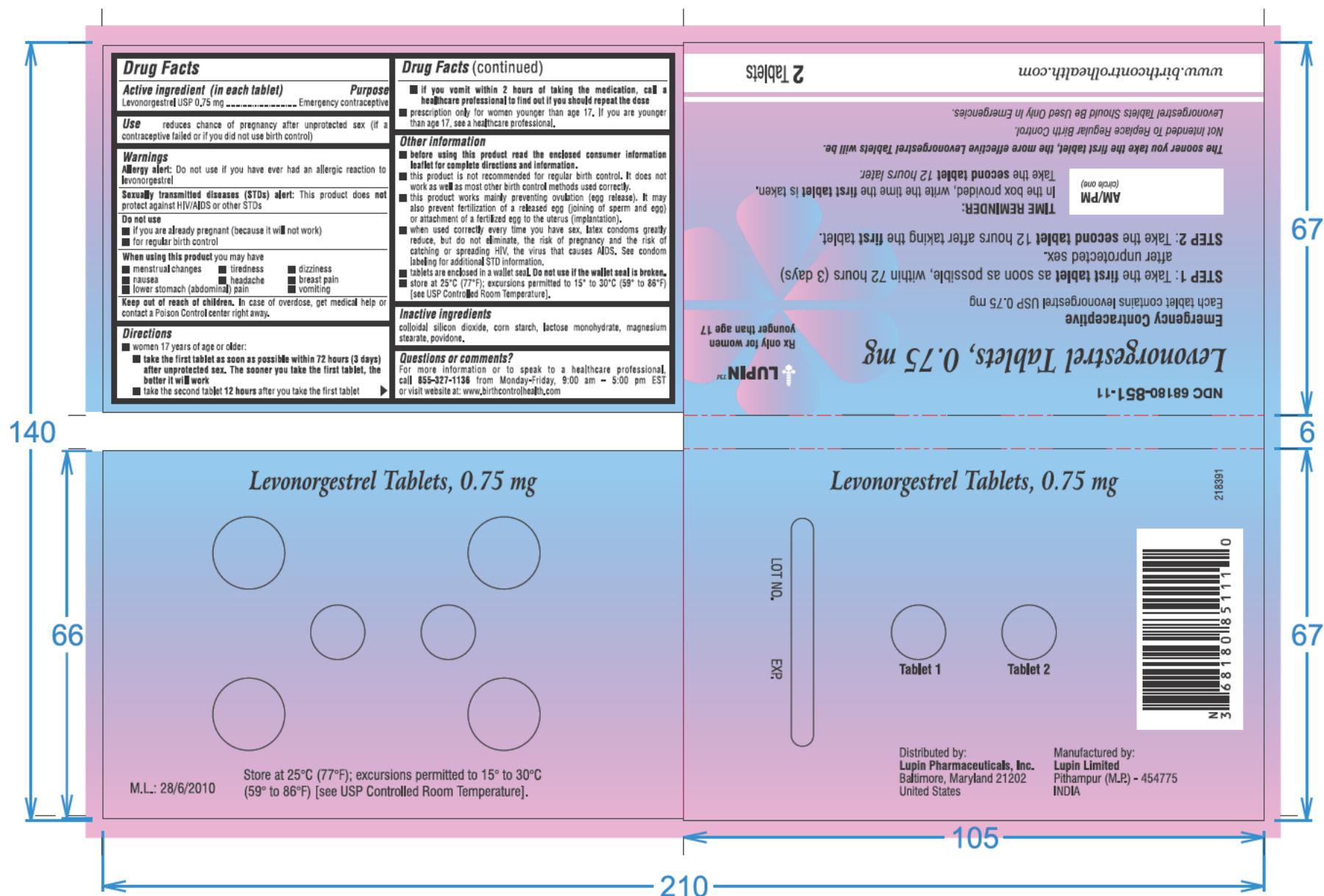
83 mm

20 mm

Lupin Pharmaceuticals					
Name	Levonorgestrel Tablets	Size	120 x 20 x 83 mm		
Type	Reverse Tuck In (Carton)	Date	14/08/12	Version	07
GSM	300	Colours	(b) (4)	(b) (4)	Black
Board	Cyber XL	Rated to	Plan B		
Molecule	Levonorgestrel Tablets 0.75 mg				

(b) (6)

D/Lupin/US/LPI Levonorgestrel/LPI Levonorgestrel Tablets 0.75 mg round 5 Carton.cdr



Lupin Pharmaceuticals				
Name	Levonorgestrel Tablets	Size	105 x 67 x 6 mm	
Type	Wallet	Date	14/08/12	Version 07
GSM	296 ± 5%	Colours	(b) (4)	(b) (4) Black
Board	Cyber XL	Rated to	Plan B	
Molecule	Levonorgestrel Tablets 0,75 mg			

(b) (6)

D:\Lupin\US\LPI Levonorgestrel\LPI Levonorgestrel Tablets 0.75 mg round 5 Wallet.cdr

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 091328

LABELING REVIEWS

**REVIEW OF PROFESSIONAL LABELING
APPROVAL SUMMARY
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number 091328
Date of Submission 08/22/2012
Applicant's Name Lupin Pharmaceuticals, Inc.
US Agent for Lupin Limited
Established Name Levonorgestrel Tablets, 0.75 mg
Proprietary Name None

REMS REQUIREMENTS:

MedGuides and/or PPIs (505-1(e))	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No	
Communication plan (505-1(e))	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No	
Elements to assure safe use (ETASU) (505-1(f)(3))	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No	
Implementation system if certain ETASU (505-1(f)(4))	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No	
Timetable for assessment (505-1(d))	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No	
ANDA REMS acceptable?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input checked="" type="checkbox"/> n/a

However this product is subject to **Marketing Support and Educational Program**. The sponsor has submitted their program (Morning After Dependable Education MADESM) for this ANDA, and a sister application (ANDA 201446). In the sister application the program was found acceptable by ONDs Division of Nonprescription Clinical Evaluation (DNCE). See Section 11.

APPROVAL SUMMARY:

Marketing Support and Educational Program.

Satisfactory with submission dated 08/22/2012

Blister Card Label (Established Name Labeling):

Satisfactory with submission dated 08/22/2012

Carton Labeling (Established Name Labeling):

Satisfactory with submission dated 08/22/2012

Package Insert Labeling (Established Name Labeling):

Satisfactory with submission dated 12/07/2011

Patient Labeling (Established Name Labeling):

Satisfactory with submission dated 12/07/2011

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Plan B[®]

NDA Number: 021045

NDA Drug Name: Ortho Plan B[®]

NDA Firm: Teva Women's Health Inc.

Date of Approval of NDA Insert and supplement #: S-015 approved July 10, 2009

Was this approval based upon an OGD labeling guidance? No

FOR THE RECORD

1. For the Record

This review was based on the labeling for Plan B[®] by Teva Women's Health Inc., NDA 021045/S-015 approved 07/10/2009. This supplemental new drug application provides for:

Over-the-counter (OTC) availability of Plan B[®] for women age 17 years and older. Plan B[®] reduces the chance of pregnancy after unprotected sex (if a contraceptive failed or if you did not use birth control).

Prescription availability of Plan B[®] for women younger than age 17 years. Plan B[®] is emergency contraception for prevention of pregnancy following unprotected intercourse or a known or suspected contraceptive failure.

2. Patents and Exclusivities (P&E)

There are no unexpired patents for this product.

There are no unexpired exclusivities for this product.

3. USP 35 (Checked 10/22/2012):

No Monograph present

4. PF 38 (Checked 10/22/2012):

No Monograph present

5. MedWatch (Checked 10/22/2012):

No entry after last supplement approval.

6. Quantitative Composition

Inactive Ingredients
Lactose Monohydrate
Corn Starch
Povidone
Colloidal Silicon Dioxide
Magnesium Stearate

Labeling Ingredients Consistent with :	
CMC submission	YES
Package Insert	YES
SPL	YES
Iron Content acceptable	N/A

7. Manufacturing Facility

The manufacturing, processing, testing and stability facilities are located at the following address:

Lupin Limited at Lupin Pharmicare Limited,
Plot No.2, Phase-II, SEZ,
Dist- Dhar, Pithampur,
Madhya Pradesh- 454774,
INDIA

8. Container system

The drug product will be packaged as follows: 2 tablets per blister per carton.

The blister consists of aluminum push-thru foil and ^{(b) (4)} film. Based on the results of long term stability studies only one pack i.e. either ^{(b) (6)} will be used for commercial batches.

9. Storage Condition

ANDA: store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

RLD: store at 20-25°C (68-77°F).

Taken from carton

10. Packaging Configuration and Description:

ANDA: Levonorgestrel Tablets, 0.75 mg are white to off white round biconvex tablets, debossed with “LU” on one side and “S24” on the other side.

Levonorgestrel Tablets, 0.75 mg are available in a wallet containing 2 tablets (NDC 68180-851-11).

Each wallet is packed in a carton (NDC 68180-851-13).

RLD: Plan B (levonorgestrel) tablets, 0.75 mg, are available for a single course of treatment in PVC/aluminum foil blister packages of two tablets each. The tablet is white, round and marked INOR on one side.

Available as: Unit-of-use NDC 51285-769-93

Taken from PI

11. Marketing Support and Educational Program:

The RLD is conducting a CARE (Convenient Access, Responsible Education) Program for Plan B[®] One-Step (NDA 021045) and Plan B[®] which are identical. A description of the program is below; taken directly from the RLD’s approval letter dated 07/10/2009. The program includes the following 4 core elements:

RLD’s CARE programs	ANDA’s submitted Morning After Dependable Education (MADE SM) Program.
Labeling/Packaging/Informational toll free number (to provide essential information to consumers in an accessible, easy to understand format. The Plan B One-Step packaging is designed to meet both prescription and OTC requirements.)	Labeling/Packaging/Informational toll free number (to provide essential information to consumers in an accessible, easy to understand format. The levonorgestrel tablets, 0.75 mg packaging is designed to meet both prescription and OTC requirements.)
Education (to provide information intended to educate physicians, pharmacists, pharmacy staff, nurse practitioners, and patients.)	Education (to provide information intended to educate physicians, pharmacists, pharmacy staff, nurse practitioners, and patients. Educational initiatives will focus on clearly instructing all audiences on the lower age requirement that women younger than age 17 obtain a prescription for levonorgestrel tablets, 0.75 mg.)
Distribution (to ensure that Plan B One-Step will be available only to licensed drug wholesalers, retail operations with pharmacy services and clinics with licensed healthcare practitioners, and to successfully facilitate the Plan B One-Step prescription-only age requirement.)	Distribution (to ensure that levonorgestrel tablets, 0.75 mg will be available only to licensed drug wholesalers, retail operations with pharmacy services and clinics with licensed healthcare practitioners, and to successfully facilitate the levonorgestrel tablets, 0.75 mg prescription-only age requirement. These settings will also provide easy access by the consumer to a pharmacist or other healthcare professional should questions arise.)
Monitoring (to evaluate the effectiveness of the program by determining if the age restriction is understood by all audiences and is properly being adhered to.)	Monitoring (to evaluate the effectiveness of the program by determining if the age restriction is understood by all audiences and is properly being adhered to.)

The sponsor’s MADESM program was reviewed by Division of Nonprescription Clinical Evaluation (DNCE), Consult dated 09/06/2012 in DARRTS and found acceptable in their sister ANDA 201446. See below:

REVIEW:

The construct of Lupin’s MADESM program mirrors that of the CARESM program in that it covers the same four core elements included in CARESM – labeling/packaging, education, distribution, and monitoring.

The following differences are noted in a side-by-side comparison of the CARESM and MADESM programs:

1. *The toll-free, Information Line for CARESM is available to consumers around the clock. Lupin's MADESM program describes the Information Line as being operational from Monday to Friday, 9:00 am to 5:00 EST.*
2. *The 2009 CARESM program described a consumer education campaign, which was to be initiated "immediately" following the approval of Plan B One-Step. This campaign was intended to address potential consumer confusion related to the simplified dosing regimen for Plan B One-Step in comparison to Plan B. Such education campaign is no longer necessary three years after the approval of Plan B One-Step.*
3. *Lupin's MADESM program does not include Continuing Education programs for the pharmacists.*
4. *Lupin does not state that new promotional materials will be submitted to the FDA's Division of Marketing, Advertising, and Communications for comment.*
5. *Unlike the CARESM program, Lupin's proposal does not explicitly state that media placements targeting audiences younger than age 17 will not be used. However, the MADESM program indicates that direct-to-consumer campaign will be designed to target those aged 17 to 44 years.*

These differences are not critical to Lupin's marketing and educational support program for the generic availability of levonorgestrel 1.5 mg tablet to be used for emergency contraception. It has been more than six years since the approval of Plan B (and more than three years since the approval of Plan B One-Step); continuing education programs for pharmacists are not necessary. In addition, given the success of label comprehension and actual use studies that FDA has reviewed for Plan B One-Step and Plan B, and given the variety of ways consumers can access information regarding emergency contraception, an Information Line in operation continuously is not necessary.

CONCLUSION AND RECOMMENDATIONS

The proposed MADESM program sufficiently parallels the existing CARESM program. No additional risk mitigation elements are needed for Lupin's generic levonorgestrel 1.5 mg product.

Taken from DNCE review dated 09/06/2012

12. Proprietary Name and DMEPA Review:

None-however DMEPA reviewed the established name dated 03/28/2012

A. WALLET BLISTER LABEL AND CARTON LABELING

1. Revise the presentation of the established name and strength, Levonorgestrel Tablets, 0.75 mg, to use a type and font size that is more prominent and does not look like script.

2. The Rx statement on your principal display panel is incorrect. Patients 17 and above may receive this product without a prescription. Therefore, we request you revise the statement to read as follows: “Rx only for women younger than age 17”.
3. Delete “USP” from the statement on the principal display panel to read:
“Each tablet contains levonorgestrel 0.75 mg”.
4. Revise the presentation of the established name and strength on the principal display panel of the Carton Labeling by deleting the comma after “Tablets” and adding “per tablet” after the strength. The revised established name and strength should read:
Levonorgestrel Tablets
0.75 mg per tablet
5. The manufacturer’s name “Lupin” and the associated logo are too prominent and compete with the proprietary name. Decrease the size of the manufacturer’s name and logo so that it is less prominent than the proprietary name.

B. WALLET BLISTER LABEL

1. Remove the words “(b) (4)” in the statement starting with **STEP 2** to read:
“Take the **second tablet** 12 hours after taking the **first** tablet.”
2. In accordance with 21 CFR 201.17, ensure the wallet blister label incorporates the expiration date and lot number.

13. Labeling Format:

Style: Helvetica-Condensed Size: 9 Sample of Medication Guide:	Style: Helvetica-Condensed Size: 6 Sample of package insert:
<p>What are levonorgestrel tablets, 0.75 mg? Levonorgestrel tablets, 0.75 mg are emergency contraception that helps prevent pregnancy after birth control failure or unprotected sex. It is a backup method of preventing pregnancy and is not to be used routinely.</p>	<p>FULL PRESCRIBING INFORMATION 1 INDICATIONS AND USAGE Levonorgestrel tablets, 0.75 mg are progestin-only emergency contraceptive indicated for prevention of pregnancy following unprotected intercourse or a known or suspected contraceptive failure. To obtain optimal efficacy, the First tablet should be taken as soon as possible within 72 hours of intercourse. The second tablet should be taken 12 hours later</p>

DRUG FACTS TEXT DEFINED IN CARTON	TYPE SIZE	TYPE FONT
DRUG FACTS Title	9	Helvetica Bold Italic, condensed
DRUG FACTS CONTINUED	8	Helvetica Bold Italic, condensed
HEADINGS	8	Helvetica Bold Italic, condensed
SUBHEADS/BODY TEXT	6	Helvetica Bold Italic, condensed
BULLETS	5	

DRUG FACTS TEXT DEFINED IN WALLET	TYPE SIZE	TYPE FONT
DRUG FACTS Title	9	Helvetica Bold Italic, condensed
DRUG FACTS CONTINUED	8	Helvetica Bold Italic, condensed
HEADINGS	6.5	Helvetica Bold Italic, condensed
SUBHEADS/BODY TEXT	5	Helvetica Bold Italic, condensed
BULLETS	5	

ALL fonts in the labeling is ACCEPTABLE

14. SPL

LEVONORGESTREL

levonorgestrel tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG LABEL	Item Code (Source)	NDC:68180- 851
Route of Administration	ORAL	DEA Schedule	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength

LEVONORGESTREL (LEVONORGESTREL)		LEVONORGESTREL	0.75 mg
Inactive Ingredients			
Ingredient Name		Strength	
SILICON DIOXIDE			
STARCH, CORN			
POVIDONE			
LACTOSE MONOHYDRATE			
MAGNESIUM STEARATE			
Product Characteristics			
Color	WHITE (White to off white)	Score	no score
Shape	ROUND (round biconvex)	Size	8mm

Flavor		Imprint Code	LU;S24
Contains			
Packaging			
#	Item Code	Package Description	
1	NDC:68180-851-13	1 BLISTER PACK (BLISTER PACK) in 1 CARTON	
1	NDC:68180-851-11	2 TABLET (TABLET) in 1 BLISTER PACK	
Marketing Information			
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA091328		
Labeler - LUPIN PHARMACEUTICALS INC (089153071)			

Registrant - LUPIN LIMITED (675923163)

Establishment

Name	Address	ID/FEI	Operations
LUPIN LIMITED		863645527	Manufacture

Revised: 12/2011

LUPIN PHARMACEUTICALS INC

Date of Review 10/22/2012
Date of Submission 08/22/2012
Primary Reviewer Malik Imam
Team Leader Lillie Golson

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

/s/

MALIK M IMAM
10/31/2012

LILLIE D GOLSON
10/31/2012

**REVIEW OF PROFESSIONAL LABELING #1
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number	091328
Date of Submission	04/15/2009, 09/30/2011, 12/07/2011, 01/03/2012, and 01/04/2012
Applicant's Name	Lupin Pharmaceuticals, Inc. US Agent for Lupin Limited
Established Name	Levonorgestrel Tablets, 0.75 mg
Proprietary Name	None

Labeling Deficiencies:

A. General Comments:

Please revise both carton and wallet labels in order to comply with the labeling format requirements of 21 CFR 201.66. Also please submit a format legend with carton and wallet labels.

B. Carton Label:

1. See GENERAL COMMENTS above.
2. In the section titled "When using this product you may have" please ensure you have the same side effects listed as the RLD.
3. Revise the presentation of the established name and strength, Levonorgestrel Tablets, 0.75 mg, to use a type and font size that is more prominent and does not look like script.
4. The Rx statement on your principal display panel is incorrect. Patients 17 and above may receive this product without a prescription. Therefore, we request you revise the statement to read as follows:
"Rx only for women younger than age 17".
5. Delete "USP" from the statement on the principal display panel to read:
"Each tablet contains levonorgestrel 0.75 mg".
6. The manufacturer's name "Lupin" and the associated logo are too prominent and compete with the proprietary name. Decrease the size of the manufacturer's name and logo so that it is less prominent than the proprietary name.

C. Blister Card:

1. See GENERAL COMMENTS above.
2. Please see note B-2 through B-6
3. Remove the words (b) (4) in the statement starting with **STEP 2** to read:
"Take the **second tablet** 12 hours after taking the **first** tablet."
4. In accordance with 21 CFR 201.17, ensure the wallet blister label incorporates the expiration date and lot number.

Please submit final printed labeling electronically.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with the last approved labeling of the **RLD** with all differences annotated and explained.

{See appended electronic signature page}

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REMS REQUIREMENTS:

- MedGuides and/or PPIs (505-1(e)) Yes No
- Communication plan (505-1(e)) Yes No
- Elements to assure safe use (ETASU) (505-1(f)(3)) Yes No
- Implementation system if certain ETASU (505-1(f)(4)) Yes No
- Timetable for assessment (505-1(d)) Yes No
- ANDA REMS acceptable? Yes No n/a

APPROVAL SUMMARY:

Blister Card Label:

See comments above.

Carton Labeling:

See comments above.

Package Insert Labeling:

Satisfactory in FPL with submission dated 12/07/2011

Medication Guide Labeling:

Satisfactory in FPL with submission dated 12/07/2011

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Plan B[®]

NDA Number: 021045

NDA Drug Name: Ortho Plan B[®]

NDA Firm: Teva Women's Health Inc.

Date of Approval of NDA Insert and supplement #: S-015 approved July 10, 2009

Was this approval based upon an OGD labeling guidance? No

FOR THE RECORD

1. For the Record

This review was based on the labeling for Plan B[®] by Teva Women's Health Inc., NDA 021045/S-015 approved 07/10/2009. This supplemental new drug application provides for:

Over-the-counter (OTC) availability of Plan B[®] for women age 17 years and older. Plan B[®] reduces the chance of pregnancy after unprotected sex (if a contraceptive failed or if you did not use birth control).

Prescription availability of Plan B[®] for women younger than age 17 years. Plan B[®] is emergency contraception for prevention of pregnancy following unprotected intercourse or a known or suspected contraceptive failure.

2. Patents and Exclusivities (P&E)

There are no unexpired patents for this product.

There are no unexpired exclusivities for this product.

3. USP 35 (Checked 05/16/2012):

Levonorgestrel

Packaging and storage-Preserve in well-closed light-resistant containers

4. PF 38 (Checked 05/09/2012):

No current issues listed

5. MedWatch (Checked 05/09/2012):

No entry after last supplement approval.

6. Quantitative Composition

Inactive Ingredients
Lactose Monohydrate
Corn Starch
Povidone
Colloidal Silicon Dioxide
Magnesium Stearate

Labeling Ingredients Consistent with :	
CMC submission	YES
Package Insert	YES
SPL	YES
Iron Content acceptable	N/A

7. Manufacturing Facility

The manufacturing, processing, testing and stability facilities are located at the following address:

Lupin Limited at Lupin Pharmicare Limited,
Plot No.2, Phase-II, SEZ,
Dist- Dhar, Pithampur,
Madhya Pradesh- 454774,
INDIA

8. Container system

The drug product will be packaged as follows: 2 tablets per blister per carton.

The blister consist of aluminum push-thru foil and (b) (4) film. Based on the results of long term stability studies only one pack i.e. either (b) (4) will be used for commercial batches.

9. Storage Condition

ANDA: store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

RLD: store at 20-25°C (68-77°F).
Taken from carton

10. Packaging Configuration and Description:

ANDA: Levonorgestrel Tablets, 0.75 mg are white to off white round biconvex tablets, debossed with "LU" on one side and "S24" on the other side.
Levonorgestrel Tablets, 0.75 mg are available in a wallet containing 2 tablets (NDC 68180-851-11). Each wallet is packed in a carton (NDC 68180-851-13).

RLD: Plan B (levonorgestrel) tablets, 0.75 mg, are available for a single course of treatment in PVC/aluminum foil blister packages of two tablets each. The tablet is white, round and marked INOR on one side.

Available as: Unit-of-use NDC 51285-769-93

Taken from PI

11. Proprietary Name and DMEPA Review:

None-however DMEPA reviewed the established name dated 03/28/2012

A. WALLET BLISTER LABEL AND CARTON LABELING

1. Revise the presentation of the established name and strength, Levonorgestrel Tablets, 0.75 mg, to use a type and font size that is more prominent and does not look like script.
2. The Rx statement on your principal display panel is incorrect. Patients 17 and above may receive this product without a prescription. Therefore, we request you revise the statement to read as follows: "Rx only for women younger than age 17".
3. Delete "USP" from the statement on the principal display panel to read:
"Each tablet contains levonorgestrel 0.75 mg".
4. Revise the presentation of the established name and strength on the principal display panel of the Carton Labeling by deleting the comma after "Tablets" and adding "per tablet" after the strength. The revised established name and strength should read:
Levonorgestrel Tablets
0.75 mg per tablet
5. The manufacturer's name "Lupin" and the associated logo are too prominent and compete with the proprietary name. Decrease the size of the manufacturer's name and logo so that it is less prominent than the proprietary name.

B. WALLET BLISTER LABEL

1. Remove the words (b) (4) in the statement starting with **STEP 2** to read:
"Take the **second tablet** 12 hours after taking the **first** tablet."
2. In accordance with 21 CFR 201.17, ensure the wallet blister label incorporates the expiration date and lot number.

12. Labeling Format:

<p>Style: Helvetica-Condensed Size: 9 Sample of Medication Guide:</p>	<p>Style: Helvetica-Condensed Size: 6 Sample of package insert:</p>
<p>What are levonorgestrel tablets, 0.75 mg? Levonorgestrel tablets, 0.75 mg are emergency contraception that helps prevent pregnancy after birth control failure or unprotected sex. It is a backup method of preventing pregnancy and is not to be used routinely.</p>	<p>FULL PRESCRIBING INFORMATION 1 INDICATIONS AND USAGE Levonorgestrel tablets, 0.75 mg are progestin-only emergency contraceptive indicated for prevention of pregnancy following unprotected intercourse or a known or suspected contraceptive failure. To obtain optimal efficacy, the First tablet should be taken as soon as possible within 72 hours of intercourse. The second tablet should be taken 12 hours later</p>

DRUG FACTS TEXT DEFINED IN CARTON	TYPE SIZE	TYPE FONT
DRUG FACTS Title	5	(b) (4)
DRUG FACTS CONTINUED	5	
HEADINGS	5	
SUBHEADS/BODY TEXT	5	
BULLETS	5	

DRUG FACTS TEXT DEFINED IN WALLET	TYPE SIZE	TYPE FONT
DRUG FACTS Title	4.5	(b) (4)
DRUG FACTS CONTINUED	4.5	
HEADINGS	4.5	
SUBHEADS/BODY TEXT	4.5	
BULLETS	4.55	

13. SPL**LEVONORGESTREL**

levonorgestrel tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG LABEL	Item Code (Source)	NDC:68180- 851
Route of Administration	ORAL	DEA Schedule	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
LEVONORGESTREL (LEVONORGESTREL)	LEVONORGESTREL	0.75 mg

Inactive Ingredients

Ingredient Name	Strength
SILICON DIOXIDE	

STARCH, CORN	
POVIDONE	
LACTOSE MONOHYDRATE	
MAGNESIUM STEARATE	

Product Characteristics

Color	WHITE (White to off white)	Score	no score
Shape	ROUND (round biconvex)	Size	8mm
Flavor		Imprint Code	LU;S24
Contains			

Packaging

#	Item Code	Package Description
---	-----------	---------------------

1	NDC:68180-851-13	1 BLISTER PACK (BLISTER PACK) in 1 CARTON
1	NDC:68180-851-11	2 TABLET (TABLET) in 1 BLISTER PACK

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA091328		

Labeler - LUPIN PHARMACEUTICALS INC (089153071)

Registrant - LUPIN LIMITED (675923163)

Establishment

Name	Address	ID/FEI	Operations
LUPIN LIMITED		863645527	Manufacture

Revised: 12/2011

LUPIN PHARMACEUTICALS INC

Date of Review	05/16/2012
Date of Submission	04/15/2009, 09/30/2011, 12/07/2011, 01/03/2012, and 01/04/2012
Primary Reviewer	Malik Imam
Team Leader	Lillie Golson

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

/s/

MALIK M IMAM
05/25/2012

LILLIE D GOLSON
05/25/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 091328

CHEMISTRY REVIEWS

Date: 1/17/2013

To: ANDA 091328
Levonorgestrel Tablets, 0.75 mg
Lupin

From: Robert Iser, Division Director, DC IV

RE: Clarification on Drug Substance and Drug Product specifications – addendum to
Rev #3

As multiple revisions of specifications can be found in Review #3, for clarification the
current Drug Substance Specification is as follows:





For clarification the current Drug Product Specification is as follows:



Current specifications were provided in the amendment dated 3/29/2012. All the proposed criteria remain acceptable from review #3.

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

/s/

ROBERT L ISER
01/17/2013
Director, DC IV

ANDA 091328

Levonorgestrel Tablets, 0.75 mg (Rx/OTC)

Lupin Limited

**Roslyn Friar Powers, Ph.D.
Office of Generic Drugs
Division of Chemistry IV
Team 44**

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Chemistry Review Data Sheet

1. ANDA #: 091328
2. REVIEW #: 3
3. REVIEW DATE: 21-MAR-2012
4. REVIEWER: Roslyn Friar Powers, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous DocumentsOriginalAmendmentDocument Date15-APR-200917-JAN-2012

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

Amendment

14-MAR-2012

Amendment

29-MAR-2012

7. NAME & ADDRESS OF APPLICANT:

Name: Lupin Limited

Address: 159, CST Road, Kalina, Santacruz (East)
Mumbai-400 098, Maharashtra, INDIA

Leslie Sands

Representative: Lupin Pharmaceuticals Inc.,
Harborplace Tower, 111 South Calvert Street, 21st Floor,
Baltimore, Maryland 21202 United States.
Tel: (410) 5762000 & Fax: (410) 5762221

Telephone: (410) 576-2000

Fax: (410) 576-2221

8. DRUG PRODUCT NAME:

a) Proprietary Name: The proposed names: (b) (4) and (b) (4) have been denied (per letter dated 01/27/12 (see DARRTS))

Chemistry Review Data Sheet

b) Non-Proprietary Name (USAN): Levonorgestrel Tablets, 0.75 mg

9. LEGAL BASIS FOR SUBMISSION:

NDA: Plan B® (Levonorgestrel) 0.75 mg

Firm: Duramed Research, Inc.

Reference Listed Drug Information	
Name	Plan B®
Active Ingredients	Levonorgestrel
Route of Administration	Oral
Dosage Form	Tablet
Strength	0.75 mg Levonorgestrel
NDA Number	021045
NDA Holder	Duramed Research Inc.

The dosage form, route of administration, indications and usage, active ingredient, strength and labeling (except for differences detailed in labeling section of this ANDA) for the proposed generic drug product are the same as those of the RLD noted above.

(a) The basis for the Lupin's proposed ANDA for Levonorgestrel Tablets, 0.75 mg is the reference listed drug (RLD) Plan B® (Levonorgestrel) Tablets, 0.75 mg covered under New Drug Application (NDA) 021045, which is held by Duramed Research, Inc. The NDA and proposed ANDA are over-the-counter drug products.

Information regarding the RLD, Plan B® (Levonorgestrel) Tablets, 0.75 mg, as noted in the 28th Edition of the *Approved Drug Product List with Therapeutic Equivalence Evaluations* (Electronic Orange Book) is included in this section.

(b) Patent and exclusivity statements are included in this section in **Module 1, Section 1.3.5.1 Patent Information on Any Patent** and **Module 1, Section 1.3.5.3 Exclusivity Statement**, respectively.

There are no unexpired patents for Plan B® (Levonorgestrel) Tablets, 0.75 mg.

Patent Information – Provided in Section 1.3.5.1

Patent Certification - Provided in Section 1.3.5.2

Exclusivity Statement – Provided in Section 1.3.5.3.

Patent Data

There are no unexpired patents for this product in the Orange Book Database.

[Note: Title I of the 1984 Amendments does not apply to drug products submitted or approved under the former Section 507 of the Federal Food, Drug and Cosmetic Act (antibiotic products). Drug products of this category will not have patents listed.]

Exclusivity Data

Chemistry Review Data Sheet

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
021045	002	NP	AUG 24, 2009

The applicant states there are no relevant patents.

10. PHARMACOL. CATEGORY: Levonorgestrel tablets reduce the chances of pregnancy after unprotected sex (if a contraceptive failed or if you did not use birth control).

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 0.75 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

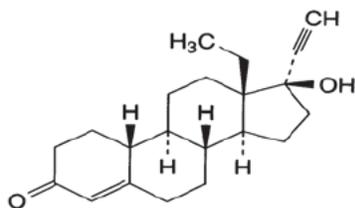
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name : 18,19-Dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-, (17 α)-(-); (-)-13-Ethyl-17-hydroxy-18,19-dinor-17 α -pregn-4-en-20-yn-3-one.

CAS# : 797-63-7

USAN : Levonorgestrel

Molecular Structure:



Molecular Formula: C₂₁H₂₈O₂
Molecular Weight: 312.45

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:
A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	3	Adequate	02-FEB-2012	Reviewed by R. Niles
	III			4			
	III			4			
	III			4			

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A
18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending		
Methods Validation	N/A		
Labeling	Approvable		
*Bioequivalence Dissolution	Pending Acceptable	30-OCT-2009	H. Mandula
EA	Acceptable	26-JUN-2011	RFPowers
Radiopharmaceutical	N/A		
Pharm/Tox	N/A		
Proprietary Name	Denied	27-JAN-2012	S. Jackson

Chemistry Review Data Sheet

*Pending DSI inspection- Outcome: Data accepted for review [4-JUN-2010]

Accepted Dissolution Information:

Medium: 0.1 N HCl with 0.1% Sodium Lauryl

Sulfate (SLS)

Volume: 1000 mL

Temperature: 37°C ± 0.5°C

USP Apparatus: II (Paddle)

Speed: 75 rpm

The test product should meet the following specification:

NLT (b) (4) (Q) of the labeled amount of Levonorgestrel in 60 minutes.

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. Yes No If no, explain reason(s) below:

The Chemistry Review for ANDA 91328

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

CMC Approvable

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable - N/A

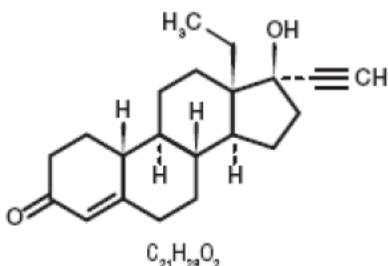
II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance:

Levonorgestrel USP is a white or practically white odorless powder, with no reported polymorphism in the literature. Levonorgestrel is the (-) form of Norgestrel; and Norgestrel USP is composed of (+) form and (-) form. The drug substance is practically insoluble in water; soluble in chloroform; slightly soluble in alcohol. There is no report in the literature on the pH dependence of the aqueous solubility. Specifications are based on USP and DMF holder (b)(4).

Levonorgestrel has a molecular weight of 312.45, and the following structural and molecular formulas:



Based on MDD of 1.5 mg, Identification threshold and Qualification threshold are DS: 0.10% and 0.15% and DP: 0.50% and 1.0%, respectively.

Drug Product:

Emergency contraceptive tablet. Each levonorgestrel tablet contains 0.75 mg of a single active steroid ingredient, levonorgestrel [18,19-Dinorpregn-4-en-20-yn-3-one-13-ethyl-17-hydroxy-, (17 α)-(-)-], a totally synthetic progestogen. The inactive ingredients present are corn starch, colloidal silicon dioxide, lactose monohydrate, magnesium stearate, and povidone.

Based on MDD of 1.5 mg,

ICH Q3A(R): Identification threshold NMT 0.10% and Qualification threshold 0.15%

Chemistry Assessment Section

ICH Q3B(R): Identification threshold NMT 0.50% and Qualification threshold 1.0%

How Supplied:

Levonorgestrel Tablets containing 0.75 mg of Levonorgestrel, are white to off white round biconvex tablets, debossed with 'LU' on one side and 'S24' on the other side. Levonorgestrel tablets are available in 2's blister pack. One blister pack in a carton.

Storage Conditions/Dispensing Recommendations:

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

USP:

No USP drug product monograph in the current USP

B. Description of How the Drug Product is Intended to be Used

Indications and Usage:

(b) (4)

Please see labeling insert for more details.

C. Basis for Approvability or Not-Approval Recommendation

CMC Approvable

Endorsements (Draft and Final with Dates):

HFD-630 / RFPowers Review/21-MAR-2012; 03-APR-2012

HFD-630 /USAtwal – Team Leader /04-05-2012

HFD-617 AKim – Project Manager /4/9/12

C:\DOCUMENTS AND SETTINGS\POWERSR\DESKTOP\91328.R002.DOC

TYPE OF LETTER: Approvable

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

/s/

ROSLYN F POWERS
04/11/2012

UPINDER S ATWAL
04/11/2012

ANDREW KIM
04/11/2012

ANDA 091328

Levonorgestrel Tablets, 0.75 mg (Rx/OTC)

Lupin Limited

**Roslyn Friar Powers, Ph.D.
Office of Generic Drugs
Division of Chemistry IV
Team 44**

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Chemistry Review Data Sheet

1. ANDA #: 091328
2. REVIEW #: 2
3. REVIEW DATE: 25-Jan-2012
4. REVIEWER: Roslyn Friar Powers, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

Original

15-APR-2009

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Amendment

17-JAN-2012

7. NAME & ADDRESS OF APPLICANT:

Name:	Lupin Limited
Address:	159, CST Road, Kalina, Santacruz (East) Mumbai-400 098, Maharashtra, INDIA
Representative:	Leslie Sands Lupin Pharmaceuticals Inc., Harborplace Tower, 111 South Calvert Street, 21 st Floor, Baltimore, Maryland 21202 United States. Tel: (410) 5762000 & Fax: (410) 5762221
Telephone:	(410) 576-2000
Fax:	(410) 576-2221

8. DRUG PRODUCT NAME:

- a) Proprietary Name: The proposed names: (b) (4) and (b) (4) have been denied (per letter dated 01/27/12 (see DARRTS))
- b) Non-Proprietary Name (USAN): Levonorgestrel Tablets, 0.75 mg

Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION:

NDA: Plan B® (Levonorgestrel) 0.75 mg
 Firm: Duramed Research, Inc.

Reference Listed Drug Information	
Name	Plan B®
Active Ingredients	Levonorgestrel
Route of Administration	Oral
Dosage Form	Tablet
Strength	0.75 mg Levonorgestrel
NDA Number	021045
NDA Holder	Duramed Research Inc.

The dosage form, route of administration, indications and usage, active ingredient, strength and labeling (except for differences detailed in labeling section of this ANDA) for the proposed generic drug product are the same as those of the RLD noted above.

(a) The basis for the Lupin’s proposed ANDA for Levonorgestrel Tablets, 0.75 mg is the reference listed drug (RLD) Plan B® (Levonorgestrel) Tablets, 0.75 mg covered under New Drug Application (NDA) 021045, which is held by Duramed Research, Inc. The NDA and proposed ANDA are over-the-counter drug products.

Information regarding the RLD, Plan B® (Levonorgestrel) Tablets, 0.75 mg, as noted in the 28th Edition of the *Approved Drug Product List with Therapeutic Equivalence Evaluations* (Electronic Orange Book) is included in this section.

(b) Patent and exclusivity statements are included in this section in **Module 1, Section 1.3.5.1 Patent Information on Any Patent** and **Module 1, Section 1.3.5.3 Exclusivity Statement**, respectively.

There are no unexpired patents for Plan B® (Levonorgestrel) Tablets, 0.75 mg.

Patent Information – Provided in Section 1.3.5.1

Patent Certification - Provided in Section 1.3.5.2

Exclusivity Statement – Provided in Section 1.3.5.3.

Patent Data

There are no unexpired patents for this product in the Orange Book Database.

[Note: Title I of the 1984 Amendments does not apply to drug products submitted or approved under the former Section 507 of the Federal Food, Drug and Cosmetic Act (antibiotic products). Drug products of this category will not have patents listed.]

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
91328.R002		4	

Chemistry Review Data Sheet

021045

002

NP

AUG 24, 2009

The applicant states there are no relevant patents.

10. PHARMACOL. CATEGORY: Levonorgestrel tablets reduce the chances of pregnancy after unprotected sex (if a contraceptive failed or if you did not use birth control).

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 0.75 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

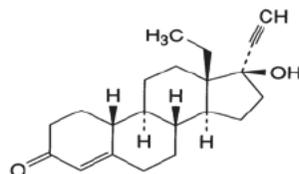
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name : 18,19-Dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-, (17 α)-(-);
(-)-13-Ethyl-17-hydroxy-18,19-dinor-17 α -pregn-4-en-20-yn-3-one.

CAS# : 797-63-7

USAN : Levonorgestrel

Molecular Structure:



Molecular Formula: C₂₁H₂₈O₂

Molecular Weight: 312.45



Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	3	Adequate	02-FEB-2012	Reviewed by R. Niles
	III			4			
	III			4			
	III			4			

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	02-APR-2010	M. Stock
Methods Validation	N/A		
Labeling	Pending		
*Bioequivalence	Pending		
Dissolution	Acceptable	30-OCT-2009	H. Mandula
EA	Acceptable	26-JUN-2011	RFPowers
Radiopharmaceutical	N/A		
Pharm/Tox	N/A		
Proprietary Name	Denied	27-JAN-2012	S. Jackson

91328.R002

6



Chemistry Review Data Sheet

*Pending DSI inspection- Outcome: Data accepted for review [4-JUN-2010]

Accepted Dissolution Information:

Medium: 0.1 N HCl with 0.1% Sodium Lauryl

Sulfate (SLS)

Volume: 1000 mL

Temperature: 37°C ± 0.5°C

USP Apparatus: II (Paddle)

Speed: 75 rpm

The test product should meet the following specification:

NLT ^{(b)(4)} (Q) of the labeled amount of Levonorgestrel in 60 minutes.

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. Yes No If no, explain reason(s) below:

The Chemistry Review for ANDA 91328

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not Approvable, Minor

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable - N/A

II. Summary of Chemistry Assessments

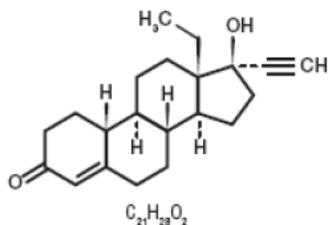
A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance:

Levonorgestrel USP is a white or practically white odorless powder, with no reported polymorphism in the literature. Levonorgestrel is the (-) form of Norgestrel; and Norgestrel USP is composed of (+) form and (-) form. The drug substance is practically insoluble in water; soluble in chloroform; slightly soluble in alcohol. There is no report in the literature on the pH dependence of the aqueous solubility.

Specifications are based on USP and DMF holder (b) (4)

Levonorgestrel has a molecular weight of 312.45, and the following structural and molecular formulas:



Based on MDD of 1.5 mg, Identification threshold and Qualification threshold are DS: 0.10% and 0.15% and DP: 0.50% and 1.0%, respectively.

Drug Product:

Emergency contraceptive tablet. Each levonorgestrel tablet contains 0.75 mg of a single active steroid ingredient, levonorgestrel [18,19-Dinorpregn-4-en-20-yn-3-one-13-ethyl-17-hydroxy-, (17 α)- (-)-], a totally synthetic progestogen. The inactive ingredients present are corn starch, colloidal silicon dioxide, lactose monohydrate, magnesium stearate, and povidone.

Based on MDD of 1.5 mg,

ICH Q3A(R): Identification threshold NMT 0.10% and Qualification threshold 0.15%

Chemistry Assessment Section

ICH Q3B(R): Identification threshold NMT 0.50% and Qualification threshold 1.0%

How Supplied:

Levonorgestrel Tablets containing 0.75 mg of Levonorgestrel, are white to off white round biconvex tablets, debossed with 'LU' on one side and 'S24' on the other side. Levonorgestrel tablets are available in 2's blister pack. One blister pack in a carton.

Storage Conditions/Dispensing Recommendations:

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

USP:

No USP drug product monograph in the current USP

B. Description of How the Drug Product is Intended to be Used

Indications and Usage:

 (b) (4)

Please see labeling insert for more details.

C. Basis for Approvability or Not-Approval Recommendation

Not Approvable, Minor

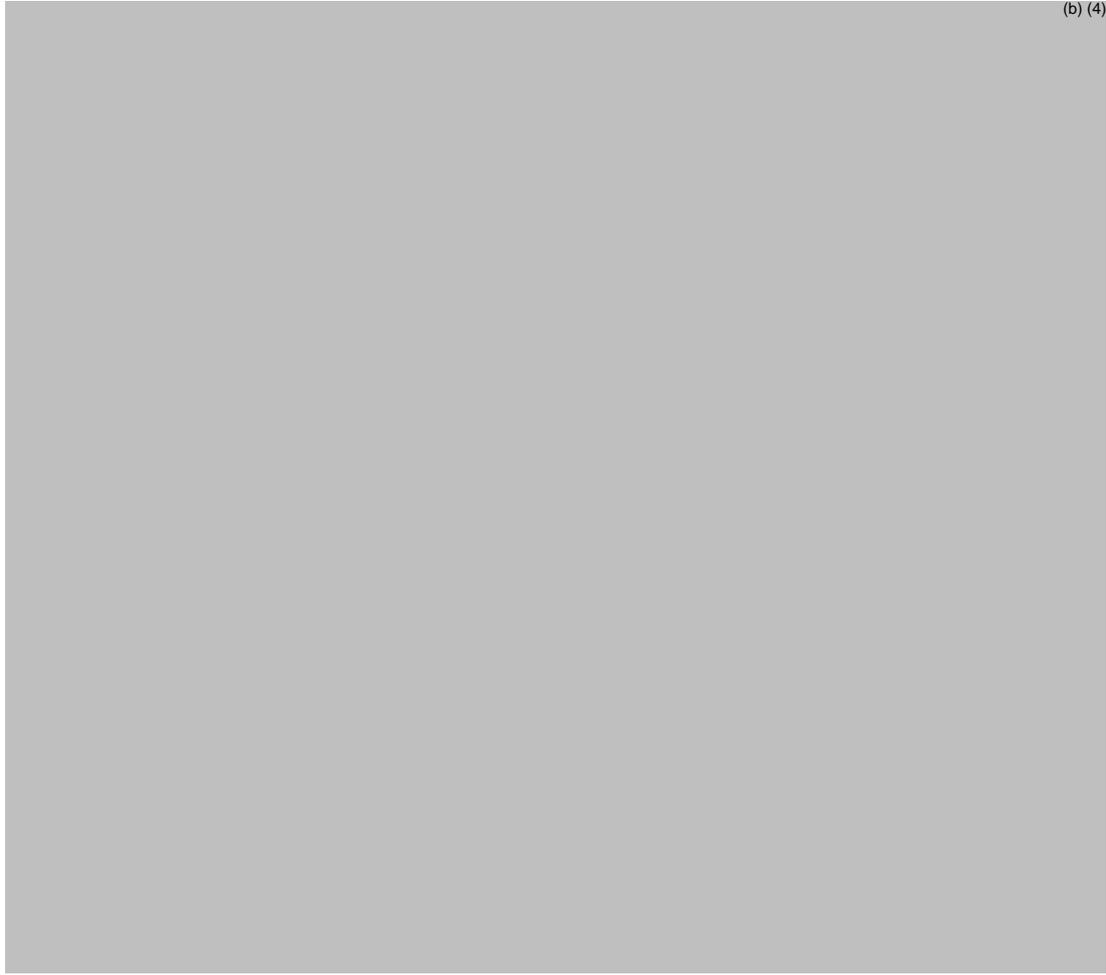
CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 91328 APPLICANT: Lupin Limited

DRUG PRODUCT: Levonorgestrel Tablets, 0.75 mg (Rx/OTC)

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:



Sincerely yours,

Robert Iser
Acting Director
Division of Chemistry IV
Office of Generic Drugs
Center for Drug Evaluation and Research

Endorsements (Draft and Final with Dates):

HFD-630 / RFPowers Review/06-FEB-2012; 13-FEB-2012
HFD-630 /USAtwal – Team Leader /02-08-2012/02-14-2012/02-15-2012
HFD-617 AKim – Project Manager /

C:\DOCUMENTS AND SETTINGS\POWERSR\DESKTOP\91328.R002.DOC

TYPE OF LETTER: Not Approvable, Minor

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

/s/

ROSLYN F POWERS
02/17/2012

ANDREW KIM
02/17/2012

UPINDER S ATWAL
02/17/2012

ANDA 091328

Levonorgestrel Tablets, 0.75 mg (Rx/OTC)

Lupin Limited

**Roslyn Friar Powers, Ph.D.
Office of Generic Drugs
Division of Chemistry IV
Team 44**

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B. Description of How the Drug Product is Intended to be Used.....	9
C. Basis for Approvability or Not-Approval Recommendation.....	9
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List Of Deficiencies To Be Communicated.....	89

Chemistry Review Data Sheet

1. ANDA #: 091328
2. REVIEW #: 1
3. REVIEW DATE: May 31, 2011; revised: 30-JUL-2011
4. REVIEWER: Roslyn Friar Powers, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

Original

15-APR-2009

7. NAME & ADDRESS OF APPLICANT:

Name:	Lupin Limited
Address:	159, CST Road, Kalina, Santacruz (East) Mumbai-400 098, Maharashtra, INDIA Leslie Sands
Representative:	Lupin Pharmaceuticals Inc., Harborplace Tower, 111 South Calvert Street, 21 st Floor, Baltimore, Maryland 21202 United States. Tel: (410) 5762000 & Fax: (410) 5762221
Telephone:	(410) 576-2000
Fax:	(410) 576-2221

8. DRUG PRODUCT NAME:

- a) Proprietary Name:
- b) Non-Proprietary Name (USAN): Levonorgestrel Tablets, 0.75 mg

9. LEGAL BASIS FOR SUBMISSION:

NDA: Plan B® (Levonorgestrel) 0.75 mg

Chemistry Review Data Sheet

Firm: Duramed Research, Inc.

Reference Listed Drug Information	
Name	Plan B®
Active Ingredients	Levonorgestrel
Route of Administration	Oral
Dosage Form	Tablet
Strength	0.75 mg Levonorgestrel
NDA Number	021045
NDA Holder	Duramed Research Inc.

The dosage form, route of administration, indications and usage, active ingredient, strength and labeling (except for differences detailed in labeling section of this ANDA) for the proposed generic drug product are the same as those of the RLD noted above.

(a) The basis for the Lupin's proposed ANDA for Levonorgestrel Tablets, 0.75 mg is the reference listed drug (RLD) Plan B® (Levonorgestrel) Tablets, 0.75 mg covered under New Drug Application (NDA) 021045, which is held by Duramed Research, Inc. The NDA and proposed ANDA are over-the-counter drug products.

Information regarding the RLD, Plan B® (Levonorgestrel) Tablets, 0.75 mg, as noted in the 28th Edition of the *Approved Drug Product List with Therapeutic Equivalence Evaluations* (Electronic Orange Book) is included in this section.

(b) Patent and exclusivity statements are included in this section in **Module 1, Section 1.3.5.1 Patent Information on Any Patent** and **Module 1, Section 1.3.5.3 Exclusivity Statement**, respectively.

There are no unexpired patents for Plan B® (Levonorgestrel) Tablets, 0.75 mg.

Patent Information – Provided in Section 1.3.5.1

Patent Certification - Provided in Section 1.3.5.2

Exclusivity Statement – Provided in Section 1.3.5.3.

Patent Data

There are no unexpired patents for this product in the Orange Book Database.

[Note: Title I of the 1984 Amendments does not apply to drug products submitted or approved under the former Section 507 of the Federal Food, Drug and Cosmetic Act (antibiotic products). Drug products of this category will not have patents listed.]

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
021045	002	NP	AUG 24, 2009

Chemistry Review Data Sheet

The applicant states there are no relevant patents.

10. PHARMACOL. CATEGORY: Levonorgestrel tablets reduce the chances of pregnancy after unprotected sex (if a contraceptive failed or if you did not use birth control).

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 0.75 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

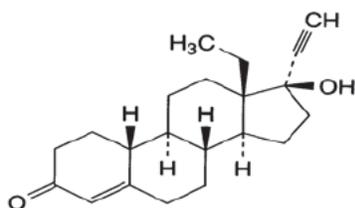
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name : 18,19-Dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-, (17 α)-(-);
(-)-13-Ethyl-17-hydroxy-18,19-dinor-17 α -pregn-4-en-20-yn-3-one.

CAS# : 797-63-7

USAN : Levonorgestrel

Molecular Structure:



Molecular Formula: C₂₁H₂₈O₂

Molecular Weight: 312.45

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

Chemistry Review Data Sheet

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Inadequate	20-JUN-2011	Reviewed by RFPowers
	III		4				
	III		4				
	III		4				

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	02-APR-2010	M. Stock
Methods Validation	N/A		
Labeling	Pending		
*Bioequivalence Dissolution	Pending Acceptable	30-OCT-2009	H. Mandula
EA	Acceptable	26-JUN-2011	RFPowers
Radiopharmaceutical	N/A		
Pharm/Tox	N/A		

*Pending DSI inspection- Outcome: Data accepted for review [4-JUN-2010]

Chemistry Review Data Sheet

Accepted Dissolution Information:

Medium: 0.1 N HCl with 0.1% Sodium Lauryl

Sulfate (SLS)

Volume: 1000 mL

Temperature: 37°C ± 0.5°C

USP Apparatus: II (Paddle)

Speed: 75 rpm

The test product should meet the following specification:

NLT (b) (4)(Q) of the labeled amount of Levonorgestrel in 60 minutes.

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. Yes No If no, explain reason(s) below:

The Chemistry Review for ANDA 91328

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not Approvable in this review cycle (#1), minor.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable - N/A

II. Summary of Chemistry Assessments

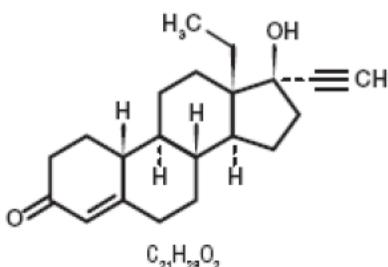
A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance:

Levonorgestrel USP is a white or practically white odorless powder, with no reported polymorphism in the literature. Levonorgestrel is the (-) form of Norgestrel; and Norgestrel USP is composed of (+) form and (-) form. The drug substance is practically insoluble in water; soluble in chloroform; slightly soluble in alcohol. There is no report in the literature on the pH dependence of the aqueous solubility.

Specifications are based on USP and DMF holder (b) (4)

Levonorgestrel has a molecular weight of 312.45, and the following structural and molecular formulas:



Based on MDD of 1.5 mg, Identification threshold and Qualification threshold are DS: 0.10% and 0.15% and DP: 0.50% and 1.0%, respectively.

Drug Product:

Emergency contraceptive tablet. Each levonorgestrel tablet contains 0.75 mg of a single active steroid ingredient, levonorgestrel [18,19-Dinorpregn-4-en-20-yn-3-one-13-ethyl-17-hydroxy-, (17 α)- (-)-], a totally synthetic progestogen. The inactive ingredients present are corn starch, colloidal silicon dioxide, lactose monohydrate, magnesium stearate, and povidone.

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ICH Q3B(R): Identification threshold NMT 0.50% and Qualification threshold 1.0%

Chemistry Assessment Section

How Supplied:

Levonorgestrel Tablets containing 0.75 mg of Levonorgestrel, are white to off white round biconvex tablets, debossed with 'LU' on one side and 'S24' on the other side. Levonorgestrel tablets are available in 2's blister pack. One blister pack in a carton.

Storage Conditions/Dispensing Recommendations:

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

USP:

No USP drug product monograph in the current USP

B. Description of How the Drug Product is Intended to be Used

Indications and Usage:

(b) (4)

Please see labeling insert for more details.

C. Basis for Approvability or Not-Approval Recommendation

CMC is not approvable, minor deficiencies.

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 91328 APPLICANT: Lupin Limited

DRUG PRODUCT: Levonorgestrel Tablets, 0.75 mg (Rx/OTC)

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:



(b) (4)

Following this page, 3 pages withheld in full (b)(4)

- B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

Please provide all available long term stability test results for your drug product. Please provide an updated and revised drug product stability specification table, forms and test methods, as applicable.

Sincerely yours,

Robert Iser
Acting Director
Division of Chemistry IV
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 91-328
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-630 / RFPowers Review/30-JUN-2011: 30-JUL-2011
HFD-630 /USAtwal – Team Leader /07-25-2011, 07-28-2011, 08-09-2011
HFD-617 AKim – Project Manager /10/4/11
NYa 8/29/2011

C:\DOCUMENTS AND SETTINGS\POWERSR\MY DOCUMENTS\DEF.91328.R001.AADOC.DOC

TYPE OF LETTER: NOT APPROVABLE – Minor

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

/s/

ROSLYN F POWERS
10/06/2011

ANDREW KIM
10/06/2011

UPINDER S ATWAL
10/13/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 091328

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	091328		
Drug Product Name	Levonorgestrel Tablets		
Strength(s)	0.75 mg		
Applicant Name	Lupin Limited		
Applicant Address	159, CST Road, Kalina, Santacruz (East) Mumbai-400 098, Maharashtra, India.		
US Agent Name and the mailing address	Authorized U.S. Agent: Leslie Sands Director, Regulatory Affairs, Harborplace Tower, 111 South Calvert Street, 21st Floor Baltimore, MD 21202, U.S.A.		
US agent's Telephone Number	410-576-2000		
US Agent's Fax Number	410-576-2221		
Original Submission Date(s)	04/15/2009		
Submission Date(s) of Amendment(s) Under Review	11/05/2009 (dissolution acknowledgement & long-term storage stability data)		
First Generic (Yes or No)	No		
Reviewer	Wayne DeHaven, Ph.D.		
Study Number (s)	CB081203		
Study Type (s)	Fasting (STF)		
Strength (s)	0.75 mg		
Clinical Site	Aizant Drug Research Solutions PVT. LTD		
Clinical Site Address	Survey No.: 172 & 173/A, Apparel Park Road, Dulapally village, Quthbullapur Mandal, Hyderabad-500014.		
Analytical Site	(b) (4)		
Analytical Site Address	(b) (4)		
OSI STATUS	ACCEPTABLE		
OVERALL REVIEW RESULT	ACCEPTABLE		
REVISED/NEW DRAFT GUIDANCE INCLUDED	NO		
BE STUDY TRACKING/SUPPORTING DOCUMENT #	STUDY/TEST TYPE	STRENGTH	REVIEW RESULT
1 and 2	Dissolution	0.75 mg	ADEQUATE
1 and 2	Fasting BE study	0.75 mg	ADEQUATE

1 EXECUTIVE SUMMARY

This application contains the results of a fasting bioequivalence (BE) study comparing the test product, Levonorgestrel Tablets, 0.75 mg, to the corresponding reference product, Plan B® (levonorgestrel) Tablets, 0.75 mg. The product-specific guidance recommends fasting *and fed* in vivo BE studies.¹ The guidance was revised (Feb 2011) to include a fed BE study. However, since this ANDA was submitted prior to this revision, the Division of Bioequivalence I (DBI) will not request a fed BE study at this time.

The BE study was designed as a single-dose, two-way crossover study in healthy female subjects. The firm's fasting study is acceptable. The results are summarized in the table below.

Levonorgestrel, 1 x 0.75 mg Fasting Bioequivalence Study No. CB081203, N=37 (All Female) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
	Least Squares Geometric Mean		Ratio	90% Confidence Intervals	
Parameter	Test (n=37)	Reference (n=37)	(T/R)	Lower	Upper
AUC _{0-t} (ng·hr/mL)	155.97	161.85	0.96	88.59	104.81
AUC _∞ (ng·hr/mL)	184.15	183.64	1.00	94.22	106.73
C _{max} (ng/mL)	11.48	10.76	1.07	100.15	113.76

The firm has conducted acceptable comparative dissolution testing using the FDA-recommended dissolution method.² On 11/05/2009, the firm has acknowledged the FDA-recommended dissolution method and specification.

No Office of Scientific Investigations (OSI) inspection is pending or necessary.³

The application is **acceptable** with no deficiencies.

Note: To the Regulatory Project Manager the comments to be provided to the applicant are provided on page 60 of this document.

¹ Draft Guidance on Levonorgestrel (Recommended Jan 2011; Revised Feb 2011): <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM240973.pdf>

² DARRTS A091328 MANDULA, HARITHA 10/30/2009 REV-BIOEQ-02(Dissolution Review)

³ **OSI Inspection History:** A routine inspection of the clinical site was requested for ANDA 91328 on 11/3/2009 and was completed on 6/4/2010 with an outcome of NAI (no action indicated). A routine inspection of the analytical site was requested for ANDA 201887 on (b)(4) and was completed on (b)(4) with an outcome of VAI. The VAI findings are specific to ANDA 201887, and do not impact the current study.

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3 SUBMISSION SUMMARY

3.1 Drug Product Information⁴

Test Product	Levonorgestrel Tablets, 0.75 mg
Reference Product	Plan B (Levonorgestrel) Tablets, 0.75 mg
RLD Manufacturer	Teva Branded Pharm (previously Duramed) ⁵
NDA No.	021045
RLD Approval Date	August 24, 2006
Indication⁶	<p>Plan B is a progestin-only emergency contraceptive indicated for prevention of pregnancy following unprotected intercourse or a known or suspected contraceptive failure. To obtain optimal efficacy, the first tablet should be taken as soon as possible within 72 hours of intercourse. The second tablet should be taken 12 hours later.</p> <p>Plan B is available only by prescription for women younger than age 17 years, and available over the counter for women 17 years and older.</p> <p>Plan B is not indicated for routine use as a contraceptive.</p>

3.2 PK/PD Information⁷

Bioavailability	<p>No specific investigation of the absolute bioavailability of Levonorgestrel in humans has been conducted. However, literature indicates that levonorgestrel is rapidly and completely absorbed after oral administration (bioavailability about 100%) and is not subject to first pass metabolism. After a single dose of Levonorgestrel 0.75 mg administered to 16 women under fasting conditions, maximum serum concentrations of levonorgestrel are 14.1 ± 7.7 ng/mL (mean \pm SD) at an average of 1.6 ± 0.7 hours.</p> <p>Levonorgestrel in serum is primarily protein bound. Approximately 50% is bound to albumin and 47.5% is bound to sex hormone binding globulin (SHBG).</p>
Food Effect	According to the RLD labeling, the effect of food on the rate and extent of levonorgestrel absorption following single oral administration of Plan B has not been evaluated.
Tmax	average of 1.6 ± 0.7 hours
Metabolism	Following absorption, levonorgestrel is conjugated at the 17 β -OH position to form sulfate conjugates and, to a lesser extent, glucuronide

⁴ Electronic Orange Book (Last Accessed 12/04/2012) Keyword Search = Levonorgestrel;
http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=021045&TABLE1=OB_Rx

⁵ DARRTS N021045 LUCARELLI, PAMELA 07/05/2011 MAIL 07/05/2011 COR-NDAACK-06(Change of Applicant Name/Address)

⁶ Drugs@FDA (Last Accessed 12/04/2012) Keyword Search = Plan B; Label was last updated 07/10/2009;
http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021045s015lbl.pdf

⁷ Labeling Repository (Last Accessed 12/04/2012) Keyword Search = Plan B;
<http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=62aace29-36a3-4a2a-aae0-61f7480095c1>

	<p>conjugates in plasma. Significant amounts of conjugated and unconjugated 3α, 5β-tetrahydrolevonorgestrel are also present in plasma, along with much smaller amounts of 3α, 5α-tetrahydrolevonorgestrel and 16βhydroxylevonorgestrel. Levonorgestrel and its phase I metabolites are excreted primarily as glucuronide conjugates.</p> <p>Metabolic clearance rates may differ among individuals by several-fold, and this may account in part for the wide variation observed in levonorgestrel concentrations among users.</p> <p><i>Following a single oral dosage, levonorgestrel does not appear to be extensively metabolized by the liver. The primary metabolites are 3α,5β- and 3α,5β-tetrahydrolevonorgestrel with 16β-hydroxynorgestrel also identified. Together, these account for less than 10% of parent plasma levels. Urinary metabolites hydroxylated at the 2α and 16β positions have also been identified. Small amounts of the metabolites are present in plasma as sulfate and glucuronide conjugates.</i></p>
Excretion	<p>About 45% of levonorgestrel and its metabolites are excreted in the urine and about 32% are excreted in feces, mostly as glucuronide conjugates.</p>
Half-life	<p>The elimination half-life of levonorgestrel following single dose administration as Plan B® (0.75 mg) is 24.4 \pm 5.3 hours.</p>
Dosage and Administration	<p>To obtain optimal efficacy, the first tablet should be taken as soon as possible within 72 hours of intercourse. The second tablet must be taken 12 hours later.</p>
Maximum Daily Dose	<p>2 tablets (packaged as 2 tablets)</p>
Drug Specific Issues	<p><u>Warnings and Precautions</u></p> <p>Ectopic Pregnancy: Women who become pregnant or complain of lower abdominal pain after taking Plan B should be evaluated for ectopic pregnancy.</p> <p>Plan B is not effective in terminating an existing pregnancy.</p> <p>Effect on menses: Plan B may alter the next expected menses. If menses is delayed beyond 1 week, pregnancy should be considered.</p> <p>STI/HIV: Plan B does not protect against STI/HIV.</p>

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	2, fasting and fed
---------------------------------------	--------------------

1.	Type of study:	Fasting
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	1.5 mg
	Subjects:	Healthy nonpregnant females, general population
	Additional Comments:	

2.	Type of study:	Fed
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	1.5 mg
	Subjects:	Healthy nonpregnant females, general population
	Additional Comments:	

Analytes to measure:	Levonorgestrel in plasma
Bioequivalence based on:	(90% CI) levonorgestrel
Waiver request of in-vivo testing:	<p>0.75 mg based on (i) acceptable fasting and fed BE studies on the 1.5 mg strength, (ii) proportional similarity in the formulations across all strengths, and (iii) acceptable dissolution testing across all strengths.</p> <p>Since Levonorgestrel Tablets, 1.5 mg and 0.75 mg are the subject of two separate applications, two separate Abbreviated New Drug Applications (ANDAs) must be submitted. A waiver of in vivo bioequivalence testing of the 0.75 mg strengths may be requested if the criteria are met. The in vivo bioequivalence studies conducted on 1.5 mg may be cross-referenced, along with the in-vivo waiver request. Refer to the Guidance for Industry, Variations in Drug Products that May Be Included in a Single ANDA located at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072892.pdf.</p> <p>If only the lower strength, 0.75 mg, is to be marketed first, please conduct the studies recommended above comparing the test 0.75 mg strength to the corresponding strength of the reference product. However, if the higher strength, 1.5 mg, is to be marketed at a later time after the in vivo studies on the 0.75 mg strength were conducted, an additional fasting study will be requested for the 1.5 mg strength.</p>
Source of most recent recommendations:	Draft Guidance on Levonorgestrel (Recommended Jan 2011; Revised Feb 2011): http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM240973.pdf

Summary of OGD or DB History:

Orange Book (OB) 0.75 mg strength only:⁸

Appl No	TE Code	RLD	Proprietary Name	Applicant
A090740	AB	No	Levonorgestrel	Perrigo
N021045	AB	Yes	Plan B	Teva
A078665	AB	Yes	Levonorgestrel	Watson
A078666	AB	No	Levonorgestrel	Watson

078665 and 078666: submitted fasting study only. These ANDAs differ only in that one is over-the-counter, while the other is prescription (cross-referencing single study). These ANDAs were approved Aug 28, 2009 and June 24, 2009 for ANDA 078665 and ANDA 078666, respectively.

090740: submitted fasting study only. Approved Dec 30, 2010

DARRTS (Pending Status – 0.75 mg strength only):⁹

ANDA #	Submitter	Status Date
		(b) (4)

Controls (Closed status – 0.75 mg strength):¹⁰

Ctl No	Description	From
03-406	Fasted study requirement	(b) (4)
05-1455	Dissolution test and BE study design	
07-0854	BE Guidance	
07-1222	Necessity of a Fed BE study?	Perrigo
10-0137	Request for BE guidance.	(b) (4)
10-0353	ANDA strategy and manufacturing site	
11-0087	Requesting BE guidance.	

Protocols (completed by the DB – 0.75 mg strength):¹¹

Protocol	Drug Name	Firm
05-031	Levonorgestrel	(b) (4)

⁸ Electronic Orange Book (OB); Keyword Search = Levonorgestrel; Last Accessed Date = 12/04/2012;

⁹ DARRTS Application Search; Keyword = Levonorgestrel; limit search to only 0.75 mg strength tablets; Last Access Date = 12/04/2012

¹⁰ Control Database; Title Search = levonorgestrel; Last Accessed 12/05/2012; <http://cdsogd1/controls/>

¹¹ Protocol Database; Drug Name Search = Levonorgestrel; Last Accessed Date = 12/04/2012; <http://fdswv04385/seltrack/Protocols.asp>

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	No	--
Steady-state	No	--
In vitro dissolution	Yes	1
Waiver requests	No	--
BCS Waivers	No	--
Clinical Endpoints	No	--
Failed Studies	No	--
Amendments	Yes	1

3.5 Pre-Study Bioanalytical Method Validation

Information Requested	Data
Analyte	Levonorgestrel
Internal standard (IS)	(b) (4)
Method description	The Principle involved in this method is "Liquid-Liquid Extraction" technique.
Limit of Quantitation	0.300ng/mL
Average Recovery of drug (%)	65.70% (LQC = 62.5%; MQC = 63.5%; and HQC = 71.0%)
Average Recovery of IS (%)	67.1%
Standard curve concentrations (ng/mL)	0.300ng/mL to 30.078ng/mL
QC concentrations (ng/mL)	0.301, 0.896, 12.766 & 22.838 (ng/mL) for LLOQQC, LQC, MQC & HQC respectively.
QC Intraday precision range (%)	<u>Levonorgestrel:</u> LLOQ QC: 2.1-12.3% LQC, MQC & HQC: 0.8-6.1%
QC Intraday accuracy range (%)	<u>Levonorgestrel:</u> LLOQ QC: 90.5-106.4% LQC, MQC & HQC: 90.6-100.1%
QC Interday precision range (%)	<u>Levonorgestrel:</u> LLOQ QC: 9.3% LQC, MQC & HQC: 4.1-4.2%
QC Interday accuracy range (%)	<u>Levonorgestrel:</u> LLOQ QC: 98.8% LQC, MQC & HQC: 93.7-97.8%
Bench-top stability (hrs)	16.25 hours @ 25°C.
In-injector stability (hrs)	40.75 hours @ 10°C.
Freeze-thaw stability (cycles)	5 cycles
Long-term storage stability (days) (In Matrix)	112 days
Dilution integrity	1/2 & 1/4 Dilutions were used. At 1/2 dilution: Precision: 5.7%; Accuracy: 95.3% At 1/4 dilution: Precision: 4.0%; Accuracy: 93.7%
Selectivity	No significant interfering peaks were observed at the RT of Levonorgestrel and Norgestrel-D6

<p>SOPs submitted</p>	<p>SOP (b)(4)-CPD-BM-156-01 (effective 04/11/2009) Estimation of Levonorgestrel in human plasma using LC-MS/MS detection method.</p> <p>SOP (b)(4)-CPD-BA-15-01 (effective 03/21/2008) Bioanalytical method validation</p> <p>SOP (b)(4)-CPD-BA-23-01 (effective 10/24/2008) Repeat analysis</p> <p>SOP (b)(4)-CPD-BA-22-01 (effective 10/25/2008) Study sample analysis and recording of raw data</p> <p>SOP (b)(4)-CPD-BA-48-00 (effective 10/21/2008) Reanalysis of incurred samples</p>
<p>Was the % recovery consistent across QC concentrations?</p>	<p>Yes</p>
<p>Is the same anticoagulant used in the pre-method validation study used in the sample assay?</p>	<p>Yes – dipotassium ethylenediaminetetraacetic acid (K₂ EDTA)</p>
<p>If not, was cross validation study conducted?</p>	<p>The same anticoagulant was used. Despite this, the firm also submitted cross validation study for K₂ EDTA and K₃ EDTA.</p>
<p>Was the dilution factor adequate for the current study sample analysis?</p>	<p>Yes</p>
<p>Was the same dilution medium (plasma/solvent) used during validation and sample analysis?</p>	<p>Yes</p>
<p>Does the duration of the each of the stability parameters support the sample preparation and assay dates</p>	<p>Yes</p>
<p>Was the pre-study validation of the bioanalytical method used for the pivotal bioequivalence studies acceptable?</p>	<p>Yes</p>

Comments on the Pre-Study Method Validation:

- In the amendment dated 11/05/2009, the firm submitted adequate long-term storage stability data. The review of these data are included at the end of Section 3.8 of this review.
- The pre-study method validation is acceptable.

3.6 In Vivo Studies

Table 1. Summary of all in vivo Bioequivalence Studies

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range))	Mean Parameters (+/-SD)						Study Report Location
					Cmax (ng/mL)	Tmax (hr)	AUC _{0-t} (ng h / mL)	AUC _{0-∞} (ng.h / mL)	T½ (hr)	Kel (hr ⁻¹)	
CB081203	To assess the single dose bioequivalence of Levonorgestrel 0.75 mg tablets manufactured by Lupin Ltd., India with Plan B® (containing 0.75 mg of Levonorgestrel) manufactured by Gedeon Richter, Ltd., Budapest, Hungary for Duramed Pharmaceuticals, Inc. Subsidiary of Barr Pharmaceuticals, Inc. Pomona in healthy, adult, female subjects under fasting conditions.	Open label, balanced, randomized, two period, two treatment, two sequence, crossover, balanced single-dose oral bioequivalence study in adult human female subjects under fasting conditions.	Test Product Levonorgestrel Tablets, 0.75mg	37 completing Healthy ,adult, female subjects mean age 31 years	12.313 ± 5.2316	Median 1.75	182.385 ± 106.2784	210.064 ± 116.8758	30.36 ± 7.575	0.024 ± 0.0055	Refer Report body pages 23,26,41, and 51 of 61
			Lupin Pharmacare Ltd., Indore.		42.49 (%CV)	1.00-4.00 (Range)	58.27 (%CV)	55.64 (%CV)	24.95 (%CV)	22.78 (%CV)	
			[Lot No. LA18001A]		11.513 ± 4.2373	Median 2.25	184.327 ± 91.7013	204.142 ± 92.1962	31.50 ± 6.906	0.023 ± 0.0048	
			Ref. Product Plan B® (containing 0.75 mg of levonorgestrel) Tablets Duramed Pharmaceuticals, Inc. Subsidiary of Barr Pharmaceuticals, Inc. Pomon, Newyork 10970, [Lot No. 306702]		36.80 (%CV)	1.00-4.00 (Range)	49.75 (%CV)	45.16 (%CV)	21.92 (%CV)	20.96 (%CV)	

Table 2. Statistical Summary of the Comparative Bioavailability Data Calculated by the Reviewer

Levonorgestrel, 1 x 0.75 mg Fasting Bioequivalence Study No. CB081203, N=37 (All Female) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter	Least Squares Geometric Mean		Ratio (T/R)	90% Confidence Intervals	
	Test (n=37)	Reference (n=37)		Lower	Upper
AUC _{0-t} (ng·hr/mL)	155.97	161.85	0.96	88.59	104.81
AUC _∞ (ng·hr/mL)	184.15	183.64	1.00	94.22	106.73
C _{max} (ng/mL)	11.48	10.76	1.07	100.15	113.76

Are the PK parameters within the acceptance limits for the 90% CI and meeting BE?

Yes

Table 3. Reanalysis of Study Samples

Reason why assay was repeated	Study No: CB081203							
	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic ¹	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Please provide detailed explanation for all repeats not related to analytical reasons.

There are no repeats.

Table 4. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
(b) (4) -CPD-BA-23-01	24/10/08	REPEAT ANALYSIS

Reanalysis SOPs submitted?	Yes
Do you agree with the reassay criteria: analytical and pharmacokinetic	N/A – There are no repeats
If not, list the criteria that you don't agree and provide additional comment below	N/A
Are the data in the summary table consistent with the data in the full analytical report?	Yes
If not, provide comment below	N/A
Did reviewer reanalyze study results?	No
Was the study outcome changed based on reviewer reanalysis?	N/A
Did the firm provide a comprehensive table of repeat samples in the format recommended by the DB?	N/A
Did the firm provide numerical raw data (e.g. peak height, peak area, response count of IS and analyte) in run sequence order (i.e. Run log)?	No

Comments from the Reviewer:

Acceptable (adequate).

3.7 Formulation

Location in appendix	Section 4.2
If a tablet, is the RLD scored?	No
If a tablet, is the test product biostudy/exhibit batch scored	No
Is the formulation acceptable?	FORMULATION ACCEPTABLE
If not acceptable, why?	N/A

3.8 In Vitro Dissolution

Location of DB Dissolution Review	DARRTS A091328 MANDULA, HARITHA 10/30/2009 REV-BIOEQ-02(Dissolution Review) and amendment (currently under review)
Submitted Method (USP, FDA, or Firm)	FDA
Recommended Method (details below) for the current ANDA	FDA
Medium	0.1 N HCl with 0.1% Sodium Lauryl Sulfate (SLS)
Volume (mL)	1000 mL
USP Apparatus type	II (Paddle)
Rotation (rpm)	75 rpm
Specifications	NLT ^{(b) (4)} (Q) in 60 minutes
Do the data meet the recommended specifications at S1, L1, A1, or B1 acceptance criteria?	Yes
If a modified-release tablet, was testing done on ½ tablets?	N/A
F2 metric calculated?	No
If no, reason why F2 not calculated	Rapidly dissolving
Is method acceptable?	METHOD ACCEPTABLE
If not then why?	N/A

Dissolution Amendment Review (Submission Dated 11/05/2009):

Deficiency 1:

Your dissolution testing using the FDA-recommended method is acceptable. We acknowledge that you will conduct dissolution testing using the following dissolution method and specification for your test product, Levonorgestrel, 0.75 mg:

Medium: 0.1 N HCl with 0.1% Sodium Lauryl Sulfate (SLS)
Volume: 1000 mL
Temp: 37°C ± 0.5°C
Apparatus: USP Type II (Paddle)

Speed: 75 rpm

The test product should meet the following specification:

NLT (b)(4)(Q) of the labeled amount of Levonorgestrel in the dosage form should be dissolved in 60 minutes

Response:

We confirm that above mentioned dissolution method will be used for dissolution testing and the above mentioned specifications will be followed.

Deficiency 2:

However, the following deficiency has been identified.

Please provide long term storage stability data for Levonorgestrel in frozen biological matrix to cover the maximum storage period of the study samples equal to the time from the first sample collection to the date the last sample was analyzed, which is at least 74 days for your BE studies.

Response:

We include the original response received from Contract Research Organization (b)(4) for the long term storage stability data of Levonorgestrel in frozen plasma for a period of one one two (112) days as **Annexure 1**.

Long term storage stability of Levonorgestrel (112 days) at -70°C in K2 EDTA:

Levonorgestrel	Long-term stability (112.53 days) at -70° C in K ₂ EDTA					
	Comparison Samples		Stability Samples		Comparison Samples	Stability Samples
Nominal Concn. (ng/mL)	(b)(4)					
QC ID						
1						
2						
3						
4						
5						
6						
Mean						
±SD						
%CV						
%Nominal						
Correction Factor						
Corrected Mean	0.8420		0.7962		21.0215	21.3899
% Stability	94.6		101.8			

Reviewer's Comments:

- The data support the long term storage of samples for the duration of the fasting BE study.
- The firm's response is acceptable.

3.9 Deficiency Comments

None

3.10 Recommendations

1. The Division of Bioequivalence I (DBI) accepts the fasting BE study No. CB081203 conducted by Lupin Limited on its Levonorgestrel Tablets, 0.75 mg (batch No. LA18001A), comparing it to Teva's Plan B® (levonorgestrel) Tablets, 0.75 mg (batch No. 306702).
2. The firm's in vitro dissolution testing is acceptable. The dissolution testing should be conducted in 1000 mL of 0.1 N HCl with 0.1% Sodium Lauryl Sulfate (SLS) at 37°C ± 0.5°C using USP Apparatus II (Paddle) at 75 rpm. The test product should meet the following specification:

NLT ^{(b) (4)} (Q) of the labeled amount of Levonorgestrel in the dosage form should be dissolved in 60 minutes
3. The DBI deems the test product Levonorgestrel Tablets, 0.75 mg, manufactured by Lupin Limited, to be bioequivalent to the reference product, Plan B® (levonorgestrel) Tablets, 0.75 mg, manufactured by Teva.

3.11 Comments for Other OGD Disciplines

Discipline	Comment
None	N/A

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-dose Fasting Bioequivalence Study

4.1.1.1 Study Design

Table 5 Study Information

Study Number	CB081203
Study Title	An open-label, randomized, two-period, two-treatment, two-sequence, crossover, balanced, Single- dose oral bioequivalence study of Levonorgestrel 0.75 mg tablets manufactured by Lupin Ltd., India and Plan B [®] tablets (containing 0.75 mg of Levonorgestrel) manufactured by Gedeon Richter, Ltd., Budapest, Hungary for Duramed Pharmaceuticals, Inc.Subsidiary of Barr Pharmaceuticals, Inc. Pomona in healthy adult female subjects under fasting conditions.
Clinical Site (Name, Address, Phone #)	AIZANT DRUG RESEARCH SOLUTIONS PVT. LTD. Survey no.: 172 &173/A, Apparel Park Road, Dulapally village, Quthbullapur mandal, Hyderabad-500014, Phone: +91- 40 -23792190 /91/92 Fax: 91-40-23792223
Principal Investigator	Dr. Nitin Kulkarni
Dosing Dates	Period I: 31 Jan 2009 Period II: 14 Feb 2009
Analytical Site (Name, Address, Phone #)	(b) (4)
Analysis Dates	05 Apr 2009-14Apr 2009
Analytical Director	(b) (6)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	74 days (Jan 31, 2009 to April 14, 2009)

Table 6. Product information

Product	Test	Reference
Treatment ID	T	R
Product Name	Levonorgestrel Tablets, 0.75mg.	Plan B® (tablet containing 0.75 mg of Levonorgestrel)
Manufacturer	Lupin Pharmacare Ltd., Indore, India	Gedeon Richter, Ltd., Budapest, Hungary for Duramed Pharmaceuticals, Inc. Subsidiary of Barr Pharmaceuticals, Inc. Pomon, New York 10970.
Batch No.	LA18001A	306702
Lot No.	-	-
Manufacture Date	NOV 2008	N/A
Expiration Date	OCT 2010	FEB 2012
Strength	0.75 mg	0.75 mg
Dosage Form	Tablet	Tablet
Bio-batch Size	(b) (4) Tablets (they will scale-up to (b) (4))	N/A
Potency	0.7864 mg/tablet (104.8%)	0.7706 mg/tablet (102.7%)
Content Uniformity (AV)	AV=6.9% Meets USP <905> requirement	N/A
Dose Administered	Single	Single
Route of Administration	Oral	Oral

Was the drug product administered per labeling (for specialized dosage forms e.g. ODT)?	Yes
Is the bio-batch size at least the recommended minimum of 100K for oral solid dosage form?	Yes

Table 7. Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	Enrolled: 38; Dosed: 38; Completed: 37; Data Analyzed: 37
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	14 days
Randomization Scheme (Sequence of T and R)	AB: 1,4,5,6,10,11,14,15,17,20,22,24,26,27,29,31,34,36,39, and 40 BA: 2,3,7,8,9,12,13,16,18,19,21,23,25,28,30,32,33,35,37, and 38
Blood Sampling Times	pre-dose (0) and at 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00, 12.00, 24.00, 36.00, 48.00, 72.00, 96.00, and 120.00 hours after administration in each period.
Blood Volume Collected/Sample	4 mL
Anticoagulant Used	K ₂ EDTA
Blood Sample Processing & Storage (include storage temperature)	After collection, the blood samples were placed in a refrigerated centrifuge within 30 minutes from the time of collection and then spun at 3000 rpm for 15 minutes at 40°C. As soon as possible, the plasma obtained from 4 mL blood sample was separated and transferred into two different polypropylene tubes/RIA vials. Each tube/vial was to be labeled with Project No., Period, Subject No., Sampling time point and Aliquot No.. All samples were stored at a temperature -20°C or below until transferred to analytical site.
IRB Approval	(b) (4) Independent Ethics Committee reviewed and approved the protocol, informed consent form for study and other appendices. The approved version bears the Version No: 00 dated 22 Dec 2008.
Informed Consent	The informed consent and other appendices submitted were approved by IEC on 20 Jan 2009.
Length of Fasting	Subjects fasted from at least 10 hours prior to first dose and up to 4 hours after dosing.
Length of Confinement	Subjects were house in the clinical facility from at least 10 hours prior to dosing until after the 24 hour sampling time-point. Samples collected at 36.00, 48.00, 72.00, 96.00 and 120.00 hours post dose were to be collected on ambulatory visits.
Safety Monitoring	During the course of the study, subjects were monitored for their well being by vital sign assessments and clinical examination. Post study safety evaluation was carried out at the end of the study.

Was the study design used for the fasting BE study acceptable?	YES
---	-----

Comments on Study Design:

- Forty subjects were planned; however, only 38 subjects were enrolled. Subjects 39 and 40 were not in the study.
- The study design is acceptable.

4.1.1.2 Clinical Results

Table 8. Demographics Profile of Subjects Completing the Bioequivalence Study

Study No. CB081203			
		Treatment Groups	
		Test Product N = 37	Reference Product N = 37
Age (years)	Mean ± SD	31± 6.8	31± 6.8
	Range	18 - 43	18 - 43
Age Groups	< 18	0(%)	0(%)
	18 – 40	32(86.49%)	32(86.49%)
	41 – 64	5(13.51%)	5(13.51%)
	65 – 75	0(%)	0(%)
	> 75	0(%)	0(%)
Sex	Male	0(%)	0(%)
	Female	37(100%)	37 (100%)
Race	Asian*	37(100%)	37 (100%)
	Black	0(%)	0(%)
	Caucasian	0(%)	0(%)
	Hispanic	0(%)	0(%)
	Other	0(%)	0(%)
BMI	Mean ± SD	22.7 ± 1.73	22.7 ±1.73
	Range	18.9 -24.7	18.9 -24.7
Other Factors		Nil	Nil

* Dravidian

N = Total number of subjects dosed and completed the study

Table 9. Dropout Information, Fasting Bioequivalence Study

Study No. CB081203				
Subject No	Reason for dropout/replacement	Period	Replaced?	Replaced with
29	Did not report for period 2	2	No	N/A

Table 10. Study Adverse Events, Fasting Bioequivalence Study

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Fasted Bioequivalence Study Study No. CB081203	
	Test	Reference
Body as a whole/Headache	2.63%	0.00%
Liver function/Bilirubin	2.63%	2.63%
Hemopoitic system/ WBC&Eosinophils	15.78%	2.63%
Gastrointestinal/Pain abdomen	2.63%	0.00%

Table 11. Protocol Deviations, Fasting Bioequivalence Study

Study No. CB081203		
Type	Subject #s (Test)	Subject #s (Ref.)
Blood Sample Deviation	08,12,14,16,22,23,25,26,34,35	02,06,08,10,13,22,23,25,28,34

Did dropouts/adverse events/protocol deviations affect the study outcome?

No.

Comments on Dropouts/Adverse Events/Protocol Deviations:

- The handling of all subjects was in accordance with the study protocol.
- There is no evidence suggesting that the test drug is less safe than the reference drug.
- There were many blood sampling deviations during fasting bioequivalence study. However, these sampling time deviations are minor deviations which occurred in less than 5% of the nominal time points, thus are considered to be insignificant. This reviewer used nominal sampling times for its PK calculation.

4.1.1.3 Bioanalytical Results

Table 12. Sample Analysis Calibration and Quality Control – Within the Fasting Bioequivalence Study

Study No: CB081203 Levonorgestrel										
Parameter	Standard Curve Samples									
	STD1-1	STD1-2	STD2	STD3	STD4	STD5	STD6	STD7	STD8-1	STD8-2
Concentration	0.300	0.300#	0.600	1.500	3.000	5.999	11.998	24.040	30.050	30.050#
Inter day Precision	1.5	5.3	3.1	1.6	1.5	1.4	1.3	1.3	1.2	2.6
Inter day Accuracy	98.7	99.4	101.5	101.3	102.6	101.2	99.6	98.2	96.9	95.7
Linearity (Range of r values)	0.9984 to 0.9999									
Linearity Range (ng/mL)	0.300ng/mL to 30.050ng/mL.									
Sensitivity/LOQ (ng/mL)	0.300ng/mL									

#- Duplicate standards not included in CC Curve.

Study No: CB081203 Levonorgestrel			
Parameter	Quality Control Samples		
	LQC	MQC	HQC
Concentration (pg/mL)	0.897	12.789	22.838
Inter day Precision (%CV)	3.9	3.5	3.6
Inter day Accuracy (%Actual)	100.3	96.9	103.0

Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?	Yes
Do you agree with the firm's accepted and rejected runs?	Yes

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serial (subjects 1-8)
Were the chromatograms submitted by the firm acceptable?	Yes

Table 13. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
(b) (4) CPD-BA-23-01	24/10/08	REPEAT ANALYSIS

Table 14. Additional Comments on Repeat Assays

Were all SOPs followed?	There were no repeats except for incurred sample reanalysis (ISR)
Did recalculation of PK parameters change the study outcome?	N/A
Does the reviewer agree with the outcome of the repeat assays?	N/A
If no, reason for disagreement	N/A

Were Calibration and Quality Control for the Sample Analysis acceptable?

Yes

Summary/Conclusions, Study Assays:

- The firm conducted incurred sample reanalysis (ISR) on 88 samples (approximately 5%). Only a single reassayed sample was not within 20% of the original value.
- The study assays are acceptable for analysis.

4.1.1.4 Pharmacokinetic Results

Table 15. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in [Table](#) and [Figure 1](#)

		Test (n=37)				Reference (n=37)				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	ng hr/mL	181.515	58.55	43.77	500.62	183.441	50.27	46.26	468.36	0.99
AUCI	ng hr/mL	209.023	56.02	57.47	556.03	203.342	45.51	58.82	480.14	1.03
C _{MAX}	ng/mL	12.313	42.49	5.24	29.26	11.513	36.80	5.24	20.58	1.07
T _{MAX}	hr	1.750	.	1.00	4.00	2.250	.	1.00	4.00	0.78
KE	hr ⁻¹	0.024	22.44	0.01	0.04	0.023	21.73	0.01	0.03	1.05
THALF	hr	30.333	24.53	18.91	51.17	31.658	23.58	21.64	51.74	0.96

*T_{max} values are presented as median, range.

Table 16. Geometric Means and 90% Confidence Intervals - Firm Calculated

Levonorgestrel CB081203 Dose (1 x Levonorgestrel Tablets 0.75 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasting Bioequivalence Study (Study No. CB081203)				
Parameter	Test	Reference	Ratio	90% C.I.
AUC _{0-t} (ng h / mL)	156.670	162.975	96.13	88.31 - 104.65
AUC _∞ (ng.h / mL)	185.133	184.523	100.33	94.39 - 106.64
C _{max} (ng / mL)	11.481	10.757	106.74	100.17 - 113.73

Table 17. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Levonorgestrel, 1 x 0.75 mg Fasting Bioequivalence Study No. CB081203, N=37 (All Female) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
	Least Squares Geometric Mean		Ratio	90% Confidence Intervals	
Parameter	Test (n=37)	Reference (n=37)	(T/R)	Lower	Upper
AUC _{0-t} (ng·hr/mL)	155.97	161.85	0.96	88.59	104.81
AUC _∞ (ng·hr/mL)	184.15	183.64	1.00	94.22	106.73
C _{max} (ng/mL)	11.48	10.76	1.07	100.15	113.76

Table 18. Additional Study Information, Fasting Study No. CB081203

DB SAS Program Macros Used (CONTINU, CONTINU2 or CALCKE)	CALCKE	
Reason(s) for Selecting Above SAS Program Macro	Please provide comment below the table	
Root mean square error, AUC _{0-t}	0.2133	
Root mean square error, AUC _∞	0.1582	
Root mean square error, C _{max}	0.1617	
	Test	Reference
If CALCKE program is used, please state how many subjects used by you for determining Kel and AUC _∞	37	37
If CALCKE program is used, please state if you agree or disagree with firm's determination of Kel and AUC _∞	AGREE	AGREE
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as C _{max}	0	0
C _{max} at the first time point	0	0
Were the subjects dosed as more than one group?	NO	

Ratio of AUC _{0-t} /AUC _∞																																		
Treatment	n	Mean	Minimum	Maximum																														
Test	37	0.85	0.62	0.98																														
Reference	37	0.88	0.72	0.98																														
<p>If the minimum ratios less than 0.8, were they due to inadequate sampling schedule? Provide additional comments below.</p>	<p>Sampling schedule is adequate. There were 9 ratios less than 0.8 (highlighted yellow on pages 50-51). This was primarily due to missing samples in the elimination phase in these few subjects. Dropping these subjects does not change the outcome of the study (see table below):</p> <table border="1" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th></th> <th colspan="2" style="text-align: center;">Least Squares Geometric Mean</th> <th style="text-align: center;">Ratio</th> <th colspan="2" style="text-align: center;">90% Confidence Intervals</th> </tr> <tr> <th style="text-align: left;">Parameter</th> <th style="text-align: center;">Test</th> <th style="text-align: center;">Reference</th> <th style="text-align: center;">(T/R)</th> <th style="text-align: center;">Lower</th> <th style="text-align: center;">Upper</th> </tr> </thead> <tbody> <tr> <td>LAUCT</td> <td style="text-align: center;">179.79</td> <td style="text-align: center;">167.32</td> <td style="text-align: center;">1.07</td> <td style="text-align: center;">99.69</td> <td style="text-align: center;">115.80</td> </tr> <tr> <td>LAUCI</td> <td style="text-align: center;">201.24</td> <td style="text-align: center;">188.29</td> <td style="text-align: center;">1.07</td> <td style="text-align: center;">100.08</td> <td style="text-align: center;">114.13</td> </tr> <tr> <td>LCMAX</td> <td style="text-align: center;">11.87</td> <td style="text-align: center;">11.06</td> <td style="text-align: center;">1.07</td> <td style="text-align: center;">99.83</td> <td style="text-align: center;">115.26</td> </tr> </tbody> </table>					Least Squares Geometric Mean		Ratio	90% Confidence Intervals		Parameter	Test	Reference	(T/R)	Lower	Upper	LAUCT	179.79	167.32	1.07	99.69	115.80	LAUCI	201.24	188.29	1.07	100.08	114.13	LCMAX	11.87	11.06	1.07	99.83	115.26
	Least Squares Geometric Mean		Ratio	90% Confidence Intervals																														
Parameter	Test	Reference	(T/R)	Lower	Upper																													
LAUCT	179.79	167.32	1.07	99.69	115.80																													
LAUCI	201.24	188.29	1.07	100.08	114.13																													
LCMAX	11.87	11.06	1.07	99.83	115.26																													

Was the fasting bioequivalence study acceptable?

Yes

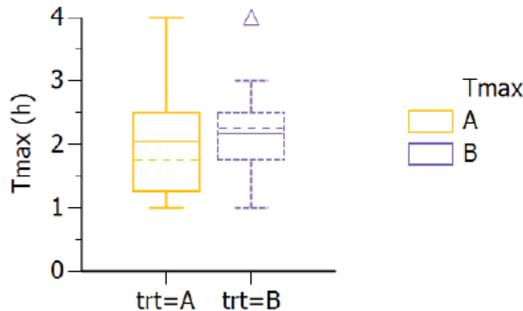
Comments on SAS Program selected, Subject variability, any Tmax differences (if applicable), Pharmacokinetic and Statistical Analysis:

- The reviewer used the SAS code CALCKE in order to estimate the elimination rate constant, K_{el} (AUC_{∞} and $THALF$ are dependent variables), along with other PK parameters. The SAS code CALCKE also compares the reviewer’s results to the firm’s (see page 55).
- The Ke_first and Ke_last used to predict K_{el} are listed in the table below (pages 30-31). The selection of the time-points for calculating the K_{el} (Ke_first and Ke_last) were based on best fits determined using Phoenix WinNonlin version 6.3.
- The reviewer’s calculations are in agreement with the firm’s calculations. The fasting study meets bioequivalence criteria of 90% CI within 80.00% to 125.00% for AUC_{0-t} , AUC_{∞} and C_{max} .
- The T_{max} values for the fasting study are the following:

Variable	trt											
	A						B					
	N	Mean	Median	CV%	Min	Max	N	Mean	Median	CV%	Min	Max
T_{max}	37.00	2.03	1.75	45.37	1.00	4.00	37.00	2.17	2.25	30.74	1.00	4.00

- The box plots compare the T_{max} values determined for the test and reference products:

Levonorgestrel box plot [showing mean (solid line), median (dashed line) and 25th and 75th percentiles (upper and lower borders of the box, respectively)]



- The minor T_{max} difference is acceptable.

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:

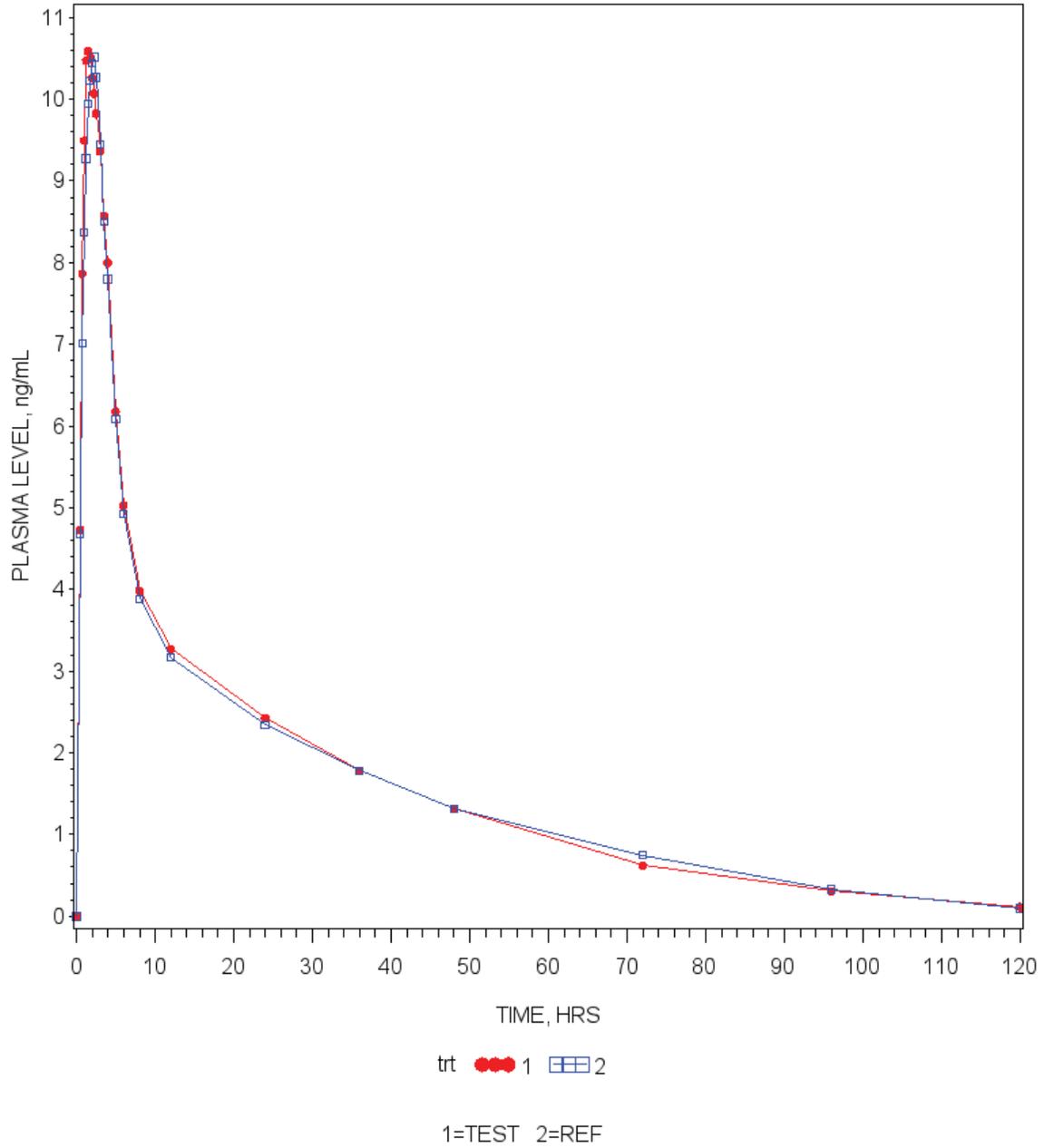
The firm’s *in vivo* fasting bioequivalence (BE) study is **acceptable (adequate)**.

Table 19. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

Time (hr)	Test (n=37)		Reference (n=37)		Ratio (T/R)
	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	
0.00	0.00	.	0.00	.	.
0.50	4.73	53.97	4.68	63.51	1.01
0.75	7.87	54.48	7.01	49.79	1.12
1.00	9.50	51.52	8.38	44.76	1.13
1.25	10.48	49.97	9.28	40.34	1.13
1.50	10.59	47.34	9.95	41.44	1.06
1.75	10.51	45.78	10.22	41.71	1.03
2.00	10.26	43.09	10.44	40.12	0.98
2.25	10.07	43.44	10.52	40.58	0.96
2.50	9.82	45.80	10.27	39.83	0.96
3.00	9.37	48.61	9.45	39.51	0.99
3.50	8.58	52.27	8.50	39.93	1.01
4.00	8.00	53.43	7.80	40.06	1.03
5.00	6.18	53.24	6.08	41.38	1.02
6.00	5.03	55.96	4.93	45.19	1.02
8.00	3.99	59.35	3.89	49.48	1.02
12.00	3.27	63.30	3.17	54.90	1.03
24.00	2.43	66.34	2.34	55.47	1.04
36.00	1.78	68.24	1.78	58.14	1.00
48.00	1.31	69.24	1.32	51.99	1.00
72.00	0.62	74.34	0.75	47.45	0.83
96.00	0.30	97.88	0.33	84.44	0.92
120.00	0.11	172.11	0.10	185.05	1.17

Figure 1. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

PLASMA Levonorgestrel LEVELS
Levonorgestrel Tablets, ANDA 091328
UNDER FASTING CONDITIONS
DOSE= 1 x 0.75 MG



Ke first and Ke last determinations from WinNonlin using best fit approach:

sub	seq	per	trt	Lambda z lower (h)	Lambda z upper (h)
1.00	1.00	1.00	A	24.00	48.00
1.00	1.00	2.00	B	12.00	48.00
2.00	2.00	1.00	B	24.00	96.00
2.00	2.00	2.00	A	5.00	96.00
3.00	2.00	1.00	B	48.00	120.00
3.00	2.00	2.00	A	72.00	120.00
4.00	1.00	1.00	A	72.00	120.00
4.00	1.00	2.00	B	24.00	96.00
5.00	1.00	1.00	A	12.00	120.00
5.00	1.00	2.00	B	48.00	120.00
6.00	1.00	1.00	A	24.00	120.00
6.00	1.00	2.00	B	24.00	96.00
7.00	2.00	1.00	B	8.00	72.00
7.00	2.00	2.00	A	6.00	72.00
8.00	2.00	1.00	B	36.00	120.00
8.00	2.00	2.00	A	48.00	96.00
9.00	2.00	1.00	B	12.00	72.00
9.00	2.00	2.00	A	8.00	48.00
10.00	1.00	1.00	A	12.00	120.00
10.00	1.00	2.00	B	36.00	96.00
11.00	1.00	1.00	A	48.00	96.00
11.00	1.00	2.00	B	36.00	96.00
12.00	2.00	1.00	B	12.00	120.00
12.00	2.00	2.00	A	72.00	120.00
13.00	2.00	1.00	B	36.00	72.00
13.00	2.00	2.00	A	12.00	48.00
14.00	1.00	1.00	A	36.00	120.00
14.00	1.00	2.00	B	48.00	96.00
15.00	1.00	1.00	A	36.00	72.00
15.00	1.00	2.00	B	8.00	72.00
16.00	2.00	1.00	B	8.00	96.00
16.00	2.00	2.00	A	8.00	96.00
17.00	1.00	1.00	A	36.00	72.00
17.00	1.00	2.00	B	24.00	72.00
18.00	2.00	1.00	B	36.00	72.00
18.00	2.00	2.00	A	12.00	48.00
19.00	2.00	1.00	B	36.00	120.00
19.00	2.00	2.00	A	36.00	96.00
20.00	1.00	1.00	A	8.00	96.00
20.00	1.00	2.00	B	36.00	96.00
21.00	2.00	1.00	B	8.00	96.00

ANDA 091328
Single-Dose Fasting Bioequivalence Study Review

sub	seq	per	trt	Lambda_z_lower (h)	Lambda_z_upper (h)
21.00	2.00	2.00	A	12.00	72.00
22.00	1.00	1.00	A	12.00	36.00
22.00	1.00	2.00	B	12.00	120.00
23.00	2.00	1.00	B	48.00	96.00
23.00	2.00	2.00	A	36.00	72.00
24.00	1.00	1.00	A	12.00	48.00
24.00	1.00	2.00	B	48.00	120.00
25.00	2.00	1.00	B	24.00	72.00
25.00	2.00	2.00	A	8.00	96.00
26.00	1.00	1.00	A	36.00	120.00
26.00	1.00	2.00	B	36.00	96.00
27.00	1.00	1.00	A	8.00	48.00
27.00	1.00	2.00	B	36.00	120.00
28.00	2.00	1.00	B	24.00	72.00
28.00	2.00	2.00	A	36.00	120.00
30.00	2.00	1.00	B	48.00	96.00
30.00	2.00	2.00	A	24.00	72.00
31.00	1.00	1.00	A	8.00	24.00
31.00	1.00	2.00	B	72.00	120.00
32.00	2.00	1.00	B	24.00	72.00
32.00	2.00	2.00	A	36.00	96.00
33.00	2.00	1.00	B	12.00	96.00
33.00	2.00	2.00	A	36.00	96.00
34.00	1.00	1.00	A	12.00	96.00
34.00	1.00	2.00	B	12.00	96.00
35.00	2.00	1.00	B	48.00	96.00
35.00	2.00	2.00	A	24.00	96.00
36.00	1.00	1.00	A	5.00	120.00
36.00	1.00	2.00	B	8.00	96.00
37.00	2.00	1.00	B	24.00	72.00
37.00	2.00	2.00	A	24.00	72.00
38.00	2.00	1.00	B	24.00	72.00
38.00	2.00	2.00	A	36.00	72.00

4.2 Formulation Data

Ingredients	0.75 mg	
	Quantity mg/tablet	% w/w
ACTIVE INGREDIENT		
Levonorgestrel *	0.75	0.429
OTHER INGREDIENTS		
(b) (4)		

IIG LIMITS:¹²

Ingredient	Amount (mg)	Amount per MDD (mg) ¹³	Maximum amount per IID (mg)	NDA/ANDA reference	Acceptable?
Lactose Monohydrate	(b) (4)	(b) (4)	587.44	(b) (4) ORAL; TABLET, FILM COATED	Yes
Corn Starch			1135.00	(b) (4) ORAL; CAPSULE	Yes
Povidone			240.0	(b) (4) ORAL; TABLET (IMMED./COMP. RELEASE), FILM COATED	Yes
Magnesium Stearate			400.748	(b) (4) ORAL; TABLET	Yes
Collodial Silicon Dioxide			100 MG	(b) (4) ORAL; GRANULE	Yes

Maximum daily dose (MDD) = 2 tablets

¹² Temporary IIG Internal Database: <http://intranetapps.test.fda.gov/scripts/iig/> (Last Accessed 12/05/2012)

¹³ Drugs@FDA (Last Accessed 12/04/2012) Keyword Search = Plan B; Label was last updated 07/10/2009; http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021045s015lbl.pdf

Is there an overage of the active pharmaceutical ingredient (API)?	No
If the answer is yes, has the appropriate chemistry division been notified?	N/A
If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?	N/A
Are the amounts of all inactive ingredients based on Maximum Daily Dose (MDD) within IIG (per unit) limits?	Yes
If no, are they all above/within IIG (per day) limits?	N/A
If no, are additional data or Pharm/Tox consult necessary?	N/A
Are all color additives and elemental iron within limits specified by CFR (if applicable) or less than 0.1% of the total unit weight (w/w)?	N/A
Are all strengths of the test product proportionally similar per the BA/BE guidance criteria?	N/A
Are all strengths of the RLD product dose-proportional?	N/A
Are all strengths of the test formulation acceptable	ACCEPTABLE

4.3 Dissolution Data

Dissolution Review Path	DARRTS A091328 MANDULA, HARITHA 10/30/2009 REV-BIOEQ-02(Dissolution Review)
-------------------------	---

Table 20. Dissolution Data

Dissolution Conditions		Apparatus:	USP Type 2 (Paddle)								
		Speed of Rotation:	75								
		Medium:	0.1 N HCl with 0.1% SLS								
		Volume:	1000 mL								
		Temperature:	37 C ± 0.5 C								
Firm's Proposed Specifications		NLT ^{(b) (4)} Q of the labeled amount of Levonorgestrel USP is dissolved in 60 minutes.									
Dissolution Testing Site (Name, Address)		Lupin Limited, at Lupin Pharmicare Plot No. 2, SEZ Phase – II, Misc.Zone Appreal Park, Pithampur (Dist - Dhar), Madhya Pradesh, 454774 INDIA									
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes or hours)					Study Report Location	
					10.	20	30	45	60		
Study Report #:	08/12/08	Levonorgestrel Tablets, 0.75 mg (B. No. LA18001) Mfg: Nov. 2008	0.75 mg Tablet	12	Mean	96	99	101	100	102 (b) (4)	m5.3.1.3
					Range	[REDACTED]					
					%CV	2.3	2.1	2.9	1.7	2.0	
Study Report #:	16/01/09	Plan B [®] Tablets, 0.75 mg (B. No. 306702) Exp: Feb. 2012	0.75 mg Tablet	12	Mean	99	100	101	101	101 (b) (4)	m5.3.1.3
					Range	[REDACTED]					
					%CV	3.5	2.4	2.2	2.1	1.3	

4.4 OSI Inspection Report Review

Analytical Site:

[Redacted] (b) (4)

This site has been inspected for ANDA 201887 (Desogestrel and Ethinyl Estradiol Tablets, USP 0.15 mg/0.03 mg) on [Redacted] (b) (4) and inspection result was VAI (voluntary action indicated).¹⁴ The study dates for ANDA 201887 were February to April 2010. The study date for the current application was April 2009, which was earlier than the study dates of ANDA 201887 and the OSI inspection dates. The OSI findings in analytical portion and the relevance to the current application are as follows:

OSI Finding:

[Redacted] (b) (4)

[Redacted] (b) (4)

¹⁴ DARRTS A201887 DASGUPTA, ARINDAM 05/04/2011 CONSULT REV-DSI-05(Bioequivalence Establishment Inspection Report Review)

The following reviewer's comments were copied and pasted from the DBI's original review of the OSI inspection report:¹⁵

Reviewer's Comments: The reviewer concurs with the OSI opinion. In the firm's response for the OSI finding, the firm [REDACTED] (b) (4) [REDACTED] So the OSI finding does not have any impact on the outcome of the current fasting and fed studies.

Reviewer's Comment for Related ANDAs: Since the finding is specific to the current ANDA 201887, the above OSI finding should have no significant impact on related ANDAs.

This reviewer agrees. No OSI-related deficiency is necessary.

¹⁵ DARRTS A201887 DANDAMUDI, SUMAN 11/30/2011 REV-BIOEQ-01(General Review); Pages 18-19

4.5 SAS Output

4.5.1 Fasting Study Data

(b) (4)



Following this page, 22 pages withheld in full (b)(4)

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 091328
APPLICANT: Lupin Limited
DRUG PRODUCT: Levonorgestrel tablets, 0.75 mg

The Division of Bioequivalence I has completed its review and has no further questions at this time.

We acknowledge that you will conduct dissolution testing in 1000 mL of 0.1 N HCl with 0.1% Sodium Lauryl Sulfate (SLS) at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ using USP Apparatus II (Paddles) at 75 rpm. The product should meet the following specification:

NLT (b) (4) (Q) of the labeled amount of Levonorgestrel in the dosage form should be dissolved in 60 minutes

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

4.6 Outcome Page

ANDA: 091328

Completed Assignment for 91328 ID: 18598

Reviewer: Dehaven, Wayne

Date Completed:

Verifier: ,

Date Verified:

Division: Division of Bioequivalence

Description: Levonorgestrel Tablets, 0.75 mg (Lupin)

Productivity:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Productivity</i>	<i>Subtotal</i>
18598	4/15/2009	Bioequivalence Study (REGULAR)	Fasting Study	1	1
18598	11/5/2009	Other (REGULAR)	Study Amendment Without Credit	0	0
				Total:	1

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

/s/

WAYNE I DEHAVEN
12/14/2012

APRIL C BRADDY
12/14/2012

HOAINHON N CARAMENICO
12/14/2012

HOAINHON N CARAMENICO on behalf of DALE P CONNER
12/14/2012

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	91-328		
Drug Product Name	Levonorgestrel Tablets		
Strength (s)	0.75 mg		
Applicant Name	Lupin Limited		
Address	159, CST Road, Kalina, Santacruz (East) Mumbai-400 098, Maharashtra, India.		
Applicant's Point of Contact	Authorized U.S. Agent: Leslie Sands Director, Regulatory Affairs, Harborplace Tower, 111 South Calvert Street, 21 st Floor Baltimore, MD 21202, U.S.A.		
Contact's Phone Number	410-576-2000		
Contact's Fax Number	410-576-2221		
Submission Date(s)	04/15/2009		
First Generic	No		
Reviewer	Haritha Mandula, Ph.D.		
Study Number (s)	CB081203		
Study Type (s)	Fasting (STF)		
Strength(s)	0.75 mg		
Clinical Site	Aizant Drug Research Solutions PVT. LTD		
Clinical Site Address	Survey No.: 172 & 173/A, Apparel Park Road, Dulapally village, Quthbullapur Mandal, Hyderabad-500014.		
Analytical Site	(b) (4)		
Analytical Address	(b) (4)		
OVERALL REVIEW RESULT	INADEQUATE		
BIOEQUIVALENCE STUDY TRACKING /SUPPORTING DOCUMENT #	STUDY/TEST TYPE	STRENGTH	REVIEW RESULT
1	DISSOLUTION	0.75 mg	ADEQUATE

I. EXECUTIVE SUMMARY

This is a review of the dissolution testing data only.

There is no USP method for this product but there is an FDA-recommended method. The firm's dissolution testing with the FDA-recommended method is acceptable at S1 level. The firm's proposed specification of Not Less Than (NLT) (b) (4) (Q) in 60 minutes is same as the FDA-recommended specification [NLT (b) (4) (Q) in 60 minutes]. The DBE acknowledges that the firm will conduct dissolution testing using the FDA-recommended method and specification for the test product.

A Division of Scientific Investigations (DSI) inspection is pending for the clinical site¹.

No Division of Scientific Investigations (DSI) inspection is pending or necessary for the analytical site².

The firm did not submit long term storage stability data. The firm will be asked to provide adequate long-term storage stability data for Levonorgestrel in the biological matrix covering at least 74 days.

The DBE will review the bioequivalence studies at a later date.

¹ For the clinical site, Aizant Drug Research Solutions PVT. LTD, a request for new site inspection was made on 10/22/09. The Project Manager was informed that this was a new site and DSI inspection should be requested.

² For the analytical site, the routine DSI inspection was requested for ANDA # 77502 on (b) (4). The DSI inspection was completed on (b) (4) and the outcome was VAI (Voluntary Action Indicated) DARRTS Search; ANDA # 77502; REV-RPM-05 (General Review); Final Date: 07/20/2007 (After reviewing the DSI report, the study was found to be acceptable; DARRTS Search: ANDA # 77502; REV-BIOEQ-01 (General Review); Final Date: 08/30/2007).

Table 1: SUBMISSION CONTENT CHECKLIST

Information		YES	NO	N/A	
Did the firm use the FDA-recommended dissolution method		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Did the firm use the USP dissolution method		<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Did the firm use 12 units of both test and reference in dissolution testing		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Did the firm provide complete dissolution data (all raw data, range, mean, % CV, dates of dissolution testing)		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Did the firm conduct dissolution testing with its own proposed method		<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Is FDA method in the public dissolution database (on the web)		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
SAS datasets submitted to the electronic document room (edr)	Fasting BE study	PK parameters	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
		Plasma concentrations	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Fed BE study	PK parameters	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
		Plasma concentrations	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
	Other study	PK parameters	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
		Plasma concentrations	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Are the DBE Summary Tables present in either PDF and/or MS Word Format?		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If any of the tables are missing or incomplete please indicate that in the comments and request the firm to provide the complete DBE Summary Tables 1-16.					
Is the Long Term Storage Stability (LTSS) sufficient to cover the maximum storage time of the study samples?		<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If the LTSS is NOT sufficient please request the firm to provide the necessary data.					

Table 2: SUMMARY OF IN VITRO DISSOLUTION DATA

Dissolution Conditions		Apparatus:	USP Type 2 (Paddle)								
		Speed of Rotation:	75								
		Medium:	0.1 N HCl with 0.1% SLS								
		Volume:	1000 mL								
		Temperature:	37 °C ± 0.5 °C								
Firm's Proposed Specifications		NLT ^{(b) (4)} Q of the labeled amount of Levonorgestrel USP is dissolved in 60 minutes.									
Dissolution Testing Site (Name, Address)		Lupin Limited, at Lupin Pharmcare Plot No. 2, SEZ Phase – II, Misc Zone Appreal Park, Pithampur (Dist - Dhar), Madhya Pradesh, 454774 INDIA									
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes or hours)					Study Report Location	
					10.	20	30	45	60		
Study Report #:	08/12/08	Levonorgestrel Tablets, 0.75 mg (B. No. LA18001) Mfg: Nov. 2008	0.75 mg Tablet	12	Mean	96	99	101	100	102	m5.3.1.3
					Range	(b) (4)					
					%CV	2.3	2.1	2.9	1.7	2.0	
Study Report #:	16/01/09	Plan B® Tablets, 0.75 mg (B. No. 306702) Exp: Feb. 2012	0.75 mg Tablet	12	Mean	99	100	101	101	101	m5.3.1.3
					Range	(b) (4)					
					%CV	3.5	2.4	2.2	2.1	1.3	

I. COMMENTS:

1. Currently, there is no USP method for Levonorgestrel Tablets but there is an FDA-recommended dissolution method. The FDA-recommended dissolution method is available in the public dissolution database on the Office of Generic Drugs website, <http://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm>.
2. The FDA-recommended dissolution method for Levonorgestrel Tablets, 0.75 mg is the same as the dissolution method of the innovator (NDA 21-045 of Duramed's, PlanB[®] (Levonorgestrel) Tablets, approved on 08/24/2006). According to our internal dissolution database, the dissolution specification for the reference product (PlanB[®]) is not less than (NLT) (b) (4) (Q) in 60 minutes (NOT TO BE RELEASED UNDER FOIA)³.
3. The firm's dissolution testing on its Levonorgestrel Tablets, 0.75 mg along with the reference product, Plan B[®] (Levonorgestrel) Tablets, 0.75 mg using the FDA-recommended dissolution method is acceptable. The firm proposed a specification of not less than (NLT) (b) (4) (Q) in 60 minutes is the same as the FDA-recommended specification. The specification is acceptable. The firm's test product meets the specification at the S₁ level.

III. DEFICIENCY COMMENTS:

The firm did not submit long term storage stability data. The firm will be asked to provide adequate long-term storage stability data for Levonorgestrel in the biological matrix covering at least 74 days.

IV. RECOMMENDATIONS:

1. The *in vitro* dissolution testing conducted by Lupin Limited, on its test product, Levonorgestrel Tablets, 0.75 mg (Lot # LA18001), comparing it to Duramed's Plan B[®] (Levonorgestrel) Tablets, 0.75 mg (Lot # 306702) is acceptable.
2. The Division of Bioequivalence (DBE) accepts the firm's proposed specification of NLT (b) (4) (Q) in 60 minutes, which is the same as the FDA-recommended specification.
3. The DBE acknowledges that the firm will conduct dissolution testing using the FDA-recommended dissolution method and specification for its test product.
4. The firm should submit sufficient long-term storage stability data.

The firm should be informed of the above deficiency comment and recommendations.

³ FDA internal dissolution database, last accessed: 10/22/2009.

Darrrts Search, ANDA # 78665, REV-BIOEQ-01 (General Review) Rec'd date: 12/10/2007. Final Date: 12/10/2007. Communication Author: Xiaojian Jiang. Last accessed: 10/26/2009.

BIOEQUIVALENCE DEFICIENCY

ANDA: 91-328
APPLICANT: Lupin Limited
DRUG PRODUCT: Levonorgestrel Tablets, 0.75 mg

The Division of Bioequivalence has completed its review of only the dissolution testing portion of your submission(s) acknowledged on the cover sheet. The review of the bioequivalence studies will be conducted later.

1. Your dissolution testing using the FDA-recommended method is acceptable. We acknowledge that you will conduct dissolution testing using the following dissolution method and specification for your test product, Levonorgestrel, 0.75 mg:

Medium: 0.1 N HCl with 0.1% Sodium Lauryl Sulfate (SLS)
Volume: 1000 mL
Temperature: 37°C ± 0.5°C
USP Apparatus: II (Paddle)
Speed: 75 rpm

The test product should meet the following specification:

NLT (b) (4) (Q) of the labeled amount of Levonorgestrel in the dosage form should be dissolved in **60 minutes**

However, the following deficiency has been identified:

2. Please provide long term storage stability data for Levonorgestrel in frozen biological matrix to cover the maximum storage period of the study samples equal to the time from the first sample collection to the data the last sample was analyzed, which is at least 74 days for your BE studies.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

V. OUTCOME

ANDA: 91-328

Completed Assignment for 91328 ID: 9513

Reviewer: Mandula, Haritha **Date Completed:**

Verifier: Braddy, April **Date Verified:**

Division: Division of Bioequivalence

Description:

Productivity:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Productivity</i>	<i>Subtotal</i>
9513	4/15/2009	Dissolution Data	Dissolution Review	1	1
				Bean Total:	1

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

/s/

HARITHA MANDULA
10/29/2009

APRIL C BRADDY
10/30/2009

HOAINHON N CARAMENICO on behalf of DALE P CONNER
10/30/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 091328

OTHER REVIEWS

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label and Labeling Review

Date: March 27, 2012

Reviewer(s): Alison Park, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis

Team Leader: Zachary Oleszczuk, PharmD, Team Leader
Division of Medication Error Prevention and Analysis

Division Director: Carol Holquist, RPh, Division Director
Division of Medication Error Prevention and Analysis

Drug Name: Levonorgestrel Tablets
0.75 mg

Application Type/Number: ANDA 091328

Applicant: Lupin Limited

OSE RCM #: 2011-3817

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review summarizes the Division of Medication Error Prevention and Analysis' (DMEPA) evaluation of the proposed labels and labeling for Levonorgestrel Tablets, 0.75 mg, for vulnerabilities that could lead to medication errors.

1.1 BACKGROUND OR REGULATORY HISTORY

The reference listed drug for this product is Plan B, NDA 021045.

1.2 PRODUCT INFORMATION

- Established Name: Levonorgestrel Tablets
- Indication of Use: Emergency Contraception
- Route of Administration: Oral
- Dosage Form: Tablet
- Strength: 0.75 mg
- Dose and Frequency of Administration: The first tablet is taken orally as soon as possible within 72 hours after unprotected intercourse. The second tablet should be taken 12 hours after the first dose.
- How Supplied: Wallet blister containing 2 tablets. Each wallet blister is packed in a carton. The wallet blister pack and the carton are not considered to be child-resistant.
- Storage: 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F)

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis¹, the principals of human factors, and post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Wallet Blister Label submitted December 7, 2011 (see Appendix A)
- Carton Labeling submitted December 7, 2011 (see Appendix B)
- Insert Labeling submitted December 7, 2011

Additionally, since the reference listed drug, Plan B, is currently marketed, DMEPA searched the FDA Adverse Event Reporting System (AERS) database to identify medication errors involving Plan B. The AERS search conducted on December 27, 2011 used the following search terms: trade name "Plan B" and "Plan B One-Step" and verbatim term "Plan%". The reaction terms used include MedDRA High Level Group Terms (HLGT) "Medication Errors" and "Product Quality Issues".

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

The reports were manually reviewed to determine if a medication error occurred. Duplicate reports were combined into cases. The cases that described a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors. If a root cause was associated with the label or labeling of the product, the case was considered pertinent to this review. Reports excluded from the case series include dose omission errors that were not due to the label or labeling, intentional overdose errors, accidental pediatric exposure errors that were not due to the label or labeling, and drug exposure via breast milk errors that were not due to the label or labeling (See Appendix C).

3 MEDICATION ERRORS EVALUATED

We considered the findings from AERS and applied principals of human factors in our analysis of the labels and labeling. Overall, the proposed labels and labeling are similar to the currently marketed products. The following sections describe the errors identified to date with Plan B and issues we identified with the proposed labels and labeling.

3.1 AERS SEARCH

Following exclusions we evaluated a total of 8 cases relevant to this review (See Appendix D). One case (ISR 5531756-2) involved a patient who was instructed by the pharmacist to take both tablets together (inappropriate schedule of drug administration). However, the patient noticed that the package insert states “to take the two tablets 12 hours apart.” The labeling for Plan B currently states to “take the second tablet **12 hours** after you take the first tablet.” This case appears to be due to a knowledge deficit of the pharmacist because the patient actually was able to identify the correct dose and frequency on the label.

The second case (ISR 5764425-4) involved a patient who took Plan B when she was already pregnant. The current labeling for Plan B states the correct Use (reduces chance of pregnancy after unprotected sex) as well as when not to use Plan B (i.e. already on regular birth control pills and if you are already pregnant). This case did not contain enough information to determine if the patient didn’t see the warning or understand the product would not work if already pregnant.

Additionally, there have been 6 cases in AERS (ISR 7313171-4, ISR 7352429-X, ISR 7353510-1, ISR 7456341-7, ISR 7486204-2, and ISR 7750580-3) of patients using expired Plan B One Step. Out of those 6 cases, 1 case stated that the patient was aware she took expired Plan B One Step and another case stated she did not realize the Plan B One Step was expired until after she had taken it. The remaining four cases did not state if the patient was aware or not aware they were taking expired medications.

3.2 WALLET BLISTER LABEL AND CARTON LABELING

- The font and use of italics for the established name decreases prominence of the information and almost looks like script which can be difficult to read.
- The statement [REDACTED] ^{(b) (4)} on the principal display panel is incorrect. Levonorgestrel Tablets 0.75 mg is prescription only for women

younger than age 17. For those that are 17, the product is still available over the counter.

- The abbreviation “USP” in the statement “Each tablet contains levonorgestrel USP 0.75 mg” on the principal display panel of the Blister Label is not necessary.
- The principal display panel of the Carton Labeling does not indicate “per tablet” after the strength which may be misleading.
- The manufacturer’s name is too prominent on the Carton Labeling.

3.3 WALLET BLISTER LABEL

- The directions for use on the principal display panel, next to **STEP 2**, is confusing and potentially misleading with the addition of (b) (4) in the statement “Take the **second tablet** 12 hours (b) (4) after taking the **first** tablet.”
- The expiration date and lot number is not on the Wallet Blister Label.

4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed label and labeling introduces vulnerability that can lead to medication errors. The type and font size used to communicate important information such as the established name and strength is difficult to read and the directions for use are incorrectly displayed. We recommend the revisions, outlined in A and B below, be implemented prior to approval.

If you have further questions or need clarifications, please contact Shawnetta Jackson, project manager, at 301-796-4952.

A. WALLET BLISTER LABEL AND CARTON LABELING

1. Revise the presentation of the established name and strength, Levonorgestrel Tablets, 0.75 mg, to use a type and font size that is more prominent and does not look like script.
2. The Rx statement on your principal display panel is incorrect. Patients 17 and above may receive this product without a prescription. Therefore, we request you revise the statement to read as follows: “Rx only for women younger than age 17”.
3. Delete “USP” from the statement on the principal display panel to read: “Each tablet contains levonorgestrel 0.75 mg”.
4. Revise the presentation of the established name and strength on the principal display panel of the Carton Labeling by deleting the comma after “Tablets” and adding “per tablet” after the strength. The revised established name and strength should read:

Levonorgestrel Tablets
0.75 mg per tablet

5. The manufacturer's name "Lupin" and the associated logo are too prominent and compete with the proprietary name. Decrease the size of the manufacturer's name and logo so that it is less prominent than the proprietary name.

B. WALLET BLISTER LABEL

1. Remove the words (b) (4) in the statement starting with **STEP 2** to read: "Take the **second tablet** 12 hours after taking the **first** tablet."
2. In accordance with 21 CFR 201.17, ensure the wallet blister label incorporates the expiration date and lot number.

APPENDICES

Appendix A: Wallet Label –



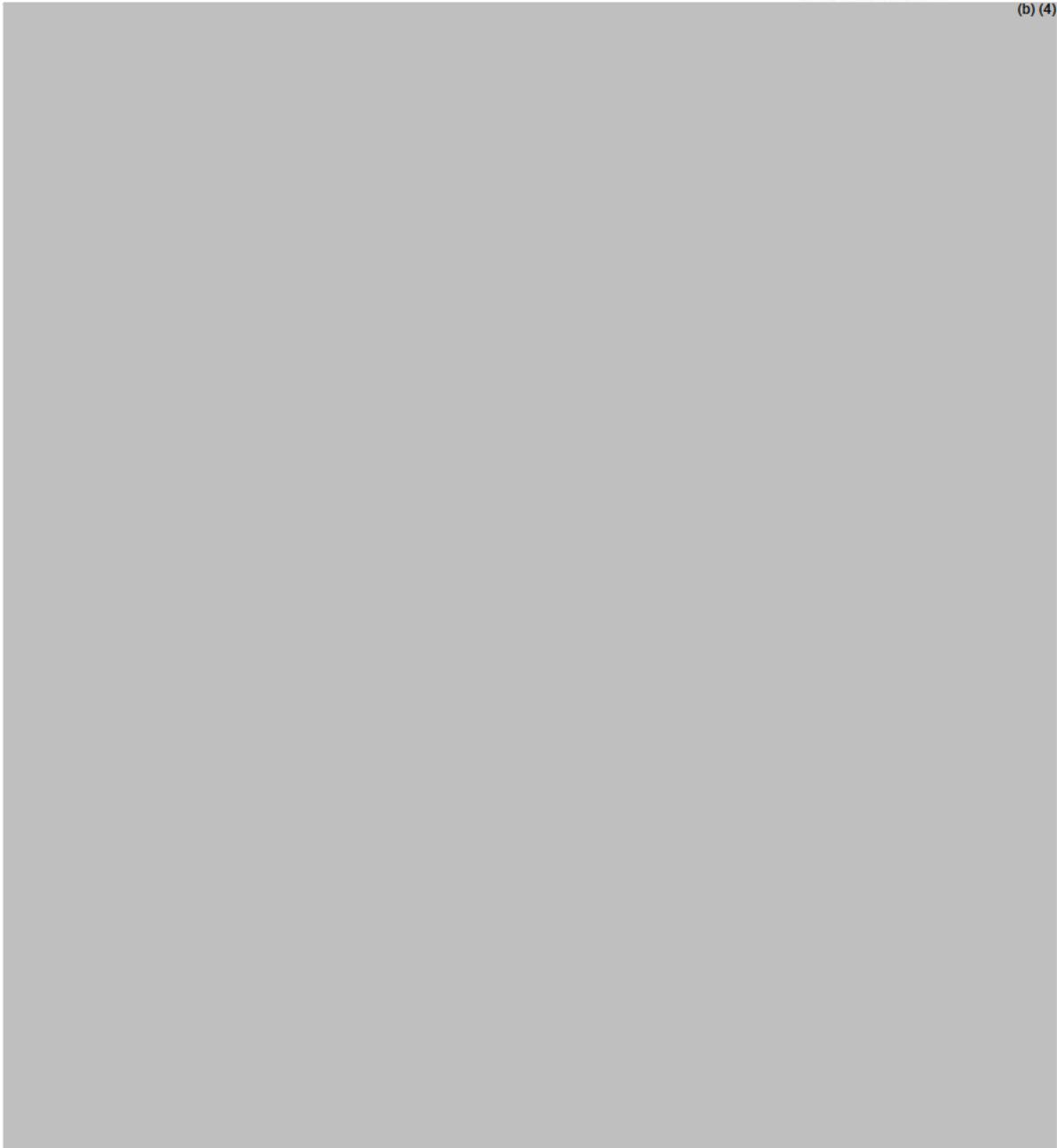
(b) (4)

No Varnish Zone

Dotted line not to be printed.

Lupin Pharmaceuticals			
Name	Levonorgestrel tablets	Size	105 x 67 x 6 mm
Type	Wallet	Date	01/12/11
GSM	200 ± 5%	Colours	(b) (4)
Board	(b) (4)	Rated to	Plan B
Molecule	Levonorgestrel Tablets 0.75		

Appendix B: Carton Labeling –



(b) (4)



(b) (4)

Appendix C: Excluded AERS ISR Numbers

ISR	ISR	ISR	ISR	ISR
5393288-4 (Dose omission)	5934830-1 (Intentional overdose)	7425677-8 (Exposure via breast milk)	7726387-x (Accidental pediatric exposure)	7757134-3 (Exposure via breast milk)
7879777-9 (Exposure via breast milk)	7876260-1 (Exposure via breast milk)	7879859-1 (Exposure via breast milk)	7944796-0 (Exposure via breast milk)	7985531-x (Intentional overdose)
7994917-9 (Prescribing error)	7996213-2 (Accidental pediatric exposure)			

Appendix D: All Relevant AERS ISR Numbers

ISR	Narrative
5531756-2	Information was received regarding a 19-year-old female patient who took Plan B (levonorgestrel tablets, 0.75 mg) for emergency contraception. The patient's last menstrual period is unknown. It was reported the patient had unprotected sexual intercourse on 11/15/2007. The patient took a single two tablet dose of Plan B on 11/16/2007. It was reported the patient was instructed by a pharmacist to take both tablets together; however, after reading the package insert, which stated to take the two tablets 12 hours apart, she returned to the pharmacy and was advised by the pharmacist to take a third tablet of Plan B 12. The patient took a second regimen of Plan B, a single one tablet dose, on 11/16/2007, 12 hours after the first regimen of Plan B. It was reported the patient experienced dizziness and passed out on 11/16/2007, after taking the third tablet of Plan B. At the time of the report on 11/16/2007, the patient was reported to be awake and talking. As of 11/16/2007, the dizziness persists. No further information is expected. This report has not been medically confirmed.
5764425-4	Information was received regarding a 34-year-old female patient who took Plan B (levonorgestrel tablets, 0.75 mg) for emergency contraception. The patient's last menstrual period began on 12-JAN-2008. It was reported the patient had unprotected sexual intercourse on an unspecified date in JAN-2008. A home urine pregnancy test performed on 15-FEB-2008, was positive. It was reported the patient took Plan B in MAR-2008, (dates, dose and frequency unspecified). It was stated the patient misunderstood the correct administration and indications for Plan B. The patient visited her doctor "a few days" after taking Plan B and was informed she had experienced a spontaneous abortion. It was further reported the doctor informed the patient the pregnancy had self-aborted, which he did not attribute to Plan B. No additional information was provided. This report has not been medically confirmed.
7313171-4	18-FEB-2011, Spontaneous Non-Serious Report Information was received from a female patient, 24 years of age, who took Plan B One-Step (levonorgestrel tablet, 1.5 mg) for emergency contraception. The patient's last menstrual period began on 08-FEB-2011. It was reported the patient had unprotected sexual intercourse on 14-FEB-2011. The patient took Plan B One-Step, 1.5 milligrams, on 14-FEB-2011. The Plan B One-Step lot number is T8B538A11, and the expiration date is NOV-2010. The patient stated she did not realize the Plan B One-Step was expired until after she had taken it. In addition, the patient reported she was diagnosed with an ear infection on 17-FEB-2011. The patient's doctor prescribed Zithromax, to be taken once daily, on 17-FEB-2011, to treat the ear infection. Additionally, the patient reported experiencing vaginal bleeding on 18-FEB-2011. As of 18-FEB-2011, the ear infection and vaginal bleeding persist. Because this is a spontaneous case, regulatory distribution will be handled as though it is a related case.
7352429-x	10-MAR-2011, Spontaneous Non-Serious Report. Information was received from a female patient, 24 years of age, who took Plan B One Step (levonorgestrel tablets, 1.5 mg) for emergency contraception. Concomitant medication includes an unspecified oral contraceptive, initiated on an unspecified date and is ongoing. The patient's last menstrual period is unknown. It was reported the patient had unprotected sexual intercourse on 06-MAR-2011. The patient takes an unspecified oral contraceptive and did not feel protected because she was on her placebo tablets; therefore, she took Plan B One Step, 1.5 milligrams, on 07-MAR-2011. The patient reported the Plan B she took expired in NOV-2010. In addition, the patient reported she was supposed to start her next period on 09-MAR-2011, which has not occurred as of 10-MAR-2011. Because this is a spontaneous case, regulatory distribution will be handled as though it is a related case.
7353510-1	10-MAR-2011, Spontaneous Non-Serious Report Information was received from a female patient, age unknown, who took Plan B One-Step (levonorgestrel tablet, 1.5 mg) for emergency contraception. Concomitant medication includes an unspecified birth control pill, for oral contraception, initiated on an unspecified date and is ongoing. The patient's last menstrual period began on 06-FEB-2011. It was reported the patient had protected sexual intercourse on 06-MAR-2011. The patient's next expected menstrual period due on 06-MAR-2011, did not occur. The patient takes an unspecified birth control pill as her regular form of contraception and was unsure if she was covered during the inactive week of her pills; therefore, she took Plan B One-Step, 1.5 milligrams, on 07-MAR-2011. The Plan B One-Step the patient took on 07-MAR-2011, had an expiration date of NOV-2010. The patient was aware she took expired Plan B One-Step. As of 10-MAR-2011, the menstrual period has not occurred. Follow-up will be attempted. Because this is a spontaneous case, regulatory distribution will be handled as though it is a related case.
7456341-7	25-APR-2011, Spontaneous Non-Serious Report Information was received from a female patient, 24 years of age, who took Plan B One-Step (levonorgestrel tablet, 1.5 mg) for emergency contraception. The patient's last menstrual period is unknown. It was reported the patient had unprotected sexual intercourse on 24-APR-2011. The patient took Plan B One-Step, 1.5 milligrams, on 24-APR-2011. The Plan B One-Step the patient took on 24-APR-2011, had an expiration date of NOV-2010. It was reported the patient experienced menses-like abdominal cramping and breast tenderness to touch on 24-APR-2011. As of 25-APR-2011, the abdominal cramping and breast tenderness persist. Follow-up will be attempted. Because this is a spontaneous case, regulatory distribution will be handled as though it is a related case. 02-MAY-2011, Spontaneous Non-Serious Report Additional information was received. The patient was contacted regarding the outcome of the events and reported the abdominal cramping and breast tenderness both resolved on 28-APR-2011. Because this is a spontaneous case, regulatory distribution will be handled as though it is a related case.
7486204-2	12-MAY-2011, Spontaneous Non-Serious Report. Information was received from a female patient, 18 years of age, who took Plan B One Step (levonorgestrel tablets, 1.5 mg) for emergency contraception. Concomitant medication includes Trivora, for oral contraception, initiated on an unspecified date and is ongoing. The patient's last menstrual period began on 13-APR-2011. It was reported the patient had unprotected sexual intercourse on 07-MAY-2011. The patient takes the oral contraceptive, Trivora, as her regular form of birth control. As a precautionary measure, the patient took Plan B One Step, 1.5 milligrams, on 07-MAY-2011. The Plan B the patient took on 07-MAY-2011, had an expiration date of NOV-2010. The patient reported experiencing a late period on 11-MAY-2011. As of 12-MAY-2011, the menstrual period has not occurred. Because this is a spontaneous case, regulatory distribution will be handled as though it is a related case.
7750580-3	10-SEP-2011, Spontaneous Non-Serious Report. Information was received from a female patient, 19 years of age, who took Plan B One Step (levonorgestrel tablets, 1.5 mg) for emergency contraception. The patient's last menstrual period began on 25-AUG-2011. It was reported the patient had unprotected sexual intercourse on 07-SEP-2011. The patient took Plan B One Step, 1.5 milligrams, on 08-SEP-2011. The Plan B One Step the patient took on 08-SEP-2011, had an expiration date of JUL-2011. The patient reported experiencing vaginal bleeding on 09-SEP-2011. As of 10-SEP-2011, the vaginal bleeding persists. Follow-up will be attempted. Because this is a spontaneous case, regulatory distribution will be handled as though it is a related case.

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/s/

ALISON J PARK
03/27/2012

ZACHARY A OLESZCZUK
03/27/2012

CAROL A HOLQUIST
03/28/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Proprietary Name Review

Date:	December 20, 2011
Reviewer(s):	Alison Park, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis
Team Leader	Zachary Oleszczuk, PharmD, Team Leader Division of Medication Error Prevention and Analysis
Deputy Division Director	Kellie Taylor, PharmD, MPH, Deputy Director Division of Medication Error Prevention and Analysis
Division Director	Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis
Drug Name(s) and Strength(s):	(b) (4) (Levonorgestrel) Tablets 0.75 mg
Application Type/Number:	ANDA 91328
Applicant/Sponsor:	Lupin Ltd.
OSE RCM #:	2011-3816

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review summarizes the evaluation of the proposed proprietary name, (b) (4) (b) (4) (Levonorgestrel) tablet for ANDA 91328. The proposed proprietary name was submitted by Lupin Ltd., for evaluation on September 30, 2011. Additionally, Lupin submitted the secondary name, (b) (4).

1.1 PRODUCT INFORMATION

(b) (4) (Levonorgestrel) is indicated for emergency contraception. It will be available as a tablet and packaged in a blister card containing two tablets. The usual dose is one tablet by mouth within 72 hours of unprotected sexual intercourse followed by a second tablet 12 hours after the first tablet. The reference listed drug for this product is Plan B (NDA 021045).

2 DISCUSSION

During the initial steps of the proprietary name review process, the Office of Prescription Drug Promotion (OPDP) did not recommend the use of the proposed proprietary name, (b) (4), because it is misleading. OPDP provided the following statement:

OPDP objects to the proposed proprietary names (b) (4) and (b) (4) (b) (4) " because they are overly fanciful and minimize the potential risks associated with the drug product.

Levonorgestrel is a common substance and the limitations of which are readily recognized when it is listed by its established name [21 CFR 201.10(c)(3)]. Therefore, the proposed proprietary names imply a unique representation over other drugs with a similar active ingredient.

(b) (4)

Please note that the Federal Food Drug and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made, whether through a proposed proprietary name or otherwise; this includes suggestions that a drug

is better, more effective, useful in a broader range of conditions or patients, safer, has fewer, or lower incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence or substantial clinical experience. [21 U.S.C. 321(n); see also 21 U.S.C. 352(a) & (n); 21 CFR 202.1(e)(5)(i);(e)(6)(i)].

This concern was shared with the Division of Reproductive and Urologic Products (DRUP), the Division of Nonprescription Clinical Evaluation (DNCE), and the Office of Generic Drugs (OGD). In an email correspondence dated October 14, 2011, we were notified that OGD does not have any issues with the proposed name. Additionally, OGD did not object to OPDP's assessment. Similarly, in an email correspondence dated November 18, 2011 and November 29, 2011, respectively, we were notified that DNCE and DRUP do not have any concerns with the proprietary name, and they also did not object to OPDP's assessment.

3 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concurs with OPDP's promotional concerns with both the primary proposed proprietary name, (b) (4), and the secondary proposed proprietary name, (b) (4). Therefore, the Division of Medication Error Prevention and Analysis will not proceed with the safety review of the proposed proprietary name. The proposed proprietary name is considered promotional. DMEPA will notify the Applicant of FDA's decision to object to the name based on promotional concerns.

3.1 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, (b) (4), and have concluded that this name is unacceptable for the following reason:

The proposed proprietary names (b) (4) and (b) (4) because they are overly fanciful and minimize the potential risks associated with the drug product. Levonorgestrel is a common substance and the limitations of which are readily recognized when it is listed by its established name [21 CFR 201.10(c)(3)]. Therefore, the proposed proprietary names imply a unique representation over other drugs with a similar active ingredient. (b) (4)

Please note that the Federal Food Drug and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made, whether through a proposed trade name or otherwise; this includes suggestions that a drug is better, more effective, useful in a broader range of conditions or patients, safer, has fewer, or lower incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence or substantial clinical experience. [21 U.S.C. 321(n); see also 21 U.S.C. 352(a) & (n); 21 CFR 202.1(e)(5)(i);(e)(6)(i)].

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/s/

ALISON J PARK
12/20/2011

ZACHARY A OLESZCZUK
12/20/2011

ZACHARY A OLESZCZUK on behalf of KELLIE A TAYLOR
12/20/2011

CAROL A HOLQUIST
12/20/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 091328

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

ROUTING SHEET

APPROVAL TENTATIVE APPROVAL SUPPLEMENTAL APPROVAL (NEW STRENGTH) CGMP

Division: **IV** Team: **44** PM: **Andrew Kim**

Electronic ANDA:
Yes No

ANDA #: **91328**

Firm Name: **Lupin Limited**

ANDA Name: **Levonorgestrel Tablets, 0.75 mg**

RLD Name: **Ortho Plan B®**

Electronic AP Routing Summary Located:

V:\Chemistry Division IV\Team 44\Electronic AP Summaries

AP/TA Letter Located:

V:\Chemistry Division IV\Team 44\Final Version For DARRTS

Project Manager Evaluation:

Date: **12/17/12** Initials: **AK**

- Previously reviewed and tentatively approved --- Date _____
 Previously reviewed and CGMP Complete Response issued -- Date _____

Original Rec'd date <u>4/17/09</u>	Date of Application <u>04/15/2009</u>	Date Acceptable for Filing <u>4/17/09</u>
Patent Certification (type) <u>PII</u>	Date Patent/Excl. expires	Citizens' Petition/Legal Case? Yes <input type="checkbox"/> No <input type="checkbox"/> (If YES, attach email from PM to CP coord)
First Generic Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> DMF#: _____ (provide MF Jackets)	Priority Approval (Top 100, PEPFAR, etc.)? Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Comment: Prepared Draft Press Release sent to Cecelia Parise Yes <input type="checkbox"/> No <input type="checkbox"/> Date:	
<input type="checkbox"/> Suitability Petition/Pediatric Waiver	Pediatric Waiver Request: Accepted <input type="checkbox"/> Rejected <input type="checkbox"/> Pending <input type="checkbox"/>	

EER Status: Pending Acceptable OAI *EES Date Acceptable: 12/14/12* Warning Letter Issued; Date:
Has there been an amendment providing for a Major change in formulation since filing? Yes No Comment:
Date of Acceptable Quality (Chemistry) 4/11/12 Addendum Needed: Yes No Comment: Tert Review Memo in DARRTS
Date of Acceptable Bio 12/14/12 Bio reviews in DARRTS: Yes No (Volume location:)
Date of Acceptable Labeling 10/31/12 Attached labeling to Letter: Yes No Comment:
Date of Acceptable Sterility Assurance (Micro) _____

Methods Val. Samples Pending: Yes No ; Commitment Rcvd. from Firm: Yes No

Post Marketing Agreement (PMA): Yes No (If yes, email PM Coordinator) Comment:

Modified-release dosage form: Yes No (If yes, enter dissolution information in Letter)

Routing:

Office of Management, Fee Verification, Date emailed: _____; Date Response in DARRTS: Met

Labeling Endorsement, Date emailed: 1/14/13 REMS Required: Yes No REMS Acceptable: Yes No

Regulatory Support

Paragraph 4 Review (Dave Read, Susan Levine), Date emailed: _____

Division

1st Generic Review

Bob West / Peter Rickman

Gregory Geba

Filed AP Routing Summary in DARRTS

Notified Firm and Faxed Copy of Approval Letter

Sent Email to "CDER-OGDAPPROVALS"
distribution list

Reference ID: 3248928

OGD APPROVAL ROUTING SUMMARY

1. **Office of Management**

CDER-OM-COLLECTIONS (cder-om-collections@fda.hhs.gov)

Date Emailed:

Date Verification response received from OM:

Fee Verification (check all that apply):

- Backlog Fee
- ANDA New Application Fee
- API Manufacturer Fee
- FDF Manufacturer Fee
- DMF Fee

- Misbranding statement required in letter for no Facility Fee payment
- Misbranding statement required in letter for Failure to Self-ID

- Backlog ANDA TA/AP'd prior to being able to collect fees statement (Limbo TA/AP)

Comments:

2. **Regulatory Support Branch Evaluation**

Martin Shimer

Date: 1/16/2013

Chief, Reg. Support Branch

Initials: MHS

Contains GDEA certification: Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> (required if sub after 6/1/92)	Determ. of Involvement? Yes <input type="checkbox"/> No <input type="checkbox"/>
Patent/Exclusivity Certification: Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> If Para. IV Certification- did applicant: Notify patent holder/NDA holder Yes <input type="checkbox"/> No <input type="checkbox"/> Was applicant sued w/in 45 days: Yes <input type="checkbox"/> No <input type="checkbox"/> Has case been settled: Yes <input type="checkbox"/> No <input type="checkbox"/> Date settled: _____ Is applicant eligible for 180 day	Pediatric Exclusivity System RLD = _____ NDA# _____ Date Checked _____ Nothing Submitted <input type="checkbox"/> Written request issued <input type="checkbox"/> Study Submitted <input type="checkbox"/>
Generic Drugs Exclusivity for each strength: Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>	
Date of latest Labeling Review/Approval Summary _____	
Any filing status changes requiring addition Labeling Review Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>	
Type of Letter: <input checked="" type="checkbox"/> APPROVAL <input type="checkbox"/> TENTATIVE APPROVAL <input type="checkbox"/> SUPPLEMENTAL APPROVAL (NEW STRENGTH) <input type="checkbox"/> CGMP <input type="checkbox"/> OTHER:	
Comments: ANDA submitted on 4/17/2009, BOS=Plan B NDA 21045, PI cert provided. ANDA ack for filing on 4/17/2009(LO dated 7/13/2009). There are no remaining unexpired patents or exclusivities which protect the RLD. This ANDA is eligible for immediate Full Approval.	

3. **Labeling Endorsement**

Reviewer, _____ :
Date _____
Initials _____

Labeling Team Leader, _____ :
Date _____
Initials _____

REMS required?
 Yes No

REMS acceptable?
 Yes No n/a

Comments:

From: Golson, Lillie D
Sent: Tuesday, January 15, 2013 12:03 PM
To: Kim, Andrew (CDER); Golson, Lillie D
Subject: FW: 91328 AP Endorsement needed

Hi Andrew,

Please endorse the AP routing form on behalf of Malik and me.

Thanks

4. ***Paragraph IV Evaluation*** **PIV's Only** Date _____
Initials _____
David Read
OGD Regulatory Counsel
Pre-MMA Language included
Post-MMA Language Included
Comments:
5. ***Quality Division Director /Deputy Director Evaluation*** Date 1/17/2013
Initials RLI
Chemistry Div. **IV (Iser)**
Comments:CMC OK
6. ***First Generic Evaluation*** **First Generics Only** Date _____
Initials _____
Frank Holcombe
Assoc. Dir. For Chemistry
Comments: (First generic drug review)

OGD Office Management Evaluation

7. ***Peter Rickman*** Date 1/23/13
Initials wpr
Director, DLPS
Para.IV Patent Cert: Yes No
Pending Legal Action: Yes No
Petition: Yes No
Comments: BOS=Plan B NDA 21045. Applicant provided a PI patent certification. There are no remaining unexpired patents or exclusivities which protect the RLD. Chemistry acceptable 4/11/2012 and 1/17/2013. Bio acceptable 12/14/2012 (fasting study). Labeling acceptable 10/31/2012, TL sign-off 1/15/2013. This ANDA is eligible for Full Approval.

AND/OR

8. ***Robert L. West*** Date _____
Initials _____
Deputy Director, OGD
Para.IV Patent Cert: Yes No
Pending Legal Action: Yes No
Petition: Yes No
Press Release Acceptable
Date PETS checked for first generic drug _____

Comments:
9. ***OGD Director Evaluation***
Gregory Geba
Deputy Director, OPS
Comments:
First Generic Approval
PD or Clinical for BE
Special Scientific or Reg.Issue

Press Release Acceptable

Comments:

10. Project Manager

Date _____

Initials _____

Check Communication and Routing Summary into DARRTS

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/s/

ANDREW KIM
01/23/2013

****Please send an email to the labeling reviewer (Malik.Imam@fda.hhs.gov) to confirm that you received the labeling comments****

Labeling Comments

ANDA 091328

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773 (240-276-8988)



TO: Lupin Pharmaceuticals Inc.,
US Agent for Lupin Limited
ATTN: Leslie Sands

TEL: 410-576-2000

FAX: 410-576-2221

FROM: Malik Imam
240-276-8964

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for:

Levonorgestrel Tablets, 0.75 mg

Pages (including cover and signature page): 4

SPECIAL INSTRUCTIONS:

Effective 01-Aug-2010, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents has become:

***Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, Maryland 20855***

ANDAs will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): <http://www.fda.gov/cder/ogd> or Federal Register: <http://www.gpoaccess.gov/ft/>

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

**REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number	091328
Date of Submission	04/15/2009, 09/30/2011, 12/07/2011, 01/03/2012, and 01/04/2012
Applicant's Name	Lupin Pharmaceuticals, Inc. US Agent for Lupin Limited
Established Name	Levonorgestrel Tablets, 0.75 mg
Proprietary Name	None

Labeling Deficiencies:

A. General Comments:

Please revise both carton and wallet labels in order to comply with the labeling format requirements of 21 CFR 201.66. Also please submit a format legend with carton and wallet labels.

B. Carton Label:

1. See GENERAL COMMENTS above.
2. In the section titled "When using this product you may have" please ensure you have the same side effects listed as the RLD.
3. Revise the presentation of the established name and strength, Levonorgestrel Tablets, 0.75 mg, to use a type and font size that is more prominent and does not look like script.
4. The Rx statement on your principal display panel is incorrect. Patients 17 and above may receive this product without a prescription. Therefore, we request you revise the statement to read as follows:
"Rx only for women younger than age 17".
5. Delete "USP" from the statement on the principal display panel to read:
"Each tablet contains levonorgestrel 0.75 mg".
6. The manufacturer's name "Lupin" and the associated logo are too prominent and compete with the proprietary name. Decrease the size of the manufacturer's name and logo so that it is less prominent than the proprietary name.

C. Blister Card:

1. See GENERAL COMMENTS above.
2. Please see note B-2 through B-6
3. Remove the words (b) (4) in the statement starting with **STEP 2** to read:
"Take the **second tablet** 12 hours after taking the **first** tablet."
4. In accordance with 21 CFR 201.17, ensure the wallet blister label incorporates the expiration date and lot number.

Please submit final printed labeling electronically.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with the last approved labeling of the **RLD** with all differences annotated and explained.

{See appended electronic signature page}

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

LILLIE D GOLSON
05/25/2012
for Wm. Peter Rickman

TELEPHONE CONFERENCE FAX

ANDA #:91-328 (Revised 3/28/12)

Date: 28-MAR-2012

Total of 2 pages



OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Lupin Limited

TEL: 410-576-2000

ATTN: Leslie Sands

FAX: 410-576-2221

FROM: Roslyn Powers, Ph.D.

FDA CONTACT PHONE: (240) 276-8417

Dear Madam:

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Levonorgestrel Tablets, 0.75 mg. Please confirm receipt of this FAX through e-mail: Roslyn.Powers@fda.hhs.gov.

The deficiencies presented below represent MINOR deficiencies identified during the ongoing review and the current review cycle will remain open. You should respond to these deficiencies with a "Telephone Amendment" within ten working days. If you have questions regarding these deficiencies please contact the Project Manager, Andrew Kim at (240) 276-8438. Please submit documentation by fax to the attention of the Project Manager at (240) 276-8440. Please also submit official hard copies of any faxed documentation to the Document Room.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents will be:*

*Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, Maryland 20857*

*After the effective date, **01-Aug-2010**, ANDAs will only be accepted at the new mailing address listed above. **DO NOT** submit your ANDA Regulatory documents to this address prior to **01-Aug-2010**. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): <http://www.fda.gov/cder/ogd> or Federal Register: <http://www.gpoaccess.gov/fr/>*

Please submit your response in electronic format. This will improve document availability to review staff.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

III. List of Deficiencies and Comments to Be Communicated:

ANDA: 91-328 APPLICANT: Lupin Limited.

DRUG PRODUCT: Levonorgestrel Tablets, 0.75 mg

The deficiencies presented below represent TELEPHONE DEFICIENCY:

Please revise the drug product release and stability related substances tests in the specifications to state the following with the proposed acceptance limit:

 (b) (4)

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/s/

ROSLYN F POWERS
03/28/2012

QUALITY DEFICIENCY - MINOR

ANDA 091328

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855



APPLICANT: Lupin Limited

TEL: (410) 576-2000

ATTN: Leslie Sands

FAX: (410) 576-2221

FROM: Andrew Kim

FDA CONTACT PHONE: (240) 276-8438

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated April 15, 2009, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Levonorgestrel Tablets, 0.75 mg.

Reference is also made to your amendment dated January 17, 2012.

The Division of Chemistry has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached ___ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

Your amendment should respond to all of the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Your cover letter should clearly indicate that the response is a **QUALITY MINOR AMENDMENT / RESPONSE TO INFORMATION REQUEST** and should appear prominently in your cover letter.

We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

Effective ~~01-Aug-2010~~, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents will be:

***Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855***

All ANDA documents will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): <http://www.fda.gov/cder/ogd> or Federal Register: <http://www.gpoaccess.gov/fr/>

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If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 91328 APPLICANT: Lupin Limited

DRUG PRODUCT: Levonorgestrel Tablets, 0.75 mg (Rx/OTC)

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:



Sincerely yours,

Robert Iser
Acting Director
Division of Chemistry IV
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

UPINDER S ATWAL
02/17/2012



ANDA 091328

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Lupin Limited
c/o:
Lupin Pharmaceuticals Inc.,
Harborplace Tower
111 South Calvert Street, 21st Floor
Baltimore, Maryland 21202

Attention: Leslie Sands
Director, Regulatory Affairs

Dear Ms. Sands:

Please refer to your Abbreviated New Drug Application (ANDA) dated April 15, 2009, received April 17, 2009, submitted under 505(j) of the Federal Food, Drug, and Cosmetic Act for Levonorgestrel Tablets, 0.75 mg.

We also refer to:

- Your September 30, 2011 correspondence, received October 3, 2011, requesting review of your proposed proprietary name, (b) (4);
- Your December 7, 2011 correspondence, received December 7, 2011, in which you submitted container and carton labeling that does not include a proposed proprietary name;
- Our letter of December 23, 2011, responding to your December 7, 2011 submission, which we interpreted as a request to withdraw the proposed proprietary name, (b) (4);
- Your correspondence, submitted on January 3, 2012, and January 4, 2012, and received on January 3, 2012 and January 4, 2012 respectively, in which you clarify that:
 - it was not your intent to withdraw the proposed proprietary name (or alternate) from review;
 - instead, you intended to provide labeling that does not incorporate a proprietary name, for use if the ANDA is approved before review of the proposed proprietary name was complete.

We have completed our review of the proposed proprietary names, (b) (4) and (b) (4) and have concluded that these names are unacceptable for the following reasons.

The proposed proprietary names (b) (4) and (b) (4) are overly fanciful and minimize the potential risks associated with the drug product. Levonorgestrel is a common substance

and the limitations of which are readily recognized when it is listed by its established name [21 CFR 201.10(c)(3)]. Therefore, the proposed proprietary name implies a unique representation over other drugs with a similar active ingredient.

(b) (4)

Please note that the Federal Food Drug and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made, whether through a proposed proprietary name or otherwise; this includes suggestions that a drug is better, more effective, useful in a broader range of conditions or patients, safer, has fewer, or lower incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence or substantial clinical experience. [21 U.S.C.321(n); see also 21 U.S.C. 352(a) & (n); 21 CFR 202.1(e)(5)(i);(e)(6)(i)].

Therefore, if you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Shawnetta Jackson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4952. For any other information regarding this application contact Andrew Kim, Product Quality Regulatory Project Manager in the Office of Generic Drugs (OGD), at (240) 276-8438.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
01/27/2012



ANDA 91328

**PROPRIETARY NAME REVIEW REQUEST
WITHDRAWN**

Lupin Limited
c/o:
Lupin Pharmaceuticals Inc.,
Harborplace Tower
111 South Calvert Street, 21st Floor
Baltimore, Maryland 21202

Attention: Leslie Sands
Director, Regulatory Affairs

Dear Ms. Sands:

Please refer to your Abbreviated New Drug Application (ANDA) dated April 15, 2009, received April 17, 2009, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Levonorgestrel Tablets, 0.75 mg.

We acknowledge receipt of your December 7, 2011, correspondence, on December 7, 2011, notifying us that you are withdrawing your request for a review of the proposed proprietary name [REDACTED] (b) (4). This proposed proprietary name request is considered withdrawn as of December 7, 2011.

We note that you have proposed an alternate proprietary name in your submission dated September 30, 2011. In order to initiate the review of the alternate proprietary name, [REDACTED] (b) (4) [REDACTED] (b) (4) submit a new complete request for proprietary name review within 14 days of this letter. The review of this alternate name will not be initiated until the new submission is received.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Shawnetta Jackson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4952. For any other information regarding this application contact Andrew Kim, Product Quality Regulatory Project Manager in the Office of Generic Drugs (OGD), at (240) 276-8438.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
12/23/2011

QUALITY DEFICIENCY - MINOR

ANDA 091328

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855



APPLICANT: Lupin Limited

TEL: (410) 576-2000

ATTN: Leslie Sands

FAX: (410) 576-2221

FROM: Andrew Kim

FDA CONTACT PHONE: (240) 276-8438

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated April 15, 2009, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Levonorgestrel Tablets, 0.75 mg.

The Division of Chemistry has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached ___ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

Your amendment should respond to all of the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Your cover letter should clearly indicate that the response is a **QUALITY MINOR AMENDMENT / RESPONSE TO INFORMATION REQUEST** and should appear prominently in your cover letter.

We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

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Rockville, Maryland 20855***

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CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 91328 APPLICANT: Lupin Limited

DRUG PRODUCT: Levonorgestrel Tablets, 0.75 mg (Rx/OTC)

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

(b) (4)



Following this page, 2 pages withheld in full (b)(4)

- B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

Please provide all available long term stability test results for your drug product. Please provide an updated and revised drug product stability specification table, forms and test methods, as applicable.

Sincerely yours,

Robert Iser
Acting Director
Division of Chemistry IV
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

UPINDER S ATWAL
10/13/2011

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

Date Requested: 11/02/2009

TO: C.T. Viswanathan, Ph.D.
Associate Director - Bioequivalence (HFD-48)
Division of Scientific Investigations

FROM: Dale P. Conner, Pharm. D or Barbara M. Davit, Ph.D., J.D.
Director or Acting Director, Division of Bioequivalence I or II, HFD-650

SUBJECT: Biopharmaceutics Compliance Program 7348.001

REQUEST FOR INSPECTION:

Electronic Submission: Yes

Priority: B

Due Date: 05/01/2010

ANDA No.	91-328
Drug Product Name	Levonorgestrel Tablets
Strength (s)	0.75 mg
Applicant Name	Lupin Limited
Address	159, CST Road, Kalina, Santacruz (East) Mumbai-400 098, Maharashtra, India.
Applicant's Point of Contact	Authorized U.S. Agent: Leslie Sands Director, Regulatory Affairs, Harborplace Tower, 111 South Calvert Street, 21 st Floor Baltimore, MD 21202, U.S.A.
Contact's Phone Number	410-576-2000
Contact's Fax Number	410-576-2221
Submission Date(s)	04/15/2009
First Generic	No
Reviewer	Haritha Mandula, Ph.D.
Study Number (s)	CB081203
Study Type (s)	Fasting (STF)

Strength(s)	0.75 mg
Clinical Site	Aizant Drug Research Solutions PVT. LTD
Clinical Site Address	Survey No.: 172 & 173/A, Apparel Park Road, Dulapally village, Quthbullapur Mandal, Hyderabad-500014.

Reason for: New site

Comments: This DSI inspection request is only for the Clinical site.

Bio Study Status: Under review

Project Manager: Teresa Vu

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- ANDA-91328	----- ORIG-1	----- LUPIN LTD	----- LEVONORGESTREL

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/s/

TERESA VU
11/02/2009

DALE P CONNER
11/03/2009

BIOEQUIVALENCE AMENDMENT

ANDA 091328

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)



APPLICANT: Lupin Pharmaceuticals Inc.

TEL: (410) 576-2000

ATTN: Leslie Sands

FAX: (410) 576-2221

FROM: Teresa Vu

FDA CONTACT PHONE: (240) 276-8782

Dear Madam:

This facsimile is in reference to the bioequivalence data submitted on April 15, 2009, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Levonorgestrel Tablets, 0.75 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached 1 page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review.** Your cover letter should clearly indicate:

Bioequivalence Response to Information Request Bioequivalence Long Term Stability

If applicable, please clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this **communication with your response.**

Please submit a copy of your amendment in an archival (blue) jacket and unless submitted electronically through the gateway, a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format. This will improve document availability to review staff.

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ANDA: 091328
APPLICANT: Lupin Limited
DRUG PRODUCT: Levonorgestrel Tablets, 0.75 mg

The Division of Bioequivalence has completed its review of only the dissolution testing portion of your submission(s) acknowledged on the cover sheet. The review of the bioequivalence studies will be conducted later.

1. Your dissolution testing using the FDA-recommended method is acceptable. We acknowledge that you will conduct dissolution testing using the following dissolution method and specification for your test product, Levonorgestrel, 0.75 mg:

Medium: 0.1 N HCl with 0.1% Sodium Lauryl Sulfate (SLS)
Volume: 1000 mL
Temperature: 37°C ± 0.5°C
USP Apparatus: II (Paddle)
Speed: 75 rpm

The test product should meet the following specification:

NLT (b) (4) (Q) of the labeled amount of Levonorgestrel in the dosage form should be dissolved in **60 minutes**

However, the following deficiency has been identified:

2. Please provide long term storage stability data for Levonorgestrel in frozen biological matrix to cover the maximum storage period of the study samples equal to the time from the first sample collection to the date the last sample was analyzed, which is at least 74 days for your BE studies.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- ANDA-91328	----- ORIG-1	----- LUPIN LTD	----- LEVONORGESTREL

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/s/

DALE P CONNER
11/03/2009



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 91-328

Lupin Pharmaceuticals Inc.
Attention: Leslie Sands
U.S. Agent for Lupin Limited
Harborplace Tower
111 South Calvert Street, 21st floor
Baltimore, MD 21202

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Levonorgestrel Tablets, 0.75 mg

DATE OF APPLICATION: April 15, 2009

DATE (RECEIVED) ACCEPTABLE FOR FILING: April 17, 2009

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Leigh Ann Bradford
Project Manager
240-276-8453

Sincerely yours,

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

Peter Chen
7/13/2009 09:12:11 AM
Signing for Wm Peter Rickman