LEVONORGESTREL- levonorgestrel tablet
Lupin Pharmaceuticals, Inc.

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%), 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 pediatric (premenarcheal) (8.4) or postmenopausal women (8.5).
- Clinical trials demonstrated a higher pregnancy rate in the Chinese population. (8.6)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 12/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

* 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 either dose of medication, 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 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 bleeding 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 infection (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 contraception; 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%), 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

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 (including primidone)
- 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. Concomitant administration of efavirenz has been found to reduce plasma levels of levonorgestrel (AUC) by around 50%, which may reduce the effectiveness of levonorgestrel tablets, 0.75 mg.

Consult the labeling of all concurrently used drugs 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 progestins pass into the breast milk of nursing mothers taking progestin-only pills for long-term contraception, resulting in detectable steroid 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 under the age of 16 and for users 16 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.

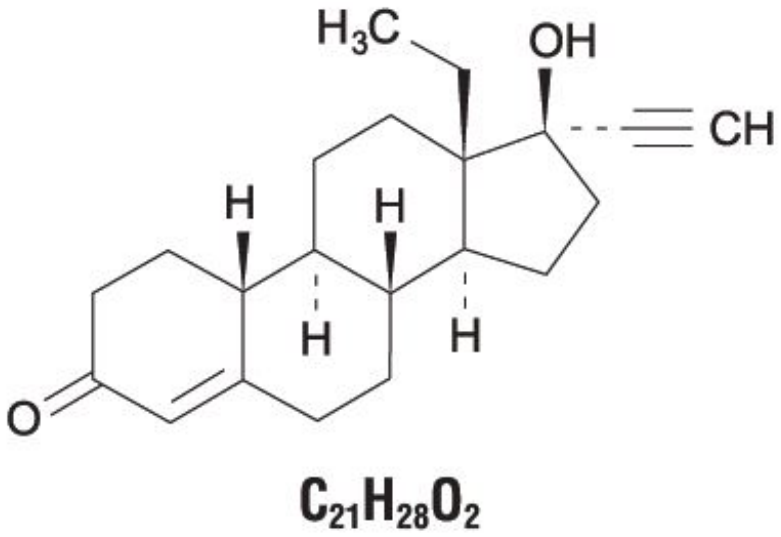
10 OVERDOSAGE

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

11 DESCRIPTION

Each levonorgestrel tablets, 0.75 mg 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 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:



$C_{21}H_{28}O_2$

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 maximum serum concentrations of levonorgestrel were 14.1 + 7.7 ng/mL (mean + SD) at an average of 1.6 + 0.7 hours.

	Mean (± SD)					
	C_{max} (ng/mL)	**T_{max} (h)**	**CL (L/h)**	**V_d (L)**	**$t_{½}$ (h)**	**AUC_{inf} (** ng/mL.h)
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
$t_{½}$ = elimination half life
AUC_{inf} = 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 17β-OH position to form sulfate conjugates and, to a lesser extent, glucuronide 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. 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 pediatric (pre-menarcheal) 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 tumorgenicity following administration of levonorgestrel to rats for 2 years at approximately 5 µg/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 µg/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 irreversible 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 bleeding similar to their 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.

Baltimore, Maryland 21202

United States

Manufactured by:

Lupin Limited

Pithampur (M.P.) - 454 775

INDIA

January 2018 ID#: 226728

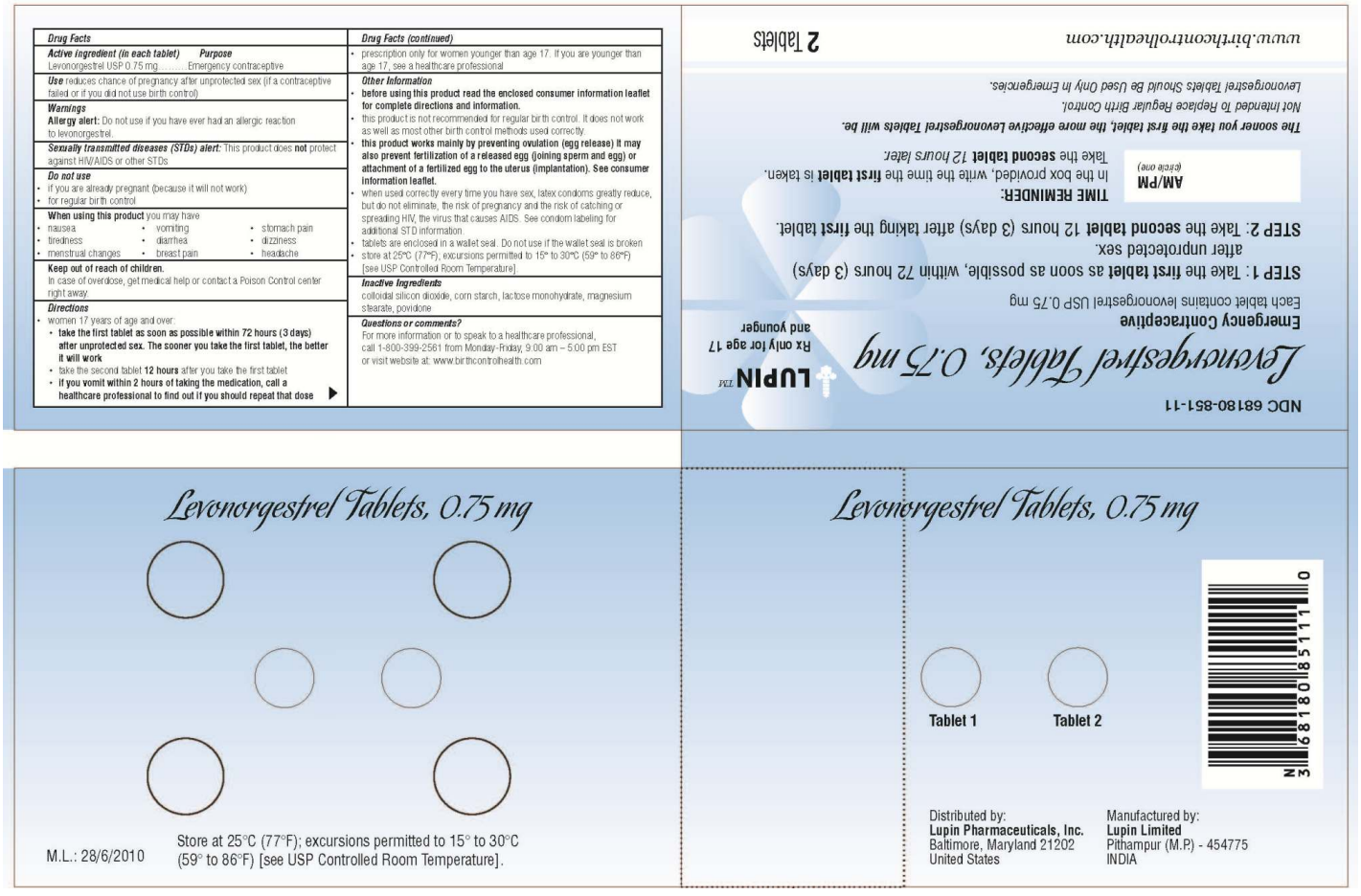
PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

Levonorgestrel Tablets, 0.75 mg

Rx only for age 17 and younger

NDC 68180-851-11

Wallet Label: 2 Tablets

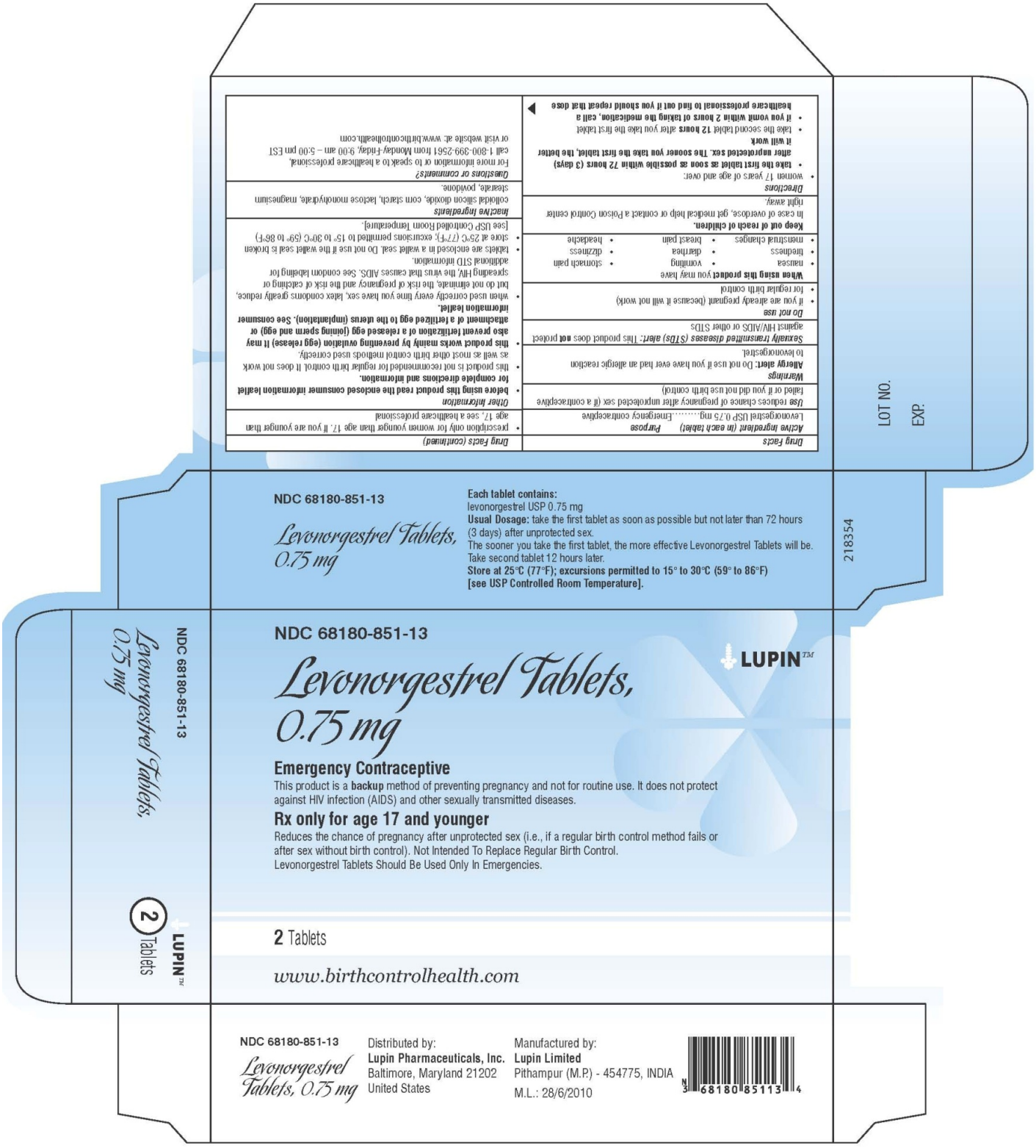


Levonorgestrel Tablets, 0.75 mg

Rx only for age 17 and younger

NDC 68180-851-13

Carton Label: 2 Tablets



LEVONORGESTREL

levonorgestrel tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:68180-851

Route of Administration	ORAL

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
LEVONORGESTREL (UNII: 5W7SIA7YZW) (LEVONORGESTREL - UNII:5W7SIA7YZW)	LEVONORGESTREL	0.75 mg

Inactive Ingredients

Ingredient Name	Strength
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
STARCH, CORN (UNII: O8232NY3SJ)	
POVIDONE (UNII: FZ989GH94E)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	

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	Marketing Start Date	Marketing End Date
1	NDC:68180-851-13	1 in 1 CARTON	01/01/2024	
1	NDC:68180-851-11	2 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA091328	01/01/2024	

Labeler - Lupin Pharmaceuticals, Inc. (089153071)

Revised: 1/2019 Lupin Pharmaceuticals, Inc.