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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use DAYSEE safely and effectively. See full prescribing information for DAYSEE.

Daysee™ [levonorgestrel and ethinyl estradiol tablets USP (0.15 mg/0.03 mg) and ethinyl estradiol tablets USP (0.01 mg)] for oral use

Initial U.S. Approval: 1982

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

See full prescribing information for complete boxed warning.

- **Women who are over 35 years old and smoke should not use Daysee.**
- **Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptive (COC) use.**

----------RECENT MAJOR CHANGES----------

Warnings and Precautions, Malignant Neoplasms (5.2) 04/2022

----------INDICATIONS AND USAGE----------

Daysee (levonorgestrel and ethinyl estradiol tablets USP, and ethinyl estradiol tablets USP) is an estrogen/progestin COC indicated for use by women to prevent pregnancy. (1)

----------DOSAGE AND ADMINISTRATION----------

Take one tablet daily by mouth at the same time every day for 91 days. (2)

----------DOSAGE FORMS AND STRENGTHS----------

Daysee consists of 84 light blue tablets containing 0.15 mg levonorgestrel and 0.03 mg ethinyl estradiol, and 7 mustard tablets containing 0.01 mg ethinyl estradiol. (3)

----------CONTRAINDICATIONS----------

- A high risk of arterial or venous thrombotic diseases (4)
- Undiagnosed abnormal genital bleeding (4)
- Breast cancer or other estrogen- or progestin-sensitive cancer (4)
- Liver tumors or liver disease (4)
- Pregnancy (4)
- Co-administration with Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir (4)

----------WARNINGS AND PRECAUTIONS----------

- Vascular risks: Stop Daysee if a thrombotic event occurs. Stop Daysee at least 4 weeks before and through 2 weeks after major surgery. Start Daysee no earlier than 4 weeks after delivery, in women who are not breastfeeding. (5.1)
- Liver disease: Discontinue Daysee if jaundice occurs. (5.3)
- High blood pressure: Do not prescribe Daysee for women with uncontrolled hypertension or hypertension with vascular disease. (5.5)
- Carbohydrate and lipid metabolic effects: Monitor prediabetic and diabetic women taking Daysee. Consider an alternate contraceptive method for women with uncontrolled dyslipidemias. (5.7)
- Headache: Evaluate significant change in headaches and discontinue Daysee if indicated. (5.8)
- Uterine bleeding: Evaluate irregular bleeding or amenorrhea. (5.9)

----------ADVERSE REACTIONS----------

The most common adverse reactions (≥5%) in clinical trials for Daysee are irregular and/or heavy uterine bleeding, weight gain, and acne. (6)

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, including CYP3A4, may decrease the effectiveness of COCs or increase breakthrough bleeding. Counsel patients to use a back-up method or alternative method of contraception when enzyme inducers are used with COCs. (7.1)

----------USE IN SPECIFIC POPULATIONS----------

- Nursing Mothers: Not recommended for nursing mothers; can decrease milk production. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-Approved Patient Labeling

Revised: 06/2022

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

FULL PRESCRIBING INFORMATION

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS
Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptives (COC) use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, COCs should not be used by women who are over 35 years of age and smoke. [See **CONTRAINDICATIONS (4).**]

1. INDICATIONS AND USAGE

Daysee™ (levonorgestrel and ethinyl estradiol tablets USP, and ethinyl estradiol tablets USP) is indicated for use by women to prevent pregnancy.

2. DOSAGE AND ADMINISTRATION

Take one tablet by mouth at the same time every day. The dosage of Daysee is one light blue tablet containing levonorgestrel and ethinyl estradiol daily for 84 consecutive days, followed by one mustard ethinyl estradiol tablet for 7 days. To achieve maximum contraceptive effectiveness, Daysee must be taken exactly as directed and at intervals not exceeding 24 hours.

Instruct the patient to begin taking Daysee on the first Sunday after the onset of menstruation. If menstruation begins on a Sunday, the first light blue tablet is taken that day. One light blue tablet should be taken daily for 84 consecutive days, followed by one mustard tablet for 7 consecutive days. A non-hormonal back-up method of contraception (such as condoms or spermicide) should be used until a light blue tablet has been taken daily for 7 consecutive days. A scheduled period should occur during the 7 days that the mustard tablets are taken.

Begin the next and all subsequent 91-day cycles without interruption on the same day of the week (Sunday) on which the patient began her first dose of Daysee, following the same schedule: 84 days taking a light blue tablet followed by 7 days taking a mustard tablet. If the patient does not immediately start her next pill pack, she should protect herself from pregnancy by using a non-hormonal back-up method of contraception until she has taken a light blue tablet daily for 7 consecutive days. If unscheduled spotting or bleeding occurs, instruct the patient to continue on the same regimen. If the bleeding is persistent or prolonged, advise the patient to consult her healthcare provider.

For patient instructions regarding missed pills, see **FDA-Approved Patient Labeling**.

For postpartum women who are not breastfeeding, start Daysee no earlier than four to six weeks postpartum due to increased risk of thromboembolism. If the patient starts on Daysee postpartum and has not yet had a period, evaluate for possible pregnancy, and instruct her to use an additional method of contraception until she has taken a light blue tablet for 7 consecutive days.

3. DOSAGE FORMS AND STRENGTHS

Daysee is available in Extended-Cycle Wallet, each containing a 13-week supply of tablets: 84 light blue tablets, each containing 0.15 mg of levonorgestrel and 0.03 mg ethinyl estradiol, and 7 mustard tablets each containing 0.01 mg of ethinyl estradiol. The light blue tablets are round, biconvex film-coated tablets, debossed with “LU” on one side and “V21” on the other side. The mustard tablets are round, biconvex film-coated tablets debossed with “LU” on one side and “V22” on the other side.

4. CONTRAINDICATIONS

Daysee is contraindicated in females who are known to have or develop the following conditions:

- A high risk of arterial or venous thrombotic diseases. Examples include women who are known to:
  - Smoke, if over age 35 [see **BOXED WARNING** and **WARNINGS AND PRECAUTIONS (5.1)**].
  - Have deep vein thrombosis or pulmonary embolism, now or in the past [see **WARNINGS AND PRECAUTIONS (5.1)**].
  - Have cerebrovascular disease [see **WARNINGS AND PRECAUTIONS (5.1)**]
  - Have coronary artery disease [see **WARNINGS AND PRECAUTIONS (5.1)**].
  - Have thrombogenic valvular or thrombogenic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease, or atrial fibrillation) [see **WARNINGS AND PRECAUTIONS (5.1)**].
  - Have inherited or acquired hypercoagulopathies [see **WARNINGS AND PRECAUTIONS (5.1)**].
  - Have uncontrolled hypertension [see **WARNINGS AND PRECAUTIONS (5.5)**].
  - Have diabetes with vascular disease [see **WARNINGS AND PRECAUTIONS (5.7)**].
  - Have headaches with focal neurological symptoms or have migraine headaches with or without aura if over age 35 [see **WARNINGS AND PRECAUTIONS (5.8)**].
- Undiagnosed abnormal genital bleeding [see **WARNINGS AND PRECAUTIONS (5.9)**].
- Current diagnosis of, or history of, breast cancer, which may be hormone-sensitive [see **WARNINGS AND PRECAUTIONS (5.2)**].
- Liver tumors, benign or malignant, or liver disease [see **WARNINGS AND PRECAUTIONS (5.3)** and **USE IN SPECIFIC POPULATIONS (8.6)**].
- Pregnancy, because there is no reason to use COCs during pregnancy [see **WARNINGS AND PRECAUTIONS (5.9)** and **USE IN SPECIFIC POPULATIONS (8.1)**].
- Use of Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to the potential for ALT elevations [see **WARNINGS AND PRECAUTIONS (5.4)**].

5. WARNINGS AND PRECAUTIONS

5.1 Thrombotic and Other Vascular Events

Stop Daysee if an arterial or deep venous thrombotic event occurs. Although the use of COCs increases the risk of venous thromboembolism, pregnancy increases the risk of venous thromboembolism as much or more than the use of COCs. The risk of venous thromboembolism in women using COCs is 3 to 9 per 10,000 woman-years. The excess risk is highest during the first year of use of a COC. Use of COCs also increases the risk of arterial thromboses such as strokes and myocardial infarctions, especially in women with other risk factors for these events. The risk of thromboembolic disease due to COCs gradually disappears after COC use is discontinued.

Use of Daysee provides women with more hormonal exposure on a yearly basis than conventional monthly oral contraceptives containing the same strength synthetic estrogens and progestins (an additional 9 and 13 weeks of exposure to progestin and estrogen, respectively, per year).

If feasible, stop Daysee at least 4 weeks before and through 2 weeks after major surgery or other surgeries known to have an elevated risk of thromboembolism.

Start Daysee no earlier than 4 to 6 weeks after delivery, in women who are not breastfeeding. The risk of postpartum thromboembolism decreases after the third postpartum week, whereas the risk of ovulation increases after the third postpartum week.
COCs have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes), although, in general, the risk is greatest among older (>35 years of age), and hypertensive women who also smoke. COCs also increase the risk for stroke in women with other underlying risk factors.
Oral contraceptives must be used with caution in women with cardiovascular disease risk factors. Stop Daysee if there is unexplained loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions. Evaluate for retinal vein thrombosis immediately.

5.2 Malignant Neoplasms

Breast Cancer

Daysee is contraindicated in females who currently have or have had breast cancer because breast cancer may be hormonally sensitive *[see Contraindications (4)]*.

Epidemiology studies have not found a consistent association between use of combined oral contraceptives (COCs) and breast cancer risk. Studies do not show an association between ever (current or past) use of COCs and risk of breast cancer. However, some studies report a small increase in the risk of breast cancer among current or recent users (<6 months since last use) and current users with longer duration of COC use *[see Postmarketing Experience (6.2)]*.

Cervical Cancer

Some studies suggest that COCs are associated with an increase in the risk of cervical cancer or intraepithelial neoplasia. However, there is controversy about the extent to which these findings are due to differences in sexual behavior and other factors.

5.3 Liver Disease

Discontinue Daysee if jaundice develops. Steroid hormones may be poorly metabolized in patients with impaired liver function. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal and COC causation has been excluded.
Hepatic adenomas are associated with COC use. An estimate of the attributable risk is 3.3 cases/100,000 COC users. Rupture of hepatic adenomas may cause death through intra-abdominal hemorrhage.
Studies have shown an increased risk of developing hepatocellular carcinoma in long-term (> 8 years) COC users. However, the attributable risk of liver cancers in COC users is less than one case per million users.
Oral contraceptive-related cholestasis may occur in women with a history of pregnancy-related cholestasis. Women with a history of COC-related cholestasis may have the condition recur with subsequent COC use.

5.4 Risk of Liver Enzyme Elevations with Concomitant Hepatitis C Treatment

During clinical trials with the Hepatitis C combination drug regimen that contains obmitasvir/paritaprevir/ritonavir, with or without dasabuvir, ALT elevations greater than 5 times the upper limit of normal (ULN), including some cases greater than 20 times the ULN, were significantly more frequent in women using ethinyl estradiol-containing medications, such as

COCs. Discontinue Daysee prior to starting therapy with the combination drug regimen ombitasvir/paritaprevir/ritonavir, with or without dasabuvir [see **CONTRAINDICATIONS (4)**]. Daysee can be restarted approximately 2 weeks following completion of treatment with the Hepatitis C combination drug regimen.

5.5 High Blood Pressure

For women with well-controlled hypertension, monitor blood pressure and stop Daysee if blood pressure rises significantly. Women with uncontrolled hypertension or hypertension with vascular disease should not use COCs.

An increase in blood pressure has been reported in women taking COCs, and this increase is more likely in older women and with extended duration of use. The incidence of hypertension increases with increasing concentration of progestin.

5.6 Gallbladder Disease

Studies suggest a small increased relative risk of developing gallbladder disease among COC users.

5.7 Carbohydrate and Lipid Metabolic Effects

Carefully monitor prediabetic and diabetic women who are taking Daysee. COCs may decrease glucose tolerance in a dose-related fashion.

Consider alternative contraception for women with uncontrolled dyslipidemias. A small proportion of women will have adverse lipid changes while on COCs.

Women with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs.

5.8 Headache

If a woman taking Daysee develops new headaches that are recurrent, persistent, or severe, evaluate the cause and discontinue Daysee if indicated.

An increase in frequency or severity of migraine during COC use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation of the COC.

5.9 Bleeding Irregularities

Unscheduled (breakthrough) bleeding and spotting sometimes occur in patients on COCs, especially during the first 3 months of use. If bleeding persists, check for causes such as pregnancy or malignancy. If pathology and pregnancy are excluded, bleeding irregularities may resolve over time or with a change to a different COC.

When prescribing Daysee, the convenience of fewer planned menses (4 per year instead of 13 per year) should be weighed against the inconvenience of increased unscheduled bleeding and/or spotting. The primary clinical trial (PSE-301) that evaluated the efficacy of Daysee also assessed unscheduled bleeding. The participants in the 12-month clinical trial (N=1,006) completed the equivalent of 8,681 28-day cycles of exposure and were composed primarily of women who had used oral contraceptives previously (89%) as opposed to new users (11%). A total of 82 (8.2%) of the women discontinued Daysee, at least in part, due to bleeding or spotting.

Scheduled (withdrawal) bleeding and/or spotting remained fairly constant over time, with an average of 3 days of bleeding and/or spotting per each 91-day cycle. Unscheduled bleeding and unscheduled spotting decreased over successive 91-day cycles. Table 1 below presents the

number of days with unscheduled bleeding in treatment cycles 1 and 4. Table 2 presents the number of days with unscheduled spotting in treatment cycles 1 and 4.

Table 1: Total Number of Days with Unscheduled Bleeding

91-Day Treatment Cycle	Days per 84-Day Interval				Days per 28-Day Interval
	Q1	Median	Q3	Mean	Mean
1st	1	4	10	6.9	1.7
4th	0	1	4	3.2	0.8

Q1 = Quartile 1: 25% of women had this number of days of unscheduled bleeding
Median: 50% of women had ≤ this number of days of unscheduled bleeding
Q3 = Quartile 3: 75% of women had ≤ this number of days of unscheduled bleeding

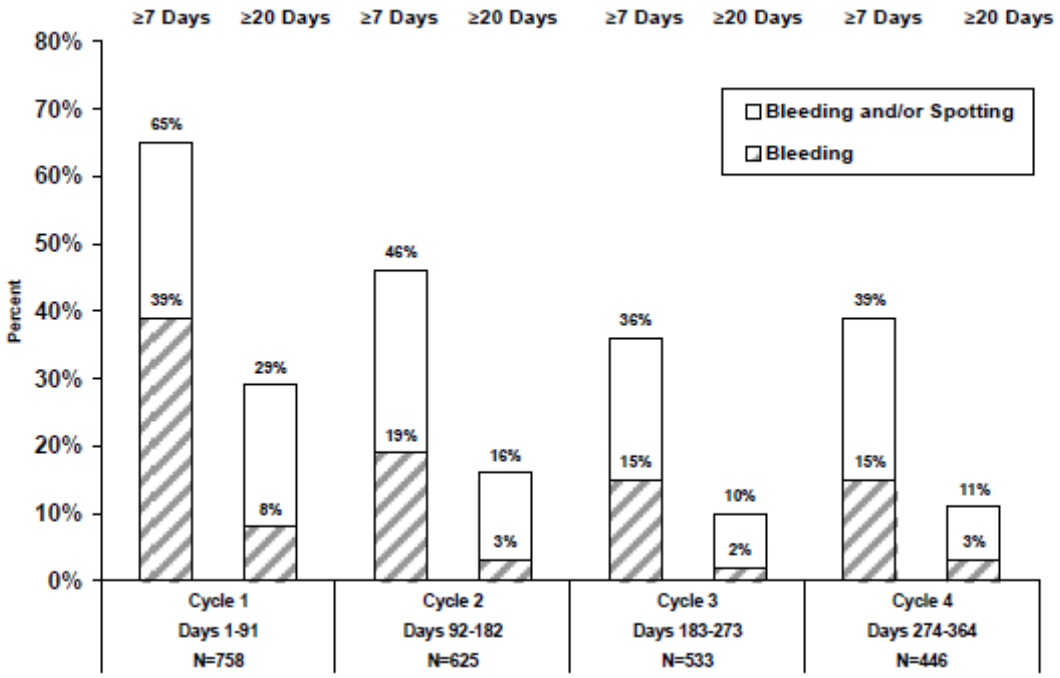
Table 2: Total Number of Days with Unscheduled Spotting

91-Day Treatment Cycle	Days per 84-Day Interval				Days per 28-Day Interval
	Q1	Median	Q3	Mean	Mean
1st	1	4	11	7.4	1.9
4th	0	2	7	4.4	1.1

Q1 = Quartile 1: 25% of women had ≤ this number of days of unscheduled spotting
Median: 50% of women had ≤ this number of days of unscheduled spotting
Q3 = Quartile 3: 75% of women had ≤ this number of days of unscheduled spotting

Figure 1 shows the percentage of Daysee subjects participating in trial PSE-301 with ≥ 7 days or ≥ 20 days of unscheduled bleeding and/or spotting, or only unscheduled bleeding, during each 91-day treatment cycle.

Figure 1: Percent of Women Taking Daysee who Reported Unscheduled Bleeding and/or Spotting or only Unscheduled Bleeding



Amenorrhea sometimes occurs in women who are using COCs. Pregnancy should be ruled out in the event of amenorrhea. Some women may encounter amenorrhea or oligomenorrhea after stopping COCs, especially when such a condition was pre-existent.

5.10 COC Use Before or During Early Pregnancy

Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. Studies also do not suggest a teratogenic effect, particularly in so far as cardiac anomalies and limb-reduction defects are concerned, when taken inadvertently during early pregnancy. Oral contraceptive use should be discontinued if pregnancy is confirmed.

The administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy [see **USE IN SPECIFIC POPULATIONS (8.1)**].

5.11 Emotional Disorders

Women with a history of depression should be carefully observed and Daysee discontinued if depression recurs to a serious degree.

5.12 Interference with Laboratory Tests

The use of COCs may change the results of some laboratory tests, such as coagulation factors, lipids, glucose tolerance, and binding proteins. Women on thyroid hormone replacement therapy may need increased doses of thyroid hormone because serum concentrations of thyroid binding globulin increase with use of COCs.

5.13 Monitoring

A woman who is taking COCs should have a yearly visit with her healthcare provider for a blood pressure check and for other indicated health care.

5.14 Other Conditions

In women with hereditary angioedema, exogenous estrogens may induce or exacerbate symptoms of angioedema. Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation while taking COCs.

6. ADVERSE REACTIONS

The following serious adverse reactions with the use of COCs are discussed elsewhere in the labeling:

- Serious cardiovascular events and smoking [see **BOXED WARNING** and **WARNINGS AND PRECAUTIONS (5.1)**]
- Vascular events [see **WARNINGS AND PRECAUTIONS (5.1)**]
- Liver disease [see **WARNINGS AND PRECAUTIONS (5.3)**]

Adverse reactions commonly reported by COC users are:

- Irregular uterine bleeding
- Nausea
- Breast tenderness
- Headache

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 the rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The clinical trial that evaluated the safety and efficacy of Daysee was a 12-month, randomized, multicenter, open-label study, which enrolled women aged 18 to 40, of whom 1,006 took at least one dose of Daysee.

Adverse Reactions Leading to Study Discontinuation

16.3% of the women discontinued from the clinical trial due to an adverse reaction; the most common adverse reactions (≥ 1% of women) leading to discontinuation were irregular and/or heavy uterine bleeding (5.9%), weight gain (2.4%), mood changes (1.5%), and acne (1.0%).

Common Treatment-Emergent Adverse Reactions (≥ 5% of women)

Irregular and/or heavy uterine bleeding (17%), weight gain (5%), acne (5%).

Serious Adverse Reactions

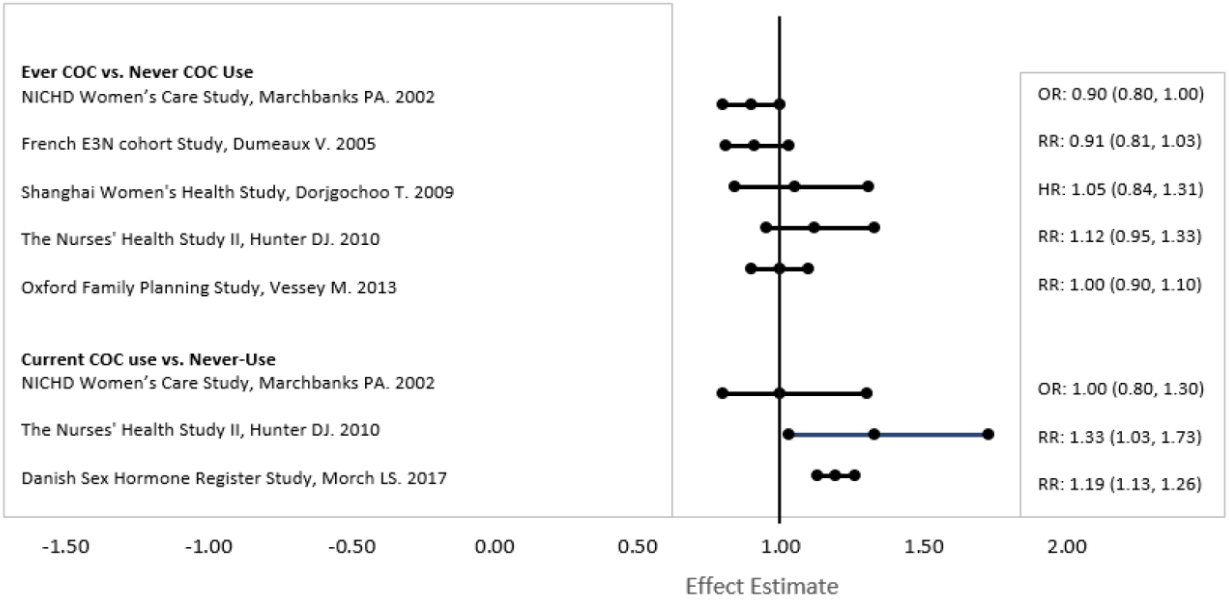
Migraine, cholecystitis, cholelithiasis, pancreatitis, abdominal pain, and major depressive disorder.

6.2 Postmarketing Experience

Five studies that compared breast cancer risk between ever-users (current or past use) of COCs and never-users of COCs reported no association between ever use of COCs and breast cancer risk, with effect estimates ranging from 0.90 - 1.12 (Figure 2).

Three studies compared breast cancer risk between current or recent COC users (<6 months since last use) and never users of COCs (Figure 2). One of these studies reported no association between breast cancer risk and COC use. The other two studies found an increased relative risk of 1.19 - 1.33 with current or recent use. Both of these studies found an increased risk of breast cancer with current use of longer duration, with relative risks ranging from 1.03 with less than one year of COC use to approximately 1.4 with more than 8-10 years of COC use.

Figure 2: Relevant Studies of Risk of Breast Cancer with Combined Oral Contraceptives



RR = relative risk; OR = odds ratio; HR = hazard ratio. “ever COC” are females with current or past COC use; “never COC use” are females that never used COCs.

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

Gastrointestinal Disorders
Abdominal distension, vomiting
General Disorders and Administration Site Conditions
Chest pain, fatigue, malaise, edema peripheral, pain
Immune System Disorders
Hypersensitivity reaction
Investigations
Blood pressure increased
Musculoskeletal and Connective Tissue Disorders
Muscle spasms, pain in extremity
Nervous System Disorders
Dizziness, loss of consciousness
Psychiatric Disorders
Insomnia
Reproductive and Breast Disorders
Dysmenorrhea
Respiratory, Thoracic and Mediastinal Disorders
Pulmonary embolism, pulmonary thrombosis
Skin and Subcutaneous Tissue Disorders
Alopecia
Vascular Disorders
Thrombosis

7. DRUG INTERACTIONS

No drug-drug interaction studies were conducted with Daysee.

7.1 Changes in Contraceptive Effectiveness Associated with Co-Administration of Other Products

If a woman on hormonal contraceptives takes a drug or herbal product that induces enzymes, including CYP3A4, that metabolize contraceptive hormones, counsel her to use additional contraception or a different method of contraception. Drugs or herbal products that induce such enzymes may decrease the plasma concentrations of contraceptive hormones, and may decrease the effectiveness of hormonal contraceptives or increase breakthrough bleeding. Some drugs or herbal products that may decrease the effectiveness of hormonal contraceptives include:

- barbiturates
- bosentan
- carbamazepine
- felbamate
- griseofulvin
- oxcarbazepine
- phenytoin

- rifampin
- St. John's wort
- topiramate

HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors

Significant changes (increase or decrease) in the plasma levels of the estrogen and progestin have been noted in some cases of co-administration of HIV protease inhibitors or with non-nucleoside reverse transcriptase inhibitors.

Antibiotics

There have been reports of pregnancy while taking hormonal contraceptives and antibiotics, but clinical pharmacokinetic studies have not shown consistent effects of antibiotics on plasma concentrations of synthetic steroids.

Consult the labeling of all concurrently-used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.

7.2 Increase in Plasma Levels of Estradiol Associated with Co-Administered Drugs

Co-administration of atorvastatin and certain COCs containing ethinyl estradiol increase AUC values for ethinyl estradiol by approximately 20%. Ascorbic acid and acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. CYP3A4 inhibitors such as itraconazole or ketoconazole may increase plasma hormone levels.

7.3 Concomitant Use with Hepatitis C Vaccine (HCV) Combination Therapy – Liver Enzyme Elevation

Do not co-administer Daysee with HCV drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to potential for ALT elevations [see **WARNINGS AND PRECAUTIONS (5.4)**].

7.4 Changes in Plasma Levels of Co-Administered Drugs

COCs containing some synthetic estrogens (e.g., ethinyl estradiol) may inhibit the metabolism of other compounds. COCs have been shown to significantly decrease plasma concentrations of lamotrigine likely due to induction of lamotrigine glucuronidation. This may reduce seizure control; therefore, dosage adjustments of lamotrigine may be necessary. Consult the labeling of the concurrently-used drug to obtain further information about interactions with COCs or the potential for enzyme alterations.

8. USE IN SPECIFIC POPULATIONS

8.1. Pregnancy

There is little or no increased risk of birth defects in women who inadvertently use COCs during early pregnancy. Epidemiologic studies and meta-analyses have not found an increased risk of genital or non-genital birth defects (including cardiac anomalies and limb-reduction defects) following exposure to low dose COCs prior to conception or during early pregnancy.

The administration of COCs to induce withdrawal bleeding should not be used as a test for pregnancy. COCs should not be used during pregnancy to treat threatened or habitual abortion.

Women who do not breastfeed may start COCs no earlier than four to six weeks postpartum.

8.3. Nursing Mothers
When possible, advise the nursing mother to use other forms of contraception until she has weaned her child. Estrogen-containing COCs can reduce milk production in breastfeeding mothers. This is less likely to occur once breastfeeding is well established; however, it can occur at any time in some women. Small amounts of oral contraceptive steroids and/or metabolites are present in breast milk.

8.4. Pediatric Use
Safety and efficacy of Daysee have been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents under the age of 18 as for users 18 years and older. Use of Daysee before menarche is not indicated.

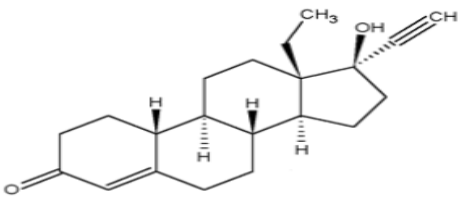
8.5. Geriatric Use
Daysee has not been studied in women who have reached menopause and is not indicated in this population.

8.6 Hepatic Impairment
No studies have been conducted to evaluate the effect of hepatic disease on the disposition of Daysee. However, steroid hormones may be poorly metabolized in patients with impaired liver function. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal. [See **CONTRAINDICATIONS (4)** and **WARNINGS AND PRECAUTIONS (5.3)**].

8.7 Renal Impairment
No studies have been conducted to evaluate the effect of renal disease on the disposition of Daysee.

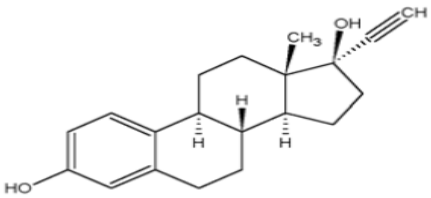
10. OVERDOSAGE
There have been no reports of serious ill effects from overdose of oral contraceptives, including ingestion by children. Overdosage may cause withdrawal bleeding in females and nausea.

11. DESCRIPTION
Daysee (levonorgestrel and ethinyl estradiol tablets USP, and ethinyl estradiol tablets USP) is an extended-cycle oral contraceptive consisting of 84 light blue tablets each containing 0.15 mg of levonorgestrel, a synthetic progestogen and 0.03 mg of ethinyl estradiol, and 7 mustard tablets containing 0.01 mg of ethinyl estradiol.
The structural formulas for the active components are:



Levonorgestrel
$C_{21}H_{28}O_2$ MW: 312.4

Levonorgestrel is chemically 18,19-Dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-,(17α)-, (-)-.



Ethinyl Estradiol
$C_{20}H_{24}O_2$ MW: 296.4

Ethinyl Estradiol is 19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17α)-.
Each light blue tablet contains the following inactive ingredients: croscarmellose sodium, hypromellose, FD and C blue No. 1, FD and C yellow No. 6, iron oxide yellow, lactose anhydrous, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone and titanium dioxide.
Each mustard tablet contains the following inactive ingredients: FD and C yellow No. 6, hypromellose, iron oxide yellow, lactose anhydrous, magnesium stearate, microcrystalline cellulose, polacrillin potassium, polyethylene glycol, polysorbate 80 and titanium dioxide.
The Mustard Tablet *i.e.* Ethinyl Estradiol Tablets USP meets USP Dissolution Test 2.

12. CLINICAL PHARMACOLOGY

12.1. Mechanism of action

COCs lower the risk of becoming pregnant primarily by suppressing ovulation. Other possible mechanisms may include cervical mucus changes that inhibit sperm penetration and endometrial changes that reduce the likelihood of implantation.

12.3. Pharmacokinetics

Absorption

Ethinyl estradiol and levonorgestrel are absorbed with maximum plasma concentrations occurring within 2 hours after Daysee administration. Levonorgestrel is completely absorbed after oral administration (bioavailability nearly 100%) and is not subject to first-pass metabolism. Ethinyl estradiol is absorbed from the gastrointestinal tract but, due to first-pass metabolism in gut mucosa and liver, the bioavailability of ethinyl estradiol is approximately 43%.
The daily exposure to levonorgestrel and ethinyl estradiol on Day 21, corresponding to the end of a typical 3-week contraceptive regimen, and on Day 84, at the end of an extended cycle regimen, were similar. There was no additional accumulation of ethinyl estradiol after dosing a 0.03 mg ethinyl estradiol tablet during Days 84 to 91. The mean plasma pharmacokinetic parameters of Daysee following a single dose of one levonorgestrel /ethinyl estradiol combination tablet, for 84 days, in normal healthy women are reported in Table 3.

Table 3: Mean Pharmacokinetic Parameters for Daysee during Daily One Tablet Dosing for 84 Days

	$AUC_{0\text{-}24\ hr}$ (mean ± SD)	C_{max} (mean ± SD)	T_{max} (mean ± SD)
	Levonorgestrel		
Day 1	18.2 ± 6.1 ng.hr/mL	3.0 ± 1.0 ng/mL	1.3 ± 0.4 hours
Day 21	64.4 ± 25.1 ng.hr/mL	6.2 ± 1.6 ng/mL	1.3 ± 0.4 hours
Day 84	60.2 ± 24.6 ng.hr/mL	5.5 ± 1.6 ng/mL	1.3± 0.3 hours
	Ethinyl Estradiol		
Day 1	509.3 ± 172.0 pg.hr/mL	69.8 ± 26 pg/mL	1.5 ± 0.3 hours
Day 21	837.1 ± 271.2 pg.hr/mL	99.6± 31 pg/mL	1.5 ± 0.3 hours
Day 84	791.5 ± 215.0 pg.hr/mL	91.3 ± 32 pg/mL	1.6 ± 0.3 hours

The effect of food on the rate and the extent of levonorgestrel and ethinyl estradiol absorption following oral administration of Daysee has not been evaluated.

Distribution

The apparent volume of distribution of levonorgestrel and ethinyl estradiol are reported to be approximately 1.8 L/kg and 4.3 L/kg, respectively. Levonorgestrel is about 97.5 to 99% protein-bound, principally to sex hormone binding globulin (SHBG) and, to a lesser extent, serum albumin. Ethinyl estradiol is about 95 to 97% bound to serum albumin. Ethinyl estradiol does not bind to SHBG, but induces SHBG synthesis, which leads to decreased levonorgestrel clearance. Following repeated daily dosing of levonorgestrel/ethinyl estradiol oral contraceptives, levonorgestrel plasma concentrations accumulate more than predicted based on single-dose pharmacokinetics, due in part, to increased SHBG levels that are induced by ethinyl estradiol, and a possible reduction in hepatic metabolic capacity.

Metabolism

Following absorption, levonorgestrel is conjugated at the 17β-OH position to form sulfate 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 16β-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.

First-pass metabolism of ethinyl estradiol involves formation of ethinyl estradiol-3-sulfate in the gut wall, followed by 2-hydroxylation of a portion of the remaining untransformed ethinyl estradiol by hepatic cytochrome P-450 3A4 (CYP3A4). Levels of CYP3A4 vary widely among individuals and can explain the variation in rates of ethinyl estradiol hydroxylation.

Hydroxylation at the 4-, 6-, and 16- positions may also occur, although to a much lesser extent than 2-hydroxylation. The various hydroxylated metabolites are subject to further methylation and/or conjugation.

Excretion

About 45% of levonorgestrel and its metabolites are excreted in the urine and about 32% are excreted in feces, mostly as glucuronide conjugates. The terminal elimination half-life for levonorgestrel after a single dose of Daysee was about 34 hours.

Ethinyl estradiol is excreted in the urine and feces as glucuronide and sulfate conjugates, and it undergoes enterohepatic recirculation. The terminal elimination half-life of ethinyl estradiol after a single dose of Daysee was found to be about 18 hours.

Race

The effect of race on the pharmacokinetics of Daysee has not been evaluated.

13. NONCLINICAL TOXICOLOGY

13.1. Carcinogenesis, Mutagenesis, Impairment of Fertility

[See **WARNINGS AND PRECAUTIONS (5.2, 5.3)**].

14. CLINICAL STUDIES

In a 12-month, multicenter, randomized, open-label clinical trial, 1,006 women aged 18 to 40 were studied to assess the safety and efficacy of Daysee, completing the equivalent of 8,681 28-day cycles of exposure. The racial demographic of those enrolled was: Caucasian (80%), African-American (11%), Hispanic (5%), Asian (2%), and Other (2%). There were no exclusions for body mass index (BMI) or weight. The weight range of those women treated was 91 to 360 lbs., with a mean weight of 156 lbs. Among the women in the trial, 63% were current or recent hormonal contraceptive users, 26% were prior users (who had used hormonal contraceptives in the past but not in the 6 months prior to enrollment), and 11% were new starts. Of treated women, 14.8% were lost to follow-up, 16.3% discontinued due to an adverse event, and 12.9% discontinued by withdrawing their consent.

The pregnancy rate (Pearl Index [PI]) in women aged 18 to 35 years was 1.34 pregnancies per 100 women-years of use (95% confidence interval 0.54 to 2.75), based on 7 pregnancies that occurred after the onset of treatment and within 14 days after the last combination pill. Cycles in which conception did not occur, but which included the use of back-up contraception, were not included in the calculation of the PI. The PI includes patients who did not take the drug correctly.

16. HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Daysee [levonorgestrel and ethinyl estradiol tablets USP (0.15 mg/0.03 mg) and ethinyl estradiol tablets USP (0.01 mg)] is available in Extended-Cycle Wallets each containing a 13-week supply of tablets: 84 light blue tablets, each containing 0.15 mg of levonorgestrel and 0.03 mg of ethinyl estradiol, and 7 mustard tablets, each containing 0.01 mg of ethinyl estradiol. The light blue tablets are round, biconvex, film-coated tablets, debossed with “LU” on one side and “V21” on the other side. The mustard tablets are round, biconvex, film-coated tablets debossed with “LU” on one side and “V22” on the other side.

They are supplied as follows:

Daysee [levonorgestrel and ethinyl estradiol tablets USP (0.15 mg/0.03 mg) and ethinyl estradiol tablets USP (0.01 mg)] is available in an extended cycle wallet of 91 tablets which is packed in a pouch (NDC 68180-846-11). Such two pouches are packed in a carton (NDC 68180-846-13).

16.2 Storage Conditions

Store 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

See **FDA- Approved Patient Labeling**

- Counsel patients that cigarette smoking increases the risk of serious cardiovascular events from COC use, and that women who are over 35 years old and smoke should not use COCs.
- Counsel patients that this product does not protect against HIV-infection (AIDS) and other sexually transmitted diseases.
- Counsel patients on Warnings and Precautions associated with COCs.
- Counsel patients to take one tablet daily by mouth at the same time every day. Instruct patients what to do in the event pills are missed. See **WHAT TO DO IF YOU MISS PILLS** section of FDA-Approved Patient Labeling.
- Counsel patients to use a back-up or alternative method of contraception when enzyme inducers are used with COCs.
- Counsel patients who are breastfeeding or who desire to breastfeed that COCs may reduce breast milk production. This is less likely to occur if breastfeeding is well established.
- Counsel any patient who starts COCs postpartum, and who has not yet had a period, to use an additional method of contraception until she has taken a light blue tablet for 7 consecutive days.
- Counsel patients that amenorrhea may occur. Pregnancy should be considered in the event of amenorrhea, and should be ruled out if amenorrhea is associated with symptoms of pregnancy, such as morning sickness or unusual breast tenderness.

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

Manufactured by:
Lupin Limited
Pithampur (M.P.) – 454 775
INDIA

Revised: June 2022

FDA-Approved Patient Labeling

Guide for Using Daysee™
[levonorgestrel and ethinyl estradiol tablets USP (0.15 mg/0.03 mg) and ethinyl estradiol tablets USP (0.01 mg)]

WARNING TO WOMEN WHO SMOKE

Do not use Daysee if you smoke cigarettes and are over 35 years old. Smoking increases your risk of serious cardiovascular side effects from birth control pills, including death from heart attack, blood clots or stroke. This risk increases with age and the number of cigarettes you smoke.

Birth control pills help to lower the chances of becoming pregnant. They do not protect against HIV infection (AIDS) and other sexually transmitted diseases.

What Is Daysee?

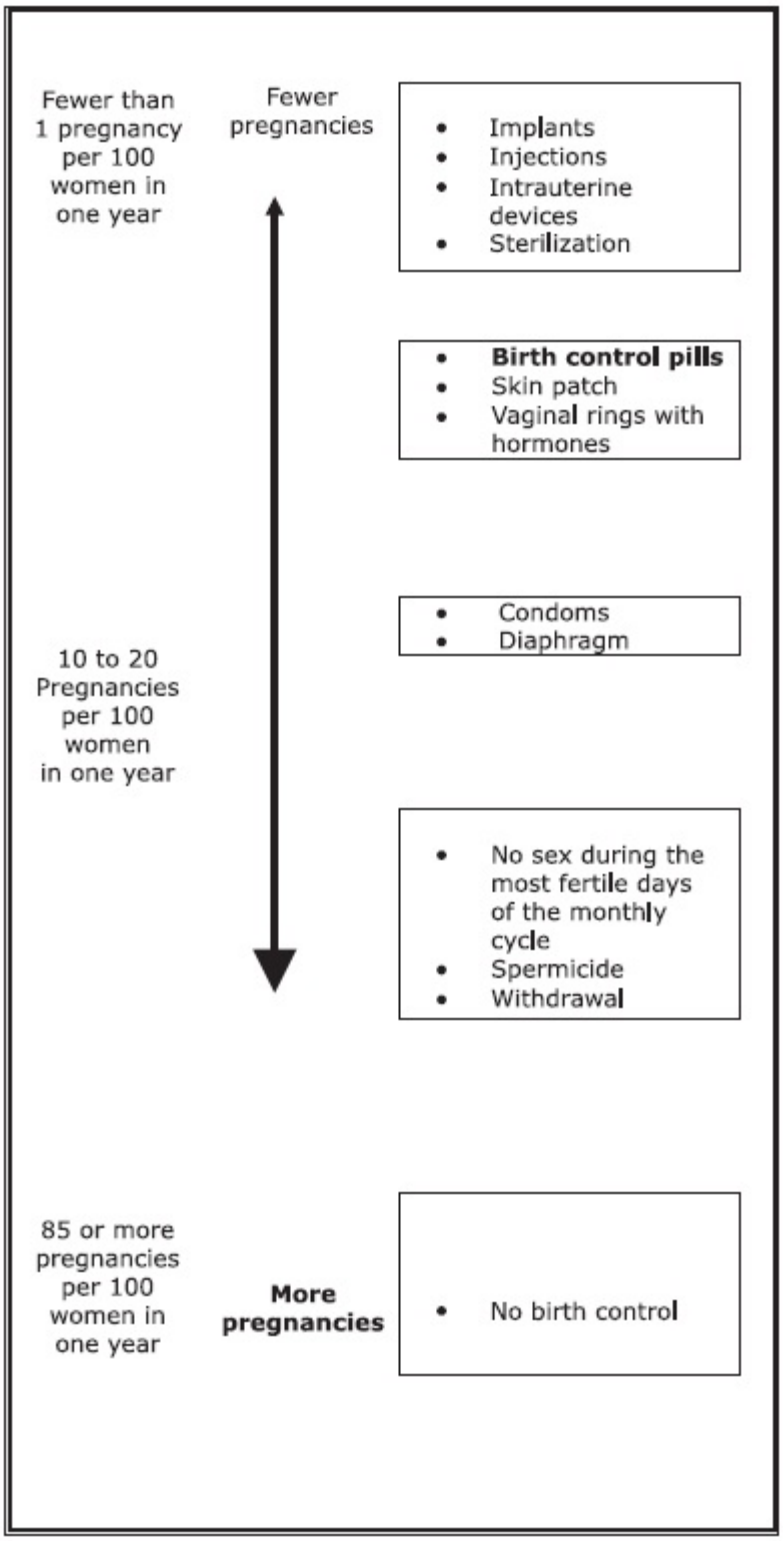
Daysee is a birth control pill. It contains two female hormones, an estrogen called ethinyl estradiol, and a progestin called levonorgestrel.

How Well Does Daysee Work?

Your chance of getting pregnant depends on how well you follow the directions for taking your birth control pills. The more carefully you follow the directions, the less chance you have of getting pregnant.

Based on the results of a single clinical study lasting 12 months, 1 to 3 women, out of 100 women, may get pregnant during the first year they use Daysee.

The following chart shows the chance of getting pregnant for women who use different methods of birth control. Each box on the chart contains a list of birth control methods that are similar in effectiveness. The most effective methods are at the top of the chart. The box on the bottom of the chart shows the chance of getting pregnant for women who do not use birth control and are trying to get pregnant.



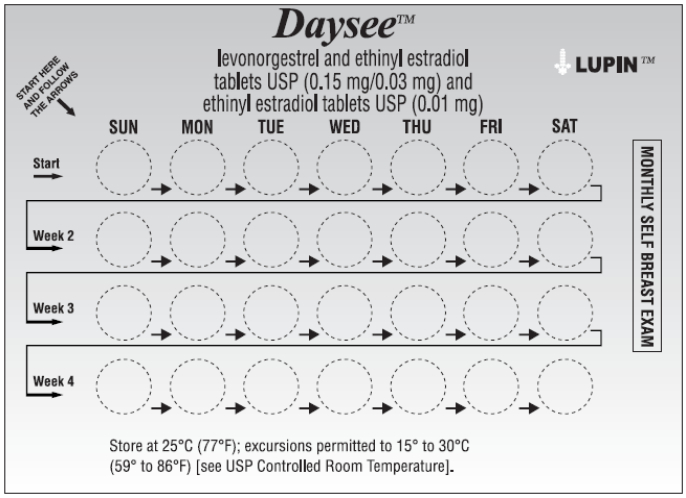
How Do I Take Daysee?

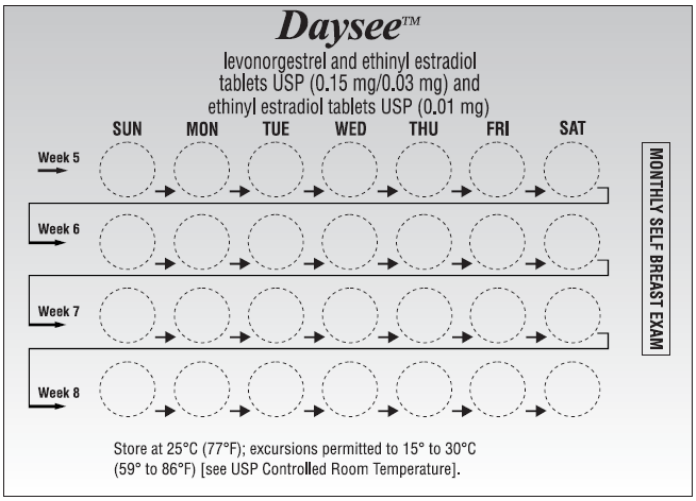
1. Take one pill every day at the same time. If you miss pills you could get pregnant. This includes starting the pack late. The more pills you miss, the more likely you are to get pregnant.

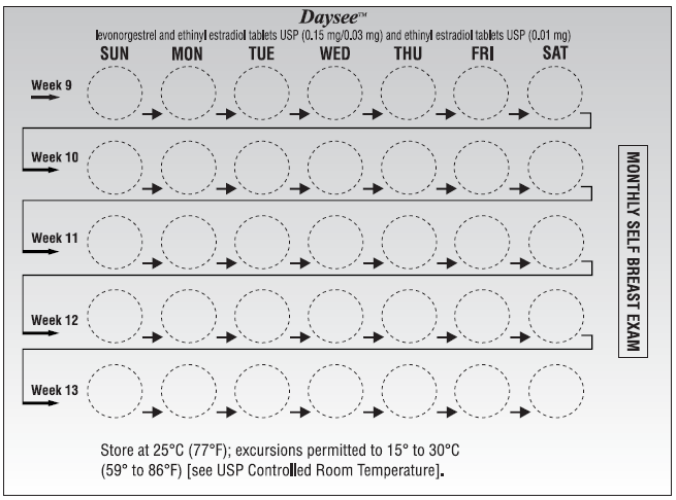
2. Many women have spotting or light bleeding, or may feel sick to their stomach during the first few months of taking Daysee. If you feel sick to your stomach, do not stop taking the pill. The problem will usually go away. If it doesn't go away, check with your healthcare provider.
3. Missing pills can also cause spotting or light bleeding, even when you take the missed pills later. On the days you take 2 pills to make up for missed pills, you could also feel a little sick to your stomach.
4. If you have trouble remembering to take Daysee, talk to your healthcare provider about how to make pill-taking easier or about using another method of birth control.

Before you start taking Daysee

1. Decide what time of day you want to take your pill. It is important to take it at about the same time every day.
2. Look at your Extended-Cycle Wallet. Your Wallet consists of 3 blister strip that hold 91 individually sealed pills (a 13-week or 91-day cycle). The 91 pills consist of 84 light blue and 7 mustard pills. Blister strips 1 and 2 each contain 28 light blue pills (4 rows of 7 pills). Blister strip 3 contains 35 pills consisting of 28 light blue pills (4 rows of 7 pills) and 7 mustard pills (1 row of 7 pills).







3. Also find:
   - Where on the first blister strip in the pack to start taking pills (upper left corner at the start arrow) and
   - In what order to take the pills (follow the weeks and arrow).
4. Be sure you have ready at all times another kind of birth control (such as condoms or spermicides), to use as a back-up in case you miss pills.

When to Start Daysee

1. Take the first light blue pill on the Sunday after your period starts, even if you are still bleeding. If your period begins on Sunday, start the first light blue pill that same day.
2. Use another method of birth control (such as condoms or spermicides) as a back-up method if you have sex anytime from the Sunday you start your first light blue pill until the next Sunday (first 7 days). If you have been using a different hormonal method of birth control (such as a different pill, the "patch," or the "vaginal ring"), you need to use another method of birth control (such as condoms or spermicides) each time you have sex after stopping your old method of birth control until you have taken Daysee for 7 days.

How to Take Daysee

1. Take one pill at the same time every day until you have taken the last pill in the Wallet.
   - Do not skip pills even if you are experiencing spotting or bleeding or feel sick to your stomach (nausea).
   - Do not skip pills even if you do not have sex very often.
2. When you finish a Wallet
   - After taking the last mustard pill, start taking the first light blue pill from a new Extended-Cycle Wallet the very next day (this should be on a Sunday) regardless of when your period started.
3. If you miss your scheduled period when you are taking the mustard pills, contact your healthcare provider because you may be pregnant. If you are pregnant, you should stop taking Daysee.

What To Do If You Miss Pills

If you **MISS 1** light blue pill:

1. Take it as soon as you remember. Take the next pill at your regular time. This means you may take 2 pills in 1 day.
2. You do not need to use a back-up birth control method if you have sex.

If you **MISS 2** light blue pills in a row:

1. Take 2 pills on the day you remember, and 2 pills the next day.
2. Then take 1 pill a day until you finish the pack.
3. You could become pregnant if you have sex in the 7 days after you miss two pills. You MUST use another birth control method (such as condoms or spermicide) as a back-up for the 7 days after you restart your pills.

If you **MISS 3 OR MORE** light blue pills in a row:

1. Do not take the missed pills. Keep taking 1 pill every day as indicated on the pack until you have completed all of the remaining pills in the pack. For example: If you resume taking the pill on Thursday, take the pill under "Thursday" and do not take the missed pills. You may experience bleeding during the week following the missed pills.
2. You could become pregnant if you have sex during the days of missed pills or during the first 7 days after restarting your pills.
3. You MUST use a non-hormonal birth control method (such as condoms or spermicide) as a back-up when you miss pills and for the first 7 days after you restart your pills. If you do not have your period when you are taking the mustard pills, call your healthcare provider because you may be pregnant.

If you **MISS ANY** of the 7 mustard pills:

1. Throw away the missed pills.
2. Keep taking the scheduled pills until the pack is finished.
3. You do not need a back-up method of birth control.

Finally, if you are still not sure what to do about the pills you have missed

1. Use a back-up method anytime you have sex.
2. Keep taking one pill each day until you contact your healthcare provider.

Who Should Not Take Daysee?

Your healthcare provider will not give you Daysee if you have:

- Ever had breast cancer or any cancer that is sensitive to female hormones
- Liver disease, including liver tumors
- Been prescribed any Hepatitis C drug combination containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir. This may increase levels of the liver enzyme “alanine aminotransferase” (ALT) in the blood
- Ever had blood clots in your arms, legs, or lungs
- Ever had a stroke
- Ever had a heart attack
- Certain heart valve problems or heart rhythm abnormalities that can cause blood clots to form in the heart
- An inherited problem with your blood that makes it clot more than normal
- High blood pressure that medicine can't control
- Diabetes with kidney, eye, or blood vessel damage

- Certain kinds of severe migraine headaches with aura, numbness, weakness or changes in vision

Also, do not take birth control pills if you:

- Smoke and are over 35 years old
- Are pregnant

Birth control pills may not be a good choice for you if you have ever had jaundice (yellowing of the skin or eyes) caused by pregnancy.

What Else Should I Know About Taking Daysee?

Birth control pills do **not** protect you against any sexually transmitted disease, including HIV, the virus that causes AIDS.

Do not skip any pills, even if you do not have sex often.

Birth control pills should not be taken during pregnancy. However, birth control pills taken by accident during pregnancy are not known to cause birth defects.

If you are breastfeeding, consider another birth control method until you are ready to stop breastfeeding. Birth control pills that contain estrogen, like Daysee, may decrease the amount of milk you make. A small amount of the pill's hormones pass into breast milk.

Tell your healthcare provider about all medicines and herbal products that you take. Some medicines and herbal products may make birth control pills less effective, including:

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

Consider using another birth control method when you take medicines that may make birth control pills less effective.

Birth control pills may interact with lamotrigine, an anticonvulsant used for epilepsy. This may increase the risk of seizures, so your physician may need to adjust the dose of lamotrigine.

If you have vomiting or diarrhea, your birth control pills may not work as well. Use another birth control method, like condoms or a spermicide, until you check with your healthcare provider.

What Are The Most Serious Risks of Taking Birth Control Pills?

Like pregnancy, birth control pills increase the risk of serious blood clots, especially in women who have other risk factors, such as smoking, obesity, or age > 35. It is possible to die from a problem caused by a blood clot, such as a heart attack or a stroke. Some examples of serious blood clots are blood clots in the:

- Legs (thrombophlebitis)
- Lungs (pulmonary embolus)
- Eyes (loss of eyesight)
- Heart (heart attack)

- Brain (stroke)

Women who take birth control pills may get:

- High blood pressure
- Gallbladder problems
- Rare cancerous or noncancerous liver tumors

All of these events are uncommon in healthy women.

Call your healthcare provider right away if you have:

- Persistent leg pain
- Sudden shortness of breath
- Sudden blindness, partial or complete
- Severe pain in your chest
- Sudden, severe headache unlike your usual headaches
- Weakness or numbness in an arm or leg, or trouble speaking
- Yellowing of the skin or eyeballs

What Are Common Side Effects of Birth Control Pills?

The most common side effects of birth control pills are:

- Spotting or bleeding between menstrual periods
- Nausea
- Breast tenderness
- Headache

These side effects are usually mild and usually disappear with time.

Less common side effects are:

- Acne
- Less sexual desire
- Bloating or fluid retention
- Blotchy darkening of the skin, especially on the face
- High blood sugar, especially in women who already have diabetes
- High fat levels in the blood
- Depression, especially if you have had depression in the past. Call your healthcare provider immediately if you have any thoughts of harming yourself.
- Problems tolerating contact lenses
- Weight changes

This is not a complete list of possible side effects. Talk to your healthcare provider if you develop any side effects that concern you. You may report side effects to the FDA at 1-800-FDA-1088. You may also report side effects to Lupin Pharmaceuticals, Inc. at 1-800-399-2561.

No serious problems have been reported from a birth control pill overdose, even when accidentally taken by children.

Do Birth Control Pills Cause Cancer?

It is not known if hormonal birth control pills cause breast cancer. Some studies, but not all, suggest that there could be a slight increase in the risk of breast cancer among current users with longer duration of use.

If you have breast cancer now, or have had it in the past, do not use hormonal birth control because some breast cancers are sensitive to hormones.Women who use birth control pills may have a slightly higher chance of getting cervical cancer. However, this may be due to other reasons such as having more sexual partners.

What Should I Know About My Period When Taking Daysee?
When you take Daysee, which has a 91-day extended dosing cycle, you should expect to have 4 scheduled periods per year (bleeding when you are taking the 7 mustard pills). Each period is likely to last about 3 days. However, you will probably have more bleeding or spotting between your scheduled periods than if you were using a birth control pill with a 28-day dosing cycle. During the first Daysee 91-day treatment cycle, about 3 in 10 women may have 20 or more days of unplanned bleeding or spotting. This bleeding or spotting tends to decrease with time. Do not stop taking Daysee because of this bleeding or spotting. If the spotting continues for more than 7 consecutive days or if the bleeding is heavy, call your healthcare provider.

What If I Miss My Scheduled Period When Taking Daysee?
You should consider the possibility that you are pregnant if you miss your scheduled period (no bleeding on the days that you are taking mustard tablets). Since scheduled periods are less frequent when you are taking Daysee, notify your healthcare provider that you have missed your period and that you are taking Daysee. Also notify your healthcare provider if you have symptoms of pregnancy such as morning sickness or unusual breast tenderness. It is important that your healthcare provider evaluates you to determine if you are pregnant. Stop taking Daysee if it is determined that you are pregnant.

What If I Want To Become Pregnant?
You may stop taking the pill whenever you wish. Consider a visit with your healthcare provider for a pre-pregnancy checkup before you stop taking the pill.

General Advice About Daysee
Your healthcare provider prescribed Daysee for you. Do not share Daysee with anyone else. Keep Daysee out of the reach of children.
If you have concerns or questions, ask your healthcare provider. You may also ask your healthcare providers for a more detailed label written for medical professionals.

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

Manufactured by:
Lupin Limited
Pithampur (M.P.) – 454 775
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Revised: June 2022 ID#: 260120