

Drospirenone (SLYND) National Drug Monograph March 2022

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information. [Drospirenone \(SLYND\) Prescribing Information 2019](#)

FDA Approval Information^{1,2}

Description/Mechanism of Action

- SLYND is a progestin-only contraceptive pill (POP) containing drospirenone (DRSP). DRSP is a fourth generation progestin and spironolactone analogue with anti-mineralocorticoid activity (comparable to 25 mg spironolactone). DRSP prevents pregnancy primarily by suppressing ovulation.

Indication(s) Under Review in This Document

- DRSP POP is indicated for use in females of reproductive potential for the prevention of pregnancy.

Dosage Form(s) Under Review

- SLYND is packaged in 28-day blister cards containing 24 active DRSP-containing oral tablets and 4 inert oral tablets providing a hormone-free interval. Patients should take one tablet daily at about the same time each day to keep a 24 hour interval between pills.
- *Note: formulations containing 3 mg DRSP in combination with estrogen and approved as contraceptive and menopausal agents are not included in this review.*

Clinical Evidence Summary

Efficacy Considerations^{1,2,3,4}

- FDA approval of the DRSP POP was based on one open-label, multicenter, noncomparative 13-cycle trial (CF111/303) conducted in the U.S. evaluating efficacy in preventing pregnancy. Enrolled women were healthy, sexually active, and aged 15 years and older with normal menstrual cycles. Breastfeeding women were allowed to be enrolled but not included in the efficacy analyses.
- The primary endpoint was the Pearl Index (number of pregnancies per 100 woman-years) for non-breastfeeding women who were 35 years of age and younger. The Pearl Index was calculated as the number of on-treatment pregnancies that occurred in evaluable cycles (cycles where sexual activity occurred and where there was no use of adjunctive contraception).
- Baseline/disposition: A total of 953 females aged 35 years or younger were included in the efficacy population and contributed 5,547 evaluable cycles. The mean age of the population was 26 years, and the mean BMI was 28.5 kg/m² (35% of subjects with BMI ≥ 30 kg/m²). About half of the participants were Caucasian and 39% were African American. Of note, 65% of subjects discontinued the study early (the anticipated discontinuation rate was 45%). The most common reasons for premature discontinuation were loss to follow-up (27%), withdrawal of consent (15%), and adverse events (11%).

- **Results:** The Pearl Index was 4.0 (95% confidence interval [CI]: 2.3 – 6.4) based on 17 reported on-treatment pregnancies.^{1,2} Subgroup analyses of patients with a higher body mass index (BMI) did not suggest a greater risk of pregnancy.²
- **Additional trials:** Two additional Phase 3 studies conducted in Europe (CF111/301 and CF111/302) were not included in the FDA efficacy analysis or U.S. label, with the FDA reasoning that the information is generally not applicable to the U.S. population.² One European study was noncomparative. The other European study included a desogestrel POP arm for safety comparison only. The desogestrel POP is not available in the U.S. Pooled analyses from both European studies showed an overall Pearl Index of 1.0 (95% CI 0.4 – 2.0) in women aged 35 years or younger for cycles where sexual activity occurred without additional contraception.⁴

Safety Considerations^{1,2,3}

- **Safety results from clinical trials:** Safety data to support FDA approval was mainly based on pooled data from 2,598 DRSP POP-treated subjects from three phase 3 studies (one U.S., two non-U.S.) and one phase 2 study. The overall mean duration of treatment was 236 days. Even though the U.S. study's completion rate of 35% was lower than the other three trials, the portion of patients discontinuing prematurely due to adverse events was comparable between the U.S. and non-U.S. trials. Hyperkalemia and thromboembolic disorders were safety issues of special interest during the FDA review.
- **Contraindications:**
 - Renal impairment
 - Adrenal insufficiency
 - Liver tumors (benign or malignant) or hepatic impairment
 - Presence or history of cervical cancer or progestin sensitive cancers
 - Undiagnosed abnormal uterine bleeding
- **Warnings and Precautions:**
 - **Hyperkalemia:** DRSP POP is contraindicated in patients with conditions that predispose them to hyperkalemia (e.g., renal impairment, hepatic impairment, and adrenal insufficiency). Monitor serum potassium levels in patients receiving concomitant daily, chronic medications that increase potassium or strong CYP3A4 inhibitors that increase DRSP exposure or who develop conditions that increase the risk for hyperkalemia.
 - **Thromboembolic disorders:** Consider the increased thromboembolic risk in the postpartum period and in patients with a history of thromboembolism when prescribing DRSP POP. Consider discontinuing DRSP POP in the setting of prolonged immobilization due to surgery or illness.
 - **Bone loss:** Progestin-only contraceptives have been associated with clinically significant bone loss. At this time, it is unclear whether DRSP POP causes clinically significant bone loss.
 - **Uterine bleeding irregularities and amenorrhea:** Vaginal bleeding irregularities are common with progestin-only contraceptives. If bleeding persists or occurs after previously regular cycles, evaluate for causes such as pregnancy or malignancy. Or, if scheduled bleeding does not occur, consider the possibility of pregnancy.
 - **Liver disease:** Discontinue DRSP if jaundice or symptoms of liver function disturbances develop.
 - **Risk of hyperglycemia in patients with diabetes**
 - **Ectopic pregnancy**
 - **Cervical cancer**
 - **Depression**

- **Adverse reactions:** The most common adverse reactions are listed in Table 1.

Table 1. Adverse reactions occurring in ≥1% of subjects in pooled studies

Adverse reaction	% of Subjects N=2,598
Acne	3.8
Metrorrhagia	2.8
Headache	2.7
Breast pain	2.2
Weight increased	1.9
Dysmenorrhea	1.9
Nausea	1.8
Vaginal hemorrhage	1.7
Libido decreased	1.3
Breast tenderness	1.2
Menstruation irregular	1.2

- **Deaths:** none
- **Serious adverse events:** Hyperkalemia was the most commonly reported serious adverse event, reported in 7 subjects (0.2%). No subjects with hyperkalemia were hospitalized or symptomatic. Other serious adverse events that were considered possibly related to study drug were uterine myoma, cholelithiasis, liver adenoma, and abdominal pain and vomiting.
- **Discontinuations due to adverse events:** In the pooled data, 11% of subjects discontinued due to adverse events. The most frequently reported adverse events leading to discontinuation included acne, metrorrhagia, irregular menstruation, increased weight, vaginal hemorrhage, and decreased libido.²
- **Adverse events of interest:**
 - **Hyperkalemia:** In the U.S. phase 3 study, 41 of 1,006 subjects reported elevated serum potassium (greater than 5.3 mm/L), with nearly half of those identified at screening. Most patients' labs returned to normal despite continued treatment on DRSP POP. Three subjects withdrew from the study prematurely due to persistently elevated serum potassium. The FDA reviewers concluded that elevated serum potassium is isolated, mild, and returns to normal even with continued treatment in many patients.² Patients with known contraindications were excluded from clinical trials. Many clinical studies evaluating DRSP-containing products have not found a clinically significant increased risk for hyperkalemia.⁵
 - **Thromboembolic disorders:** Epidemiologic studies have not identified an increased risk of arterial or venous thromboembolism (VTE) with progestin-only contraceptives. There were no thromboembolic events reported in the clinical development program with DRSP POP. Preparations of ethinyl estradiol plus DRSP may be associated with a higher risk of VTE than other estrogen/progestin combinations. It is unknown whether there is a higher risk of VTE with DRSP alone.
 - **Bone loss:** Safety concerns were not identified in the evaluation of surrogate markers of bone metabolism with DRSP POP treatment during the clinical development program. However, FDA is requiring a post marketing study to evaluate the impact of DRSP POP on bone mineral density.

Other Considerations

- **Pregnancy:** Epidemiologic studies and meta-analysis have not found an increased risk of birth defects in offspring of females who inadvertently use progestin early in pregnancy. DRSP POP should be discontinued if pregnancy occurs.
- **Lactation:** Negligible amounts of DRSP are excreted in breast milk. In general, no adverse effects have been found on milk production or in the health and development of infants with the use of progestin-only contraceptives.
- **Renal impairment:** Subjects with mild renal impairment (creatinine clearance [CrCL] of 50-80 ml/min) had DRSP concentrations that were comparable to subjects with CrCL greater than 80 ml/min. DRSP serum concentrations were increased by 37% in patients with a creatinine clearance of 30-49 ml/min.
- **Hepatic impairment:** DRSP exposure was increased 3-fold in patients with moderate hepatic impairment.
- **Effect on uterine bleeding patterns^{1,2}** Irregular uterine bleeding is a common adverse effect with POPs. In the phase 3 studies, the portion of patients experiencing scheduled bleeding decreased over time, from 81% in cycle 1 to 26% in cycle 13. The portion of patients experiencing unscheduled bleeding or spotting decreased from 61% in cycle 1 to 40% in cycle 13. Minimal changes in bleeding patterns were seen after cycle 10. A total of 91 patients (4%) discontinued DRSP POP because of bleeding problems or amenorrhea. In one of the European studies, DRSP POP was associated with lower rates of overall and unscheduled bleeding compared to a desogestrel-POP administered in a continuous regimen and not available in the U.S.⁴
- **Drug interactions¹**
 - DRSP is a substrate of CYP3A4. Drugs or herbal products that induce CYP3A4 (e.g., phenytoin, carbamazepine, barbiturates) may decrease DRSP concentrations, potentially reduce the contraceptive effectiveness and increase breakthrough bleeding. CYP3A4 inhibitors (e.g., ketoconazole) may increase DRSP systemic exposure.
 - Consider the potential for increased potassium concentrations when DRSP POP is administered in patients taking other drugs that increase serum potassium (e.g., angiotensin-converting enzyme inhibitors, angiotensin-II receptor antagonists, potassium-sparing diuretics, potassium supplements, heparin, aldosterone antagonists, and non-steroidal anti-inflammatory drugs [NSAIDs]).
- **Missed pill forgiveness:** Ovulation inhibition was maintained in a study evaluating four single, intentional missed doses of DRSP POP in one cycle.⁶ Instructions for missed pills for DRSP POP include a 24-hour pill forgiveness. If more than one tablet is missed, then a back-up method of contraception should be used for 7 days.¹
- **Dosing and regimen:** Other FDA approved DRSP-containing combination contraceptive products (estrogen plus DRSP) contain 3 mg of DRSP per pill in either a 21-day (and 7 days off) or 24-day (and 4 days off) cycle. Per the FDA review, pharmacodynamics studies support a 4 mg dose of DRSP POP (without an estrogen) administered daily in a 24-day on, 4-day off regimen to adequately suppress ovulation.²

Other Therapeutic Options

Table 2. Progestin-Only Contraceptive Alternatives⁷

Drug	VANF	Other Considerations
Drospirenone 4 mg tablet (SLYND)	TBD	<ul style="list-style-type: none"> • POP administered in 24 days on/ 4 days off each cycle • Primary MOA: ovulation suppression • 24 hr pill forgiveness for missed or late doses
Norethindrone 0.35 mg tablet (Camila, Errin, etc.)	Yes	<ul style="list-style-type: none"> • POP administered daily (no hormone-free interval) • Suppresses ovulation in about half of users; relies on thickening cervical mucus and altering endometrium for contraception • Must be taken at the same time daily; 3 hr pill forgiveness • May be less effective than combination contraceptives
DMPA injection (Depo-Provera)	Yes	<ul style="list-style-type: none"> • IM or SC Injection that lasts 12 wks • Typically requires healthcare visit
Levonorgestrel-releasing IUD (Kyleena, Liletta, Mirena, Skyla)	n/a*	<ul style="list-style-type: none"> • Long-acting reversible contraceptive (LARC) • Requires provider visit for insertion/removal • Highly effective, lasts up to 3 to 7 yrs (product-specific durations)
Nexplanon Implant	n/a*	<ul style="list-style-type: none"> • Long-acting reversible contraceptive (LARC) • Requires provider visit for insertion/removal • Highly effective, lasts up to 3 yrs

DMPA=depo-medroxyprogesterone; IUD=intrauterine device; IM=intramuscular; MOA=mechanism of action; OTC=over the counter; POP=progestin only pill; SC=subcutaneous

*procured by Prosthetics in VA

Projected Place in Therapy

- In the U.S., the rate of unintended pregnancy was nearly 45% based on data from 2011.⁸
- Progestin-only contraceptives (without estrogen) are available in multiple formulations including pills, injections, IUDs, and an implant. Progestin-only contraceptives are desirable for breastfeeding women and women with contraindications or a desire to avoid estrogen-containing contraceptive products (e.g., history of venous thromboembolism, migraine with aura, smokers over 35 yrs, old).⁹ Effectiveness varies between products. Irregular menstrual bleeding and unscheduled bleeding are common side effects and a frequent cause for discontinuation.
- In the U.S., available POPs are norethindrone POP and DRSP POP. There are no direct comparator studies. The contraceptive effectiveness of POPs is usually reported as part of the “oral contraceptives” class that includes both POPs and combination hormonal products (estrogen plus progestin). It is thought that POPs may be less effective than combination products with real-world use given the strict dosing schedule and lack of forgiveness for nonadherence with traditional POPs (e.g., norethindrone POP).¹⁰
- DRSP is an analog of spironolactone with anti-mineralocorticoid activity comparable to 25 mg of spironolactone. DRSP is also available in combination with estrogen for contraceptive and menopausal use.
- In the single, noncomparative, open-label U.S. study of DRSP used for FDA approval, the Pearl Index with DRSP POP was 4.0 (95% CI 2.3 – 6.4) pregnancies per 100 woman-years in women 35 years and younger and not breastfeeding.
- Risk of hyperkalemia is a unique consideration of DRSP-containing products. DRSP POP is contraindicated in conditions that predispose patients to hyperkalemia including renal and hepatic impairment and adrenal insufficiency. Caution is recommended when co-prescribing medications that elevate serum potassium or increase DRSP exposure. In observations from clinical trials (where high risk patients were excluded), elevated serum potassium levels were isolated and mild and often returned to normal despite continued use of DRSP POP.
- Increased risk of thromboembolism has not been identified with POPs. There were no arterial or venous events reported in the DRSP POP clinical trials, though these events are uncommon in the studied population. DRSP-estrogen combinations may be associated with a higher risk of thromboembolism than other progestin-estrogen combinations.
- Unscheduled bleeding or spotting decreased over time in clinical trials but was still reported in 40% of patients in cycle 13. Nearly three-quarter of the subjects reported amenorrhea by the end of the study. Four percent of patients discontinued DRSP POP due to bleeding issues or amenorrhea.
- DRSP POP is administered in an extended cycle regimen of 24 days on (active tablets) and 4 days off (inert tablets) and should be taken at the same time daily. In comparison, the norethindrone POP is administered continuously at the same time each day with no hormone-free interval.
- DRSP POP has a 24-hr pill forgiveness window for late doses. In contrast, norethindrone POP instructions recommend use of back-up contraception if a dose is more than 3 hours late.¹¹ It is unclear whether the increased flexibility of late or missed doses of DRSP POP vs. norethindrone POPs translates to improved outcomes.
- There is moderate quality evidence to support the effectiveness of DRSP POP as a contraceptive based on data from three open-label studies evaluating pregnancy as an outcome (one U.S., two European studies).
- The acquisition cost of DRSP POP is significantly higher than norethindrone POP.
- **Summary:** DRSP POP has been shown to be effective in preventing pregnancy without any new or unexpected safety signals. Given the lack of head to head study, it is unclear how DRSP POP compares to

norethindrone POP for efficacy, safety, and tolerability. Unscheduled spotting and bleeding with DRSP POP remain common despite the extended cycle regimen including a hormone free interval. It is unknown whether the extended window for effectiveness following a late or missed pill with DRSP POP compared to norethindrone POP will translate to improved clinical outcomes. There are several formulations of progestin-only contraceptives available including pills, injections, IUDs, and an implant to suit the needs of patients desiring avoidance of estrogen. DRSP POP may be considered in patients desiring a daily POP but who are unable to use or intolerant of norethindrone POP.

- **Patient examples provided by women's health providers (not all inclusive):**
 - Patients with tolerance issues on norethindrone (e.g., unscheduled bleeding/spotting); note these could also occur on drospirenone.
 - Patients with contraindication to estrogen and who are not good candidates for the progestin shot, implant, IUD and with history of failure/intolerance to norethindrone
 - Patients with an indication for ovulation suppression (e.g., recurrent ovarian cysts) and who have contraindications to or are unable to tolerate other options for ovulation suppression.
 - Patients with difficulties adhering to the daily dosing within the 3 hour window to norethindrone despite reasonable efforts (e.g., newborn or irregular work schedules) who could benefit from extended window for taking late/missed pill with drospirenone.

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