CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216285Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	06/23/2022
From	Gerald Willett, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	216285
Applicant	Exeltis USA, Inc.
Date of Submission	August 30, 2021
PDUFA Goal Date	June 30, 2022
Proprietary Name	Pending
Established or Proper Name	Drospirenone Chewable Tablets
Dosage Form(s)	Chewable tablets
Applicant Proposed Indication(s)/Population(s)	Prevention of pregnancy
Applicant Proposed Dosing Regimen(s)	Drospirenone (DRSP) 3.5 mg once daily x 24 days followed by one inactive tablet once daily x 4 days
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Females of childbearing potential
Recommended Dosing Regimen(s) (if applicable)	Drospirenone (DRSP) 3.5 mg once daily x 24 days followed by one inactive tablet once daily x 4 days

Risk-Benefit Analysis

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Applications for chewable dosage forms of approved orally swallowed contraceptive products have been evaluated by the Division in the past based on bioequivalence, an oral irritation study and a safety review of the marketed orally swallowed tablet. This application met the regulatory requirement for bioequivalence per 21 CFR §320.1. Study BLCL-DRS-FDA-04 demonstrated that the pharmacokinetics of drospirenone 3.5 mg chewable tablets are within the bioequivalence margin of the swallowed product Slynd.

There were no deaths, serious or severe adverse events in the three clinical studies supporting this application. Review of six discontinuations due to adverse events indicated no causation due to study drug. No clinically symptomatic or significant potassium elevations were seen in the studies. No clinically significant oral irritation was found with this chewable tablet.

Evaluation of the voluntary safety reporting system (FAERS) for Slynd by the Division of Pharmacovigilance II found a few cases of hypersensitivity. This adverse reaction will be incorporated into the product labels fo (b) (4) the chewable (b) (4) products. The 4-month safety report and the Applicant's postmarketing safety reports reveal no other new safety concerns.

Additionally, the Applicant in response to an information request calculated the VTE incidence for Slynd since its approval in 2019. The Applicant calculated a VTE incidence of 0.4 events per 10,000 patient-years. This is reassuring in light of the potential increased VTE risk seen when drospirenone is combined with ethinyl estradiol. The prescription and provider labels were reviewed by the Agency and found to be acceptable on 06/23/22

In addition to the other disciplines reviewing this application and the primary clinical reviewer, I recommend approval of drospirenone 3.5 mg chewable tablets for the prevention of pregnancy in females of childbearing potential. In agreement with the Applicant, this product will also be evaluated in a required bone mineral density assessment study in conjunction with Slynd for both adults and adolescents.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Unintended pregnancy poses a significant reproductive health risk for females and their families. Progestin-only contraception historically has been somewhat less effective in terms of pregnancy protection as compared to combination hormonal contraceptive products, but is associated with fewer serious adverse reactions (e.g. venous thromboembolic events and lower risk of stroke in women over 35 who smoke)	**This chewable modification of an approved progestin-only contraceptive may be better tolerated in patients who have trouble swallowing tablets.**
Current Treatment Options	• DRSP-containing contraceptives (swallowed tablets) include 5 combination products and one progestin-only product (Slynd). • Chewable contraceptive tablets to date have all been combination products	**This is the first chewable progestin-only product**
Benefit	• This product was found to be bioequivalent to the approved cross-referenced product Slynd and therefore the expected pregnancy rate should be similar, if not identical. Additional potential benefit may result for patients who have trouble swallowing whole tablets and/or seek a progestin-only product which may have less safety concerns.	**Bioequivalence was demonstrated for this chewable progestin-only contraceptive product. Potential ease of "swallowing" and tolerability benefits may result for certain patients.**
Risk and Risk Management	<u>Venous Thromboembolism</u> Combination oral contraceptives containing drospirenone and ethinyl estradiol may be associated with a higher risk of venous thromboembolism (VTE) than those containing other estrogen-progestin combinations. It is unknown whether the risk of VTE is increased with drospirenone alone; however, no cases of VTE or arterial thromboembolism (ATE) were reported in the developmental studies of the approved "swallowed" product Slynd) or drospirenone 3.5 mg chewable tablets. Additionally the reported postmarketing cases of VTE reported for Slynd have been rare. <u>Hyperkalemia</u> The progestin drospirenone has anti-mineralocorticoid activity, including the potential for hyperkalemia in high risk females. There were four cases of mild hyperkalemia during the clinical development of drospirenone 3.5 mg chewable tablets. All cases involved mild serum potassium elevations and/or isolated increases that resolved spontaneously while still on study medication. None were associated with clinically significant adverse reactions or evidence	**Labeling regarding thromboembolic disorders for the chewable product will be the identical to that ofas the approved Slynd. Postmarketing safety evaluation of Slynd has only shown rare VTE events. Current postmarketing data suggests that Slynd is similar to other progestin-only oral contraceptives in having a low risk for VTE. Routine postmarketing surveillance of DRSP 3.5 mg chewable tablets in regard to VTEs and ATEs is acceptable.** **The current restrictions regarding the potential for hyperkalemia that are present in the labeling for DRSP-containing products (including Slynd) should be maintained in the product label for the DRSP chewable tablet.**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	of electrocardiogram (ECG) changes. Bone Loss Some progestin-only products have been associated with clinically significant bone loss due to a chronic hypoestrogenic state. Post marketing bone mineral density studies of Slynd are currently underway (see section 13.0 for specifics and the plan for the chewable dosage form). The postmarketing study will be revised to allow inclusion of women who use this chewable drosperinone product. Postmarketing Safety of Slynd Review of Slynd post-approval periodic adverse event reports (PADERS) has not shown any new safety signals or trends. There is no evidence of an increased risk for VTEs, ATEs, or hyperkalemic adverse events that requires further investigation or new safety labeling changes. Clinical Pharmacology Studies and Oral Irritation Study There were no safety concerns identified in these studies.	

1. Background

The Applicant seeks approval of a progestin-only oral contraceptive (POC) containing 3.5 mg of drospirenone (DRSP) in the form of a chewable tablet. The indication is prevention of pregnancy in females of childbearing potential. This product will be referred to as DRSP 3.5 in this review as a Tradename for this product is currently under review.

The Applicant received approval for their 4.0 mg DRSP POC (product name = Slynd) in May 2019. Slynd was designed as a tablet to be swallowed and was the first POC approved in many years by the Division. Slynd is approved and marketed in 48 countries including Europe, Middle East, Australia, Latin America and the US. There have been no regulatory actions taken in any country for safety concerns relating to Slynd usage. Since the data for the reference product Slynd is owned by the Applicant some information from the Slynd submission will be used in this review in addition to information from the Slynd label.

The Applicant found that a slightly reduced dosage of 3.5 mg for the chewable tablet was equivalent to 4.0 mg for the swallowed approved tablet. This will be the first chewable POC to be marketed in the U.S. and may have the added benefit for those individuals who have difficulty swallowing tablets. This chewable product was developed under IND 146207. There were no significant regulatory difficulties encountered during the development period.

POCs tend have to a somewhat higher pregnancy rate than combination oral contraceptives (COCs), but this is balanced by having lower safety risks (e.g., less thromboembolic complications and lower risk of stroke in smokers over 35). Historically, POCs tend to be more efficacious when patients carefully take the product at the same time each day.

Older POCs were taken continuously without a break. Slynd and DRSP 3.5 both are dosed with active tablets for 24 days followed by 4 days of inactive tablets. On page 8 of the clinical overview for Slynd (NDA 21137) the Applicant stated that a favorable bleeding pattern was sought by dosing in a 24/4 pattern. They were hoping to induce some scheduled bleeding and reduce unscheduled bleeding episodes.

The approved Slynd label, however, indicates that the percentage of subjects with unscheduled bleeding was still around 40% by cycle 13 (approximately 1 year after initiation). This unscheduled bleeding is probably due to fact that it is a progestin-only product and there is a lack of enough estrogen to stabilize the endometrial lining. It should be noted that this bleeding is rarely heavy and many patients who discontinue progestin-only products for bleeding reasons do so because of unpredictable bleeding/spotting that can affect clothing and social situations.

The Division has over a twenty year experience with hormonal contraceptives containing drospirenone. Combination products containing drospirenone and ethinyl estradiol include in their label that drospirenone-containing products may have a greater risk for VTE than other

COC progestins. The data for this statement in COC labels was derived from epidemiologic studies including one sponsored by the FDA and discussed in an advisory committee in December, 2011. Postmarketing studies of Slynd to date, however, have not shown any safety signals of an increased VTE risk.

Hyperkalemia is a potential risk with drospirenone-containing hormonal contraceptives due to anti-mineralocorticoid activity but postmarketing studies and voluntary reporting over a twenty year period have not shown this to be a clinically significant safety risk.

2. Product Quality

The review submitted by Product Quality recommends approval for NDA 216285 (Drospirenone Chewable Tablets 3.5mg). Reviewers include:

Application Technical Lead = Hamid Shafiei, PhD
Drug Substance = Sukhamaya, Bain, PhD / Donna Christner, PhD
Drug Product = Hitesh Shroff, PhD / Hong Cai, PhD
Manufaturing = Loqman Mohamed, PhD/ Vaikunth Prabhu, PhD
Microbiology = Loqman Mohamed, PhD/ Vaikunth Prabhu, PhD
Biopharmaceutics = Bryan Ericksen, PhD / Tapash Ghosh, PhD
Environmental = Hitesh Schroff, PhD/ Hong Cai, PhD

The OPQ executive summary has the following verbatim bullet points:

- The applicant of this 505(b)(2) new drug application has provided sufficient CMC information to assure the identity, strength, purity and quality of the drug substance, drospirenone and the drug product, Drospirenone Chewable Tablets, 3.5 mg.
- The Office Pharmaceutical Manufacturing Assessment has made the overall recommendation of adequate for the facilities involved in this application.
- The CMC issues on labels/labeling have been satisfactorily resolved.
- The applicant's request for the categorical exclusion from the preparation of the environmental assessment has been granted

3. Nonclinical Pharmacology/Toxicology

Andrea L. Benedict, PhD and Kimberly P Hatfield, PhD recommended approval of Drospirenone 3.5 mg chewable tablet for the indication of prevention of pregnancy in females of reproductive potential. No additional nonclinical studies or labeling for new nonclinical issues were recommended.

They noted the following:

"In the pivotal comparative BA study, the Applicant demonstrated that the DRSP exposure after single doses of DRSP 3.5 mg chewable tablet administered was less than or comparable to the reference drug SLYND. Therefore, it is appropriate for the applicant to rely on the Agency's previous findings of nonclinical safety for SLYND and YAZ® in support of this 505(b)(2) NDA."

4. Clinical Pharmacology

Mohammed Akbar, PhD and Yanhui Lu, PhD found the current application acceptable for approval from a clinical pharmacology standpoint.

The clinical pharmacology reviewers found that the Applicant demonstrated an acceptable bioequivalent range of 80 to 125% when comparing the 3.5 mg chewable tablet to the 4 mg Slynd swallowed tablet in study 2020-FLE1-SLINC-PK-04. The reviewers also evaluated the Applicant's food effect study 2020-FLEi-SLINC-PK-06 and found that effect of food on the PK of DRSP was not clinically meaningful. In terms of labeling this translates to the recommendation that DRSP chewable tablets can be taken without regard to meals.

Labeling containing the pharmacokinetics and food effect study results from DRSP 3.5 were incorporated into the final approved provider label.

5. Clinical Microbiology

See section 3.

6. Clinical/Statistical- Efficacy

The Clinical Studies submitted to this NDA to support approval of DRSP 3.5 are shown in the following table:

Study	Design
2020-FLE1-SLINC-PK-**04**	Comparative bioavailability & bioequivalence
2020-FLE1-SLINC-PK-**06**	Comparative bioavailability, food effects
2020-FLE1-SLINC-CE-**07**	Oral irritation, safety, tolerability

Notes: The studies in the above table will be listed as 04, 06 and 07 in this review. Studies 01 and 03 (not listed above) evaluated a 4 mg chewable product which is not to be marketed.

The efficacy of DRSP 3.5 is based on bioequivalence to the approved Slynd product. See Section 5 for a summary of the Clinical Pharmacology review of studies 04 and 06. Safety assessments of the Clinical Pharmacology studies and the oral irritation study are described in Section 8 of this review.

CDTL note: The above studies conducted in Portugal are acceptable by the Division for clinical pharmacology and oral irritation evaluations. The study population in Portugal consisted of females who were primarily caucasian and whose mean BMI was approximately 25 kg/m^2 (i.e. normal range). However, these demographics are balanced by the bioequivalence bridge to the large CF111/303 study conducted for Slynd in the US. In study CF111/303, the racial distribution was more consistent with the US population (53.3% caucasian, 38.5% African American and 8.2% other). Similarly, study CF111/303 had a much more representative population based on BMI with 35% having a BMI ≥ 30 kg/m^2 and 18% having a BMI ≥ 35 kg/m^2. Although the Slynd data were insufficient to fully analyze the Pearl Index by BMI subgroups in Study 303, there were actually more pregnancies in subjects with BMI < 30 kg/m^2 (12 pregnancies) compared to those with BMI > 30 kg/m^2 (5 pregnancies). This is reassuring that this product is likely to be used in a reproductive aged population in the US that is increasingly likely to be overweight or obese.

Since efficacy is being bridged through bioequivalence, a biostatistical review is not required.

7. Safety

The primary safety review for DRSP 3.5 entailed the following:

- Adverse events data collected from the Clinical Pharmacology studies (04 & 06)
- Oral irritation results and other adverse events from Study 07
- 4-month safety update (incorporated with a developmental safety update)
- Postmarketing safety review of Slynd (via Applicant's reports and separate DPV analysis of FAERS

The Applicant also provided safety information from 70 subjects in studies 01 and 03 in which the chewable table had a slightly higher dosage of 4 mg. There were no deaths or serious adverse events reported in studies 01 and 03. There were 4 discontinuations for adverse events which included 2 cases of influenza, one case of tonsillitis and one case with rash and angioedema thought likely to be drug-related. The pharmacokinetic results from the 4 mg tablet were not bioequivalent with the reference product Slynd and therefore the Applicant moved to the 3.5 mg dose as the to-be-marketed product.

Overall exposure for study drug DRSP 3.5 in Studies 04, 06 and 07 was 103 subjects. These studies were performed in Portugal. Subjects in pharmacokinetic studies 04 and 06 received a single dose of study product or reference product. Subjects in the oral irritation study received study drug for 24 consecutive days followed by 4 days of placebo as per the intended label dosing. This duration of exposure is adequate to assess oral irritation.

In the safety population of Studies 04, 06 and 07 there were no deaths or serious adverse events.

The primary reviewer, Ioanna Comstock MD, identified 5 subjects in Study 04 and one subject in Study 06 who prematurely discontinued due to adverse events. The adverse events included urinary tract infection (2), dental infection (2), tonsillitis (1), and fever syndrome (1). She contacted the Applicant to obtain additional safety information (narratives) for subjects who experienced dental or infection-related adverse events. After her review of the Applicant's response she determined that there was no apparent relationship of any of these events to the study drug DRSP 3.5.

The treatment emergent adverse events (TEAEs) and adverse reaction determinations in Studies 04, 06 and 07 were consistent with findings in similar contraceptive trials where the basis of the application is a bioequivalence bridge. All of the TEAEs were classified as mild or moderate in severity. The two most frequent events were headache and menstrual irregularities.

> **CDTL Note:** The adverse reaction section of the chewable DRSP 3.5 mg label will maintain the same adverse reaction table as Slynd since there is a bridge to the approved clinical safety profile of SLYND containing a larger number of subjects (2598 compared to 103 in these smaller studies).

Four subjects in the safety population for this application had mild serum potassium elevations in the aforementioned clinical studies. For three subjects the elevations were single isolated events that returned to normal. One subject in the oral irritation study had an elevation at day 1 and at the end of study. None of the subjects were symptomatic or had abnormal electrocardiograms.

> **CDTL note**: These findings of isolated laboratory elevations with no clinical symptomatology are similar to findings from other drospirenone applications that the Division has reviewed. It is possible that these results could potentially be impacted by mild (not gross) hemolysis of the specimen and/or delay in running the test. Although drospirenone has the potential for hyperkalemia the Division has not seen a significant safety signal for potassium-related problems in women with normal renal function since this progestin was first marketed approximately twenty years ago.

In regard to the oral irritation results, the primary reviewer, Ioanna Comstock MD, had the following statement:

"Following administration of the drospirenone 3.5 mg chewable active and inactive tablets, none of the 40 subjects had evidence of irritation at the examination of the attached gingivae, buccal mucosa, hard/soft palate, labial mucosa, oropharynx, sublingual mucosa, tongue or uvula. Only one (2.5%) subject (study subject ID (b) (6)) showed slight erythema without edema on the lips at the Day 8 pre-dose oral irritation assessment (active tablet).

This was reported as a TEAE ("Herpes virus infection").

Postmarketing Safety of Slynd

The primary clinical reviewer, Ioanna Comstock MD, performed an extensive review of global postmarketing data for Slynd including Periodic Adverse Drug Experience Reports, Annual Reports and Development Safety Update Reports (one of which was sent with the 4-month safety update in December 2021). She found no evidence of any new safety signals or trends in these reports.

However, the Division of Pharmacovigilance II in their FAERS database review for Slynd from May 23, 2019 through January 24, 2022 did identify four cases of interest that reported hypersensitivity with drospirenone use.

> **CDTL Note**: The clinical team will recommend that language regarding hypersensitivity be added to the WARNINGS/PRECAUTION section of both the Slynd label and the new label for DRSP 3.5 chewable.

An information request was sent to the Applicant on January 13, 2022, requesting a calculation incidence of VTE worldwide in female users since the approval of Slynd in May of 2019. The Applicant identified 17 cases of VTE. Based on a total world-wide patient exposure estimated at over 420,000 patient-years the reporting incidence of VTE was calculated at 0.4 per 10,000 patient-years. This estimate is far below the expected incidence for combination hormonal contraceptives at 6-9 per 10,000 patient-years.

CDTL Note: This safety data is reassuring considering the clinical concern for a potential increase risk for VTE with drospirenone in combination hormonal products. No new or revised labeling for this safety issue is necessary.

8. Advisory Committee Meeting

There are no issues in this application that require the assistance of expert advice from an advisory committee.

9. Pediatrics

DUOG discussed this application with the Pediatric Review Committee (PERC). The PeRC was advised of the ongoing postmarketing requirement (PMR) that the Applicant is performing for the assessment of bone mineral density in adults and adolescents for the approved swallowed tablet - Slynd. The Committee supported the Division's plan to enroll females who choose to use the chewable tablet into the ongoing study and add data to that analysis.

10. Other Relevant Regulatory Issues

There were no financial disclosures to report. An Office of Scientific Investigations audit was not deemed necessary. The studies were performed in compliance with Good Clinical Practice.

11. Labeling

Labeling negotiations are complete. A revised prescriber label, patient package insert and instructions for use were received from the Applicant on June 17, 2022. Upon final review, the review team and I found the labeling acceptable for approval.

12. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

Risk mitigation strategies are not required for this product.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

The Division will request the Applicant include both the 3.5 mg chewable tablet and Slynd in an ongoing prospective, controlled, long-term trial to assess bone mineral density change in adults and adolescents compared to users of non-hormonal contraceptive methods.

CDTL Note: On 6/16/22 the Applicant sent an email stating that they agree to Division's proposed milestones:

Draft protocol submission: 08/2022
Final protocol submission: 10/2022
Trial completion: 07/2026
Final report submission: 10/2026

The final study report containing both cohorts (Slynd + chewable) will be submitted to both NDA 211367 and 216285

13. Recommended Comments to the Applicant

Approval is recommended for this product. No other comments need to be relayed to the Applicant regarding this application.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

GERALD D WILLETT
06/23/2022 11:32:12 AM

AUDREY L GASSMAN
06/29/2022 09:17:55 AM
I concur with the CDTL's approval recommendation and labeling is complete