CLINICAL PHARMACOLOGY REVIEW

Application Type	NDA efficacy supplement
Application Number(s)	021529/S027
Priority or Standard	Standard
Submit Date(s)	December 16, 2024
PDUFA Goal Date	October 16, 2025
Division/Office	Division of Urology, Obstetrics, and Gynecology (DUOG) Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (ORPURM)
Review Completion Date	September 17, 2025
Established/Proper Name	Etonogestrel implant
(Proposed) Trade Name	Nexplanon
Pharmacologic Class	Progestin
Applicant	Organon USA LLC
Dosage form	A single, radiopaque, rod-shaped implant, containing 68 mg etonogestrel, pre-loaded in the needle of a disposable applicator
Applicant proposed Dosing Regimen	Insert one NEXPLANON subdermally just under the skin at the inner side of the non-dominant upper arm. NEXPLANON must be removed no later than by the end of the fifth year
Applicant Proposed Indication(s)/Population(s)	Prevention of pregnancy for up to 5 years
Recommendation on Regulatory Action	Approval
OCP Division	Division of Cardiometabolic and Endocrine Pharmacology
Primary reviewer	Li Wang, PhD
Secondary reviewer	Yanhui Lu, PhD

1. EXECUTIVE SUMMARY

Organon USA LLC (hereafter referred to as the Applicant) is seeking approval to extend the duration of Nexplanon use for up to 5 years for prevention of pregnancy (i.e., contraception). Nexplanon is an implant containing 68 mg etonogestrel (ENG) approved in 2011 for prevention of pregnancy for use by women for a period of 3 years. The Applicant submitted a supplemental New Drug Application (sNDA) on December 16, 2024.

In this sNDA, the Applicant submitted the results of a single arm, open-label Phase 3 pivotal study MK-8415-060 entitled "A Phase 3, Open label, Multi-center, Single Arm Study to Assess Contraceptive Efficacy and Safety of the Etonogestrel (MK-8415) Implant During Extended Use Beyond 3 Years in Premenopausal Females 18 to 35 Years of Age" to support the efficacy and safety of the extended use of NEXPLANON implant for Years 4 and 5. In the study, the Applicant measured etonogestrel serum concentrations in subjects from 3 to 5 years after insertion of NEXPLANON, explored the impact of body mass index (BMI) of study subjects at baseline on etonogestrel serum concentrations, and proposed labeling changes in Section 12.3 Pharmacokinetics.

1.1 Recommendations

The Office of Clinical Pharmacology, Division of Cardiometabolic and Endocrine Pharmacology have reviewed the information contained in the sNDA and finds the sNDA acceptable from a clinical pharmacology perspective.

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

No dedicated clinical pharmacology studies were conducted in the current submission. The Applicant collected blood samples in the Phase 3 Study MK-8415-060 to determine etonogestrel concentrations during the Years 3 to 5 of NEXPLANON use. Table 1 shows the mean (± standard deviation) etonogestrel serum concentrations after including data obtained from the Phase 3 study.

Table 1: Etonogestrel serum concentrations after NEXPLANON insertion

Time after insertion	Mean (±standard deviation) Etonogestrel Concentrations [pg/mL]	
	Study 34528[a]	Study MK-8415-060[b]
2 weeks	1200 (± 604)	NA
1 year	202 (± 55)	NA
2 years	164 (± 58)	NA
3 years	138 (± 43)	143 (± 74)
4 years	NA	123 (± 45)
5 years	NA	111 (± 51)

NA = not available
[a]Data contained in the labeling of prior approval; NEXPLANON use duration: 3 years.
[b]Data submitted in this supplement; subjects had used NEXPLANON for 3 years (± 2 weeks) at time of study enrollment.

A post-hoc analysis was performed to assess the potential impact of baseline BMI on etonogestrel serum concentrations among the 215 study treatment completers. No clinically significant differences in the pharmacokinetics of etonogestrel were observed based on BMI (17.4 to 63.9 kg/m^2).

2.2 General Dosing and Therapeutic Individualization

2.2.1 General Dosing

NEXPLANON consists of a single, radiopaque, rod-shaped implant, containing 68 mg etonogestrel, pre-loaded in the needle of a disposable applicator. A single NEXPLANON implant is inserted subdermally just under the skin at the inner side of the non-dominant upper arm for prevention of pregnancy for up to 5 years.

2.2.2 Therapeutic Individualization

N/A.

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

In 12.3 Pharmacokinetics, we recommend (b) (4) the description of etonogestrel concentrations in (b) (4) a table.

In the subsection of Specific Populations, we recommend the following language:

(b) (4)

3 Comprehensive Clinical Pharmacology Review

3.1 General Pharmacology and Pharmacokinetic Characteristics

In the Phase 3 study MK-8415-060, blood samples for determination of etonogestrel serum concentrations were collected at each study visit (every 3 months), from Visit 2 (Month 0 of the extended duration study = 36 months [±2 weeks] implant in situ) to Visit 10 (Month 24 of the extended duration study = 5 years [±2 weeks] implant in situ) from 215 participants who completed Study MK-8415-060 (Table 1). In general, mean etonogestrel serum concentrations declined over the 2-year extended treatment duration from a mean (SD) value of 143.4 (73.89) pg/mL at Year 3 (Visit 2) to 110.7 (51.49) pg/mL at Year 5 (Visit 10). Additionally, etonogestrel serum concentrations had a high variability, with CV% ranging from 36.3% to 51.5% across study visits.

Table 1. Measured etonogestrel concentrations at Visit 2 to Visit 10 in Study MK-8415-060

Visit	Months After NEXPLANON Insertion	Number N	Mean (pg/mL)	SD (pg/mL)	Median (pg/mL)	Range (pg/mL)	CV (%)
Visit 2	36	214	143.4	73.885	129	24.8-832	51.5
Visit 3	39	210	134.2	52.253	123	56.3-464	38.9
Visit 4	42	209	126.9	49.631	113	48.2-292	39.1
Visit 5	45	208	124.5	49.46	115	42.9-312	39.7
Visit 6	48	213	123.3	44.738	113	46.2-289	36.3
Visit 7	51	205	120.8	47.304	111	52.2-324	39.2
Visit 8	54	204	115.9	46.132	106.5	43.3-323	39.8
Visit 9	57	202	113.9	45.548	101.5	47.6-377	40
Visit 10	60	207	110.7	51.492	96.8	33.0-455	46.5

Source: Table 11-16, page 87, MK-8415-060 CSR

The Applicant conducted an analysis to show the difference in drug exposure in subjects with different baseline BMI. The median (range) BMI at baseline for the 215 completers was 27.9 (17.4 to 63.9) kg/m^2. Of the 215 completers, there were 129 participants with a BMI at baseline < 30 kg/m^2 and 86 participants with a BMI at baseline ≥ 30 kg/m^2, 23 of whom had a BMI at baseline ≥ 40 kg/m^2. As shown in Figure 1, mean etonogestrel serum concentrations were lower in participants with a BMI at baseline ≥ 30 kg/m^2 compared with those with a BMI at baseline < 30 kg/m^2.

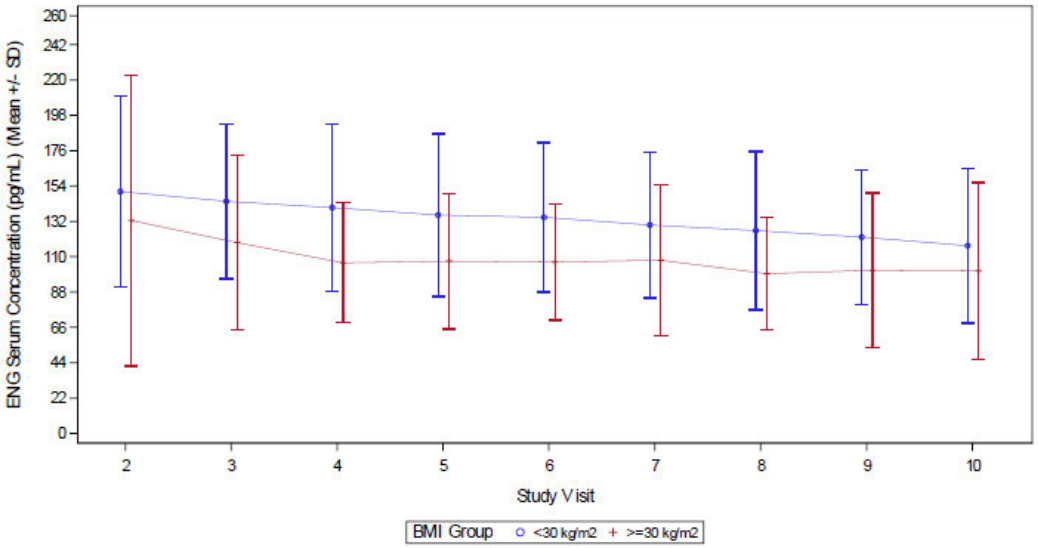

Figure 1. Mean (±SD) Etonogestrel Serum Concentrations over Time From 3 to 5 Years (Visit 2 to Visit 10) by Baseline BMI Category (<30 kg/m^2 vs ≥ 30 kg/m^2) for the Study Treatment Completers Population (n=215).

Source: Figure 2.7.2-contracept5y, page 16, Summary of Clinical Pharmacology Studies.

3.2 Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

The Applicant conducted a Phase 3 trial to evaluate the safety and efficacy of the proposed 5-year use of Nexplanon. Refer to the Clinical Review Team regarding the evidence of effectiveness. Pharmacokinetic samples were collected in the study and the results showed that mean etonogestrel serum concentrations declined over the 2-year extended treatment duration from 143.4 (73.89) pg/mL at Year 3 to 110.7 (51.49) pg/mL at Year 5.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Not applicable.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Not applicable.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Not applicable.

Is the bioanalytical assay for etonogestrel acceptable?

Yes. The Applicant used a validated bioanalytical method to determine etonogestrel concentrations for samples from Study MK-8415-060. The Applicant submitted a validation and bioanalytical report in the submission package. Refer to **Section 4** Appendix for more information.

4 Appendix

The method for quantification of the etonogestrel was originally developed by Merck (Merck PPDM Validation Report No. DM-1016). This method was partially validated at contract research organization (b) (4) and applied to quantify samples from Study MK-8415-060. The analyte was isolated from liquid-liquid extraction after addition of stable isotope labeled internal standards. Detection was done by tandem mass spectrometry in the multiple reaction monitoring mode using the positive ion mode. The summary of bioanalytical method and validation metrics are presented in Table 2.

The bioanalytical methods used are adequately validated.

Table 1. Summary review of bioanalytical methods measuring etonogestrel in human serum.

Parameter	Etonogestrel
Bioanalytical method validation report	201124PVJHM_MWP_R1
Validation assay range (ng/mL)	20 to 2000
QCs (ng/mL)	20, 60, 190, 600, and 1500
Inter-day precision (% CV)	≤ 7.6%
Inter-day accuracy (% Bias)	-6.5 to 1.3
Intra-day precision (% CV)	≤ 9.9%
Intra-day accuracy (% Bias)	-8.0 to 2.5
Reference standard	Lot Number: Lot R138H0 / R138H1
Specificity	No interference observed in the blank matrix
Freeze/thaw stability	5 freeze (-70/-20°C)-thaw (ambient temperature) cycles
Bench-top/process stability	24 hours at room temperature
Long-term storage stability	742 days at -70°C

Source: Validation Report 201124PVJHM_MWP_R1
Abbreviations: CV, coefficient of variation; QC, quality control

Bioanalytical performance for etonogestrel

The concentrations of etonogestrel were determined in a total of 3339 human serum samples obtained from Study MK-8415-060. Four levels of quality controls were analyzed in each run and the results of precision/accuracy met the preset criteria. The period between first sample collection and last sample analysis was 576 days. The established long-term stability of the samples was for 742 days. Samples were analyzed within established long-term stability.

A total of 225 study samples (approximately 7%) were selected for incurred sample reanalysis (ISR). Among them, 98.2% met the predefined criteria of having a difference within ±20% from the initial values.

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