

NDA 218201

NDA APPROVAL

Sebela Women's Health Inc.
Attention: Sandra Matsumoto, PhD, RAC, FRAPS
Vice President, Regulatory Affairs & Clinical Quality
645 Hembree Parkway, Suite I
Roswell, GA 30076

Dear Dr. Matsumoto:

Please refer to your new drug application (NDA) dated and received March 31, 2023, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Miudella (copper intrauterine system).

We acknowledge receipt of your amendment dated May 24, 2024, which constituted a complete response to our January 30, 2024, action letter.

We acknowledge receipt of your major amendment dated November 18, 2024, which extended the goal date by three months.

This NDA provides for the use of Miudella (copper intrauterine system) for prevention of pregnancy in females of childbearing potential for up to 3 years.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.¹ Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Patient Package Insert) as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling*

¹ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

*Technical Qs and As.*²

The SPL will be accessible via publicly available labeling repositories.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling as soon as they are available, but no more than 30 days after they are printed. Submit these labeling electronically according to the guidance for industry *SPL Standard for Content of Labeling Technical Qs & As*. For administrative purposes, designate this submission “**Final Printed Carton and Container Labeling for approved NDA 218201.**” Approval of this submission by FDA is not required before the labeling is used.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Miudella (copper intrauterine system) shall be 24 months from the date of manufacture when stored at 20°C-25°C (68°F-77°F); excursions permitted 15°C - 30°C (59°F - 86°F) [See USP Controlled Room Temperature].

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the Food Drug Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks.

² We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database at: <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Miudella to ensure the benefits of drug outweigh the risk of complications due to improper placement of Miudella including risk of perforation, infection, undiagnosed abnormal bleeding, pregnancy loss (if pregnancy occurs with IUS in situ), and expulsion.

Your proposed REMS must also include the following:

Elements to assure safe use: Pursuant to 505-1(f)(1), we have determined that Miudella can be approved only if elements necessary to assure safe use are required as part of the REMS to mitigate the risk of complications due to improper placement of Miudella including risk of perforation, infection, undiagnosed abnormal bleeding, pregnancy loss (if pregnancy occurs with IUS in situ), and expulsion listed in the labeling of the drug.

Your REMS includes the following elements to mitigate these risks:

- Pharmacies, practitioners, and healthcare settings that dispense the drug are specially certified
- The drug is dispensed to patients only in certain healthcare settings

Implementation System: The REMS must include an implementation system to monitor, evaluate, and work to improve the implementation of the elements to assure safe use (outlined above) that require pharmacies, practitioners, and healthcare settings that dispense the drug be specially certified and the drug be dispensed to patients only in certain health care settings.

Your proposed REMS, submitted on May 24, 2024, amended and appended to this letter, is approved.

The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your REMS must be fully operational before you introduce Miudella into interstate commerce.

The REMS Assessment Plan must include, but is not limited to, the following:

For each metric, provide the two previous, current, and cumulative reporting periods (if applicable) unless otherwise noted.

1. REMS Implementation (for the first REMS Assessment only)
 - a. Date(s) of Miudella REMS launch including:
 - i. The date when the certification process for healthcare settings, healthcare providers who dispense Miudella for insertion, and pharmacies became active.

- ii. The date when wholesalers-distributors were authorized to distribute drug
 - b. Date of first commercial distribution of Miudella
 - c. Date when the REMS Coordinating Center became operational
 - d. Date when the REMS Website became live and fully operational
- 2. REMS Certification Statistics
 - a. Healthcare providers who dispense Miudella for insertion
 - i. Number and percentage of newly certified healthcare providers stratified by professional designation (i.e., Doctor of Medicine (MD), Doctor of Osteopathic Medicine (DO), Physician Assistant (PA), Nurse Practitioner (NP), other [specify])
 - ii. Number and percentage of active (i.e., dispensed Miudella for insertion at least once during the reporting period) healthcare providers stratified by professional designation (i.e., MD, DO, PA, NP, Other [specify])
 - iii. Total number of certified healthcare providers at the end of the reporting period
 - iv. Number of healthcare providers who dispense Miudella for insertion who recertified (i.e., maintained certification)_after two years of inactivity
 - b. Pharmacies that dispense Miudella
 - i. Number and percentage of newly certified pharmacies
 - ii. Number and percentage of active (i.e., dispensed Miudella at least once during the reporting period) pharmacies
 - iii. Total number of certified pharmacies that dispense at the end of the reporting period
 - c. Healthcare settings that dispense Miudella
 - i. Number and percentage of newly certified healthcare settings that dispense Miudella
 - ii. Number and percentage of active (i.e., that received a shipment of Miudella at least once during the reporting period) healthcare settings that dispense Miudella
 - iii. Total number of certified healthcare settings that dispense Miudella at the end of the reporting period

d. Authorized Wholesalers-Distributors

- i. Number of newly contracted wholesalers-distributors
- ii. Number of active (i.e., have shipped Miudella at least once during the reporting period) wholesalers-distributors
- iii. Total number of authorized wholesalers/distributors

e. Post-Training Knowledge Assessment for Healthcare Providers

- i. Number of healthcare providers who successfully completed post-training knowledge assessment.
 1. Method of completion
 2. Descriptive statistics regarding the number of completed knowledge assessments, the number of attempts needed to successfully complete, and the mean/median/range for number of attempts required
- ii. Number of healthcare providers who did not pass the knowledge assessment on one or more attempts.
 1. Method of attempted completion
 2. Number of failed knowledge assessments
 3. Number of incomplete/abandoned knowledge assessments
- iii. A summary of the most frequently missed questions.
- iv. A summary of potential comprehension or perception issues identified with the knowledge assessment (first assessment report only).

3. REMS Operation and Performance Data

a. REMS Coordinating Center

- i. Number and percentage of contacts by type (e.g., healthcare providers, pharmacies, healthcare settings, patients, wholesalers-distributors, other [specify])
- ii. Summary of reasons for call (e.g., certification question, certified pharmacy/healthcare setting list), stratified by participant type (e.g., healthcare provider, pharmacy, healthcare setting, wholesaler-distributor); limit to the top five reasons for call by participant group

4. Utilization

- a. Number of Miudella shipments from wholesalers/distributors stratified by shipment location (i.e., healthcare setting, pharmacy)
- b. Number of Miudella units dispensed by pharmacies
- c. Number of Miudella units dispensed by healthcare settings

5. REMS Compliance

- a. Audits: Summary of audit activities, including but not limited to the following:
 - i. Copy of audit plan for pharmacies that dispense Miudella, healthcare settings that dispense Miudella, and wholesalers-distributors that distribute Miudella
 - ii. Number of audits expected per the REMS Document and number of audits performed.
 - 1. Reasons for any discrepancies between number of audits expected versus performed and any remedial actions taken
 - iii. Number and type (e.g., critical, major, or minor findings) of deficiencies noted
 - 1. Status of corrective and preventive action (CAPA) proposed to address deficiencies, including completion dates
 - 2. For any that did not complete the CAPA within the timeframe specified in the audit plan, describe actions taken
 - iv. Confirmation of documentation of completion of training for relevant staff
 - v. Verification of the existence of documented processes and procedures for complying with the REMS

A comparison of the findings to findings of previous audits and an assessment of whether any trends are observed
- b. Non-compliance: provide a summary of the non-compliance identified, including but not limited to the following:
 - i. A copy of the Non-Compliance Plan, which addresses the criteria for non-compliance for each participant, actions taken to address

non-compliance for each event, and under what circumstances a participant would be suspended or de-certified from the REMS

- ii. The number of instances of non-compliance accompanied by a description of each instance and the reason for the occurrence (if provided). For each instance of non-compliance, report the following information:
 1. The unique identifier(s) (ID(s)) of the participant(s) associated with the non-compliance event or deviation to enable tracking over time
 2. The source of the non-compliance data
 3. The results of the root cause analysis
 4. What action(s) were taken in response and whether any follow-up is planned
- iii. Number and percentage of certified healthcare providers who were identified through program operations and/or audits as non-compliant with the REMS requirements including but not limited to:
 1. Number of certified healthcare providers that had certification suspended or revoked, including the reasons for the action.
 2. Number of healthcare providers who dispensed Miudella for insertion without having recertified (i.e., maintained certification) after two years of inactivity
- iv. Number and percentage of authorized wholesalers-distributors that were non-compliant with the REMS requirements
 1. Number of shipments sent to non-certified pharmacies and/or noncertified healthcare settings. Include the source of the report, corrective actions taken to prevent future occurrences, and the outcome of such actions
- v. Number and percentage of certified pharmacies that were non-compliant with the REMS requirements including but not limited to:
 1. Number of certified pharmacies that had certification suspended or revoked; include the reasons for the action
 2. Number of prescriptions that were dispensed to noncertified healthcare settings. Include the source of the report,

corrective actions taken to prevent future occurrences, and the outcome of such actions

3. Number of times Miudella was loaned or transferred to a noncertified pharmacy. Include the source of the report, corrective actions taken to prevent future occurrences, the outcome of such actions, and disposition of the drug
 4. The number and percentage of pharmacies that were noncompliant with the requirement to dispense Miudella only to certified healthcare settings that dispense Miudella. Stratify the results by number of events per pharmacy
- vi. Number and percentage of certified healthcare settings that were non-compliant with the REMS requirements including but not limited to:
1. Number of certified healthcare settings that had certification suspended or revoked; include the reasons for the action
 2. The number of expected annual verifications of Authorized Representatives of certified healthcare settings and number of completed verifications. Include any follow up that was done (and any corrective actions taken) to address noncompliant participants. For each Assessment Report include the methodology that was used to verify that every healthcare setting had in place and followed all required processes and procedures.
 3. Number of healthcare settings that were noncompliant with the requirement to monitor healthcare providers who are certified to dispense Miudella for insertion and identify providers with a two-year period of inactivity
- vii. The number and percentage of audited healthcare settings that were noncompliant with the requirement to dispense Miudella only to certified healthcare providers who dispense Miudella for insertion. Stratify the results by number of events per healthcare provider and number of events per healthcare setting
- viii. The number and percentage of audited healthcare settings that were noncompliant with the requirement to dispense Miudella only to certified healthcare providers who dispense Miudella for insertion

prior to their first insertion. Stratify the results by number of events per healthcare setting.

- ix. Number and percentage (and 95% confidence interval) of Miudella prescriptions dispensed by audited certified healthcare settings to certified healthcare providers.
- x. Using dispensing data, the number and percentage of Miudella prescriptions dispensed by a certified pharmacy to a certified healthcare setting.
- xi. The data source used to inform each noncompliance metric above is described below:
 - 1. A copy of the Non-Compliance Plan: FDA-reviewed Non-Compliance Plan agreed upon post-approval
 - 2. The number of instances of non-compliance and the reason for the occurrence (if provided): Internal tools used by the Sebela REMS Compliance Committee to record, monitor, and take action upon non-compliance, such as a report of potential non-compliance events identified in program operations or via audits and a corrective and preventative action (CAPA) tracker.
 - 3. Number and percentage of certified healthcare providers that were non-compliant with the REMS requirements: Internal tools used by the Sebela REMS Compliance Committee to record, monitor, and take action upon non-compliance, such as a report of potential non-compliance events identified in program operations or via audits and a corrective and preventative action (CAPA) tracker.
 - 4. Number of certified healthcare providers that had certification suspended or revoked, including the reasons for the action: Internal tools used by the Sebela REMS Compliance Committee to record, monitor, and take action upon non-compliance, such as a report of potential non-compliance events identified in program operations or via audits and a corrective and preventative action (CAPA) tracker.

5. Number and percentage of authorized wholesalers-distributors that were non-compliant with the REMS requirements: Audit reporting, Sebela shipment records, and HCS audit reporting
 6. Number and percentage of certified pharmacies that were non-compliant with the REMS requirements: Contact center records, audit reporting (pharmacies and HCSs); dispense data from pharmacies, and internal tools used by the Sebela REMS Compliance Committee to record, monitor, and take action upon non-compliance, such as a report of potential non-compliance events identified in program operations or via audits and a corrective and preventative action (CAPA) tracker
 7. Number and percentage of audited, certified healthcare settings that were non-compliant with the REMS requirements: Contact center records, audit reporting (pharmacies and HCSs); and internal tools used by the Sebela REMS Compliance Committee to record, monitor, and take action upon non-compliance, such as a report of potential non-compliance events identified in program operations or via audits and a corrective and preventative action (CAPA) tracker
 8. Audit reporting (pharmacies and HCSs); dispense data from pharmacies, and internal tools used by the Sebela REMS Compliance Committee to record, monitor, and take action upon non-compliance, such as a report of potential non-compliance events identified in program operations or via audits and a corrective and preventative action (CAPA) tracker
- xii. For all other non-compliance with the REMS requirements, provide source of non-compliance report, and the corrective action taken

6. Overall Assessment of REMS Effectiveness

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or elements should be modified.

If the information provided in an assessment is insufficient to allow FDA to determine whether the REMS is meeting its goals or whether the REMS must be modified, FDA may require the submission of a new assessment plan that contains the metrics and/or methods necessary to make such a determination. Therefore, FDA strongly recommends obtaining FDA feedback on the details of your proposed assessment plan to ensure its success. To that end, we recommend that methodological approaches, study protocols, other analysis plans and assessment approaches used to assess a REMS program be submitted for FDA review as follows:

Submit your proposed audit plan and non-compliance plan for FDA review within 60 days of this letter.

Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA 218201 REMS ASSESSMENT METHODOLOGY

(insert concise description of content in bold capital letters, e.g.,

ASSESSMENT METHODOLOGY, PROTOCOL, SURVEY METHODOLOGIES, AUDIT PLAN, DRUG USE STUDY)

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A). This assessment should include:

- a) An evaluation of how the benefit-risk profile will or will not change with the new indication;
- b) A determination of the implications of a change in the benefit-risk profile for the current REMS;
- c) *If the new, proposed indication for use introduces unexpected risks:* A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.
- d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* A statement about whether the REMS was meeting its goals at the time of the last assessment and if any modifications of the REMS have been proposed since that assessment.

- e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:*
Provision of as many of the currently listed assessment plan items as is feasible.

- f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including:* Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing a REMS modification, provide a rationale for why the REMS does not need to be modified.*

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 218201 REMS ASSESSMENT

or

**NEW SUPPLEMENT FOR NDA 218201/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION**

or

**NEW SUPPLEMENT FOR NDA 218201/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION**

or

NEW SUPPLEMENT FOR NDA 218201/S-000

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

**PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING
CHANGES SUBMITTED IN SUPPLEMENT XXX**

or

**NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 218201/S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)**

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISION FOR NDA 218201

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

As soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in Structured Product Labeling (SPL) format using the FDA automated drug registration and listing system (eLIST). Content of the REMS document must be identical to the approved REMS document. The SPL will be publicly available.

Information on submitting REMS in SPL format may be found in the guidance for industry *Providing Regulatory Submission in Electronic Format – Content of the Risk Evaluation and Mitigation Strategies Document Using Structured Product Labeling*.

For additional information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulators in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs*.³

³ For the most recent version of a guidance, check the FDA guidance web page at: <https://www.fda.gov/media/128163/download>.

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.⁴ Information and Instructions for completing the form can be found at FDA.gov.⁵

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

Your product is a Part 3 combination product (21 CFR 3.2(e)); therefore, you must also comply with postmarketing safety reporting requirements for an approved combination product (21 CFR 4, Subpart B). Additional information on combination product postmarketing safety reporting is available at FDA.gov.⁶

COMPENDIAL STANDARDS

A drug with a name recognized in the official United States Pharmacopeia or official National Formulary (USP-NF) generally must comply with the compendial standards for strength, quality, and purity, unless the difference in strength, quality, or purity is plainly stated on its label (see FD&C Act § 501(b), 21 USC 351(b)). FDA typically cannot share application-specific information contained in submitted regulatory filings with third parties, which includes USP-NF. To help ensure that a drug continues to comply with compendial standards, application holders may work directly with USP-NF to revise official USP monographs. More information on the USP-NF is available on USP's website⁷.

⁴ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

⁵ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

⁶ <https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products>

⁷ <https://www.uspnf.com/>

If you have any questions, call Dorsa Jalali, Regulatory Project Manager, at 240-402-0543, or dorsa.jalali@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Audrey Gassman, MD
Deputy Director
Division of Urology, Obstetrics, and Gynecology
Office of Rare Diseases, Pediatrics,
Urologic and Reproductive Medicine
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
 - Prescribing Information
 - Patient Package Insert
- Carton and Container Labeling
- REMS

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/

AUDREY L GASSMAN
02/24/2025 01:40:30 PM