Risk Evaluation and Mitigation Strategy (REMS) Document
DSUVIA® (sufentanil) REMS Program

I. Administrative Information

Application Number: NDA 209128
Application Holder: AcelRx Pharmaceuticals, Inc.
Initial REMS Approval: 11/2018
Most Recent REMS Update: 04/2022

II. REMS Goal

The goal of the DSVIA REMS is to mitigate the risk of respiratory depression resulting from accidental exposure by:

- Ensuring that DSVIA is dispensed only to patients in certified medically supervised healthcare settings.

III. REMS Requirements

AcelRx Pharmaceuticals, Inc. must ensure that healthcare settings and wholesalers-distributors comply with the following requirements:

1. Healthcare settings that dispense DSVIA must:

<table>
<thead>
<tr>
<th>To become certified to dispense</th>
<th>1. Be able to manage acute opioid overdose, including respiratory depression.</th>
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<tbody>
<tr>
<td></td>
<td>2. Designate an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS Program on behalf of the healthcare setting.</td>
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<td>3. Have the authorized representative enroll in the REMS Program by completing the Healthcare Setting Enrollment Form and submitting it to the REMS Program.</td>
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<td>4. Train all relevant staff that DSVIA must not be dispensed for use outside of the certified healthcare setting.</td>
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<td>5. Train all relevant staff involved in administration of DSVIA to refer to the Directions for Use prior to administration.</td>
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6. Establish processes and procedures to verify that DSUVIA is not dispensed for use outside of the certified healthcare setting.

To maintain certification to dispense

7. Have a new authorized representative enroll in the REMS Program by completing the Healthcare Setting Enrollment Form if the authorized representative changes.

At all times

8. Not dispense DSUVIA for use outside the certified healthcare setting.

9. Not distribute, transfer, loan or sell DSUVIA.

10. Maintain records of staff training.

11. Maintain records of all processes and procedures including compliance with those processes and procedures.

12. Comply with audits by AcelRx Pharmaceuticals, Inc. or a third party acting on behalf of AcelRx Pharmaceuticals, Inc. to ensure that all processes and procedures are in place and are being followed.

2. Wholesalers-distributors that distribute DSUVIA must:

To be able to distribute

1. Establish processes and procedures to ensure that DSUVIA is distributed only to certified healthcare settings.

2. Train all relevant staff involved in distributing DSUVIA on the processes and procedures to verify the healthcare settings are certified.

At all times

3. Distribute only to certified healthcare settings.

4. Maintain and submit records of all shipments of DSUVIA to AcelRx Pharmaceuticals, Inc.

5. Comply with audits carried out by AcelRx Pharmaceuticals, Inc. or a third party acting on behalf of AcelRx Pharmaceuticals, Inc. to ensure that all processes and procedures are in place and are being followed.

To support REMS Program operations, AcelRx Pharmaceuticals, Inc. must:

1. Establish and maintain a REMS Program website, www.DSUVIAREMS.com. The REMS Program website must include the capability to complete healthcare setting certification online and, the option to print the Prescribing Information, Directions for Use, and REMS materials. All product websites for consumers and healthcare providers must include prominent REMS-specific links to the REMS Program website. The REMS Program website must not link back to the promotional product website.

2. Make the REMS Program website fully operational and all REMS materials available through website and call center by the date DSUVIA is first commercially distributed.
3. Establish and maintain a REMS Program call center for REMS participants at 1-855-925-8476.

4. Establish and maintain a validated, secure database of all REMS participants who are certified in the DSUVIA REMS.

5. Ensure healthcare settings are able to enroll by fax, mail, and online.

6. Provide Healthcare Setting Enrollment Form and the Prescribing Information to healthcare settings that (1) attempt to order DSUVIA and are not yet certified or (2) inquire about how to become certified.

7. Notify healthcare settings, confirming certification, within 7 calendar days after they become certified in the REMS Program.

8. Provide wholesalers-distributors access to the database of certified healthcare settings.

**To ensure REMS participants’ compliance with the REMS Program, AcelRx Pharmaceuticals, Inc. must:**

9. Verify annually that the authorized representative’s name and contact information correspond to those of the current designated authorized representative for the healthcare setting. If different, the healthcare setting must be required to re-certify with a new authorized representative.

10. Maintain adequate records to demonstrate that REMS requirements have been met, including, but not limited to records of: DSUVIA distribution; certification of healthcare settings; and audits of REMS participants.

11. Establish a plan for addressing noncompliance with REMS Program requirements.

12. Monitor healthcare settings and wholesaler-distributors on an ongoing basis to ensure the requirements of the REMS are being met. Take corrective action if non-compliance is identified, including de-certification.

13. Annually audit all certified healthcare settings, or a maximum of 400, that have received at least one shipment of DSUVIA in the past 6 months to ensure that all REMS processes and procedures are in place, functioning, and support the REMS Program requirements.

14. Audit wholesalers-distributors no later than 90 calendar days after they become authorized to distribute the drug or from the date DSUVIA is first commercially distributed (whichever is later) to ensure that all REMS processes and procedures are in place, functioning, and support the REMS Program requirements.

15. Take reasonable steps to improve operation of and compliance with the requirements in the DSUVIA REMS Program based on monitoring and evaluation of the DSUVIA REMS Program.
IV. REMS Assessment Timetable

AcelRx Pharmaceuticals, Inc. must submit REMS Assessments at 6 months, 12 months, and annually thereafter from the date of the initial approval of the REMS (11/02/2018). To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 calendar days before the submission date for that assessment. AcelRx Pharmaceuticals, Inc. must submit each assessment so that it will be received by the FDA on or before the due date.

V. REMS Materials

The following materials are part of the DSUVIA REMS:

Enrollment Forms

Healthcare Setting:

1. Healthcare Setting Enrollment Form

Other Materials

2. REMS Program Website
DSUVIA® REMS

DSUVIA (sufentanil sublingual tablet 30 mcg) is only available through the DSUVIA Risk Evaluation and Mitigation Strategy (REMS). DSUVIA can only be dispensed and/or administered in healthcare settings that are enrolled in the REMS.

To enroll your healthcare setting,

1) Designate an Authorized Representative (e.g. Pharmacy and Therapeutics Chair, Pharmacy Director, Medical Director, Medical Chief-of-Staff, Director of Nursing, etc.)

2) Complete, sign, and submit this **Healthcare Setting Enrollment Form** to the DSUVIA REMS.

Once your healthcare setting is officially enrolled, a notification will be provided to the Authorized Representative.

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**HEALTHCARE SETTING AGREEMENT**

I am the Authorized Representative designated by my healthcare setting to coordinate the certification process and oversee implementation of and compliance with the REMS. By signing this form, I agree to comply, on behalf of my healthcare setting, with the following REMS requirements:

- I am authorized to complete the **Healthcare Setting Enrollment Form** and submit it to the REMS Program on behalf of this healthcare setting.

- This healthcare setting is able to manage acute opioid overdose, including respiratory depression.

- This healthcare setting must not dispense DSUVIA for outpatient use.
  - Train all relevant staff that DSUVIA must not be dispensed for use outside of this healthcare setting.
  - Establish processes and procedures to verify that DSUVIA is not dispensed for use outside of this healthcare setting.

- This healthcare setting must train all relevant staff involved in administration of DSUVIA to read the Directions for Use prior to administering DSUVIA.

- This healthcare setting must not distribute, transfer, loan, or sell DSUVIA.

- This healthcare setting must maintain records of staff training and of all processes and procedures including compliance with those processes and procedures.

- This healthcare setting must comply with audits by AcelRx Pharmaceuticals, Inc. or a third party acting on behalf of AcelRx Pharmaceuticals, Inc. to ensure that all processes and procedures are in place and are being followed for the DSUVIA REMS. Failure to comply may result in decertification of the healthcare setting.

- If the Authorized Representative changes, this healthcare setting will have a new Authorized Representative enroll in the REMS by completing the **Healthcare Setting Enrollment Form**.

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**AUTHORIZED REPRESENTATIVE INFORMATION**

Signature: ___________________________ Date: ___________________________

Printed Name, Credentials: ___________________________ Title: ___________________________

Phone Number: ___________________________ Fax Number: ___________________________

Email Address: ___________________________ Preferred Method of Communications: [ ] EMAIL [ ] FAX

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**HEALTHCARE SETTING INFORMATION**

Name: ___________________________

Street Address: ___________________________ City: ___________________________

State: ___________________________ ZIP: ___________________________ DEA License Number: ___________________________

Reference ID: 4972271
If you have any questions or require additional information or further copies of DSUVIA REMS materials, please visit www.DSUVIDSUVIAREMS.com, or contact the DSUVIA REMS at:

AcelRx Pharmaceuticals, Inc.
Attn: REMS Administrator
25821 Industrial Blvd, Suite 400
Hayward, CA 94545

Phone: 1-855-925-8476
Email: DSUVIAREMS@acelrx.com
Fax: (650) 649-1855

This form is part of an FDA-approved REMS. For more information about DSUVIA, please see Prescribing Information, including Boxed Warnings.
Risk Evaluation and Mitigation Strategy (REMS)

What is the DSUVIA REMS (Risk Evaluation and Mitigation Strategy)?

A REMS is a risk management plan that is put into place if a drug is determined to be at risk of serious health risks. The DSUVIA REMS is intended for prolonged delivery only by a healthcare provider. DSUVIA is available only through a Risk Evaluation and Mitigation Strategy called the DSUVIA REMS in order to prevent respiratory depression resulting from accidental exposure.

What are the DSUVIA REMS requirements?

Healthcare settings that dispense DSUVIA must:

1. Be in a management or a clinical setting, including a pharmacy.
2. Designate a designated representative to carry out the certification process and implementation and compliance with the REMS. This person must be qualified by the Healthcare Setting's pharmaceutical compliance team.
3. Have all staff, including the designated representative, access to the DSUVIA REMS program.
4. Be familiar with and agree to comply with the DSUVIA REMS Program by completing the Healthcare Setting Enrollment Form.
5. Not allow DSUVIA to be used outside of a certified healthcare setting.
6. Maintain records of all training on and use of DSUVIA.
7. Train all relevant staff in the use of DSUVIA.
8. Establish processes and procedures to verify that DSUVIA is not dispensed for use outside of the certified healthcare setting.
9. Train new or substituted healthcare providers on the DSUVIA REMS.
10. Maintain record of all training on and use of DSUVIA.
11. Comply with audits by local pharmaceutical compliance teams to ensure that all processes and procedures are in place and being followed.

How does my healthcare setting become certified in the DSUVIA REMS?

To become certified in the DSUVIA REMS, healthcare settings must:

1. Sign and submit a Healthcare Setting Enrollment Form.
2. Ensure that all staff involved in the use of DSUVIA have completed the appropriate training.
3. Maintain records of all training on and use of DSUVIA.
4. Comply with all local pharmaceutical compliance requirements.

Healthcare Setting Resources

DSUVIA is only available through the DSUVIA Risk Evaluation and Mitigation Strategy (REMS) developed by AcelRx Pharmaceuticals, Inc. DSUVIA certified healthcare settings must complete the DSUVIA REMS in order to become certified to dispense DSUVIA. This section includes important product information.

Product Information:

Indications and Usage

DSUVIA is indicated for use in adults in a medically supervised healthcare setting, such as a hospital, and emergency department, for up to seven days to manage severe pain in a setting where the patient cannot self-administer opioids in order to prevent opioid misuse, opioid overdose, and opioid-related mortality.

Contraindications:

DSUVIA is contraindicated in the following circumstances:

1. Hypersensitivity to the active ingredient,
2. Known or suspected opioid abuse or addiction,
3. Known or suspected concurrent use of an opioid agonist or agonist-antagonist analgesic, and
4. Known or suspected concurrent use of an opioid antagonist.

Adverse Reactions Reporting:

AcellRx Pharmaceuticals, Inc. is committed to patient safety. To report suspected adverse reactions with DSUVIA, please:

- Refer to the DSUVIA REMS for the Healthcare Setting’s administrative and compliance processes.
- Visit the DSUVIA REMS website for additional information.
- Call 1-800-FDA-1088 to report a suspected adverse reaction.
- Email ACELRX.PHARMACUS@ACELRX.COM.
- Report the suspected adverse reaction to the FDA through the MedWatch program at: www.fda.gov/medwatch or call 1-800-FDA-1088.
DSUVIA® REMS Healthcare Setting Enrollment Form

DSUVIA (sufentanil sublingual tablet 30 mcg) is only available through the DSUVIA Risk Evaluation and Mitigation Strategy (REMS). DSUVIA can only be dispensed and/or administered in healthcare settings that are enrolled in the REMS.

To enroll your healthcare setting,

1) Designate an Authorized Representative (e.g. Pharmacy and Therapeutics Chair, Pharmacy Director, Medical Director, Medical Chief-of-Staff, Director of Nursing, etc.)

2) Complete, sign, and submit this Healthcare Setting Enrollment Form to the DSUVIA REMS.

Once your healthcare setting is officially enrolled, a notification will be provided to the Authorized Representative.

HEALTHCARE SETTING AGREEMENT

I am the Authorized Representative designated by my healthcare setting to coordinate the certification process and oversee implementation of and compliance with the REMS. By signing this form, I agree to comply, on behalf of my healthcare setting, with the following REMS requirements:

• I am authorized to complete the Healthcare Setting Enrollment Form and submit it to the REMS Program on behalf of this healthcare setting.

• This healthcare setting is able to manage acute opioid overdose, including respiratory depression.

• This healthcare setting must not dispense DSUVIA for outpatient use.
  ◦ Train all relevant staff that DSUVIA must not be dispensed for use outside of this healthcare setting.
  ◦ Establish processes and procedures to verify that DSUVIA is not dispensed for use outside of this healthcare setting.

• This healthcare setting must train all relevant staff involved in administration of DSUVIA to read the Directions for Use prior to administering DSUVIA.

• This healthcare setting must not distribute, transfer, loan, or sell DSUVIA.

• This healthcare setting must maintain records of staff training and of all processes and procedures including compliance with those processes and procedures.

• This healthcare setting must comply with audits by AcelRx Pharmaceuticals, Inc. or a third party acting on behalf of AcelRx Pharmaceuticals, Inc. to ensure that all processes and procedures are in place and are being followed for the DSUVIA REMS. Failure to comply may result in decertification of the healthcare setting.

• If the Authorized Representative changes, this healthcare setting will have a new Authorized Representative enroll in the REMS by completing the Healthcare Setting Enrollment Form.

AUTHORIZED REpresentative INFORMATION

Signature: __________________________ Date: __________________________
Printed Name, Credentials: __________________________ Title: __________________________
Phone Number: __________________________ Fax Number: __________________________
Email Address: __________________________ Preferred Method of Communications: ☐ EMAIL ☐ FAX

HEALTHCARE SETTING INFORMATION

Name: __________________________
Street Address: __________________________ City: __________________________
State: __________________________ ZIP: __________________________ DEA License Number: __________________________
If you have any questions or require additional information or further copies of DSUVIA REMS materials, please visit www.DSUVIAREMS.com, or contact the DSUVIA REMS at:

AcelRx Pharmaceuticals, Inc.
Attn: REMS Administrator
25821 Industrial Blvd, Suite 400
Hayward, CA 94545

Phone: 1-855-925-8476
Email: DSUVIAREMS@acelrx.com
Fax: (650) 649-1855

This form is part of an FDA-approved REMS. For more information about DSUVIA, please see Prescribing Information, including Boxed Warnings.
Please review & sign your document. To begin the process of reviewing and signing your documents, please click the button below. Signing will not be complete until you have reviewed the agreement and you have confirmed your signature.

Please review the documents below.

DSUVIA® REMS

DSUVIA (etorphine hydrobromide, 30 mg) is only available through the DSUVIA® REMS exclusion and mitigation strategy (REMS). DSUVIA cannot be dispensed and/or administered in healthcare settings that are not enrolled in the REMS.

To enroll in a healthcare setting:
1. Designate an Authorized Representative (Pharmacy and Therapeutics Chair, Pharmacy Director, Medical Director, Medical Chief of Staff, Director of Nursing, etc.)
2. Complete, sign, and submit the Healthcare Setting Enrollment Form to the DSUVIA REMS.

Once your healthcare setting has officially enrolled, a notification will be provided to the Authorized Representative.

HEALTHCARE SETTING AGREEMENT

I am the Authorized Representative delegated by my healthcare setting to coordinate the contribution process and oversee implementation of data compliance with the DSUVIA® REMS. By signing this form, I agree to comply on behalf of my healthcare setting, with the following REMS requirements:

• I am authorized to complete the Healthcare Setting Enrollment Form and submit it to the REMS Program on behalf of this healthcare setting.
• This healthcare setting is able to manage DSUVIA product stewardship, including respiratory depression.
• The healthcare setting must not dispense DSUVIA to patients who:
  - Have all emergency staff that DSUVIA must not be dispensed for that patient at this healthcare setting.
  - Establish an internal procedure to ensure that DSUVIA is not dispensed for non-eligible patients at healthcare settings.
• This healthcare setting must have all eligible staff trained on the use of DSUVIA and trained to refer DSUVIA to the Director for the product administrator (DSUVIA).
• This healthcare setting must maintain records of all processes and procedures including compliance with these processes and procedures.
• This healthcare setting must comply with audits by Atracle Pharmaceuticals, Inc., or a designee acting on behalf of Atracle Pharmaceuticals, Inc., for all processes and procedures including compliance with these processes and procedures.
• If the Authorized Representative or changes, this healthcare setting will address these changes in the DSUVIA REMS by completing the Healthcare Setting Enrollment Form.

AUTHORIZED REPRESENTATIVE INFORMATION
Please review the documents below.

DSUVIA REMS Healthcare Setting Enrollment Form

DSUVIA sublingual tablet 30 mcg is only available through the DSVIA Risk Evaluation and Mitigation Strategy (REMS). DSVIA can only be dispensed and/or administered in healthcare settings that are enrolled in the REMS.

To enroll your healthcare setting:
1) Designate an Authorized Representative (e.g., Pharmacy and Therapeutics Chair, Pharmacy Director, Medical Director, Medical Chief of Staff, Director of Nursing, etc.)
2) Complete, sign, and submit this Healthcare Setting Enrollment Form to the DSVIA REMS.

Once your healthcare setting is officially enrolled, notification will be provided to the Authorized Representative.

HEALTHCARE SETTING AGREEMENT

I, the Authorized Representative designated by my healthcare setting to coordinate the certification process and oversee implementation of and compliance with the REMS, by signing this form, agree to comply on behalf of this healthcare setting, with the following REMS requirements:

1. I am authorized to complete the Healthcare Setting Enrollment Form and submit it to the REMS Program on behalf of this healthcare setting.
2. The healthcare setting is able to manage acute opioid overdose, including resuscitation.
3. This healthcare setting must not dispense DSVIA for outpatient use.
4. The healthcare setting must not distribute, transfer, loan, or sell DSVIA.
5. The healthcare setting must maintain records of staff training and all processes and procedures including compliance with these processes and procedures.
6. The healthcare setting must comply with audits by AccelRx Pharmacovigilance, Inc., or a third party acting on behalf of AccelRx Pharmacovigilance, Inc. to ensure that all processes and procedures are in place and are being followed for the DSVIA REMS. Failure to comply may result in decertification of the healthcare setting.
7. If the Authorized Representative changes, this healthcare setting will have a new Authorized Representative enroll in the REMS by completing the Healthcare Setting Enrollment Form.

AUTHORIZED REPRESENTATIVE INFORMATION

Signature: ____________________________ Date: ____________________________

Printed Name, Credential: ____________________________

Phone Number: ____________________________ Fax Number: ____________________________

Email Address: ____________________________ Preferred Method of Communication: [ ] EMAIL [ ] FAX

HEALTHCARE SETTING INFORMATION

Name: ____________________________

Street Address: ____________________________ City: ____________________________

State: ____________________________ ZIP: ____________________________ DEA License Number: ____________________________

Reference ID: 4972271
Please review the documents below.

If you have any questions or require additional information or further copies of DSUVIA REMS materials, please visit www.DSVIAAREMS.com or contact the OSUVIA REMS at:
Acellix Pharmaceuticals, Inc.
28621 Industrial Blvd, Suite 400
Haywood, CA 94545

Ph: 1-855-823-8476
Email: DSUVIAHSA@acellix.com
Fax: 650-641-9857

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