NDA 22-266 ONSOLIS™ (fentanyl buccal soluble film)

Opioid Analgesic

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RISK EVALUATION AND MITIGATION STRATEGY (REMS)

FOCUS™ Program for ONSOLIS™

I. GOALS

The goal of the FOCUS™ Program for ONSOLIS™ is to mitigate the risk of ONSOLIS™ overdose, abuse, addiction, and serious complications due to medication errors by:

1. Helping to assure proper patient selection, including avoidance of the use of ONSOLIS™ in opioid non-tolerant patients;
2. Reducing the risk of exposure to ONSOLIS™ in persons for whom it was not prescribed, including accidental exposure in children; and
3. Training prescribers, pharmacists, and patients about proper dosing and administration.

II. REMS ELEMENTS

A. Medication Guide

A Medication Guide for ONSOLIS™ (MG) is dispensed with each prescription for ONSOLIS™ in accordance with 21CFR208.24 and by the Healthcare Provider (HCP) as described below.

ONSOLIS™ is packaged as individual films in child-resistant foil packages. The foil packages are supplied in cartons containing 30 films. Three copies of the MG are distributed with every 30-film carton of ONSOLIS™. One copy is included as part of the Prescribing Information for ONSOLIS™ (PI) and two extra copies are separated from the combined PI/MG by perforations. If fewer than 30-films are dispensed, the FOCUS™ pharmacist separates a perforated MG and supplies it to the patient with their ONSOLIS™. FOCUS™ pharmacies are also provided with additional copies of the MG to ensure that every patient receives a MG with each prescription.

Please see the appended MG.

B. Communication Plan

In accordance with the United States (US) federal Food, Drug, and Cosmetic Act (FDCA) 505-1(e)(3), BioDelivery Sciences International, Inc. (BDSI) will execute a communication plan to HCPs to support implementation of the FOCUS™ Program for the first year following approval of the NDA for ONSOLIS™.

The HCPs include Pain Management Specialists (comprised of Anesthesiologists, Physical Medicine and Rehabilitation Physicians, and General Practitioners), Oncologists, Oncology Nurse Practitioners who treat breakthrough pain in patients with cancer, and physicians and other appropriately licensed HCPs who prescribe oral transmucosal fentanyl products. These HCPs will receive the following FOCUS™ Program material:

1. Dear Prescriber Letter (provided at product launch).

C. Elements to Assure Safe Use

1. Healthcare providers who <u>prescribe</u> ONSOLIS™ are specially certified under FDCA 505-1(f)(3)(A)

a. BDSI will ensure that physicians and other appropriately licensed HCPs who prescribe ONSOLIS™ are specially certified. To become certified, each prescriber will be educated and enrolled in the FOCUS™ Program.

The FOCUS™ Program prescriber education and enrollment process is comprised of the following steps that must be completed prior to prescribing ONSOLIS™:

1. The prescriber reviews the educational materials (Website Educational Materials or Printed Educational Materials).
2. The prescriber completes and signs the Prescriber Enrollment Form (including Prescriber Knowledge Assessment) and faxes it to the FOCUS™ Program. In signing the Prescriber Enrollment Form, each prescriber is required to indicate they understand that ONSOLIS™ is available only through the FOCUS™ Program, that they must comply with program requirements, and acknowledge that:
   i. I have reviewed the Prescribing Information for ONSOLIS™ and the educational materials for the FOCUS™ Program. I have completed the Prescriber Knowledge Assessment, and I understand the risks and benefits of chronic opioid therapy.
   ii. I understand that ONSOLIS™ can be abused and this should be considered when prescribing or dispensing ONSOLIS™ in situations where I am concerned about an increased risk of misuse, abuse, or overdose, whether accidental or intentional.
   iii. I understand that ONSOLIS™ is indicated only for the management of breakthrough pain in patients with cancer, 18 years of age and older, who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.

iv. I understand that ONSOLIS™ is not bioequivalent with any other oral transmucosal fentanyl citrate product and therefore should not be converted from other oral transmucosal fentanyl citrate products on a microgram-per-microgram basis.

v. I will prescribe ONSOLIS™ to patients only after obtaining a signed FOCUS™ Program for ONSOLIS™ Patient Enrollment Form for each patient that documents the following safe use conditions:

a) Patients have been using around-the-clock opioid analgesia for at least 1 week;

b) Patients are opioid tolerant: patients considered opioid tolerant are those who are regularly taking at least: 60 mg oral morphine/day, 25 mcg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day, or an equianalgesic dose of another opioid for one week or longer;

c) Patients or legally authorized representatives have been counseled about the risks and benefits and appropriate use of ONSOLIS™, and about the risk of overdose due to giving ONSOLIS™ to someone for whom it has not been prescribed as described in the Medication Guide for ONSOLIS™; and

d) Patients or legally authorized representatives have been provided and reviewed the Medication Guide for ONSOLIS™.

vi. I will provide a completed, signed copy of the patient enrollment form for each patient to the FOCUS™ Program for ONSOLIS™.

vii. I will promptly respond to requests for additional information from the FOCUS™ Program.

3. A FOCUS™ Program professional reviews the form, requests any missing or illegible information, and, when the necessary forms have been verified to be accurate and complete (including successful completion of the Prescriber Knowledge Assessment), the prescriber is notified of activation.

b. BDSI will maintain a database containing a list of all enrolled prescribers and their status (ie, active or inactive) to help ensure that ONSOLIS™ is only prescribed by active prescribers.

c. Upon initial activation, prescribers remain active until a corrective action of inactivation occurs or expiration of the enrollment period. BDSI will monitor education and enrollment requirements for prescribers and may inactivate non-compliant prescribers.

d. If a previously active prescriber becomes inactive, the prescriber will become active again by successfully completing the standard prescriber education and enrollment (including Prescriber Knowledge Assessment) process in its entirety.

e. While a prescriber is inactive, prescriptions from that prescriber can no longer be filled by the FOCUS™ Program. If the prescriber is providing care for patients using ONSOLIS™ at the time of prescriber inactivation, it is the prescriber's responsibility to ensure that the patients continue to receive appropriate pain medication, either an alternate medication or via referral to another prescriber in the FOCUS™ Program.

f. Prescribers are re-educated (complete review of all educational materials) and re-enrolled (including Prescriber Knowledge Assessment) following substantial changes to the FOCUS™ Program or at least every 2 years. Substantial changes to the FOCUS™ Program are defined as:

    1. changes to the operation of the FOCUS™ Program that affect the manner in which eligible prescribers and patients are identified and screened for enrollment;
    2. changes to the PI and MG that require modification of the educational materials; or
    3. changes that modify the operation of the FOCUS™ Program in a way that changes FOCUS™ Program procedures for the prescriber or patient.

g. In addition, prescribers who write a prescription for ONSOLIS™ and have not written a prescription for ONSOLIS™ to any patient, or enrolled/re-enrolled in the FOCUS™ Program, within the last year will receive a telephone call from a FOCUS™ Program professional reminding them of the prescriber responsibilities under the FOCUS™ Program and asking if they have any questions.

h. The following prescriber materials are part of the REMS and are appended:

    1. Healthcare Professional Program Overview;
    2. Prescriber Enrollment Form (including Prescriber Knowledge Assessment);
    3. Website Educational Materials;
    4. Printed Educational Materials; and
    5. Dear Prescriber Letter.

2. ONSOLIS™ will only be dispensed by particular pharmacies under 505-1(f)(3)(C) that are specially certified under FDCA 505-1(f)(3)(B)

a. BDSI will ensure that ONSOLIS™ is dispensed from certified pharmacies via a secure, traceable courier only. ONSOLIS™ will not be available in other healthcare settings, such as retail outlet pharmacies or hospitals. To become certified, pharmacies will be educated and enrolled in the FOCUS™ Program.

The FOCUS™ pharmacy education and enrollment process is comprised of the following steps that must be completed prior to receiving ONSOLIS™ inventory for dispensing:

    1. The Pharmacist-in-Charge reviews the pharmacy, practitioner, or healthcare setting materials (Website Educational Materials or Printed Educational Materials and Dear Pharmacist Letter).

2. The Pharmacist-in-Charge completes and signs the Pharmacy Enrollment Form and faxes it to the FOCUS™ Program. In signing the Pharmacy Enrollment Form, the Pharmacist-in-Charge is required to indicate they understand that ONSOLIS™ is available only through the FOCUS™ Program, agree to comply with program requirements, and acknowledge that:
   i. I will ensure and document that all pharmacy staff who will process or dispense prescriptions for ONSOLIS™ are trained about the FOCUS™ Program for ONSOLIS™ procedures and educational materials. This training documentation is subject to audit.
   ii. I will ensure that pharmacy staff dispense ONSOLIS™ only after confirming (via FOCUS™ Program database authorization) that patients have met the following safe use conditions:
      a) Patients have been enrolled in the program, based on a valid prescription from an active prescriber;
      b) Patients or legally authorized representatives have been counseled regarding the importance of being on an around-the-clock opioid regimen for an adequate amount of time to ensure that they are opioid tolerant. Patients considered opioid tolerant are those who are regularly taking at least: 60 mg oral morphine/day, 25 mcg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day, or an equianalgesic dose of another opioid for one week or longer; and
      c) Patients or legally authorized representatives have been counseled on appropriate ONSOLIS™ product use.
   iii. I will ensure that pharmacy staff provide a Medication Guide for ONSOLIS™ to every patient each time a prescription is dispensed.
   iv. I will ensure that pharmacy staff will not substitute ONSOLIS™ for any other oral transmucosal fentanyl citrate product.
   v. I will provide reports of ONSOLIS™ prescription activity to the FOCUS™ Program for ONSOLIS™.
   vi. I will permit a program-related audit of my pharmacy to establish that ONSOLIS™ is dispensed only after documenting the above safe use conditions.
3. A FOCUS™ Program professional reviews the form, requests any missing or illegible information, and, when the form has been verified to be accurate and successfully completed, the pharmacy is notified of activation.

4. The FOCUS™ Program prescription process is comprised of the following steps:
   i. Prescriber faxes the initial prescription information for ONSOLIS™ to the FOCUS™ Program to start the verification process.
   ii. Prescriber sends the original, hardcopy prescription for ONSOLIS™ to a FOCUS™ pharmacy via courier using the supplied, pre-paid shipping label/airbill for a FOCUS™ Program courier.
   iii. The following FOCUS™ pharmacy steps generally may be completed while the original, hardcopy prescription is in transit:
      a) Confirm accuracy of prescription;
      b) Ensure that the patient and prescriber are active in the FOCUS™ Program database, the patient is enrolled through the current prescriber, and the FOCUS™ Program patient counseling call has been successfully completed. A unique FOCUS™ Program database authorization number will be issued to allow fulfillment of the prescription;
      c) Schedule ONSOLIS™ delivery to the patient;
      d) Prepare, label, and check the medication;
      e) Provide standard pharmacy practice fulfillment quality assurance check; and
      f) Ensure that a MG is enclosed in the package.
   iv. Upon receipt of the original, hardcopy prescription, the FOCUS™ pharmacy dispenses ONSOLIS™ and delivers the medication directly to the patient via a secure, traceable courier (with adult signature required).

b. BDSI will maintain a database containing a list of all enrolled FOCUS™ pharmacies and their status (ie, active or inactive) to help ensure that ONSOLIS™ is only dispensed by active FOCUS™ pharmacies.

c. Upon initial activation, FOCUS™ pharmacies remain active until a corrective action of inactivation occurs or expiration of the enrollment period.

d. If a previously active FOCUS™ pharmacy becomes inactive, the FOCUS™ pharmacy will become active again by completing the standard FOCUS™ pharmacy education and enrollment process in its entirety.

e. FOCUS™ pharmacies are re-educated (complete review of all educational materials) and re-enrolled following substantial changes to the program or at least every 2 years. Substantial changes to the FOCUS™ Program are defined as:
   1. changes to the PI and MG that require modification of the educational materials; or
   2. changes that modify the operation of the FOCUS™ Program in a way that changes FOCUS™ Program procedures for FOCUS™ pharmacies.

f. The following pharmacy materials are part of the REMS and are appended:

1. Healthcare Professional Program Overview;
2. Pharmacy Enrollment Form;
3. Website Educational Materials;
4. Printed Educational Materials; and
5. Dear Pharmacist Letter.

3. ONSOLIS™ will be dispensed to patients with evidence or other documentation of safe-use conditions under FDCA 505-1(f)(3)(D)

a. BDSI will ensure that each patient treated with ONSOLIS™ is counseled and enrolled in the FOCUS™ Program for documentation of safe use conditions.

The FOCUS™ Program patient counseling and enrollment process is comprised of the following steps that must be completed prior dispensing the patient's first prescription of ONSOLIS™:

1. The prescriber counsels the patient on the MG.
2. The prescriber and patient complete and sign the Patient Enrollment Form and the prescriber faxes it to the FOCUS™ Program. In signing the Patient Enrollment Form, prescribers are required to acknowledge that:
   i. This patient being prescribed ONSOLIS™ is opioid tolerant: patients considered opioid tolerant are those who are regularly taking at least: 60 mg oral morphine/day, 25 mcg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day, or an equianalgesic dose of another opioid for one week or longer.
   ii. This patient has been using around-the-clock opioid analgesia for at least 1 week.
   iii. This patient or a legally authorized representative has been counseled about the risks and benefits and appropriate use of ONSOLIS™, and about the risks of overdose due to giving ONSOLIS™ to someone for whom it has not been prescribed as described in the Medication Guide for ONSOLIS™.
   iv. I have provided and reviewed the Medication Guide for ONSOLIS™ with this patient or a legally authorized representative.
3. In signing the Patient Enrollment Form, patients being prescribed ONSOLIS™ or a legally authorized representative are required to acknowledge that:
   i. My prescriber gave me a copy of the Medication Guide for ONSOLIS™ and reviewed it with me. I have asked my prescriber all the questions I have about ONSOLIS™. I will ask my prescriber if I have any additional questions in the future about the use of ONSOLIS™.
   ii. I understand that there can be serious risks, especially if I do not take ONSOLIS™ as directed.

iii. I understand that I must be regularly using another opioid ("narcotic") pain medicine for my constant pain. This is important because my body must become used to opioid medicine before I can take ONSOLIS™ (I am "opioid tolerant").

iv. I agree that I will never give ONSOLIS™ to anyone else, even if they have the same symptoms, since it may harm them or even cause death.

v. I will store ONSOLIS™ in a safe place away from children because accidental use by a child is a medical emergency and can result in death.

vi. I have reviewed the Patient Authorization for Disclosure and Use of Health Information Statement and I agree to its terms and conditions to authorize my healthcare providers and health plans to disclose my personal and medical information to BioDelivery Sciences International, Inc. (BDSI; sponsor)/MEDA Pharmaceuticals Inc. (Meda; licensee) and their agents and contractors, to the extent permitted by applicable law.

4. A FOCUS™ Program professional reviews the form and requests any missing or illegible information.

5. Trained staff at the FOCUS™ Program call center counsels the patient using scripted interactions.

6. When the previous steps have been successfully completed, the prescriber and pharmacy are notified of patient activation.

b. The patient will be counseled by the prescriber and personally sign the enrollment form unless they are unable to act on their own behalf. For incapacitated patients, the patient counseling and enrollment can be provided to, and the enrollment form can be signed by, the patient's legally authorized representative or medical guardian. A patient's prescription for ONSOLIS™ may be delivered to a designated caregiver or family member of the patient. At the time of enrollment, the patient will be counseled by the FOCUS™ Program professional.

c. The FOCUS™ Program database assigns each patient a unique identification number and maintain a list of all enrolled patients and their status (ie, active or inactive) to help ensure that ONSOLIS™ is only dispensed to active patients.

d. Upon initial activation, patients remain active until a trigger for inactivation occurs or expiration of the enrollment period. Triggers for patient inactivation include: a prescription has not been filled for more than 3 months; the patient receives prescriptions for ONSOLIS™ from multiple prescribers within an overlapping time frame that is suggestive of misuse, abuse, overdose, or addiction; the prescriber requests patient inactivation; the patient or patient's legally authorized representative requests patient inactivation; or a report is received of patient ONSOLIS™ misuse, abuse, or overdose. In addition, triggers for inactivation of an individual prescription include but are not limited to: there is no answer to the counseling call or a failed delivery of medication.

e. If a previously active patient becomes inactive, the patient will become active again by completing the standard patient counseling and enrollment process in its entirety.

f. Patients are re-counseled (complete review of the current MG) and re-enrolled following substantial changes to the FOCUS™ Program or at least every 2 years. Substantial changes to the FOCUS™ Program are defined as:

   1. changes to the operation of the FOCUS™ Program that affect the manner in which eligible patients are identified and screened for enrollment;
   2. changes to the MG that require modification of the educational materials; or
   3. changes that modify the operation of the FOCUS™ Program in a way that changes FOCUS™ Program procedures for the patient.

g. If an active patient transfers to another active prescriber, the patient and new prescriber must complete a new Patient Enrollment Form. If an active patient transfers from an enrolled prescriber to a non-enrolled or inactive prescriber, the FOCUS™ Program can not fill the prescription for ONSOLIS™ until the new prescriber is active in the FOCUS™ Program database. An individual patient may have more than one current prescriber (eg, the patient's Pain Management Specialist as well as the patient's General Practitioner) provided that prescriptions for ONSOLIS™ are not for the same period of treatment.

h. The following pharmacy materials are part of the REMS and are appended:

   1. Patient Program Overview; and
   2. Patient Enrollment Form [including Health Insurance Portability and Accountability Act (HIPAA) authorization].

D. Implementation System

BDSI must:

1. Ensure that wholesalers/distributors who distribute ONSOLIS™ are specially certified. To become certified, wholesalers/distributors will be enrolled in the FOCUS™ Program.

   a. The FOCUS™ Program wholesaler/distributor enrollment process is comprised of the following steps that must be completed prior to receiving ONSOLIS™ inventory for distribution:

      1. The Wholesaler's/Distributor's Authorized Representative reviews the wholesaler/distributor FOCUS™ Program materials.

2. Prior to receiving ONSOLIS™, the Wholesaler's/Distributor's Authorized Representative completes and signs the Wholesaler/Distributor Enrollment Form and faxes it to the FOCUS™ Program. In signing the enrollment form, the Authorized Representative is required to indicate they understand that ONSOLIS™ is available only through the FOCUS™ Program, agree to comply with program requirements, and acknowledge that:
    i. I will ensure that relevant staff are trained about the FOCUS™ Program for ONSOLIS™ procedures.
    ii. I will ensure that relevant staff distribute ONSOLIS™ only to FOCUS™ pharmacies that are active in the database.
    iii. I will provide monthly records of ONSOLIS™ shipments to each FOCUS™ pharmacy.
    iv. I will permit a program-related audit of our shipping records to corroborate that we are shipping ONSOLIS™ only to FOCUS™ pharmacies.
3. A FOCUS™ Program professional reviews the form, requests any missing or illegible information, and, when the form has been verified to be accurate and successfully completed, the wholesaler/distributor is notified of activation.

b. Upon initial activation, wholesalers/distributors remain active until a corrective action of inactivation occurs or expiration of the enrollment period.

c. If a previously active wholesaler/distributor becomes inactive, the wholesaler/distributor will become active again by completing the standard wholesaler/distributor enrollment process in its entirety.

d. Wholesalers/distributors are re-enrolled following substantial changes to the program or at least every 2 years. Substantial changes to the FOCUS™ Program are defined as:
    1. changes that modify the operation of the FOCUS™ Program in a way that changes FOCUS™ Program procedures for wholesalers/distributors.

e. The following wholesaler/distributor material is part of the REMS and is appended:
    1. Wholesaler/Distributor Enrollment Form.

2. Maintain a database of enrolled entities to monitor and evaluate implementation of the elements provided for under the elements to assure safe use described in Sections C.2. and C.3. above. In addition, BDSI will ensure that the FOCUS™ Program database maintains a list of all enrolled wholesalers/distributors and their status (ie, active or inactive) to help ensure that ONSOLIS™ is only distributed to active wholesalers/distributors.

3. Monitor the distribution of ONSOLIS™ to ensure that the drug is only shipped to active FOCUS™ pharmacies and will institute corrective actions if non-compliance is found.

4. Monitor the dispensing of ONSOLIS™ by active FOCUS™ pharmacies to ensure only active patients are receiving ONSOLIS™ and only active prescribers are prescribing ONSOLIS™. If a dispensing entity is found to be non-compliant with the FOCUS™ Program, BDSI will institute corrective actions.
5. Monitor, audit, and evaluate all active FOCUS™ pharmacies, wholesalers/distributors, and the FOCUS™ Program vendor at the initiation of the program to ensure they implement the program as directed.
6. Monitor and evaluate the elements to assure safe use described in Sections C.2. and C.3. above in the manner described in the REMS supporting document, and take reasonable steps to work to improve implementation of these elements.

E. Timetable for Submission of Assessments

BDSI submits the assessment of the FOCUS™ Program for analysis 6 months and 1 year after the approval date of the NDA for ONSOLIS™ and annually thereafter. 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 days before the submission date for that assessment time interval. The assessment is to be received by the US Food and Drug Administration (FDA) on the due date.