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.

Important Prescribing Information About ONSOLIS™ (fentanyl buccal soluble film).

Dear Prescriber:

MEDA Pharmaceuticals Inc. is introducing ONSOLIS™, a new treatment indicated only for breakthrough pain in patients with cancer, 18 years of age and older. ONSOLIS™ can only be used in patients who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain. Patients considered opioid tolerant are those who are 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.

ONSOLIS™ contains fentanyl, an opioid agonist and a Schedule II controlled substance, with abuse liability similar to other opioid analgesics. This should be considered when prescribing or dispensing ONSOLIS™ in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances, which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone, have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Serious adverse events, including deaths, in patients treated with other oral transmucosal fentanyl products have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of ONSOLIS™ for any other fentanyl product may result in fatal overdose.

ONSOLIS™ is contraindicated for use in opioid non-tolerant patients including those using opioids intermittently, on an as needed basis.

ONSOLIS™ is contraindicated in the management of acute or postoperative pain, including headache/migraine, dental pain, or use in the emergency room. Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients treated with other fentanyl products.

When prescribing, do not convert patients on a mcg per mcg basis from any other oral transmucosal fentanyl product to ONSOLIS™. Patients beginning treatment with ONSOLIS™ must begin with titration from the 200 mcg dose.

Special care must be used when dosing ONSOLIS™. If the breakthrough pain episode is not relieved, patients should wait at least 2 hours before taking another dose.

ONSOLIS™ is intended to be used only in the care of opioid tolerant patients with cancer and only by healthcare professionals who are knowledgeable of, and skilled in, the use of Schedule II opioids to treat cancer pain.

Patients and their caregivers must be instructed that ONSOLIS™ contains a medicine in an amount which can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid tolerant. All ONSOLIS™ films must be kept out of the reach of children.

The concomitant use of ONSOLIS™ with CYP3A4 inhibitors may result in an increase in fentanyl plasma concentrations and may cause potentially fatal respiratory depression.

Because of the risk for misuse, abuse, and overdose, ONSOLIS™ is available only through a restricted distribution program, called the FOCUS™ Program. Under the FOCUS™ Program, only prescribers, pharmacies, and patients registered with the program are able to prescribe, dispense, and receive ONSOLIS™. To enroll in the FOCUS™ Program, call 1-877-466-7654 (1-877-4ONSOLIS) or visit www.OnsolisFocus.com.

The FOCUS™ Program has been implemented to mitigate the risk of ONSOLIS™ overdose, abuse, addiction, and serious complications due to medication errors by: helping to assure proper patient selection, including avoidance of the use of ONSOLIS™ in opioid non-tolerant patients; reducing the risk of exposure to ONSOLIS™ in persons for whom it was not prescribed, including accidental exposure in children; and training prescribers, pharmacists, and patients about proper dosing and administration. Enrolled patients receive ONSOLIS™ directly from a specialty pharmacy, which delivers the medication via a secure, traceable courier.

Adverse Reactions

The adverse reactions seen with ONSOLIS™ are typical opioid side effects in a population with cancer. Frequently, opioid-associated adverse reactions will cease or decrease in intensity with continued use of ONSOLIS™. **Expect opioid side effects and manage them accordingly.** The most serious adverse reactions associated with all opioids including ONSOLIS™ are respiratory depression (potentially leading to apnea or respiratory arrest), circulatory depression, hypotension, and shock. Follow all patients for symptoms of respiratory depression.

The most common adverse reactions are: nausea, vomiting, dizziness, anemia, dehydration, peripheral edema, dyspnea, and somnolence.

We appreciate your time and consideration and look forward to offering you and your patients continued support.

Sincerely,

[signature]

[name, title, MEDA Pharmaceuticals Inc.]

200 mcg 400 mcg 600 mcg 800 mcg 1200 mcg

(Films shown actual size)

Please see accompanying Full Prescribing Information, including BOXED WARNINGS.

MEDA PHARMACEUTICALS®

Healthcare Professional Program Overview
The FOCUS™ Program for ONSOLIS™

Onsolis
fentanyl buccal soluble film ©

The FOCUS™ Program for ONSOLIS™

The program requires the education of prescribers, pharmacists, patients, and caregivers regarding the safe use of ONSOLIS™. For information on the FOCUS™ Program call 1-877-466-7654 (1-877-4ONSOLIS) or visit www.OnsolisFocus.com.

The FOCUS™ Program for ONSOLIS™ has the following goal:

To mitigate the risk of ONSOLIS™ overdose, abuse, addiction, and serious complications due to medication errors by:

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

The 3-Step FOCUS™ Program Process

1. Complete Prescriber Education, Assessment, and Enrollment

- Review the educational materials on proper use of ONSOLIS™
- Complete the Prescriber Knowledge Assessment; sign and fax the Prescriber Enrollment Form

  Satisfactory completion of the Prescriber Knowledge Assessment is required

2. Complete Patient Counseling and Enrollment

- Determine that the patient meets the necessary requirements and is an appropriate candidate for treatment with ONSOLIS™
- Counsel the patient (or legally authorized representative) about the benefits and risks, and review the Medication Guide for ONSOLIS™
- Provide the patient with the Patient Authorization for Disclosure and Use of Health Information Statement (HIPAA)
- Complete and fax a copy of the Patient Enrollment Form

3. Initiate Delivery Process

- Fax a copy of the initial prescription for ONSOLIS™ to expedite the dispensing process
- Send the original, hardcopy prescription for ONSOLIS™ via courier using the supplied, pre-paid shipping label/airbill to initiate secure delivery of ONSOLIS™ directly to the patient or their caregiver

For further information please contact the **FOCUS™ Program for ONSOLIS™** directly at **1-877-466-7654 (1-877-4ONSOLIS)** or visit **www.OnsolisFocus.com**

For more information about ONSOLIS™, please see Full Prescribing Information, including BOXED WARNINGS

MEDA PHARMACEUTICALS

Prescriber Enrollment Form
The FOCUS™ Program for ONSOLIS™

Onsolis® fentanyl buccal soluble film ©

I understand that ONSOLIS™ is available only through the FOCUS™ Program, I must comply with the program requirements, and acknowledge that:

1. 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.
2. 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.
3. 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.
4. 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.
5. 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™.
6. I will provide a completed, signed copy of the patient enrollment form for each patient to the FOCUS™ Program for ONSOLIS™.
7. I will promptly respond to requests for additional information from the FOCUS™ Program.

_____ _____

Prescriber Signature Date

Prescriber Information

Prescriber Name, Credentials _____

DEA Registration Number _____ Specialty _____

Affiliation _____

Address _____

City _____ State _____ Zip Code _____

Office Phone _____ Office Fax _____

E-mail _____ Office Manager Name _____

How do you want to be confidentially informed of the results of your knowledge assessment? _____via e-mail _____via fax

Please fax this completed prescriber enrollment form (3 pages) to the FOCUS™ Program for ONSOLIS™ at **1-800-558-6302**. For questions regarding the FOCUS™ Program for ONSOLIS™, call **1-877-466-7654 (1-877-4ONSOLIS).**

MEDA PHARMACEUTICALS®

For more information about ONSOLIS™, please see Full Prescribing Information, including BOXED WARNINGS.

Prescriber Enrollment Form
The FOCUS™ Program for ONSOLIS™

Onsolis®
fentanyl buccal soluble film ©

Prescriber Name (print): _____

Prescriber Knowledge Assessment

1. When converted to a morphine equivalent dose, what is the minimal daily total dose (mg) of background opioid (also known as around-the-clock or baseline opioid) to render a patient "opioid tolerant"?
   - ☐ A. 60 mg
   - ☐ B. 15 mg
   - ☐ C. 120 mg

2. Contraindications for ONSOLIS™ include:
   - ☐ A. treatment of headache or migraine
   - ☐ B. treatment of dental pain
   - ☐ C. treatment of acute or postoperative pain, or emergency room use
   - ☐ D. all of the above

3. The most important reason why ONSOLIS™ should not be given to opioid NON-tolerant patients is because it may cause:
   - ☐ A. life-threatening respiratory depression
   - ☐ B. nausea
   - ☐ C. headache
   - ☐ D. constipation

4. If a patient has been using a different transmucosal fentanyl product and the dose is known (such as Actiq® 600 mcg), what is the proper way to determine the dose of ONSOLIS™?
   - ☐ A. the ONSOLIS™ dose is the same as other transmucosal fentanyl products
   - ☐ B. due to differences in bioavailability, the ONSOLIS™ dose is 2/3 the dose of other transmucosal fentanyl products
   - ☐ C. the ONSOLIS™ starting dose is always 200 mcg and the patient should titrate to an effective and tolerable dose of ONSOLIS™ regardless of previous medications

The FOCUS™ Program for ONSOLIS™

Onsolis™ fentanyl buccal soluble film ©

The program requires the education of prescribers, pharmacists, patients, and caregivers regarding the safe use of ONSOLIS™.

The FOCUS™ Program for ONSOLIS™ has the following goal:

To mitigate the risk of ONSOLIS™ overdose, abuse, addiction, and serious complications due to medication errors by:

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

Information for prescribers | Information for pharmacists | Information for patients

For information on the FOCUS™ Program, call 1-877-466-7654 (1-877-4ONSOLIS).

Please see full prescribing information including boxed warnings by clicking the link below.

Important Safety Information

The most serious adverse reactions associated with all opioids are respiratory depression (potentially leading to apnea or respiratory arrest), circulatory depression, hypotension, and shock. Follow all patients for symptoms of respiratory depression. In ONSOLIS™ trials, the most common adverse reactions were: nausea, vomiting, dizziness, anemia, dehydration, peripheral edema, dyspnea, and somnolence.