

Risk Evaluation and Mitigation Strategy (REMS) Document

A. NDA 204410 Opsumit¹ (macitentan) REMS Program

I. Administrative Information

Application Number: NDA 204410

Application Holder: Actelion Pharmaceuticals Ltd Initial

REMS Approval: 10/2013

Most Recent REMS Update: 04/2020

II. REMS Goal

The goal of the Opsumit REMS Program is to mitigate the risk of embryo-fetal toxicity associated with Opsumit by:

1. Ensuring prescribers are educated on the following:
 - the risks of embryo-fetal toxicity
2. Ensuring prescribers are educated on and adhere to the following:
 - counseling patients about these risks and the need for monthly monitoring
 - enrolling patients in the Opsumit REMS Program
 - monitoring patients at baseline and monthly
3. Ensuring that pharmacies are educated on the following:
 - the risks of embryo-fetal toxicity
4. Ensuring that pharmacies are educated on and adhere to the following:
 - confirming that the appropriate patient monitoring and counseling has occurred before dispensing Opsumit
5. Ensuring that patients are informed about:
 - the risks of embryo-fetal toxicity
 - appropriate baseline and monthly patient monitoring
 - appropriate contraception

III. REMS Requirements

Actelion Pharmaceuticals Ltd must ensure that healthcare providers, patients, pharmacies, and wholesalers-distributors comply with the following requirements:

1. Healthcare providers who prescribe Opsumit must:

To become certified to prescribe

1. Review the drug's Prescribing Information
2. Review the following: [Prescriber and Pharmacy Guide](#).
3. Enroll in the REMS by completing the [Prescriber Enrollment Form](#) and submitting it to the REMS Program
4. For all females: Assess the patient's reproductive status using the

¹ Opsumit-specific requirements contained in this document apply until the date of full approval of the first abbreviated new drug application (ANDA) joining a shared system REMS with Opsumit.

definitions in the [Prescriber and Pharmacy Guide](#). Document and submit the results to the REMS Program using the [Patient Enrollment Form](#).

5. For all females: Counsel the patient that the drug is only available through a restricted distribution program.
6. For females of reproductive potential: Assess the patient's pregnancy status by ordering and reviewing her pregnancy test result
7. For females of reproductive potential: Counsel the patient on the risk of embryo-fetal toxicity, the need to use reliable contraception, and emergency contraception using the [Guide for Female Patients](#).
8. For pre-pubertal females: Counsel the patient on the risk of embryo- fetal toxicity and to immediately contact her prescriber if she begins to menstruate - using the [Guide for Female Patients](#).
9. Enroll all female patients by completing and submitting the [Patient Enrollment Form](#) and submitting it to the REMS Program.

During treatment;
before each
prescription

10. For females of reproductive potential: Counsel the patient if she is not complying with required testing, if she is not using appropriate contraception, and to contact her prescriber if she misses a menstrual period or suspects that she is pregnant.
11. For females of reproductive potential: Assess the patient's pregnancy status by ordering and reviewing her pregnancy test result.

During treatment;
at least annually

12. For pre-pubertal females at least age 8 years or older: Document reproductive potential status and submit to the REMS Program using the [Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form](#).

After treatment
discontinuation;
one month

13. For females of reproductive potential: Assess the patient's pregnancy status by ordering and reviewing her pregnancy test result.

At all times

14. For pre-pubertal females: Assess the patient's reproductive status.
15. Report pregnancies to Actelion Pharmaceuticals Ltd.

At all times; within
10 business days

16. Report a change or misclassification in reproductive status to the REMS Program using the [Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form](#).

2. Females of reproductive potential who are prescribed Opsumit:

Before treatment
initiation

1. Review the [Guide for Female Patients](#).
2. Get a pregnancy test.
3. Enroll in the REMS by completing the [Patient Enrollment Form](#) with the

prescriber. Enrollment information will be provided to the REMS Program.

4. Receive counseling from the prescriber on the risk of embryo-fetal toxicity, the need to use reliable contraception, and emergency contraception using the [Guide for Female Patients](#).
5. Adhere to the safe use condition: Communicate with the pharmacy to confirm completion of pregnancy testing.

During treatment;
before each
dispensing

6. Receive counseling from the pharmacy or healthcare provider who dispenses Opsumit on the risk of embryo-fetal toxicity, the need for reliable contraception during treatment and for one month after stopping treatment, to get monthly pregnancy tests, and to report a pregnancy immediately.
7. Get a pregnancy test.
8. Adhere to the safe use condition: Communicate with the pharmacy to confirm completion of pregnancy testing.

During treatment
and after
treatment
discontinuation for
one month

9. Adhere to the safe use condition: Use reliable contraception as described in the [Guide for Female Patients](#).
10. Agree to be contacted by the manufacturer if you become pregnant.

After treatment
discontinuation;
one month

11. Get a pregnancy test.

At all times

12. Inform the prescriber immediately if you miss a menstrual period or suspect a pregnancy.

3. Pre-pubertal females who are prescribed Opsumit:

Before treatment
initiation

1. Review the [Guide for Female Patients](#).
 2. Enroll in the REMS Program by completing the [Patient Enrollment Form](#) with the prescriber. Enrollment information will be provided to the REMS Program.
 3. Receive counseling from the prescriber on the risk of embryo-fetal toxicity and to contact your prescriber if you begin to menstruate using the [Guide for Female Patients](#).
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| At all times | <ol style="list-style-type: none">4. If over the age of 8: Be monitored for a change in reproductive status.5. Inform the prescriber if there is a change in reproductive status. |
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4. Post-menopausal females or females with other medical reason for permanent, irreversible infertility who are prescribed Opsumit:

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| Before treatment initiation | <ol style="list-style-type: none">1. Review the Guide for Female Patients.2. Enroll in the REMS Program by completing the Patient Enrollment Form with the prescriber. Enrollment information will be provided to the REMS Program. |
| At all times | <ol style="list-style-type: none">3. Inform the prescriber if there is a change in your reproductive status. |
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5. Outpatient pharmacies that dispense Opsumit must:

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| To become certified to dispense | <ol style="list-style-type: none">1. Designate an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS Program on behalf of the pharmacy.2. Train all relevant staff involved in dispensing on the Opsumit REMS Program requirements, procedures and REMS materials.3. Establish processes and procedures to verify the female patient is enrolled, the reproductive status of the patient has not changed, and the prescriber is certified.4. For females of reproductive potential: Establish processes and procedures to verify that pregnancy testing is complete or the prescriber authorizes the refill. |
| Before dispensing | <ol style="list-style-type: none">5. For females of reproductive potential: Counsel the patient on the risk of embryo-fetal toxicity, the need to use reliable contraception during treatment and for one month after stopping treatment, to get monthly pregnancy tests, and inform the prescriber of a pregnancy immediately.6. Verify the female patient is enrolled, the reproductive status has not changed, and the prescriber is certified through the processes and procedures established as a requirement of the REMS Program.7. For females of reproductive potential: Verify that pregnancy testing is complete or the prescriber authorizes the refill through the processes and |
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procedures established as a requirement of the REMS Program.

8. For females of reproductive potential: Dispense no more than a 30-days' supply.

At all times

9. Report pregnancies to Actelion Pharmaceuticals, Ltd.
10. Not distribute, transfer, loan, or sell Opsumit except to certified dispensers.
11. For females of reproductive potential: Maintain and submit records of daily product dispensing data.
12. Maintain records that all processes and procedures are in place and are being followed.
13. Comply with audits carried out by the manufacturer or a third party acting on behalf of the manufacturer to ensure that all processes and procedures are in place and are being followed.

6. Inpatient pharmacies that dispense Opsumit must:

To become certified to dispense

1. Designate an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS Program on behalf of the pharmacy.
 2. Have the authorized representative enroll in the REMS Program by completing the [Inpatient Pharmacy Enrollment Form](#) and submitting it to the REMS Program.
 3. Have the authorized representative review the Prescribing Information and the [Prescriber and Pharmacy Guide](#).
 4. Train all relevant staff involved in dispensing Opsumit on the REMS Program requirements, procedures and REMS materials.
 5. Establish processes and procedures to verify the female patient is enrolled in the REMS program or will be enrolled prior to discharge, her reproductive status, and the female patient is under the supervision and care of a certified prescriber.
 6. For females of reproductive potential: establish processes and procedures to verify pregnancy testing is complete, and that the patient is counseled on the risk of embryo-fetal toxicity, the need to use reliable contraception, to get monthly pregnancy tests, and to inform the prescriber of a
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pregnancy immediately.

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| Before dispensing | <ol style="list-style-type: none">7. Verify the female patient is under the supervision and care of a certified prescriber, and that she is enrolled or will be enrolled in the REMS Program prior to discharge through the processes and procedures established as a requirement of the REMS.
8. For females of reproductive potential: Verify the pregnancy testing is complete, and that the patient is counseled on the risk of embryo-fetal toxicity, the need to use reliable contraception, to get monthly pregnancy tests, and to inform the prescriber of a pregnancy immediately through the processes and procedures established as a requirement of the REMS Program. |
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| To maintain certification to dispense | <ol style="list-style-type: none">9. Have a new authorized representative enroll in the REMS Program by completing the Inpatient Pharmacy Enrollment Form if the authorized representative changes. |
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| At discharge | <ol style="list-style-type: none">10. Dispense no more than a 15-days' supply. |
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| At all times | <ol style="list-style-type: none">11. Report pregnancies to Actelion Pharmaceuticals, Ltd.
12. Not distribute, transfer, loan, or sell Opsumit expect to certified dispensers.
13. Maintain records that all processes and procedures are in place and are being followed.
14. Comply with audits carried out by the manufacturer or a third party acting on behalf of the manufacturer to ensure that all processes and procedures are in place and are being followed. |
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7. Wholesalers-distributors that distribute Opsumit must:

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| To be able to distribute | <ol style="list-style-type: none">1. Establish processes and procedures to ensure that the drug is distributed only to certified pharmacies.
2. Train all relevant staff involved in distribution on the Opsumit REMS Program requirements. |
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| At all times | <ol style="list-style-type: none">3. Distribute only to certified pharmacies.
4. Maintain records of drug distribution. |
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5. Comply with audits carried out by the manufacturer or a third party acting on behalf of the manufacturer to ensure that all processes and procedures are in place and are being followed.

Actelion Pharmaceuticals Ltd must provide training to healthcare providers who prescribe Opsumit.

The training includes the following educational materials: Prescribing Information and Prescriber and Pharmacy Guide. The training must be available online or by calling the REMS Program.

Actelion Pharmaceuticals Ltd must provide training to pharmacies that dispense Opsumit. The training includes the following educational material: Prescribing Information and Prescriber and Pharmacy Guide. The training must be available online or by calling the REMS Program.

To support REMS Program operations, Actelion Pharmaceuticals Ltd must:

1. Establish and maintain a REMS Program website, www.OpsumitREMS.com. The REMS Program website must include the capability to print the Prescribing Information, Medication Guide, 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 the REMS Program website or coordinating center within 90 calendar days of REMS modification approval (06/10/2019).
3. Establish and maintain a REMS Program coordinating center for REMS participants at 1-866-228-3546.
4. Establish and maintain a validated, secure database of all REMS participants who are enrolled and/or certified in the Opsumit REMS Program.
5. Ensure prescribers are able to certify by submitting a completed Prescriber Enrollment Form by fax and phone.
6. Ensure outpatient pharmacies are able to certify by contracting with the manufacturer and agreeing to comply with the requirements of the REMS Program.
7. Ensure inpatient pharmacies are able to certify by submitting a completed Inpatient Pharmacy Enrollment Form by fax and phone.
8. Ensure prescribers are able to report change in reproductive status by fax and phone.
9. Ensure prescribers are able to complete the patient enrollment process online, by phone, or by fax.
10. Ensure pharmacies are able to confirm patient enrollment, prescriber certification, and safe use conditions are met prior to dispensing of Opsumit online.
11. Ensure pharmacies are able to enroll as inpatient (including, but not limited to, pharmacies in hospitals, long-term care facilities, prisons, and state psychiatric units) or as outpatient pharmacies.
12. Ensure inpatient pharmacies are able to contact the coordinating center for assistance in obtaining up to a 15-day supply of drug for a specific inpatient while the inpatient pharmacy completes the certification process.
13. Provide the Prescriber Enrollment Form and Prescriber and Pharmacy Guide to prescribers who (1) attempt to prescribe Opsumit and are not yet certified or (2) inquire about how to become certified.

14. Notify certified pharmacies of a patient's change or misclassification in reproductive status within one business day of receipt of a completed Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form.
15. Provide certified prescribers access to the database of certified pharmacies and enrolled patients.
16. Provide certified pharmacies access to the database of certified prescribers and enrolled patients.

To ensure REMS participants' compliance with the REMS Program, Actelion Pharmaceuticals Ltd must:

17. Maintain adequate records to demonstrate that REMS requirements have been met, including, but not limited to records of: Opsumit distribution and dispensing; certification of prescribers and pharmacies; enrolled patients; and audits of REMS pharmacies and wholesalers-distributors. These records must be readily available for FDA inspections.
18. Establish a plan for addressing noncompliance with REMS Program requirements.
19. Monitor prescribers, pharmacies, and wholesaler-distributors on an ongoing basis to ensure the requirements of the REMS are being met. Take corrective action if noncompliance is identified, including de-certification.
20. Audit all certified outpatient pharmacies and wholesaler-distributors within 180 days after they become certified, to ensure that all REMS processes and procedures are in place, functioning, and support the REMS Program requirements.
21. Audit all certified outpatient pharmacies, all wholesaler-distributors, the coordinating center for Opsumit, and at least 10% of certified inpatient pharmacies that have ordered Opsumit annually to ensure that all REMS processes and procedures are in place, functioning, and support the REMS Program requirements.
22. Take reasonable steps to improve operation of and compliance with the requirements in the Opsumit REMS Program based on monitoring and evaluation of the Opsumit REMS Program.

IV. REMS Assessment Timetable

Actelion Pharmaceuticals Ltd must submit REMS Assessments at 6 months and 1 year from the date of the initial REMS approval (10/18/2013), and then 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 calendar days before the submission date for that assessment. Actelion Pharmaceuticals Ltd 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 Opsumit REMS:

Enrollment Forms:

Prescriber:

1. [Prescriber Enrollment and Agreement Form](#)

Patient:

2. [Patient Enrollment and Consent Form](#)
3. [Patient Enrollment and Consent Form for VA use only](#)

Pharmacy:

4. [Inpatient Pharmacy Enrollment Form](#)

Training and Educational Materials

Prescriber:

5. [Prescriber and Pharmacy Guide](#)

Patient:

6. [Guide for Female Patients](#)

Pharmacy:

7. [Prescriber and Pharmacy Guide](#)

Patient Care Form

8. [Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form](#)

Other Materials

9. [REMS Program website \(www.OpsumitREMS.com\)](http://www.OpsumitREMS.com)