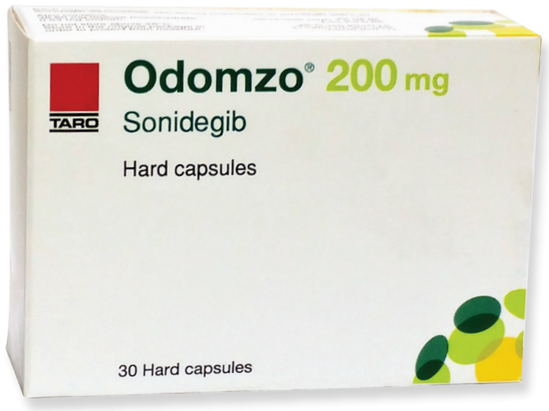
ODOMZO



Years of tumor response

INDICATION

Odomzo 200 mg is indicated for the treatment of adult patients with locally advanced basal cell carcinoma which cannot be treated with curative surgery or radiation therapy.

TARO
www.taro.co.il

Odomzo®
(sonidegib) capsules 200mg

ODOMZO

Odomzo®
(sonidegib) capsules 200mg

TABLE OF CONTENTS

Letter

for healthcare professional

Odomzo 200 mg (sonidegib) capsules:
Important information to minimise the risk of teratogenicity

צוות רפואי נכבד,

חברת תרו, בשיתוף משרד הבריאות, מביאה לידיעתכם מידע בטיחותי חשוב לגבי ההשפעות הטרטוגניות של אודומזו 200 מ"ג ואת התכנית למניעת היריון אשר יש ליישמה על מנת להקטין את הסיכון.

להלן עיקרי הדברים:

- **אודומזו עלולה לגרום למוות עוברי או למומים קשים ביילוד ואין להשתמש בתרופה במשך ההיריון.**
- **בנשים המסוגלות להרות נדרשת בדיקת היריון עד 7 ימים לפני תחילת הטיפול ואחת לחודש במשך הטיפול באודומזו.**
- **נשים המסוגלות להרות חייבות להשתמש בשתי שיטות של אמצעי מניעה מומלצים במשך הטיפול באודומזו ובמשך 20 חודשים אחרי המנה האחרונה, אלא אם כן הן נמנעות מיחסי מין.**
- **מטופלים גברים חייבים להשתמש בקונדום (עם קוטל זרע, במידת האפשר) בעת קיום יחסי מין עם בת זוג במשך הטיפול באודומזו ובמשך 6 חודשים לאחר סיום הטיפול.**
- **ודא שכל המטופלים:**
  - מיודעים באופן מספק לגבי ההשפעות הטרטוגניות של אודומזו.
  - מקבלים את 'חוברת המידע למטופל' אשר כוללת את ה'כרטיס למטופל'.

Dear Healthcare Professional,

This letter is sent in agreement with the Israeli Ministry of Health to inform you of important safety information regarding the teratogenic effects of Odomzo 200 mg and the Pregnancy Prevention Programme (PPP), which must be implemented to minimise this risk.

SUMMARY

- Odomzo 200 mg may cause embryo-foetal death or severe birth defects and must not be used during pregnancy.
- Pregnancy testing is required in women of childbearing potential within 7 days before and monthly during treatment with Odomzo.
- Women of childbearing potential must use two methods of recommended contraception during Odomzo therapy and for 20 months after the final dose unless they abstain from sexual intercourse.
- Male patients must use a condom (with spermicide, if available) when having sex with a female partner while taking Odomzo and for 6 months after ending treatment.
- Ensure that all patients:
  – Are appropriately informed regarding the teratogenic effects of Odomzo.
  – Receive the Patient Information Brochure which includes the Patient Reminder Card.

Further Information

Odomzo is indicated for the treatment of adult patients with locally advanced basal cell carcinoma who are not amenable to curative surgery or radiotherapy. Hedgehog pathway inhibitors such as Odomzo have been demonstrated to be embryotoxic and/or teratogenic in multiple animal species and can cause severe malformations. Therefore a PPP (which includes this communication, educational materials and the product information) has been developed to reinforce the warnings about the expected teratogenic risk of Odomzo, provide advice on contraception, pregnancy testing and other measures to minimise this risk.

Women of child bearing potential (WCBP)

Please refer to the Summary of Product Characteristics for the definition of a WCBP.

Pregnancy testing

Pregnancy status must be established within 7 days prior to the initiation of Odomzo treatment and monthly during treatment by means of a test performed by a healthcare professional. Patients who present with amenorrhoea during treatment should continue monthly pregnancy testing. Pregnancy tests should have a minimum sensitivity of 25 mIU/ml as per local availability. In the event of pregnancy, treatment must not be initiated. In case of pregnancy occurring during treatment, Odomzo must be stopped immediately.

Methods of contraception
Women of childbearing potential must use two methods of recommended contraception, a highly effective method (tubal sterilisation, IUD or vasectomy) and a barrier method (male condom or diaphragm, with spermicide if available). These contraceptive measures must be used during Odomzo therapy and for 20 months after the final dose unless they abstain from sexual intercourse.

Prescribing and dispensing
The initial prescription and dispensing of Odomzo should occur within 7 days of a negative pregnancy test. Prescriptions of Odomzo should be limited to 30 days of treatment, with continuation of treatment requiring a new prescription.

In case of pregnancy or missed menstrual periods
A patient who becomes pregnant, misses a menstrual period, or suspects for any reason that she may be pregnant must notify her treating healthcare professional immediately. Persistent lack of menses during treatment should be assumed to indicate a pregnancy until medically evaluated and confirmed. In cases of pregnancy or suspicion of pregnancy, treatment must be stopped immediately.

Breastfeeding
Women must not breastfeed while taking Odomzo or for 20 months after ending treatment.

Men
Male patients, even those who have had a vasectomy, must use a condom (with spermicide, if available) when having sex with a female partner while taking Odomzo and for 6 months after ending treatment. Male patients should not donate semen while taking Odomzo and for at least 6 months after ending treatment.

All patients
All patients must not donate blood while taking Odomzo and for at least 20 months after the final dose.

Additional precautions
Patients must be advised that Odomzo should not be given to another person, and that they must dispose of any unused capsules at the end of treatment in accordance with local requirements (e.g. by returning the capsules to their pharmacist or physician).

Educational material and SmPC (Summary of Product Characteristics)
Further detailed information about the measures that must be taken to minimise the risk of teratogenicity can be found in the SmPC (Summary of Product Characteristics) and educational materials, which comprise an educational brochure for healthcare professionals and patients. Please ensure that you carefully read these materials before prescribing Odomzo.

Call for reporting
Healthcare professionals should report any pregnancy and also all adverse events suspected to be associated with the use of Odomzo to Taro International Ltd (drug.safety@taro.co.il).
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

Sincerely yours,
Taro International Ltd.

Enclosures
1. Odomzo (sonidegib) Healthcare Professional Education Brochure with integrated Reminder Card.
2. Odomzo (sonidegib) Patient Education Brochure with integrated Reminder Card.

Important information

for healthcare providers

Important information for healthcare providers to minimize the risk of teratogenicity with Odomzo (sonidegib) 200 mg capsules

Odomzo may cause embryo-fetal death or severe birth defects when administered to a pregnant woman. Hedgehog pathway inhibitors, such as Odomzo, have been demonstrated to be embryotoxic and/or teratogenic in animals. Odomzo must not be used during pregnancy.

Please refer to the SmPC (Summary of Product Characteristics) for comprehensive safety information.
Odomzo is contraindicated in women who are pregnant or breastfeeding.
Odomzo is contraindicated in women of childbearing potential who do not comply with the Odomzo Pregnancy Prevention Programme.

About Odomzo (sonidegib) capsules

Indications and usage
Odomzo is indicated for the treatment of adult patients with:
Locally advanced basal cell carcinoma (BCC) who are not amenable to curative surgery or radiation therapy.

Odomzo mechanism of action
Odomzo is a potent, selective, and orally bioavailable Smoothened (Smo) antagonist.
Smo is a G protein-coupled receptor-line molecule that positively regulates the Hedgehog (Hh) signal transduction pathway. The Hh pathway activation at or upstream of Smo is linked to the pathogenesis of several types of cancer, including basal cell carcinoma.

Please refer to the **SmPC (Summary of Product Characteristics)** for a complete list of treatment risks associated with Odomzo.

Infertility, fetal toxicity, and teratogenicity

Hedgehog pathway inhibitors such as sonidegib have been demonstrated to be embryotoxic and/or teratogenic in multiple animal species and can cause severe malformations. Odomzo may cause embryo-fetal death or severe birth defects when administered to a pregnant woman. Odomzo must not be used during pregnancy.

Odomzo has also been found to be teratogenic and fetotoxic, as evidenced by the occurrence of abortion and/or complete resorption of fetuses in animal studies. **To minimise the risk of teratogenic effects, Odomzo must not be given to pregnant or lactating women. Women receiving Odomzo should be made aware of this risk prior to treatment and instructed to use highly effective methods of contraception while receiving Odomzo, and for 20 months after ending treatment.**

The fertility effects of Odomzo were studied in animal models. These effects included delayed or arrested maturation of testes, prostate, ovary, and uterus. Based on findings from animal studies, male and female fertility may be compromised with Odomzo. Additionally, amenorrhoea has been observed in clinical trials in women of childbearing potential (WCBP). **Fertility preservation options should be discussed prior to starting treatment with Odomzo with any patient wanting to maintain reproductivity after treatment.**

Recommendations for women taking Odomzo

Advise female patients of the risks of embryo-fetal death and severe birth defects and the need for contraception during and after treatment. Women of childbearing potential should be counselled regarding pregnancy prevention and planning. If pregnancy occurs, treatment must be stopped immediately. Advise patients to contact their healthcare provider immediately if they suspect they may be pregnant.

A **woman of childbearing potential** (WCBP) is defined in the Odomzo Pregnancy Prevention Programme as a sexually mature female who

- has menstruated at any time during the previous 12 consecutive months
- has not undergone a hysterectomy or a bilateral oophorectomy, or who does not have medically confirmed permanent premature ovarian failure
- does not have an XY genotype, Turner syndrome, or uterine agenesis
- has become amenorrhoeic following cancer therapy, including treatment with Odomzo.

CONSIDERATIONS	WOMEN Of childbearing potential	WOMEN NOT of child bearing potential	MEN
RISK OF TERATOGENICITY The risk of teratogenicity is relevant to female patients of childbearing potential, in addition to female patients not of childbearing potential, and male patients.	✓	✓	✓
RISK OF INFERTILITY The potential for sonidegib to cause infertility in male and female patients is unknown. Based on findings from animal studies, male and female fertility may be compromised with sonidegib. Fertility preservation options should be discussed prior to starting treatment with sonidegib with any patient wanting to maintain reproductivity after treatment.	✓		✓

CONSIDERATIONS	WOMEN Of childbearing potential	WOMEN NOT of child bearing potential	MEN
PREGNANCY TESTING In women of childbearing potential, a pregnancy test conducted by a healthcare professional must be done within 7 days before starting Odomzo treatment, and, subsequently, medically supervised monthly pregnancy tests. Patients who present with amenorrhea during treatment with Odomzo should continue monthly pregnancy testing while on treatment.	✓		
PRESCRIBING AND DISPENSING RESTRICTIONS The initial prescription and dispensing of Odomzo should occur after a negative pregnancy test.	✓		
CONTRACEPTION – WOMEN Women of childbearing potential must abstain from sexual intercourse or use highly effective contraceptive measures during treatment and for 20 months after the final dose.	✓		
IN CASE OF PREGNANCY OR MISSED MENSTRUAL PERIODS A patient who becomes pregnant, misses a menstrual period, or suspects for any reason that she may be pregnant must notify her treating physician immediately. Any menstrual irregularities during treatment should be assumed to indicate a pregnancy until medically evaluated and confirmed or ruled out. In case of pregnancy or suspicion of pregnancy, treatment must be stopped immediately. Healthcare professionals should report any pregnancy to Taro International Ltd.	✓		
BREASTFEEDING The extent to which Odomzo (sonidegib) capsules is excreted in breast milk is not known. However, because of its potential to cause serious developmental defects, women must not breastfeed while taking Odomzo and for 20 months after the final dose.	✓		

CONSIDERATIONS	WOMEN Of childbearing potential	WOMEN NOT of child bearing potential	MEN
CONTRACEPTION – MEN Odomzo may be present in the semen. To avoid potential fetal exposure during pregnancy, male patients must always use a condom, even after a vasectomy, when having sexual intercourse with a female partner while taking Odomzo and for 6 months after ending treatment to prevent exposure of female partners to the medicinal product via seminal fluid.			✓
DONATING SEMEN Men should not father a child or donate semen while taking Odomzo and for 6 months after the final dose.			✓
DONATING BLOOD All patients should be advised not to donate blood during treatment, or for 20 months after the final dose.	✓	✓	✓
RETURN UNUSED CAPSULES All patients should dispose of any unused capsules at the end of treatment in accordance with local requirements (if applicable, e.g., by returning the capsules to their pharmacist or physician).	✓	✓	✓

RECOMMENDED METHODS OF CONTRACEPTION

It is important that WCBP are counselled about the importance of recommended contraception and the avoidance of pregnancy. Unless they commit to not having sexual intercourse (abstinence), they must use 2 recommended forms of birth control at the same time, one of which must be a barrier method.

2 FORMS OF CONTRACEPTION MUST BE USED; 1 FROM EACH COLUMN

BARRIER METHODS		HIGHLY EFFECTIVE FORMS OF CONTRACEPTION
Male condom (with spermicide, if available) **OR** Intrauterine device (IUD) **OR** Diaphragm with spermicide	**AND**	• Intrauterine device (IUD) **OR** • Tubal sterilisation **OR** • Vasectomy

WHAT TO DO IF PREGNANCY OCCURS

Women who miss a menstrual period or think they may be pregnant should be directed to stop taking Odomzo immediately and talk to their healthcare provider as soon as possible. Healthcare providers must report to Taro International for any pregnancy that occurs:

- During treatment
- Within 20 months after treatment

Also, be sure to notify the patient's physician (if you are not the physician) and obtain a consult from an obstetrics specialist.

The initial prescription and dispensing of Odomzo should occur within 7 days following a negative pregnancy test. Prescriptions of Odomzo should be limited to 30 days of treatment, and continuation of treatment requires a new prescription.

Recommendations for men taking Odomzo

Advise male patients of the risks of embryo-fetal death and severe birth defects and the need for contraception during and after treatment. Male patients with partners of reproductive potential should be counselled regarding pregnancy prevention and planning. If a male patient's female partner becomes pregnant, the patient and his partner should be apprised of the potential hazard to the fetus. Advise male patients to contact their healthcare provider immediately if they suspect their female partner may be pregnant.
Sexually active males being treated with Odomzo must use a condom during sexual intercourse, regardless of their vasectomy status. Men should not father a child or donate semen while taking Odomzo and for 6 months after ending treatment.

What to tell your patients about Odomzo

REMEMBER TO TELL EVERY PATIENT:

- **Keep the medicine out of sight and reach of children**
- **Never give Odomzo to another person**
- **Dispose of any unused capsules at the end of treatment** in accordance with local requirements (if applicable, e.g., by returning the capsules to his or her pharmacist or physician)
- Do not donate blood during treatment, **AND** for 20 months after the final dose

REMEMBER TO TELL FEMALE PATIENTS:

During treatment and for **20 months after the final dose…**

- Odomzo can cause birth defects
- It is unknown if Odomzo can be found in breast milk
- **Do not** become pregnant
- **Do not** breastfeed
- **Do not** have unprotected sexual intercourse, even if you have undergone a tubal ligation

- **Always use pregnancy prevention measures**, such as abstaining from sexual intercourse **OR** using 2 recommended methods of contraception (see table in section RECOMMENDED METHODS OF CONTRACEPTION)

REMEMBER TO TELL MALE PATIENTS:

During treatment and for 6 months after the final dose…

- It is unknown if Odomzo can be found in semen
- **Do not** donate semen
- **Do not** have unprotected sexual intercourse, even if you have undergone a vasectomy

Additional safety information

Please refer to the Odomzo **SmPC (Summary of Product Characteristics)** for a detailed list of the known side effects.

Call for reporting

Healthcare professionals should report any pregnancy and also all adverse events suspected to be associated with the use of Odomzo to Taro International Ltd (drug.safety@taro.co.il).
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:
http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

This Prescriber Brochure, format and content was checked and approved by the Ministry of Health in November 2017

Reminder Card

for healthcare providers

Odomzo 200 mg (sonidegib) capsules reminder card for healthcare providers

Odomzo may cause embryo-fetal death or severe birth defects when administered to a pregnant woman. Hedgehog pathway inhibitors, such as Odomzo, have been demonstrated to be embryotoxic and/or teratogenic in animals. Odomzo must not be used during pregnancy.

Please refer to the SmPC (Summary of Product Characteristics) or contact Taro International Ltd.
Odomzo is contraindicated in women who are pregnant or breastfeeding.

Please refer to the SmPC (Summary of Product Characteristics) for comprehensive safety information.

Remind patients taking Odomzo (sonidegib) capsules of the following:

- **Do not** become pregnant
- **Do not** breastfeed
- **Do not** donate semen
- **Do not** have unprotected sexual intercourse, even if you are a woman who has undergone a tubal ligation **OR** a man who has undergone a vasectomy
- **Women of childbearing potential should always use pregnancy prevention measures**, such as abstaining from sexual intercourse **OR** using 2 recommended methods of contraception
- Female patients must take a pregnancy test within 7 days before starting Odomzo treatment and monthly during treatment

Also remember to tell your patients to:

- **Keep medicine out of sight and reach of children**
- **Never give capsules** to anyone who is not a healthcare provider
- **Dispose of any unused capsules at the end of treatment** in accordance with local requirements (if applicable, e.g., by returning the capsules to their pharmacist or physician)
- **Refrain from donating blood while on treatment**, and for 20 months after the final dose

2 FORMS OF CONTRACEPTION MUST BE USED; 1 FROM EACH COLUMN

BARRIER METHODS		HIGHLY EFFECTIVE FORMS OF CONTRACEPTION
Male condom (with spermicide, if available) **OR** Diaphragm with spermicide	**AND**	• Intrauterine device (IUD) **OR** • Tubal sterilisation **OR** • Vasectomy

This Safety Reminder Card, format and content was checked and approved by the Ministry of Health in November 2017

Remarks:


TARO