

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

Pr**ODOMZO**®

Sonidegib Capsules

200 mg sonidegib (as phosphate), oral

Antineoplastic agent (ATC code: L01XX48)

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RECENT MAJOR LABEL CHANGES

Not applicable

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

ODOMZO (sonidegib) is indicated for:

- The treatment of adult patients with histologically confirmed locally advanced basal cell carcinoma (laBCC) that is not amenable to radiation therapy or curative surgery.

The indication is granted market authorization based on objective response rate (ORR) demonstrated in a non-comparative Phase II trial (see Section 14 Clinical Trials). Overall survival (OS) benefit in this trial cannot be confirmed.

Distribution Restrictions

ODOMZO is only available through a controlled distribution program called the ODOMZO Pregnancy Prevention Program. Under this program, only prescribers and pharmacies registered with the program are able to prescribe and dispense the product, respectively. In addition, ODOMZO can only be dispensed to patients who are registered and meet all the conditions of the ODOMZO Pregnancy Prevention Program (OPPP). For more information please contact the ODOMZO Pregnancy Prevention Program at 1-844-266-2974 or log onto www.Odomzo.ca.

1.1 Pediatrics

Pediatrics (<18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of ODOMZO in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use (see Section 7.1 Special Populations – 7.1.3 Pediatrics).

1.2 Geriatrics

Geriatrics (≥65 years of age): No overall differences in effectiveness were observed between geriatric patients and younger patients. However, there was a higher incidence of serious adverse reactions, Grade 3 and 4 adverse reactions, and adverse reactions requiring dose interruption or discontinuation in elderly patients compared with younger patients. This was not attributed to an increase in any specific adverse event (see Section 7.1 Special Populations – 7.1.4 Geriatrics and Section 8 Adverse Reactions).

2 CONTRAINDICATIONS

ODOMZO (sonidegib) is contraindicated in:

- Female patients who are pregnant and females at risk of becoming pregnant (see Section 7.1 Special Populations - 7.1.1 Pregnant Women).
- Breast-feeding female patients (see Section 7.1 Special Populations - 7.1.2 Breast-feeding).
- Female patients of childbearing potential who do not comply with the ODOMZO Pregnancy Prevention Program (see Section 7 Warnings and Precautions).

- Male patients who do not comply with the contraceptive measures of the ODOMZO Pregnancy Prevention Program (see Section 7 Warnings and Precautions).
- Children and adolescents aged below 18 years (see Section 16 Non-Clinical Toxicology and Section 7.1 Special Populations – 7.1.3 Pediatrics).
- Patients who are hypersensitive to sonidegib or to any ingredient in the formulation (see Section 6 Dosage Forms, Strengths, Composition and Packaging for a complete listing).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

ODOMZO (sonidegib) should be initiated and monitored only under the supervision of a physician qualified in the use of cancer therapies and with a full understanding of the risks of ODOMZO therapy and monitoring requirements.

- ODOMZO can cause embryo-fetal death or severe birth defects (see Section 7 Warnings and Precautions – 7.1.1 Pregnant Women).
- ODOMZO has not been studied in patients with severe renal impairment (see Section 4 Dosage and Administration).
- ODOMZO is available only through a controlled distribution program called the ODOMZO Pregnancy Prevention Program.
- ODOMZO can cause irreversible premature fusion of the epiphyses in pediatric patients (see Section 2 Contraindications, Section 7 Warnings and Precautions - 7.1.3 Pediatrics, and Section 16 Non-Clinical Toxicology).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Verify the pregnancy status of females of reproductive potential prior to initiating ODOMZO (see Section 7 Warnings and Precautions - *Reproduction*).
- Obtain baseline serum creatine phosphokinase (CPK) levels and renal function tests prior to initiating ODOMZO in all patients (see Section 7 Warnings and Precautions - Musculoskeletal).

4.2 Recommended Dose and Dosage Adjustment

Recommended Dose

The recommended dosage of ODOMZO is 200 mg taken orally once daily on an empty stomach, at least 1 hour before or 2 hours after a meal. Patients should be treated until disease progression or unacceptable toxicity.

Dosage Adjustment

Dose modifications for creatine phosphokinase (CPK) elevations and muscle-related adverse events

Temporary dose interruption of ODOMZO therapy may be required for CPK elevations and muscle-related adverse events.

Table 1 summarises recommendations for dose interruption of ODOMZO therapy in the management of CPK elevations and muscle-related adverse events (such as myalgia, myopathy, and/or spasm).

Table 1 Recommended Dose Modifications and Management for CPK Elevations and Muscle-related Adverse Events

Severity of CPK elevation	Dose modifications* and management recommendations
Grade 1 [CPK elevation >ULN - 2.5 x ULN]	<ul style="list-style-type: none">Continue treatment at the same dose and monitor CPK levels weekly until resolution to baseline level and then monthly thereafter. Monitor muscle symptoms for changes until resolution to baseline.Check renal function (serum creatinine) regularly and ensure that patient is adequately hydrated.
Grade 2 without renal impairment (serum Cr ≤ ULN) [CPK elevation >2.5 x ULN - 5 x ULN]	<ul style="list-style-type: none">Interrupt treatment and monitor CPK levels weekly until resolution to baseline level.Monitor muscle symptoms for changes until resolution to baseline. Upon resolution, resume treatment at the same dose level and measure CPK monthly thereafter.Check renal function (serum creatinine) regularly and ensure that patient is adequately hydrated.If symptoms re-occur, interrupt treatment until resolution to baseline. If symptoms persist despite dose interruption, consider discontinuing treatment.
Grade 2 with renal impairment (serum Cr > ULN)	<ul style="list-style-type: none">If renal function is impaired, interrupt treatment and ensure that the patient is adequately hydrated and evaluate other secondary causes of renal impairment.Monitor CPK and serum creatinine levels weekly until resolution to baseline. Monitor muscle symptoms for changes until resolution to baseline.If CPK and serum creatinine levels return to baseline, treatment can be resumed. Measure CPK levels weekly for 2 months and monthly thereafter. If symptoms persist despite dose interruption, discontinue treatment permanently.
Grade 3 or 4 without renal impairment (serum Cr ≤ ULN) [Grade 3 (CPK elevation >5 x ULN - 10 x ULN)] [Grade 4 (CPK elevation >10 x ULN)]	<ul style="list-style-type: none">Interrupt treatment and monitor CPK levels weekly until resolution to baseline. Monitor muscle symptoms for changes until resolution to baseline.Check renal function (serum creatinine) regularly and ensure that patient is adequately hydrated.If renal function is not impaired and CPK resolves to baseline, treatment can be resumed. CPK levels should be measured weekly for 2 months after re-administration of ODOMZO and monthly thereafter. If symptoms persist despite dose interruption, consider discontinuing treatment.

Severity of CPK elevation	Dose modifications* and management recommendations
Grade 3 or 4 with renal impairment (serum Cr > ULN)	<ul style="list-style-type: none"> • If renal function is impaired, discontinue treatment and ensure that the patient is adequately hydrated and evaluate other secondary causes of renal impairment. • Monitor CPK and serum creatinine levels weekly until resolution to baseline. Monitor muscle symptoms for changes until resolution to baseline.

*The above recommendations for dose modifications are based on the Common Terminology Criteria for Adverse Events (CTCAE) v4.03.

CPK: creatine phosphokinase; Cr: creatinine; ULN: upper limit of normal.

Other dose interruptions

Management of severe or intolerable adverse reactions may require temporary dose interruption or treatment discontinuation.

When dose interruption is required, consider resuming ODOMZO at the same dose after resolution of the adverse reaction to \leq Grade 1. Due to the long half-life of ODOMZO the full effect of a dose interruption of ODOMZO on several adverse events is expected to generally occur after a few weeks (see Section 10.3 Pharmacokinetics).

Special Populations

Patients with hepatic impairment

No initial dose adjustment is necessary in patients with hepatic impairment. Based on a single dose PK study, sonidegib half-life was prolonged in subjects with moderate or severe hepatic impairment when compared to subjects with normal hepatic function (see Section 10 Action and Clinical Pharmacology – Pharmacokinetics - Special Populations and Conditions). Therefore, higher drug accumulation and exposures at steady state of sonidegib following repeated doses are expected. Patients with baseline hepatic impairment should be closely monitored for sonidegib toxicity and hepatic function. ODOMZO should be permanently discontinued if liver function deteriorates. No efficacy and safety data are available in patients with severe hepatic impairment.

Patients with renal impairment

ODOMZO has not been studied in a dedicated pharmacokinetic study in patients with renal impairment. Based on the available data, ODOMZO elimination via the kidney is negligible. A population pharmacokinetic analysis found that mild or moderate renal impairment did not have a significant effect on the exposure of ODOMZO, suggesting that dose adjustment is not necessary in those patients. No clinical data are available in patients with severe renal impairment.

Geriatric (≥ 65 years)

Safety and efficacy data in patients aged 65 years and older do not suggest that a dosage adjustment is required in these patients.

Pediatric

The safety and efficacy of ODOMZO in children and adolescents aged below 18 years with basal cell carcinoma have not been established. No data are available. Due to the safety concerns (see Section 16 Non-Clinical Toxicology), ODOMZO is contraindicated in children and adolescents aged below 18 years.

4.3 Administration

Swallow ODOMZO capsules whole. Do not chew or crush. The capsules must not be opened due to risk of teratogenicity.

Do not administer ODOMZO with food. ODOMZO should be taken orally once daily on an empty stomach, at least 1 hour before or 2 hours after a meal.

If vomiting occurs during the course of the treatment, patients should resume dosing with the next scheduled dose.

4.4 Reconstitution

Not applicable

4.5 Missed Dose

If a dose of ODOMZO is missed, patients should be instructed not to take the missed dose but to resume dosing with the next scheduled dose.

5 OVERDOSAGE

There is no antidote for sonidegib. In earlier clinical trials, patients were administered ODOMZO at doses above the clinically recommended dose. Serious adverse events including abnormal hepatic function, rhabdomyolysis, and depressed level of consciousness were reported in those patients. Rhabdomyolysis was reported as a serious adverse reaction in some patients leading to treatment discontinuation (see Section 7 Warnings and Precautions).

Patients should be monitored closely for adverse events and given appropriate supportive measures in all cases of overdose.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Capsules / 200 mg sonidegib (as phosphate)	Colloidal silicon dioxide, crospovidone, lactose monohydrate, magnesium stearate, poloxamer, sodium lauryl sulfate. Hard-capsule shell: gelatin, red iron oxide, titanium dioxide. Printing ink: ammonium hydroxide, black iron oxide, propylene glycol, shellac.

Each ODOMZO capsule has an opaque pink color with 'SONIDEGIB 200MG' printed on the capsule body and 'NVR' printed on the cap in black ink. ODOMZO capsules are supplied as a bottle of 30 capsules.

7 WARNINGS AND PRECAUTIONS

Please see the Serious Warnings and Precautions Box at the beginning of Part I: Health Professional Information.

Carcinogenesis and Mutagenesis

Patients with advanced BCC have an increased risk of developing cutaneous squamous cell carcinoma (cuSCC). Cases of cuSCC have been reported in advanced BCC patients treated with ODOMZO. It has not been determined whether cuSCC is related to ODOMZO treatment. Therefore, all patients should be monitored routinely while taking ODOMZO and cuSCC should be treated according to the standard of care.

Monitoring and Laboratory Tests

Obtain baseline serum creatine phosphokinase (CPK) and creatinine levels prior to initiating ODOMZO, periodically during treatment, and as clinically indicated (e.g., if muscle symptoms are reported). Obtain serum creatinine and CPK levels at least weekly in patients with musculoskeletal adverse reactions with concurrent serum CPK elevation greater than 2.5 times ULN until resolution of clinical signs and symptoms (see Section 7 Warnings and Precautions - Musculoskeletal).

For pregnancy test requirements for Females of Childbearing Potential (FCBP), see Section 7 Warnings and Precautions - Sexual Health, *Reproduction*.

Musculoskeletal

Skeletal muscle toxicity

Musculoskeletal adverse reactions, which may be accompanied by serum creatine phosphokinase (CPK) elevations, occur with ODOMZO and other drugs which inhibit the hedgehog pathway.

Muscle spasms, myalgia, and cases of CPK elevations were very commonly observed in the BOLT trial. The majority of patients treated with ODOMZO 200 mg daily who had Grade 2 or higher CPK elevations developed muscle symptoms prior to the CPK elevations. For most patients, muscle symptoms and CPK elevations resolved with appropriate management.

In the pivotal trial (BOLT), at the 42-month analysis, musculoskeletal adverse reactions occurred in 76% (60/79) of patients treated with ODOMZO 200 mg daily with 5% (4/79) reported as Grade 3 or 4. The most frequent manifestations of musculoskeletal adverse reactions reported as an adverse event were muscle spasms (56%), musculoskeletal pain (39%), and myalgia (19%). Overall, 6% of patients treated with ODOMZO 200 mg were discontinued from the study due to musculoskeletal events. Increased serum CPK laboratory values occurred in 61% (48/79) of patients with 8% (6/79) of patients having Grade 3 or 4 serum CPK elevations (see Section 8 Adverse Reactions). Musculoskeletal pain and myalgia usually preceded serum CPK elevation. Among patients with Grade 2 or higher CPK elevations, the median time to onset was 13 weeks (range: 2 to 39 weeks) and the median time to resolution (to ≤ Grade 1) was 12 days (95% confidence interval [CI]: 8 to 14 days).

Rhabdomyolysis was reported in 1 patient (1%) in the 200 mg cohort and 5 patients (3%) in the 800 mg cohort. At least 5 cases of rhabdomyolysis were reported in patients treated with above the clinically recommended dose in 2 Phase I studies. Some cases were reported as serious, leading to treatment discontinuation. In a retrospective analysis, rhabdomyolysis was defined as

CPK levels >10-fold above the pre-treatment or baseline level plus a 1.5-fold increase in serum creatinine from the pre-treatment or baseline level, or >10x upper limit of normal if no baseline level reported. No reported cases in the BOLT study were confirmed based on this definition. One reported case in a patient treated with ODOMZO 800 mg in a Phase I study was confirmed.

Obtain baseline serum CPK and creatinine levels prior to initiating ODOMZO, periodically during treatment, and as clinically indicated (e.g., if muscle symptoms are reported). Obtain serum creatinine and CPK levels at least weekly in patients with musculoskeletal adverse reactions with concurrent serum CPK elevation greater than 2.5 times ULN until resolution of clinical signs and symptoms. Depending on the severity of symptoms, temporary dose interruption or discontinuation may be required for musculoskeletal adverse reactions or serum CPK elevation (see Section 4 Dosage and Administration - Section 4.2 Recommended Dose).

Advise patients starting therapy with ODOMZO of the risk of muscle-related adverse reactions. Advise patients to report promptly any new unexplained muscle pain, tenderness or weakness occurring during treatment or that persists after discontinuing ODOMZO.

Sexual Health

Reproduction

Embryo-fetal death or severe birth defects

ODOMZO can cause embryo-fetal death or severe birth defects when administered to a pregnant woman. In animal reproduction studies, sonidegib was embryotoxic, fetotoxic, and teratogenic at maternal exposures below the recommended human dose of 200 mg (see Section 16 Non-Clinical Toxicology).

Because of the risk of embryo-fetal toxicity, a female patients of childbearing potential must not be given ODOMZO until pregnancy is excluded. ODOMZO is only available through a controlled distribution program called the ODOMZO Pregnancy Prevention Program (OPPP). The OPPP is designed to assist healthcare professionals and patients to avoid embryo-fetal exposure to ODOMZO.

Female of Childbearing Potential (FCBP)

Definition of FCBP in the OPPP

A FCBP is defined as a female who meets at least one of the following criteria:

- Is menstruating,
- Is amenorrhoic and has not entered clinically confirmed menopause,
- Is pre-menopausal, and
- Does not qualify as a Female of Non-Childbearing Potential (FNCPB).

A FNCPB is defined in the OPPP as a female who does not meet one of the above FCBP criteria, and:

- Has entered clinically confirmed menopause (e.g., in natural menopause for ≥12 months), or
- Has had a hysterectomy and/or a bilateral oophorectomy, or
- Has premature ovarian failure confirmed by a gynecologist, or
- Has one of the following:
 - An XY genotype,

- Turner's syndrome, or
- Uterine agenesis

For FCBP, ODOMZO is contraindicated unless **ALL** of the following conditions are met:

- She is capable of understanding and carrying out instructions. In some cases, the patient will need a competent support person to ensure OPPP compliance.
- She must agree to comply with all OPPP requirements.
- She must be informed of and understands that ODOMZO exposes a teratogenic risk to the unborn child.
- She must be willing and able to comply with the pregnancy testing requirements noted in detail below, which includes negative pregnancy test within 7 days prior to initiating ODOMZO treatment, on-going monthly pregnancy tests during the treatment and monthly tests for 20 months following discontinuation of treatment.
- She has a consultation with an appropriate specialist to discuss the most appropriate **two** simultaneous contraceptive methods to be used.
- She must be willing and able to comply with the effective contraceptive measures noted in detail below, which includes the simultaneous use of **two** methods of recommended contraception, unless she commits to not having sexual intercourse (abstinence).
- She understands that she must contact her physician immediately if any of the following occur during treatment and during the 20 months after her final dose:
 - She becomes pregnant or thinks for any reason that she may be pregnant,
 - She misses her expected menstrual period,
 - She stops using contraception unless she commits to not having sexual intercourse (abstinence),
 - She needs to change contraception.

Pregnancy testing requirements for FCBP

- A FCBP must not be given ODOMZO until pregnancy is excluded.
- Even if abstinence is the chosen method of contraception, a medically supervised pregnancy test with a minimum sensitivity of 25 mIU/mL must be performed:
 - Within 7 days prior to initiating ODOMZO treatment,
 - Monthly during treatment (including dose interruption), and
 - Monthly, for 20 months, after stopping treatment with ODOMZO.
- Patients who present with amenorrhea or abnormal menstrual bleeding during treatment with ODOMZO should continue monthly pregnancy testing unless confirmed as having changed to a risk classification of FNCBP.
- Dates and results of all pregnancy tests must be documented and kept in the patient's medical charts.
- For FCBP, continuation of treatment will require a new prescription each month to allow for monthly pregnancy testing.

Contraception requirements for FCBP

- Unless otherwise recommended by their healthcare professional for medical reasons, FCBP must use **two** acceptable forms of contraception together (1 acceptable form of highly effective primary contraception and 1 acceptable form of barrier method contraception) every time they have sex with a male:
 - For at least 4 weeks before starting treatment with ODOMZO,
 - During ODOMZO treatment (including during dose interruption), and
 - Monthly, for 20 months, after stopping treatment with ODOMZO.

- Contraceptive advice must be given to the individual patient by a healthcare professional as effectiveness of contraception methods can vary.
- The acceptable forms of primary contraception in the OPPP (where medically appropriate) are:
 - Intrauterine device
 - Sterilization (tubal ligation for females, vasectomy for male partners)
 - Hormonal methods (combination oral contraceptives, hormonal patches, hormonal injections, vaginal rings, implants)
- The acceptable forms of barrier method contraception are:
 - Male condom with spermicide
 - Diaphragm with spermicide
 - Cervical cap with spermicide
 - Contraceptive sponge with male condom

Pregnancy reporting requirements for FCBP

- Female patients must contact their physician immediately if they suspect they may be pregnant.
- If ODOMZO is used during pregnancy or if a patient becomes pregnant while taking ODOMZO, treatment must be immediately discontinued.
- The patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity, for further evaluation and counseling.
- Report any suspected exposure to ODOMZO during pregnancy immediately to the OPPP at 1-844-266-2974. Pregnancy reporting forms are also available for healthcare professionals on www.Odomzo.ca.
- Advise the patient to share information pertaining to her pregnancy outcomes when she is contacted by the OPPP.

Male Patients

To avoid potential fetal exposure during pregnancy:

- He is capable of understanding and carrying out instructions. In some cases, the patient will need a competent support person to ensure OPPP compliance.
- He must agree to comply with all OPPP requirements.
- He must be informed and understand that ODOMZO may pass into the semen and ODOMZO exposes a teratogenic risk to the unborn child if he engages in unprotected sexual activity with a pregnant woman.
- He must inform his female sexual partner(s) that he is taking ODOMZO and the potential serious risks to a developing fetus should the partner(s) become pregnant during his course of treatment with ODOMZO (including dose interruption) and 6 months after stopping treatment with ODOMZO.
- He must always use the recommended contraception and for at least 6 months after his final dose.
- He will tell his healthcare provider if his female partner becomes pregnant while he is taking ODOMZO or for at least 6 months after his final dose.

Contraception requirement for male patients

Male patients, even those who have had a vasectomy, must always use a condom (with spermicide, if available) when having sex with a female partner while taking ODOMZO (including dose interruptions) and for 6 months after ending treatment.

Pregnancy reporting requirements for male patients

- The male patient must contact his physician immediately if his female sexual partner(s) may be pregnant.
- If the male patient's female sexual partner was exposed to his semen and becomes pregnant, she should be referred to an obstetrician/gynecologist experienced in reproductive toxicity, for further evaluation and counseling.
- Any suspected exposure to ODOMZO during pregnancy should be reported immediately to the OPPP at 1-844-266-2974. Pregnancy reporting forms are also available for healthcare professionals on www.Odomzo.ca.
- Advise females who may have been exposed to ODOMZO during pregnancy through seminal fluid to share information pertaining to her pregnancy outcomes when she is contacted by the OPPP.

Semen Donation

Male patients must not donate semen while taking ODOMZO (including dose interruptions) and for at least 6 months after ending treatment.

Blood Donation

Advise all patients not to donate blood or blood products while taking ODOMZO (including dose interruptions) and for at least 20 months after the last dose of ODOMZO, because their blood or blood products might be given to a female of reproductive potential.

Fertility

- ODOMZO can cause amenorrhea (absence of menstrual periods) in females who are able to become pregnant (see Section 8.2 Clinical Trial Adverse Reactions, *Amenorrhea*). It is not known if amenorrhea is permanent.
- ODOMZO may irreversibly impair fertility (see Section 16 Non-Clinical Toxicology).
- Fertility preservation strategies should be discussed with women of childbearing potential prior to starting treatment with ODOMZO.

7.1 Special Populations

7.1.1 Pregnant Women

Based on its mechanism of action and data from animal reproduction studies, ODOMZO can cause fetal harm when administered to a pregnant woman. There are no available data on the use of ODOMZO in pregnant women. In animal reproduction studies, oral administration of sonidegib during organogenesis at doses substantially below the recommended human dose of 200 mg resulted in embryotoxicity, fetotoxicity, and teratogenicity in rabbits. Teratogenic effects observed included severe midline defects, missing digits, and other irreversible malformations. Advise pregnant women of the potential risk to a fetus (see Section 16 Non-Clinical Toxicology).

Due to the risk of embryofetal death or severe birth defects caused by sonidegib, women taking ODOMZO must not be pregnant or become pregnant during treatment and for 20 months after ending treatment (see Section 2 Contraindications and Section 7 Warnings and Precautions - *Reproduction*).

ODOMZO is contraindicated in woman of childbearing potential who do not comply with the ODOMZO Pregnancy Prevention Program.

In case of pregnancy or missed menstrual periods

If the patient does become pregnant, misses a menstrual period, or suspects for any reason that she may be pregnant, she must notify her treating physician immediately.

Persistent lack of menses during treatment with ODOMZO should be assumed to indicate pregnancy until medical evaluation and confirmation.

7.1.2 Breast-feeding

No data are available regarding the presence of sonidegib in human milk, the effects of the drug on the breast-fed infant, or the effects of the drug on milk production. Because of the potential for serious adverse reactions in breast-fed infants, advise women to avoid breast-feeding during treatment with ODOMZO and for 20 months after the last dose.

7.1.3 Pediatrics

Pediatrics (<18 years of age): The safety and effectiveness of ODOMZO have not been established in pediatric patients; therefore, Health Canada has not authorized an indication for pediatric use.

Effects on Post-Natal Development

Epiphyseal disorders, including premature fusion of the epiphyses, have been reported in pediatric patients exposed to ODOMZO in a clinical trial. In some cases, pediatric patients treated with other hedgehog pathway inhibitors have experienced progression of epiphyseal fusion despite discontinuation of the hedgehog pathway inhibitor. Precocious puberty has been reported with other hedgehog pathway inhibitors. Due to the safety concerns (see Section 16 Non-Clinical Toxicology), ODOMZO is contraindicated in children and adolescents below the age of 18 (see Section 2 Contraindications).

7.1.4 Geriatrics

Of the 229 patients who received ODOMZO (79 patients receiving 200 mg daily and 150 patients receiving 800 mg daily) in the BOLT trial, 54% were 65 years and older, while 28% were 75 years and older. No overall differences in effectiveness were observed between these patients and younger patients. There was a higher incidence of serious adverse reactions, Grade 3 and 4 adverse reactions, and adverse reactions requiring dose interruption or discontinuation in patients ≥ 65 years compared with younger patients; this was not attributable to an increase in any specific adverse event.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety of ODOMZO (sonidegib) was evaluated in 229 adult patients with locally advanced BCC (laBCC) or metastatic BCC (mBCC) who were randomized to treatment with ODOMZO 200 mg/day (n=79) or ODOMZO 800 mg/day (n=150). The data described below reflect the cohort of ODOMZO 200 mg daily in 79 patients with laBCC (n=66) or mBCC (n=13) enrolled in the BOLT trial.

Overall, 98% of patients treated with ODOMZO 200 mg reported at least one adverse event.

The most common adverse reactions occurring in $\geq 10\%$ of patients treated with ODOMZO 200 mg were muscle spasms, alopecia, fatigue, dysgeusia, nausea, musculoskeletal pain, diarrhea, weight decreased, decreased appetite, myalgia, abdominal pain, headache, pain, vomiting and pruritus (Table 3).

Overall, 43% of patients treated with ODOMZO 200 mg reported Grade 3 or 4 adverse events. The most common Grade 3 adverse reactions occurring in $\geq 2\%$ of patients treated with ODOMZO 200 mg were fatigue, weight decreased, muscle spasms, and hypotension (Table 3).

One death occurred in a laBCC patient while on treatment with sonidegib 200 mg which was determined by the investigator to not be related to study drug. Overall, 20% of patients treated with ODOMZO 200 mg reported serious adverse events (SAEs). SAEs in the sonidegib 200 mg group occurred as single incidences (i.e., $< 2\%$) except for pneumonia which occurred in two patients (3%). Four patients (5%) in the 200 mg experienced SAEs that were considered related by the investigator (blood CPK increased [2 patients], rhabdomyolysis, dyspnea, and hypoglycemia).

Overall, 43% of patients treated with ODOMZO 200 mg required a dose interruption or a dose adjustment due to an adverse event. The most common ($\geq 5\%$) adverse events leading to a dose interruption/adjustment were nausea, vomiting, diarrhea, blood CPK increased and lipase increased. Overall, 30% of patients in the 200 mg group with laBCC or mBCC discontinued due to an adverse event. The most common ($\geq 2\%$) adverse events leading to discontinuation were muscle spasms, asthenia, dysgeusia, nausea, fatigue, decreased weight and decreased appetite.

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Patients were followed for at least 42 months unless discontinued earlier. The median duration of exposure with ODOMZO 200 mg was 11.0 months (range 1.3 to 53.2 months). The study population characteristics for patients in the sonidegib 200 mg group were: median age of 67 years (range 25 to 92; 60% were ≥ 65 years), 61% male, and 90% White.

Table 3 Adverse Reactions Occurring in ≥5% of laBCC and mBCC Patients in the BOLT Trial

Adverse Reaction*	ODOMZO 200 mg (N=79)	
	All Grades ^a n (%)	Grade 3 n (%)
Gastrointestinal disorders		
Nausea	31 (39)	1 (1)
Diarrhea	25 (32)	1 (1)
Abdominal pain ^b	15 (19)	0 (0)
Vomiting	9 (11)	1 (1)
Dyspepsia	7 (9)	1 (1)
Constipation	6 (8)	1 (1)
Dry mouth	4 (5)	0 (0)
General disorders and administration site conditions		
Fatigue ^c	39 (49)	4 (5)
Pain ^d	12 (15)	1 (1)
Investigations		
Weight decreased	24 (30)	4 (5)
Metabolism and nutrition disorders		
Decreased appetite	18 (23)	1 (1)
Musculoskeletal and connective tissue disorders		
Muscle spasms ^e	44 (56)	2 (3)
Musculoskeletal pain ^f	31 (39)	1 (1)
Myalgia	15 (19)	0 (0)
Myopathy ^g	4 (5)	0 (0)
Nervous system disorders		
Dysgeusia ^h	36 (46)	0 (0)
Headache	12 (15)	1 (1)
Dizziness	7 (9)	1 (1)
Paresthesia	4 (5)	0 (0)
Psychiatric disorders		
Depression	5 (6)	0 (0)
Skin and subcutaneous tissue disorders		
Alopecia ⁱ	42 (53)	0 (0)

Adverse Reaction*	ODOMZO 200 mg (N=79)	
	All Grades ^a n (%)	Grade 3 n (%)
Pruritus ^j	9 (11)	0 (0)
Rash ^k	7 (9)	0 (0)
Vascular disorders		
Hypotension	4 (5)	2 (3)

* Adverse reactions are reported as preferred terms based on Medical Dictionary for Regulatory Activities (MedDRA) terminology, Version 23.0, except grouped terms where indicated; the frequency of an adverse reaction is derived from all treatment-emergent adverse events. No Grade 4 adverse reactions were reported.

^a Based on Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.

^b Abdominal pain includes abdominal pain and abdominal pain upper.

^c Fatigue includes asthenia, fatigue, lethargy, and malaise.

^d Pain includes ear pain, eye pain, facial pain, gingival pain, oral pain, oropharyngeal pain, pain, and pain of skin.

^e Muscle spasms includes muscle spasms and muscle tightness.

^f Musculoskeletal pain includes arthralgia, back pain, musculoskeletal chest pain, musculoskeletal pain, pain in extremity, and pain in jaw.

^g Myopathy includes muscular weakness.

^h Dysgeusia includes ageusia.

ⁱ Alopecia includes alopecia and madarosis.

^j Pruritus includes pruritus, pruritus generalized, and eye pruritus.

^k Rash includes dermatitis acneiform, dry skin, rash, and rash pruritic.

Amenorrhea

Amenorrhea lasting for at least 18 months occurred in 2 of 14 pre-menopausal women treated with ODOMZO 200 mg or 800 mg once daily.

8.3 Less Common Clinical Trial Adverse Reactions

Adverse reactions occurring in <5% of patients treated with ODOMZO 200 mg in the BOLT trial:

Eye disorders: dry eye

Gastrointestinal disorders: gastrointestinal reflux disease

Metabolism and nutrition disorders: dehydration

Musculoskeletal and connective tissue disorders: rhabdomyolysis, trigger finger

Nervous system disorders: peripheral neuropathy

Skin and subcutaneous tissue disorders: hair growth abnormal

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Changes in laboratory parameters were observed in the clinical trials conducted (see Table 4). The most commonly reported Grade 3/4 laboratory abnormalities with an incidence of $\geq 5\%$ occurring in patients treated with ODOMZO 200 mg were lipase increased and serum creatine phosphokinase (CPK) increased (Table 4).

Table 4 Key Laboratory Abnormalities^a Seen in $\geq 5\%$ of Patients in the BOLT Trial

Laboratory Test	ODOMZO 200 mg (N=79)	
	All Grades n (%)	Grades 3/4 n (%)
Chemistry		
Serum creatinine increased	73 (92 ^b)	0 (0)
Serum creatine phosphokinase (CPK) increased	48 (61)	6 (8)
Blood glucose increased	40 (51)	3 (4)
Lipase increased	35 (44)	10 (13)
Alanine aminotransferase (ALT) increased	16 (20)	3 (4)
Aspartate aminotransferase (AST) increased	16 (20)	3 (4)
Potassium increased	14 (18)	3 (4)
Amylase increased	13 (17)	1 (1)
Hematology		
Hemoglobin decreased	25 (32)	0 (0)
Lymphocyte count decreased	22 (28)	2 (3)

^a Based on worst post-treatment laboratory value regardless of baseline; grading by CTCAE v4.03.

^b The serum creatinine level remained within normal range in 76% (60/79) of patients.

8.5 Clinical Trial Adverse Reactions (Pediatrics)

Epiphyseal disorders, including premature fusion of the epiphyses, have been reported in pediatric patients exposed to ODOMZO in a clinical trial. In some cases, pediatric patients treated with other hedgehog pathway inhibitors have experienced progression of epiphyseal fusion despite discontinuation of the hedgehog pathway inhibitor. Precocious puberty has been reported with other hedgehog pathway inhibitors.

8.6 Post-Market Adverse Reactions

No new adverse reactions have been observed post-market that are attributable to ODOMZO.

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions Box

Not applicable

9.2 Overview

Sonidegib is eliminated predominantly by metabolism, involving CYP3A as a primary enzyme. Strong CYP3A inhibitors or long-term use (greater than 14 days) of moderate CYP3A inhibitors should be avoided. Strong and moderate CYP3A inducers should also be avoided (see Section 9.2 Drug-Drug Interactions below).

9.3 Drug-Drug Interactions

Effects of Other Drugs on Sonidegib

Strong and Moderate CYP3A Inhibitors

Ketoconazole increased sonidegib AUC_{0-10d} by 2.2-fold and the C_{max} by 1.5-fold. The magnitude of exposure change of sonidegib was estimated to be even higher following repeated doses of sonidegib and with continuous dosing of ketoconazole. Avoid concomitant administration of ODOMZO with strong CYP3A inhibitors. Strong CYP3A inhibitors include, but are not limited to, ritonavir, saquinavir, telithromycin, ketoconazole, itraconazole, voriconazole, and posaconazole.

Avoid concomitant administration of ODOMZO with moderate CYP3A inhibitors. If a moderate CYP3A inhibitor must be used, administer the moderate CYP3A inhibitor for less than 14 days and monitor closely for adverse reactions particularly musculoskeletal adverse reactions.

Strong and Moderate CYP3A Inducers

Rifampicin decreased sonidegib AUC_{0-10d} by 72% and C_{max} by 54%. Avoid concomitant administration of ODOMZO with strong or moderate CYP3A inducers, including but not limited to carbamazepine, efavirenz, modafinil, phenobarbital, phenytoin, rifabutin, rifampin and St. John's Wort (*Hypericum perforatum*).

Gastric Acid Reducing Agents

Esomeprazole, a proton pump inhibitor, decreased ODOMZO exposure by 32% - 38%. Concomitant administration of an acid reducing agent reduced sonidegib bioavailability by 31% based on a population PK analysis. Patients may experience reduced efficacy when an acid reducing agent is concomitantly used with ODOMZO.

Effects of Sonidegib on Other Drugs

Effect of Sonidegib on Cytochrome P450 Enzymes

Concomitant administration of ODOMZO, a competitive inhibitor of CYP2B6 and CYP2C9 in vitro, did not alter the systemic exposure of bupropion (a CYP2B6 substrate) or warfarin (a CYP2C9 substrate) in patients. The peak concentration of S- and R-warfarin, however, was delayed from 1 to 2 hours post dose.

In vitro studies suggested that sonidegib does not induce CYP1A2, CYP2B6 or CYP3A expression or activity.

Effect of Sonidegib on Transporters

Sonidegib is an inhibitor of breast cancer resistance protein (BCRP) in vitro. Concomitant use of BCRP transporter substrates with narrow therapeutic index should be avoided. Drugs that are BCRP substrates with narrow therapeutic index include but not limited to methotrexate, mitoxantrone, irinotecan, and topotecan.

In vitro studies suggested that sonidegib does not inhibit P-glycoprotein, MRP2, OATP1B1, OATP1B3, OAT1, OAT3, OCT1 or OCT2.

9.4 Drug-Food Interactions

The bioavailability of sonidegib is increased by over 7-fold with a high-fat meal and by 2-fold with a light meal (see Section 10.3 Pharmacokinetics, Absorption, Effect of Food). ODOMZO must be taken at least 1 hour before or 2 hours after a meal.

Avoid grapefruit products/juice, and Seville oranges/juice when treated with ODOMZO.

9.5 Drug-Herb Interactions

Patients should avoid using St. John's Wort (*Hypericum perforatum*) as it is a CYP3A inducer (see Section 9.3 Strong and Moderate CYP3A Inducers above). Interactions with other herbal products have not been established.

9.6 Drug-Laboratory Test Interactions

Interactions of ODOMZO with laboratory tests have not been established.

9.7 Drug-Lifestyle Interactions

Interactions of ODOMZO with lifestyle have not been established.

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Sonidegib is an inhibitor of the Hedgehog (Hh) pathway. Sonidegib binds to and inhibits Smoothened (SMO), a transmembrane protein involved in the Hh signal transduction pathway. SMO leads to the activation and nuclear localization of glioma-associated oncogene (Gli) transcription factors and induction of Hh target genes. Many of these genes are involved in proliferation, survival, and differentiation. SMO inhibition by sonidegib prevents Hh signal transduction resulting from either inactivating mutations in PTCH1 or activating mutations in SMO.

10.2 Pharmacodynamics

Tumour response was independent of ODOMZO dose or plasma trough concentration in the dose range of 200 mg to 800 mg with data obtained from the BOLT study. A logistic regression analysis of the probability of objective response (CR or PR) vs. Week 5 sonidegib C_{min} did not show a relationship between exposure and efficacy based on the Phase II pivotal study in patients with BCC. The median time to tumor response was 4 months (see Section 14. Clinical Trials) when steady state PK of sonidegib was reached (see Section 10.3 Pharmacokinetics

below). However, a logistic regression analysis of objective response vs. sonidegib C_{min} at Week 17 was not conducted.

Effects on creatine phosphokinase (CPK)

The relationship between sonidegib plasma exposure and occurrence of grade 3 or 4 CPK was assessed from data obtained from 4 clinical studies comprising 336 patients. The results indicate a higher sonidegib exposure poses a higher risk for grade 3 or 4 CPK elevation. In addition, male patients have a higher risk of experiencing grade 3 or 4 CPK elevation than female patients.

Cardiac Electrophysiology

The sonidegib plasma concentration-QTc analysis showed that the upper bound of one-sided 95% confidence interval for increase in QT interval corrected using Fridericia method (QTcF) was below 5 msec at steady-state C_{max} for 800 mg daily doses, which provide 2.3-fold plasma exposure compared with the recommended 200 mg dose. Therefore, the therapeutic dose of ODOMZO is not expected to cause clinically significant QTc prolongation.

10.3 Pharmacokinetics

Following oral administration under fasted condition in patients, sonidegib exhibited dose-proportional increases in the area under the curve (AUC) and the maximal concentration (C_{max}) over the dose range of 100 mg to 400 mg, but less than dose-proportional increases at doses greater than 400 mg. Based on a population PK analysis, steady-state was reached approximately 4 months after starting ODOMZO and the estimated accumulation at steady-state was 19-fold. Following a once daily dose of 200 mg sonidegib, the estimated mean steady-state C_{max} is 1030 ng/mL, AUC_{0-24h} is 22 $\mu\text{g}\cdot\text{h/mL}$ and minimal concentration (C_{min}) is 890 ng/mL (Table 5).

Table 5 Estimated Sonidegib Pharmacokinetic Parameters at Steady State in Patients based on Population PK Analysis

Dose	C_{max} (ng/mL)	$t_{1/2}$ (days)	AUC_{0-24h} ($\mu\text{g}\cdot\text{h/mL}$)	C_{min} (ng/mL)	CL/F (L/h)	Vss/F (L)
200 mg qd at steady state	858 (317, 2351)	28 (7, 120)	18 (6, 53)	705 (224, 2170)	10 (4, 28)	9166 (3166, 27881)

Values are presented as geometric mean (5th, 95th percentile).

Absorption:

Less than 10% of an oral dose of ODOMZO is absorbed. Following the administration of a single ODOMZO dose (100 mg to 3000 mg) under fasted conditions in patients, the median time-to-peak concentration (T_{max}) was 2 to 4 hours.

Effect of Food

A high-fat meal (approximately 1000 calories with 50% of calories from fat) increased exposure to sonidegib (geometric mean AUC_{inf} and C_{max}) by 7.4- to 7.8-fold. Administration of sonidegib with a light meal increases sonidegib exposures by 1.8-2.5-fold compared with fasted conditions. A moderate-fat meal taken 2 hours before administration of sonidegib increases exposures by 55-77% compared with fasted conditions whereas, a moderate-fat meal taken 1 hour after administration of sonidegib provides exposure similar to the fasted conditions.

Distribution:

Based on the population PK analysis, the estimated apparent steady-state volume of distribution (V_{ss}/F) was 9,166 L. In vitro, sonidegib was greater than 99% bound to human plasma proteins or albumin and the binding was concentration independent up to 20 ng/mL of sonidegib.

Sonidegib binding to alpha-1 acid glycoprotein (AGP) was dependent on the concentrations of AGP (0.15 – 5 g/L) with a binding range of 92-99%.

In vitro studies suggested that sonidegib is not a substrate of P-glycoprotein, MRP2 or BCRP suggesting passive transport of sonidegib across the intestinal tract epithelial cells.

Metabolism:

Sonidegib is primarily metabolized by CYP3A. The main circulating compound was unchanged sonidegib (36% of total circulating radioactivity) in healthy male Caucasians in a mass balance study. The most prominent plasma metabolites were the amide hydrolysis product, LGE899 (15% of circulating radioactivity) and the oxidative morpholine cleavage product, LNC119 (13% of circulating radioactivity). The contributions to the pharmacological activity of sonidegib from these two metabolites is minimal.

Elimination:

The elimination of absorbed sonidegib occurred predominantly by metabolism. In the mass balance study, urinary excretion of the radioactivity was low (<5% of administered dose) and unchanged sonidegib could not be detected in the urine. Up to 89% of radioactivity administered was excreted as unchanged sonidegib via the feces.

The elimination half-life ($t_{1/2}$) of sonidegib estimated from population pharmacokinetic (PK) modeling was approximately 28 days.

Special Populations and Conditions

Age (median: 58 years; range: 20-93 years), body weight (median: 73 kg; range: 42-181 kg), and sex had no clinically meaningful effect on sonidegib steady-state exposure based on population PK analysis.

Pediatrics (<18 years of age): The safety, effectiveness and pharmacokinetics of ODOMZO have not been established in pediatric patients. Health Canada has not authorized an indication for pediatric use (see Section 1.1 Indications - Pediatrics).

Geriatrics (≥65 years of age): No clinically relevant difference in the steady-state AUC_{0-24h} of sonidegib was inferred between patients aged ≥65 years and aged <65 years based on population PK analysis.

Ethnic origin: A cross study comparison revealed that AUC_{inf} and C_{max} of sonidegib are 1.7- and 1.6-fold higher, respectively, in Japanese healthy subjects compared to Western healthy subjects (Whites and Blacks) following a single 200 mg dose of ODOMZO.

Hepatic Impairment:

The pharmacokinetics of sonidegib were examined in subjects with mild (Child-Pugh class A; n=8), moderate (Child-Pugh class B; n=8) or severe (Child-Pugh class C; n=9) hepatic impairment and in 8 healthy subjects with normal hepatic function. After a single oral dose administration, total C_{max} of sonidegib was 20%, 21% and 60% lower in mild, moderate and

severe hepatic impairment, respectively, compared to normal hepatic function. AUC_{last} was 35% lower in mild hepatic impairment, 14% higher in moderate hepatic impairment and 23% lower in severe hepatic impairment. AUC_{inf} of sonidegib was 31% lower, 44% higher and 16% lower in mild, moderate and severe hepatic impairment respectively. The median half-life of unbound sonidegib was prolonged by 2.2- and 2.5-fold in moderate and severe hepatic impairment, respectively, compared to normal hepatic function, suggesting a reduced clearance in those subjects. Therefore, increased drug accumulation and exposures of sonidegib at steady state following daily dosing cannot be excluded in subjects with moderate or severe hepatic impairment.

Renal Impairment: ODOMZO has not been studied in a dedicated PK study in patients with renal impairment. Based on population PK analysis, mild to moderate renal impairment (creatinine clearance 30 to 89 mL/min) had no clinically meaningful effect on sonidegib steady-state exposure. The effect of severe renal impairment (creatinine clearance <30 mL/min) on sonidegib pharmacokinetics is unknown.

11 STORAGE, STABILITY AND DISPOSAL

Store ODOMZO at 15°C to 30°C. Protect from moisture.

Keep out of sight and reach of children.

Disposal of unused/expired medicines: The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Use established “collection systems”, if available in your location.

12 SPECIAL HANDLING INSTRUCTIONS

No special handling instructions are required for ODOMZO.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

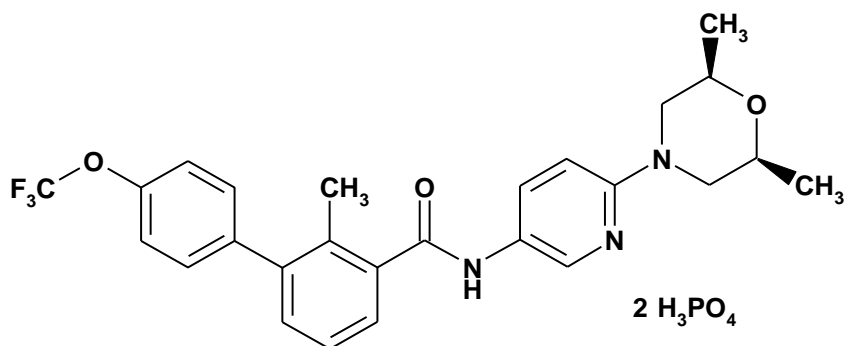
Common name: Sonidegib phosphate

Chemical name: N-[6-(cis-2,6-dimethylmorpholin-4-yl)pyridine-3-yl]-2-methyl-4'-(trifluoromethoxy) [1,1'-biphenyl]-3-carboxamide diphosphate

Molecular formula and molecular mass: $C_{26}H_{26}F_3N_3O_3 \cdot 2H_3PO_4$
681.49 daltons

Molecular formula and molecular mass of the free base:
 $C_{26}H_{26}F_3N_3O_3$
485.50 daltons

Structural formula:



Physicochemical properties: Sonidegib phosphate is a white to slightly yellow powder, and is practically insoluble.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Table 6 Summary of Patient Demographics for Clinical Trial in Patients with laBCC or mBCC, 42-month analysis (FAS)

Study	Trial design	Dosage, route of administration and duration	Study subjects (n)	Median age (Range)	Sex
BOLT	Phase II, randomized, multicentre, double-blind, multiple cohort clinical trial	ODOMZO 800 mg or 200 mg orally, once daily, until disease progression or intolerable toxicity	Patients with locally advanced basal cell carcinoma (laBCC) (n=194) or metastatic basal cell carcinoma (mBCC) (n=36) Total: n=230	66 (24, 93)	M (63%) F (37%)

The safety and efficacy of ODOMZO were evaluated in a single, multicentre, double-blind, multiple cohort clinical trial conducted in adult patients with laBCC (n=194) or mBCC (n=36) (Basal cell carcinoma Outcomes with LDE225 Treatment [BOLT] trial). Patients were randomized (2:1) to receive either ODOMZO 800 mg or 200 mg orally, once daily, until disease progression or intolerable toxicity. Randomization was stratified by stage of disease (laBCC or mBCC), laBCC disease histology (aggressive or non-aggressive), and geographic region (Australia, Europe, or North America). Patients with laBCC were required to have lesions for which radiotherapy was contraindicated or inappropriate (e.g., Gorlin syndrome or limitations because of location of tumor), that had recurred after radiotherapy, that were unresectable or for which surgical resection would result in substantial deformity, or that had recurred after prior surgical resection. Eligible patients had World Health Organization performance status ≤ 2 and adequate bone marrow, liver and renal function. Patients with neuromuscular disorders (e.g., inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis and spinal muscular atrophy) were excluded from the study. Concomitant use of drugs causing rhabdomyolysis was not permitted, except for pravastatin which could be used with caution. Patients were advised not to embark on strenuous exercise while on ODOMZO treatment.

Of the 230 patients randomised, 79 patients were assigned to ODOMZO 200 mg and 151 assigned to ODOMZO 800 mg (Full Analysis Set [FAS]). Of the 79 patients, 66 (83.5%) were laBCC patients and 13 (16.5%) were mBCC patients. Of the 66 laBCC patients randomized to ODOMZO 200 mg daily, three of these patients had a diagnosis of Gorlin Syndrome. The demographic characteristics of the 66 patients with laBCC were: median age of 67 years (range: 25 to 92 years; 58% were ≥ 65 years); 58% male, 89% White, and ECOG performance status of 0 (67%). Seventy-six percent of patients had prior therapy for treatment of BCC; this included surgery (73%), radiotherapy (18%), and topical/photodynamic therapies (21%). Approximately half of these patients (56%) had aggressive histology. No patients had received prior treatment with a Hedgehog pathway inhibitor.

The primary efficacy endpoint of the trial was objective response rate (ORR) as determined by blinded central review according to modified Response Evaluation Criteria in Solid Tumors (mRECIST) for patients with laBCC or RECIST version 1.1 for patients with mBCC. The key secondary efficacy endpoints included duration of response (DoR) and rate of complete response (CRR) according to mRECIST in patients with laBCC and RECIST 1.1 in patients with mBCC, as determined by central review. No statistical analyses were planned to compare efficacy results between the two dose cohorts. Other secondary endpoints included time to tumour response (TTR).

For patients with laBCC, the Independent Review Committee (IRC) Composite Overall Response was integrated from centrally evaluated magnetic resonance imaging (MRI) scans, digital clinical photographs and histopathology according to mRECIST. For laBCC, multiple punch biopsies were taken each time a response assessment was confounded by presence of lesion ulceration, cyst, and or scarring/fibrosis. MRI tumour response was evaluated by RECIST 1.1. Response by digital clinical photography was evaluated by World Health Organization (WHO) adapted criteria [partial response (PR): $\geq 50\%$ decrease in the sum of the product of perpendicular diameters (SPD) of the lesions, CR: disappearance of all lesions, progressive disease (PD): $\geq 25\%$ increase in the SPD of the lesions]. All modalities used must have demonstrated absence of tumor to achieve a composite assessment of complete response (CR).

14.2 Study Results

Table 7 Efficacy Results: laBCC Cohort per Central Review Assessment by FAS^a

	ODOMZO 200 mg
	Primary (6-month) analysis
	laBCC
	N=66
Objective response rate, n (%)	31 (47.0)
95% CI	(34.6, 59.7)
Best overall response, n (%)	
Complete response	2 (3.0)
Partial response	29 (43.9)
Disease stabilization	29 (43.9)
Disease progression	1 (1.5)
Unknown	5 (7.6)
Duration of response	
Median (months)	NE
95% CI	NE
^a FAS: Full analysis set; FAS included all randomised patients (intent-to-treat population). CI: confidence interval NE: not estimable	

42-month analysis

Patients with laBCC randomized to receive ODOMZO 200 mg daily were followed for at least 42 months unless discontinued earlier. The ORR was 56% (95% confidence interval: 43%, 68%), consisting of 3 (5%) complete responses and 34 (52%) partial responses. Based on the 42-month analysis, median duration of response was 26.1 months (95% CI: NE) and median time to tumour response was 4.0 months (95% CI: 3.8, 5.6) for patients with laBCC in the ODOMZO 200 mg group.

14.3 Comparative Bioavailability Studies

Not applicable

15 MICROBIOLOGY

Not applicable

16 NON-CLINICAL TOXICOLOGY

General Toxicology (Repeat dose toxicity)

The toxicity of daily doses of oral sonidegib was assessed by conducting repeat-dose toxicity studies of up to 26-weeks in duration in rats and dogs.

The majority of adverse effects of sonidegib can be attributed to its pharmacological mechanism of action on developmental pathways and effects in rats and dogs were similar. Most effects occurred close to the intended human exposures. These effects observed at clinically relevant exposures include closure of bone growth plates, effects on growing teeth (dentine dysplasia, ectopic dentin in the pulp, irregular dentin, altered shape of tooth and loss of incisors), effects on the male and female reproductive tract (see Reproductive and Developmental Toxicology), atrophy of the hair follicles with alopecia, gastrointestinal toxicity with body weight loss (distention of stomach and duodenum, hemorrhage in the stomach wall, loss of mucosa with inflammation, ulcerations, emesis and diarrhea with single cell necrosis and thinning of intestinal epithelium) and effects on lymph nodes (lymphoid depletion in the thymus and spleen, lymphocytolysis/lymphophagocytosis, GALT, and Peyer's patches). At exposures well above the clinical exposure, an additional target organ was the kidney (acute tubular necrosis and mineralization of tubular epithelium).

Body tremors along with significant increases in creatine phosphokinase were observed in rats administered oral sonidegib for 13 weeks or longer at ≥ 10 mg/kg/day (approximately ≥ 2 times the recommended human dose based on AUC).

Carcinogenicity

Carcinogenicity studies with sonidegib have not been performed.

Genotoxicity

Sonidegib was not mutagenic in the in vitro bacterial reverse mutation (Ames) assay and was not clastogenic or aneugenic in the in vitro human chromosome aberration assay or in vivo rat bone marrow micronucleus assay.

Reproductive and Developmental Toxicology

Sonidegib resulted in a lack of fertility when administered to female rats at ≥ 20 mg/kg/day (approximately 1.3 times the recommended human dose based on body surface area (BSA)). A reduction of the number of pregnant females, an increase in the number of early resorptions, and a decrease in the number of viable fetuses was also noted at 2 mg/kg/day (approximately 0.12 times the recommended human dose based on BSA). In addition, in a 6 month repeat-dose toxicology study in rats, effects on female reproductive organs included atrophy of the uterus and ovaries at doses of 10 mg/kg (approximately ≥ 2 times the exposure in humans at the recommended dose of 200 mg based on AUC). No adverse effects on fertility were noted when male rats were administered sonidegib at doses up to 20 mg/kg/day, the highest dose tested.

Daily oral administration of sonidegib to pregnant rabbits resulted in abortion, complete resorption of fetuses, or severe malformations at ≥ 5 mg/kg/day (approximately 0.05 times the recommended human dose based on AUC). Teratogenic effects included vertebral, distal limb and digit malformations, severe craniofacial malformations, and other severe midline defects. Skeletal variations were observed when maternal exposure to sonidegib was below the limit of detection.

Phototoxicity

ODOMZO was negative in an in vitro Balb/c mouse 3T3 fibroblast phototoxicity bioassay.

Juvenile Toxicity

In a 5-week juvenile rat toxicology study, effects of sonidegib were observed in bone, teeth, reproductive tissues, GI tract, lymphoid tissues and nerves at doses ≥ 10 mg/kg/day (approximately 1.2 times the recommended human dose based on AUC). Bone findings included thinning/closure of bone growth plate, decreased bone length and width, and hyperostosis. Findings in teeth included missing or fractured teeth, and atrophy. Reproductive tissue toxicity was evidenced by atrophy of testes, ovaries, and uterus, partial development of the prostate gland and seminal vesicles, and inflammation and aspermia of the epididymis. GI toxicity included abdominal distension, fecal changes including varying degrees of diarrhea with intestinal cryptal necrosis. Effect on lymphoid tissues included decrease in thymus weight, thymic lymphoid depletion and extramedullary hematopoiesis in the spleen. Nerve degeneration was also noted.

17 SUPPORTING PRODUCT MONOGRAPHS

Not applicable

**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION**

Pr**ODOMZO**®

Sonidegib Capsules

Read this carefully before you start taking ODOMZO and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about ODOMZO.

Serious Warnings and Precautions

ODOMZO should only be prescribed to you under the supervision of a doctor:

- who is qualified in the use of cancer therapies and
- has a full understanding of the risks of ODOMZO therapy and the patient monitoring requirements for this medicine
- ODOMZO can cause your baby to die before it is born (be stillborn) or cause your baby to have severe birth defects.
- ODOMZO is only available under a controlled distribution program called the ODOMZO Pregnancy Prevention Program (OPPP).
- ODOMZO has not been studied in patients with severe kidney problems.
- In children ODOMZO can cause bones to stop growing. This is called epiphyses premature fusion. It can happen even after stopping ODOMZO. This is a permanent condition.

What is ODOMZO used for?

ODOMZO is used to:

- treat adults with a type of skin cancer, called basal cell carcinoma. It is used when the cancer has spread to surrounding areas (called “locally advanced” basal cell carcinoma (BCC)) and it cannot be treated with surgery or radiation.

How does ODOMZO work?

The DNA in skin cells can become damaged. This damage can change how certain proteins in your cell work and it can turn these damaged cells into skin cancer. ODOMZO works by controlling a key protein involved in cancer. This may stop the cancer cells from growing or may kill them. As a result, your skin cancer may shrink.

What are the ingredients in ODOMZO?

Medicinal ingredients: sonidegib

Non-medicinal ingredients: colloidal silicon dioxide, crospovidone, lactose monohydrate, magnesium stearate, poloxamer, and sodium lauryl sulfate. The capsule shell contains gelatin, red iron oxide, and titanium dioxide. The black printing ink contains ammonium hydroxide, black iron oxide, propylene glycol, and shellac.

ODOMZO comes in the following dosage forms:

Capsules: 200 mg sonidegib (as phosphate)

Do not use ODOMZO if:

- You are pregnant or think you may be pregnant
- You are breast-feeding
- You are able to become pregnant but you are unable or unwilling to follow the necessary pregnancy prevention measures that are listed in the ODOMZO Pregnancy Prevention Program
- You are a male and you are unwilling to follow the necessary contraceptive measures listed in the ODOMZO Pregnancy Prevention Program
- You are under the age of 18 years
- You are allergic to sonidegib. This medicine contains lactose and other ingredients – see **What are the ingredients in ODOMZO?** for the complete list of ingredients.

Do not take ODOMZO if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking ODOMZO.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ODOMZO. Talk about any health conditions or problems you may have, including if you:

- Have muscle pain or spasms, or have a history of a muscle disorder called rhabdomyolysis or myopathy. Your doctor should do a blood test to check for muscle problems and to check how well your kidneys are working:
 - before you start taking ODOMZO
 - during treatment and
 - if you develop muscle problems
- Have kidney problems
- Have any other medical conditions
- Are pregnant or plan to become pregnant
- Are breast-feeding

Other warnings you should know about:

Cutaneous squamous cell carcinoma (cuSCC): Patients with advanced BCC have an increased risk of developing cutaneous squamous cell carcinoma (cuSCC). Your doctor should monitor you regularly while you are taking ODOMZO.

Donating Blood: You should not donate blood while taking ODOMZO and for 20 months after you have stopped taking ODOMZO.

Abnormal test results: ODOMZO can cause abnormal blood test results. Your doctor will do a blood test before you start taking ODOMZO and periodically during treatment and will interpret the results.

For female patients who can become pregnant (are of childbearing age):**Pregnancy:**

- Before starting ODOMZO, ask your doctor if you are able to become pregnant, even if your periods have stopped (menopause). It is important to check with your doctor whether there is a risk that you could become pregnant.
- **ODOMZO may cause your baby to have severe birth defects or lead to the death of your unborn baby.**

- Do not take ODOMZO if you are pregnant, think you may be pregnant, or are planning to become pregnant while taking ODOMZO and for 20 months after you have taken your last dose.
- You must stop taking ODOMZO and talk to your doctor **right away** if while taking ODOMZO or within 20 months after you have taken your last dose you:
 - become pregnant
 - think you could be pregnant
 - miss your menstrual period

Pregnancy Testing:

Your doctor will do pregnancy tests:

- within 7 days before you start treatment to make sure you are not pregnant
- every month while you are taking ODOMZO (including if there is an interruption in your treatment)
- every month for 20 months after you stop taking ODOMZO

Breast-feeding:

- Do not breast-feed while taking ODOMZO and for 20 months after you have taken your last dose. It is not known whether ODOMZO can pass into your breast milk and cause harm to your baby.

Fertility:

- ODOMZO may affect your ability to have children. Some women taking ODOMZO have stopped having their menstrual period. If this happens to you, it is not known if your period will come back. Talk to your doctor if you wish to have children in the future.

Contraception:

Your healthcare provider will talk to you about what contraceptive methods are right for you and will give you educational materials on the contraception requirements and risks of ODOMZO in pregnancy.

If you are able to become pregnant:

- You must take precautions so that you do not become pregnant while taking ODOMZO
- Unless you commit to not having sex (abstinence), you **must use 2 methods of contraception**, one highly effective method and one barrier method every time you have sex with a male:
 - for 4 weeks before you start taking ODOMZO
 - while you are taking ODOMZO (including if there is an interruption in your treatment)
 - for 20 months after you have taken your last dose because traces of the medicine remain in the body for a long time
- If your periods have stopped, are irregular or you have abnormal menstrual bleeding, you must continue to use 2 methods of contraception
- Talk to your doctor **right away** if while taking ODOMZO or within 20 months after you have taken your last dose you:
 - have stopped using contraception
 - previously chosen to not have sex as a way to prevent pregnancy but you have changed your mind
 - need to change the type of contraception you are using or
 - think your contraception has failed or had unprotected sex

For male patients:

ODOMZO is present in semen. **You must** let your female sexual partners know that you are taking ODOMZO and of the potential serious risks to an unborn baby if she becomes pregnant by you:

- while you are taking this medicine (including if there is an interruption in your treatment) and
- within 6 months after you have stopped taking ODOMZO

Contraception:

- To protect your female partner from being exposed to ODOMZO, you **must always** use a condom (with spermicide, if available) when you have sex with a female partner while taking ODOMZO. You must do this:
 - even if you have had a vasectomy
 - for at least 6 months after you have taken your last dose
- Your doctor will counsel you and give you educational materials on the contraception requirements and risks of ODOMZO in pregnancy.
- Talk to your doctor **right away** if while taking ODOMZO or for 6 months after you have taken your last dose:
 - your female partner gets pregnant or thinks she is pregnant
 - you think your contraception has failed or had unprotected sex

Sperm donation:

- You should not donate semen during your treatment and for at least 6 months after your treatment has finished.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with ODOMZO:

- Strong and moderate CYP3A inhibitors (such as ritonavir, saquinavir, telithromycin, ketoconazole, itraconazole, voriconazole, posaconazole)
- Strong and moderate CYP3A inducers (such as carbamazepine, efavirenz, modafinil, phenobarbital, phenytoin, rifabutin, rifampin)
- St. John's Wart (*Hypericum perforatum*)
- Warfarin (used to treat blood clots)
- Medicines used to treat too much acid in your stomach/heartburn (such as esomeprazole)
- Medicines used to treat other types of cancer (such as methotrexate, mitoxantrone, irinotecan, topotecan)
- Grapefruit products and juice
- Seville oranges and juice

How to take ODOMZO:

ONLY take this medicine if you are registered in and agreed to meet all the conditions set out in the ODOMZO Pregnancy Prevention Program. Information on the OPMP can be found:

- by calling 1-844-266-2974 or
- online at www.Odomzo.ca

ODOMZO should only be prescribed to you under the supervision of a doctor who:

- is qualified in the use of cancer therapies
- has a full understanding of the risks of ODOMZO therapy and the patient monitoring requirements for this medicine

Before you start treatment with ODOMZO your doctor will do blood tests to verify that you are not pregnant and how well your kidneys are working.

- Take ODOMZO exactly as your healthcare provider tells you
- Swallow the capsule whole. **Do not open, chew or crush the capsule.**

Usual Adult dose: Take 1 capsule once a day on an empty stomach, at least 1 hour before or 2 hours after a meal.

Overdose:

If you think you have taken too much ODOMZO, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose, skip the missed dose. Take your next dose as scheduled.

What are possible side effects from using ODOMZO?

The most common side effects (those that may affect 1 or more in every 20 patients) include:

- | | |
|---|---------------------------------|
| • a sensation of tingling or prickling ("pins and needles") | • hypotension |
| • absence of menstrual period (amenorrhea) in females | • itching |
| • change in taste | • muscle pain |
| • constipation | • muscle spasms |
| • decreased appetite | • muscle weakness |
| • decrease in weight | • rash |
| • depression | • stomach area (abdominal) pain |
| • diarrhea | • upset stomach or indigestion |
| • dry mouth | • vomiting |
| • feeling dizzy | • weight loss |
| • feeling sick (nausea) | |
| • feeling tired | |
| • hair loss | |
| • headache | |

Less common side effects include:

- abnormal hair growth
- acid reflux
- dry eye
- nerve damage (peripheral neuropathy)
- thirst, not passing much urine, weight loss, dry flushed skin, irritability (possible symptoms of low levels of fluids in the body, known as dehydration).
- trigger finger (condition in which one of your fingers gets stuck in a bent position)

These are not all the possible side effects you may feel when taking ODOMZO. If you experience any side effects not listed here, contact your healthcare professional.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON (occurring between 1 and 10 in every 100 patients) Rhabdomyolysis (breakdown of damaged muscle): muscle tenderness, weakness, red-brown (tea-coloured) urine			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store ODOMZO at room temperature between 15°C to 30°C. Protect from moisture. Keep out of reach and sight of children.

If you want more information about ODOMZO:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (<https://health-products.canada.ca/dpd-bdpp/index-eng.jsp>); the manufacturer's website www.sunpharma.com/canada, or by calling 1-844-924-0656.

For more information about the ODOMZO Pregnancy Prevention Program, contact 1-844-266-2974 or visit website www.Odomzo.ca.

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