New Zealand Datasheet

1 PRODUCT NAME
ODOMZO ®

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Odomzo capsules contain 200 mg of sonidegib as the diphosphate salt.

Excipient with known effect
Each hard capsule contains 38.6 mg lactose monohydrate.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
200 mg hard gelatin capsule: Size #00 Coni-snap, opaque pink capsule, cap imprinted in black ink with “NVR,” body imprinted in black ink with “SONIDEGIB 200MG,” containing white to practically white powder with granules.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
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.
- Metastatic BCC.

4.2 Dose and method of administration
Dosage
General target population
The recommended dose of Odomzo is 200 mg taken orally once daily on an empty stomach, at the same time each day. Odomzo should be taken at least 1 hour before, or two hours after a meal. Odomzo capsules must be swallowed whole. They must not be chewed or crushed.

If a dose is missed, the recommended dose of Odomzo should be taken within 6 hours after the missed dose. If more than 6 hours have passed, the patient should be instructed not to take the missed dose. The patient should continue treatment with the next prescribed dose.

Continue treatment as long as clinical benefit is observed or until unacceptable toxicity develops.

Dose modifications for creatine phosphokinase (CK) elevations and muscle related adverse events
Temporary dose interruption and/or dose reduction of Odomzo therapy may be required for CK elevations and muscle related adverse events.

Table 1 summarizes recommendations for dose interruption and/or dose reduction of Odomzo treatment in the management of symptomatic CK elevations and muscle related adverse events (such as myalgia, myopathy, and/or spasm).

Table 1: Recommended dose modifications and management for symptomatic CK elevations and muscle related adverse events

Severity of CK elevation	Dose modifications* and management recommendations
Grade1 [CK elevation >ULN - 2.5 x ULN)]	• Continue treatment at the same dose and monitor CK 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 the patient is adequately hydrated.
Grade 2 without renal impairment (serum Cr ≤ ULN) [CK elevation >2.5 x ULN - 5 x ULN]	• Interrupt treatment and monitor CK levels weekly until resolution to baseline. Monitor muscle symptoms for changes until resolution to baseline. Upon resolution resume treatment at the same dose level and measure CK monthly thereafter. • Check renal function (serum creatinine) regularly; and ensure that the patient is adequately hydrated. • If symptoms re-occur, interrupt treatment until resolution to baseline. Re-introduce Odomzo at 200 mg every other day and follow the same monitoring recommendations. If symptoms persist despite alternate day dosing, consider discontinuing treatment.
Grade 3 or 4 **without** renal impairment (serum Cr ≤ ULN) [Grade 3 (CK elevation >5 x ULN - 10 x ULN)] [Grade 4 (CK elevation >10 x ULN)]	• Interrupt treatment and monitor CK levels weekly until resolution to baseline. Monitor muscle symptoms for changes until resolution to baseline. • Check renal function (serum creatinine) regularly; and ensure that the patient is adequately hydrated. • If renal function is not impaired and CK resolves to baseline consider resuming treatment at 200 mg every other day. CK levels should be measured weekly for 2 months after re-administration of Odomzo and monthly thereafter.
Grade 2, 3 or 4 with renal impairment (serum Cr > ULN)	• If renal function is impaired, interrupt treatment and ensure that the patient is adequately hydrated and evaluate other secondary causes of renal impairment. • Monitor CK and serum creatinine levels weekly until resolution to baseline. Monitor muscle symptoms for changes until resolution to baseline. • If CK and serum creatinine levels return to baseline consider resuming treatment at 200 mg every other day and measure CK levels weekly for 2 months and monthly thereafter; otherwise discontinue treatment permanently.

*Recommendations for dose modifications contained within the chart above based on the Common Terminology Criteria for Adverse Events (CTCAE) v4.03, developed by the National Cancer Institute (USA). The CTCAE is a standardized classification of side effects used in assessing drugs for cancer therapy.
Cr: creatinine; ULN: Upper limit of normal

Other dose modifications

If dose reduction is required due to any other adverse drug reaction, then the recommended dose of Odomzo should be reduced to 200 mg every other day. If the same adverse drug reaction occurs following the switch to alternate-daily dosing and does not improve, consider discontinuing treatment with Odomzo.

Patients with Renal Impairment

Sonidegib has not been studied in patients with renal impairment. Based on the available data, sonidegib elimination via the kidney is negligible. A population pharmacokinetic analysis did not find significant influence of renal function on the apparent clearance (CL/F) of sonidegib

suggesting that dose adjustment is not necessary in patients with renal impairment (see section 5.1).

Patients with Hepatic Impairment
No dose adjustment is necessary in patients with hepatic impairment (see section 5.1).

4.3 Contraindications
Women who are pregnant or breast-feeding (see section 4.6 – **Use in Pregnancy, and Use in Lactation**).

Women of child-bearing potential, unless two reliable methods of contraception are used during treatment and for 20 months after the last dose (see section 4.4 - **Women of child-bearing potential and sexually active men**).

4.4 Special warnings and precautions for use
Muscle related adverse events
Advise all patients starting therapy with Odomzo of the risk of muscle related adverse events including the potential for rhabdomyolysis. Advise all patients to report promptly any new unexplained muscle pain, tenderness or weakness occurring during treatment with Odomzo or if symptoms persist after discontinuing treatment.

Check CK levels prior to starting treatment and as clinically indicated thereafter, e.g. if muscle related symptoms are reported. If clinically notable elevation of CK is detected, renal function should be assessed (see section 4.2).

Follow dose modification or interruption guidelines (see Dosage and administration, Dose adjustment). Management of high grade CK elevation using supportive therapy, including proper hydration, should be considered according to local standards of medical practice and treatment guidelines.
In the phase II pivotal study, muscle spasms, myalgia, myopathy and cases of CK elevations were observed. The majority of patients treated with Odomzo 200 mg daily who had Grade 2 or higher CK elevations developed muscle symptoms prior to the CK elevations. For most patients, muscle symptoms and CK elevations resolved with appropriate proper management.

Closely monitor patients for muscle related symptoms if Odomzo is used in combination with certain medications that may increase the potential risk of developing muscle toxicity (e.g. CYP3A inhibitors, chloroquine, hydroxychloroquine, fibric acid derivatives, penicillamine, zidovudine, niacin, HMG-CoA reductase inhibitors) (see section 4.5).

Closely monitor patients with neuromuscular disorders (e.g. inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis and spinal muscular atrophy) due to an increased risk of muscle toxicity.

Paediatric Use
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.

Use in the Elderly
The safety and effectiveness data of Odomzo in patients aged 65 years and older do not suggest that a dosage adjustment is required in elderly patients (see section 5.1).

Blood donation
Patients should be instructed not to donate blood while taking Odomzo and for at least 20 months after ending treatment.

Premature Fusion of the Epiphyses
Premature fusion of the epiphyses has been reported in paediatric patients exposed to Hedgehog (Hh) pathway inhibitors. In some cases, fusion progressed after drug discontinuation (see Section 4.8 **Undesirable Effects**).

Women of child-bearing potential and sexually active men
Odomzo may cause embryo-fetal death or severe birth defects when administered to pregnant women. Based on the mechanism of action, in animal studies, sonidegib has been shown to be teratogenic and fetotoxic. Odomzo must not be administered to women who are, or planning to become, pregnant. Women who have received Odomzo should not become pregnant for at least 20 months following their last Odomzo dose. Verify pregnancy status of women of childbearing potential within 7 days prior to the initiation of Odomzo treatment and monthly during treatment by a test performed by a healthcare professional. Women of child-bearing potential must be instructed to use two methods of contraception, including one highly effective method and a barrier method while taking Odomzo. Contraception must be continued for 20 months after ending treatment. Women whose periods are irregular or have stopped must follow all the advice on effective contraception. In case of pregnancy occurring during treatment, Odomzo must be stopped immediately.

Sexually active males being treated with Odomzo must use a condom with spermicide (if available), regardless of vasectomy status, during intercourse and for 6 months after ending treatment to prevent exposure of female partners to the drug via seminal fluid. They should not father a child or donate semen while taking Odomzo or for at least 6 months after ending treatment.

Advise male and female patients of the risks of embryo-fetal death and severe birth defects and the need for contraception during and after treatment. Advise female patients (and female partners of male patients) to contact their healthcare provider immediately if they suspect that they may be pregnant. Female and male patients of reproductive potential should be counseled regarding pregnancy prevention and planning. If Odomzo is used during pregnancy or if a patient (or the female partner of a male patient) becomes pregnant while taking Odomzo, the expectant mother should be apprised of the potential hazard to the fetus.

Encourage women who may be exposed to Odomzo during pregnancy, either directly or through seminal fluid to report this to their treating physician immediately.

Advice to handler
Do not open capsules due to risk of teratogenicity.

4.5 Interaction with other medicines and other forms of interaction
Sonidegib undergoes metabolism primarily by CYP3A4, and concomitant administration of strong inhibitors or inducers of CYP3A4 can increase or decrease sonidegib concentrations significantly.

Agents that may increase sonidegib plasma concentration
In healthy subjects, co-administration of a single 800 mg dose of Odomzo with ketoconazole (200 mg twice daily for 14 days), a strong CYP3A inhibitor, resulted in a 2.25 fold and a 1.49-fold increase in sonidegib AUC and Cmax, respectively, compared to when Odomzo was given alone. Co-administration of Odomzo with strong CYP3A inhibitors increases sonidegib plasma concentration. Avoid concomitant use of strong CYP3A inhibitors, including but not limited to, ritonavir, saquinavir, telithromycin, ketoconazole, itraconazole, voriconazole, posaconazole and nefazodone. Patients should be carefully monitored for adverse events if one of these agents is used together with sonidegib. Recommended dose reductions should be considered if muscle related symptoms develop.

Agents that may decrease sonidegib plasma concentration
In healthy subjects, co-administration of a single dose of 800 mg Odomzo with rifampicin (600 mg daily for 14 days), a strong CYP3A inducer, resulted in 72% and 54% decreases in sonidegib AUC and Cmax respectively, compared with when Odomzo was given alone. Co-administration of Odomzo with strong CYP3A inducers decreases sonidegib plasma concentration. Avoid concomitant use of strong CYP3A inducers, including but not limited to carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin and St John's Wort *(Hypericum perforatum).* If a strong CYP3A inducer must be used concomitantly with sonidegib, consider increasing the dose of sonidegib by 200 mg increments to a maximum daily dose of 800 mg. This dose of sonidegib is predicted to adjust the AUC to the range observed without inducers based on pharmacokinetic data. The dose of Odomzo used prior to initiation of the strong inducer should be resumed if the strong inducer is discontinued.

Results from a clinical study demonstrated a change in sonidegib exposure (32% and 38% decrease in AUC and C_{max}) after co-administration of a single dose of Odomzo 200 mg with esomeprazole (a proton pump inhibitor) at 40 mg daily for 6 days in healthy subjects. The effect of this interaction upon clinical efficacy has not been determined.

Anticipated interactions to be considered
Sonidegib is a competitive inhibitor of CYP2B6 and CYP2C9 *in vitro*. However, results of a drug-drug interaction study in cancer patients demonstrate that the systemic exposure of bupropion (a CYP2B6 substrate) and warfarin (a CYP2C9 substrate) is not altered when co-administered with sonidegib. Sonidegib is also a breast cancer resistance protein (BCRP) inhibitor. Patients should be carefully monitored for adverse drug reactions with concomitant use of substrates of BCRP transporter, especially those with a narrow therapeutic range.

Agents that are substrates of transporters
Based on *in vitro* data, sonidegib did not inhibit apical efflux transporters, P-gp or MRP2, hepatic uptake transporters OATP1B1 or OATP1B3, renal organic anion uptake transporters OAT1 and OAT3, or the organic cation uptake transporters OCT1 or OCT2 at clinically relevant concentrations. Therefore, clinical drug-drug interactions as a result of sonidegib-mediated inhibition of substrates for these transporters are unlikely to occur.

Agents that may increase muscle related adverse events
Due to overlapping toxicities, patients taking Odomzo who are also taking medications known to increase the risk of muscle related toxicity may be at increased risk of developing muscle related adverse events. Patients should be closely monitored and dose adjustments should be considered if muscle symptoms develop.

In the phase II pivotal study, 12 (15.2%) patients treated with Odomzo 200 mg took concomitant HMG-CoA reductase inhibitors. Of the patients on HMG-CoA reductase inhibitors, 7 (58.3%) had up to Grade 1 muscle symptoms while 43 (64.2%) patients not taking HMG-CoA reductase inhibitors experienced up to Grade 3 symptoms. No patient taking HMG-CoA reductase inhibitors experienced Grade 3/4 CK elevations, as opposed to 6 (9.0%) patients not taking HMG-CoA reductase inhibitors.

Drug-food interaction
The bioavailability of Odomzo is increased in the presence of food (see section 5.1). Odomzo should be taken at least 1 hour before, or two hours after a meal.

4.6 Fertility, pregnancy and lactation
Use in Pregnancy (Category X)
Odomzo may cause embryo-foetal death or severe birth defects when administered to pregnant women. Based on the mechanism of action, in animal studies, sonidegib has been shown to be teratogenic and foetotoxic. Odomzo must not be administered to women who are,

or planning to become, pregnant. Women who have received Odomzo should not become pregnant for at least 20 months following their last Odomzo dose.

Sonidegib was shown to be foeto-toxic in rabbits as evidenced by abortion and/or complete resorption of fetuses and teratogenic resulting in severe malformations at ≥ 5 mg/kg/day (approx. 0.05 times the clinical exposure based on AUC). Teratogenic effects included vertebral, distal limb and digit malformations, severe craniofacial malformations and other severe midline defects. Foeto-toxicity in rabbits was seen at low maternal doses (0.01 mg/kg/day) where maternal exposure was below the limit of detection.

Use in Lactation
It is unknown whether Odomzo is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse drug reactions in breastfed newborns/infants from Odomzo, women must not breast feed while taking Odomzo or for at least 20 months after ending treatment.

Effects on Fertility
The potential for Odomzo to cause infertility in male and female patients is unknown. Based on findings from animal studies, male and female fertility may be compromised by Odomzo. Fertility preservation strategies should be discussed prior to starting treatment with Odomzo.

In a fertility study in rats, sonidegib administered to female rats at 20 mg/kg resulted in a complete lack of fertility even though estrous cycling was within normal ranges and the precoital interval was comparable to concurrent controls. There was also a reduction of the number of pregnant females and a decrease in the number of viable fetuses at 2 mg/kg/day (exposure below the clinical exposure based on AUC). The no observed effect level (NOEL) for female fertility was 0.2 mg/kg. For sonidegib-treated males, the 20 mg/kg/day (high) dose (exposure approx. 3 times the clinical exposure based on AUC) did not impact the ability of the male rat to impregnate the untreated females and therefore, the 20 mg/kg/day dose is considered the NOEL for fertility and reproduction in the male rat. Repeat dose toxicity studies in rats and dogs at around clinical exposure levels showed various reproductive tract changes such as delayed or arrested maturation as well as atrophy of testes, seminal vesicles, prostate, ovary and uterus.

4.7 Effects on ability to drive and use machines
Odomzo has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects
Summary of the safety profile
Pivotal Clinical Studies
The phase II pivotal study evaluated the safety of Odomzo in a total of 229 adult patients with locally advanced or metastatic BCC. Patients were treated with Odomzo 200 mg daily (n=79) or with Odomzo 800 mg daily (n=150). The following safety analysis is based on data collected after all patients were followed for at least 30 months unless discontinued earlier. The median duration of treatment was 11.0 months for patients treated with Odomzo at the recommended dose of 200 mg (range 1.3 to 41.3 months). Thirteen (13) (16.5%) patients had a dose reduction and 23 (29.1%) discontinued treatment due to adverse events. One death occurred while on treatment or within 30 days of the last dose taken in either the metastatic BCC or locally advanced BCC patients taking Odomzo 200 mg.

The most common adverse drug reactions occurring in ≥10% in patients treated with Odomzo 200 mg were muscle spasms, alopecia, dysgeusia, fatigue, nausea, musculoskeletal pain, diarrhoea, weight decreased, decreased appetite, myalgia, abdominal pain, headache, pain, vomiting and pruritus.

The most common Grade 3/4 adverse drug reactions occurring in ≥ 2% of patients treated with Odomzo 200 mg were fatigue, weight decreased and muscle spasms.

Among adverse drug reactions reported, the frequency was greater in patients taking Odomzo 800 mg than in patients taking Odomzo than 200 mg except musculoskeletal pain, diarrhea, abdominal pain, headache and pruritus. This was also true for Grade 3/4 adverse reactions, except fatigue.

Tabulated summary of adverse drug reactions

Adverse drug reactions for the recommended dose from the phase II pivotal clinical study (Table 2) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Table 2: Adverse drug reactions observed in the phase II pivotal study

Primary System Organ Class **Preferred Term**	**Odomzo 200 mg N=79** **all grades n (%)**	**grade 3 n (%)**	**grade 4 n (%)**	**Frequency** **all grades**
Metabolism and nutrition disorders				
Decreased appetite	18 (23)	1 (1)	0	Very common
Dehydration	1 (1)	1 (1)	0	Common
Nervous system disorders				
Dysgeusia	36 (46)	0	0	Very common
Headache	12 (15)	1 (1)	0	Very common
Gastrointestinal disorders				
Nausea	31 (39)	1 (1)	0	Very common
Diarrhea	25 (32)	1 (1)	0	Very common
Abdominal pain	14 (18)	0	0	Very common
Vomiting	9 (11)	1 (1)	0	Very common
Dyspepsia	7 (9)	1 (1)	0	Common
Constipation	6 (8)	1 (1)	0	Common
Gastroesophageal reflux disorder	3 (4)	0	0	Common
Skin and subcutaneous tissue disorders				
Alopecia	42 (53)	0	0	Very common
Pruritus	8 (10)	0	0	Very common
Rash	6 (8)	0	0	Common
Abnormal hair growth	3 (4)	0	0	Common
Musculoskeletal and connective tissue disorders				
Muscle spasms	43 (54)	2 (3)	0	Very common
Musculoskeletal pain	26 (33)	1 (1)	0	Very common
Myalgia	15 (19)	0	0	Very common
Myopathy [muscular fatigue and muscular weakness]	4 (5)	0	0	Common
General disorders and administration site conditions				
Fatigue	33 (42)	3 (4)	0	Very common
Pain	12 (15)	1 (1)	0	Very common
Investigations				
Weight decreased	24 (30)	4 (5)	0	Very common

Clinically relevant laboratory abnormalities
The most commonly reported Grade 3/4 laboratory abnormalities with an incidence of ≥5% occurring in patients treated with Odomzo 200 mg were lipase increase and blood CK increase (Table 3).

Table 3: Laboratory abnormalities*

Laboratory test	Odomzo 200 mg Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Frequency all grades
Hematological parameters					
Hemoglobin decreased	19 (24)	6 (8)	0	0	Very common
Lymphocyte count decreased	13 (16)	7 (9)	2 (3)	0	Very common
Biochemistry parameters					
Serum creatinine increased	71 (90)	2 (3)	0	0	Very common
Serum creatine phosphokinase (CK) increased	34 (43)	8 (10)	4 (5)	2 (3)	Very common
Blood glucose increased	31 (39)	6 (8)	3 (4)	0	Very common
Lipase increased	18 (23)	7 (9)	9 (11)	1 (1)	Very common
Alanine amino transaminase (ALT) increased	13 (16)	0	3 (4)	0	Very common
Aspartate amino transaminase (AST) increased	13 (16)	0	2 (3)	1 (1)	Very common
Amylase increased	9 (11)	3 (4)	1 (1)	0	Very common

*Based on worst laboratory value post-treatment regardless of baseline, grading by CTCAE version 4.03

Description of selected adverse drug reactions
Muscle-related adverse events including CK elevation
Muscle-related adverse reactions are the most clinically relevant side effect reported in patients receiving Odomzo therapy, and are a class effect of inhibitors of the Hh signaling pathway. In the phase II pivotal study muscle spasms were the most common 'muscle-related' adverse events, and were reported in fewer patients in the Odomzo 200 mg group (54%) than in the Odomzo 800 mg group (69%).

Grade 3/4 increase in blood CK was reported in 8% of patients taking Odomzo 200 mg. The majority of patients who had Grade 2 or higher CK elevations developed muscle symptoms prior to the CK elevations. In these patients, increases in laboratory values of CK to Grade 2 and higher severity had a median time to onset of 12.9 weeks (range 2 to 39 weeks) after initiating Odomzo therapy and a median time to resolution (to normalization or Grade 1) of 12 days (95% confidence interval 8 to 14 days).

One patient receiving Odomzo 200 mg experienced muscle symptoms and CK elevations above 10x ULN and required intravenous fluids, compared to 6 patients receiving Odomzo 800 mg.

After at least 18 months follow up for all patients unless discontinued earlier, the phase II pivotal study had no reported cases of rhabdomyolysis confirmed (defined as CK levels >10 fold above the pre-treatment or baseline level or >10 x ULN if no baseline level reported plus a 1.5 fold increase in serum creatinine from the pre-treatment or baseline level). However, 1 reported case in a patient treated with Odomzo 800 mg in a non-pivotal study was confirmed.

Amenorrhea
In the phase II pivotal study, 2 out of 14 (14.3%) women of either childbearing potential or of child-bearing age sterilized by tubal ligation, developed amenorrhea while on treatment with Odomzo 200 mg or 800 mg once daily.

All Clinical Studies
Pooled analysis of cumulative drug-related treatment-emergent adverse events recorded in clinical trials with all tested doses of ODOMZO, is presented in Table 4.

Table 4: Pooled analysis of Cumulative Drug-related Treatment-emergent Adverse Events Recorded in Clinical Trials

Primary System Organ Class Preferred Term	all grades %	Odomzo N=665 grade 3 %	grade 4 %	Frequency all grades
Blood and lymphatic system disorders				
Anaemia*	3.0	0.9	0	Common
Gastrointestinal disorders				
Nausea*	26.0	0.9	0	Very common
Vomiting*	13.2	0.8	0	Very common
Constipation	4.7	0.2	0	Common
Dyspepsia	3.6	0.2	0	Common
Abdominal pain*	1.8	0	0	Common
Abdominal pain upper*	3.2	0	0	Common
Diarrhoea*	10.1	0	0	Very common
Dry mouth*	1.8	0	0	Common
Stomatitis	1.1	0	0	Common
General disorders and administration site conditions				
Fatigue*	22.4	2.0	0	Very common
Asthenia*	5.9	0.8	0.2	Common
Investigations				
Blood creatine phosphokinase increased*	28.1	6.2	7.1	Very common
Aspartate aminotransferase increased	5.7	2.1	0.6	Common
Lipase increased*	3.6	2.3	0.5	Common
Alanine aminotransferase increased	5.1	1.8	0.3	Common
Weight decreased*	14.6	1.8	0	Very common
Myoglobin blood increased	2.1	0.6	0.9	Common
Amylase increased	1.5	0.3	0.2	Common
Blood alkaline phosphatase increased	1.5	0	0	Common
Blood bilirubin increased	1.1	0	0	Common
Blood creatinine increased	1.2	0	0	Common
Metabolism and nutrition disorders				
Decreased appetite*	17.6	1.4	0	Very common
Musculoskeletal and connective tissue disorders				
Rhabdomyolysis*	2.1	1.1	0.9	Common
Muscle spasms*	34.0	1.8	0	Very common
Myalgia*	19.2	1.1	0	Very common
Muscular weakness*	3.5	0.9	0	Common
Arthralgia*	3.8	0.5	0	Common
Myositis*	1.1	0.3	0.2	Common
Pain in extremity*	2.7	0	0	Common
Nervous system disorders				
Dizziness*	3.3	0.5	0	Common
Headache*	4.4	0.2	0	Common
Ageusia*	2.6	0	0	Common
Dysgeusia*	28.4	0	0	Very common

Hypogeusia	2.0	0	0	Common
Lethargy	1.5	0	0	Common
Paraesthesia	1.5	0	0	Common
Psychiatric disorders				
Depression*	1.2	0	0	Common
Skin and subcutaneous tissue disorders				
Alopecia*	23.8	0	0	Very common
Dermatitis acneiform	1.1	0	0	Common
Dry skin	2.0	0	0	Common
Madarosis	1.4	0	0	Common
Pruritus*	1.7	0	0	Common
Rash	2.0	0	0	Common

*Adverse events also reported in patients during postmarketing

The most common reported grade ¾ laboratory abnormalities with an incidence of ≥5% occurring in patients treated with ODOMZO 200 mg were lipase increase and blood CK increase (Table 5).

Table 5: Laboratory Abnormalities

Laboratory test	all grades %	Odomzo N=665 grade 3 %	grade 4 %	Frequency all grades
Investigations				
Blood creatine phosphokinase increased*	5.1	0.8	4.2	Common
Myoglobin blood increased	1.1	0.2	0.9	Common

*Adverse events also reported in patients during postmarketing

Postmarketing
Due to limited data from post-marketing experience, frequency of the reported adverse drug reactions cannot be estimated:

Musculoskeletal and connective tissue disorders: Muscle spasm, Rhabdomyolysis, Myalgia/Myositis

General disorders and administration site conditions: Fatigue

Nervous system disorders: Dysgeusia

Investigations: Blood creatine phosphokinase increased

Gastrointestinal disorders: Vomiting

Premature fusion of epiphyses
Three cases (one case of cartilage injury, one case of epiphyseal disorder and one case of epiphyseal fracture) of epiphyseal growth plate disorders were reported in paediatric patients with sonidegib during clinical study but causal association with sonidegib cannot be ascertained conclusively. Premature fusion of the epiphyses has been reported in paediatric patients exposed to Hh (Hedgehog) pathway inhibitors. ODOMZO (sonidegib) should not be used in these paediatric patients as safety and effectiveness is not established in paediatric patients.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/.

4.9 Overdose

In dose escalation studies, Odomzo was administered up to 3000 mg orally once daily. Patients should be monitored closely for adverse events and given appropriate supportive measures in all cases of overdose.

Contact the Poisons Information Centre on 13 11 26 in Australia or 0800 POISON, 0800 764 766 in NZ for advice on management.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, other antineoplastic agents, ATC code: L01XX48

Mechanism of action

Sonidegib is a selective and orally bioavailable Smoothened (Smo) antagonist. Smo is a G protein-coupled receptor-like molecule that positively regulates the Hedgehog (Hh) signal transduction pathway. Hh pathway activation of Smo leads to activation and nuclear localization of Glioma-Associated Oncogene (GLI) transcription factors, and is linked to the pathogenesis of several types of cancer including basal cell carcinoma (BCC). Sonidegib binds Smo with high affinity to inhibit GLI mediated target gene activation thereby inhibiting Hh signaling.

Pharmacodynamics

The sonidegib plasma concentration-QTc analysis showed that the upper bound of one-sided 95% confidence interval for QTc increase 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. Further, sonidegib plasma concentrations above those achieved with the therapeutic doses were not associated with life threatening arrhythmias or Torsades de pointes.

In the pivotal study A2201, a postbaseline QTcF > 500 ms was reported for one patient in the sonidegib 200 mg group. This patient had prolonged QTcF intervals at baseline which present consistently throughout the study; there were no associated cardiac-related AEs. Increases from baseline of >30 ms were reported for 7.6% of patients in the sonidegib 200 mg group. No increases from baseline in QTcF of > 60 ms were observed.

Tumor response was independent of sonidegib dose or plasma concentration in the dose range of 200 mg to 800 mg.

Clinical Trials

A phase II, randomized double-blind study of two dose levels (200 mg or 800 mg) of Odomzo was conducted in 230 patients with either locally advanced basal cell carcinoma (laBCC) (n=194) or metastatic basal cell carcinoma (mBCC) (n=36). Of the 230 patients, 16 had a diagnosis of Gorlin Syndrome (15 laBCC and 1 mBCC). Adult patients with laBCC or mBCC (≥18 years of age) who were not candidates for radiotherapy, surgery or other local therapies, were randomized to receive either Odomzo 200 mg or 800 mg daily until disease progression or unacceptable toxicity.

The primary efficacy endpoint of the trial was objective response rate (ORR) according to modified Response Evaluation Criteria in Solid Tumors (mRECIST) in patients with laBCC and RECIST 1.1 in patients with mBCC as determined by central review. The secondary endpoints included duration of response (DoR), time to tumor response (TTR) and progression free survival (PFS) according to mRECIST in patients with laBCC and RECIST 1.1 in patients with mBCC as determined by central review.

For patients with laBCC, the Independent Review Committee (IRC) Composite Overall Response was integrated from centrally evaluated MRI scans, digital clinical photographs, and histopathology according to mRECIST. For LaBCC, multiple punch biopsies of target lesions were taken to confirm a complete response (CR) or each time a response assessment was confounded by presence of lesion ulceration, cyst, and or scarring/fibrosis. MRI tumor response was evaluated by RECIST 1.1. Response by digital clinical photograph was evaluated by World Health Organization (WHO) adapted criteria [partial response (PR): ≥ 50% decrease in the sum of the product of perpendicular diameters (SPD) of lesions, complete response (CR): disappearance of all lesions, progressive disease (PD): ≥ 25% increase in the SPD of lesions]. The criteria for CR were highly stringent for mRECIST. Negative biopsy alone was not sufficient for a composite overall response of CR; all modalities used for assessment must have demonstrated absence of tumor.

Of the 230 patients randomized, 79 patients were assigned to Odomzo 200mg. Of these 79 patients, 66 (83.5%) were laBCC patients (37 [46.8%] with aggressive histology and 29 [36.7%] with non-aggressive histology) and 13 (16.5%) were mBCC patients. The median age of all patients receiving Odomzo 200 mg was 67 years (59.5% were >65 years of age), 60.8% were male and 89.9% Caucasian. The majority of patients (laBCC 74%, mBCC 92%) had undergone prior therapies including surgery (laBCC 73%, mBCC 85%), radiotherapy (laBCC 18%, mBCC 54%), and antineoplastic therapies (laBCC 23%, mBCC 23%).

The following efficacy analysis includes data collected after all patients were followed for at least 30 months unless discontinued earlier. The key efficacy results per central review and local investigator assessment are presented in Table 4.

Table 4 Efficacy overview per central review and local investigator assessment by FAS[a]

	Odomzo 200 mg			
	Central		Local Investigator	
	laBCC N=66	mBCC N=13	laBCC N=66	mBCC N=13
Primary Endpoint				
Overall objective response rate, n (%)	**38 (48.1)**		**50 (63.3)**	
Secondary Endpoints				
Objective response rate, n (%)	**37 (56.1)**	**1 (7.7)**	**47 (71.2)**	**3 (23.1)**
95% CI	(43.3, 68.3)	(0.2, 36.0)	(58.7, 81.7)	(5.0, 53.8)
Best overall response, n (%)				
Complete response[b]	3 (4.5)	0	6 (9.1)	0
Partial response	34 (51.5)	1 (7.7)	41 (62.1)	3 (23.1)
Disease stabilization	23 (34.8)	11 (84.6)	13 (19.7)	8 (61.5)
Disease progression	1 (1.5)	0	1 (1.5)	2 (15.4)
Unknown	5 (7.6)	1 (7.7)	5 (7.6)	0
Time to tumor response (months)				
Median	4.0	9.2	2.5	1.0
95% CI	(3.8, 5.6)	NE	(1.9, 3.7)	(0.9, 3.7)
Duration of response				
No. of events*	11	1	22	2
No. censored	26	0	25	1
Median (months)	26.1	24	15.7	18.1
95% CI	(NE)	(NE)	(12.0,20.2)	(17.7, 18.4)
Event-free probability (%), (95% CI)				
6 months	86.4 (67.7,94.7)	100 (NE)	89.8 (74.8, 96.1)	100 (NE)
9 months	74.9 (54.4,87.2)	100 (NE)	80.7 (63.5,90.4)	100 (NE)
12 months	64.9 (42.3,80.4)	100 (NE)	71.4 (53.1,83.6)	100 (NE)
Progression-free survival				
No. of events*	16	8	28	9
No. censored	50	5	38	4
Median (months)	22.1	13.1	19.4	13.1
95% CI	(NE)	(5.6, 33.1)	(16.6, 23.6)	(9.2, 19.4)
Progression-free survival probability (%), (95% CI)				
6 months	94.8 (84.6, 98.3)	80.8 (42.3, 94.9)	94.7 (84.5, 98.3)	84.6 (51.2, 95.9)
12 months	82.0 (66.7, 90.7)	58.9 (23.4, 82.5)	75.5 (60.7, 85.4)	57.1 (25.1, 79.7)

[a]Full analysis set included all randomized patients. *Event refers to disease progression or death due to any reason

[b]Using only negative histology to define CR among patients who have at least a PR from other modalities (MRI or photography) resulted in a CRR of 21.2% (laBCC, central review) and 28.8% (laBCC, investigator review), respectively

CI: confidence interval

NE: not estimable

Figures 1 and 2 show the best change in target lesion size for each patient with laBCC (Figure 1) and mBCC (Figure 2) at the dose of 200 mg per central review.

Figure 1: Best change from baseline in the target lesions of laBCC patients per central review by FAS

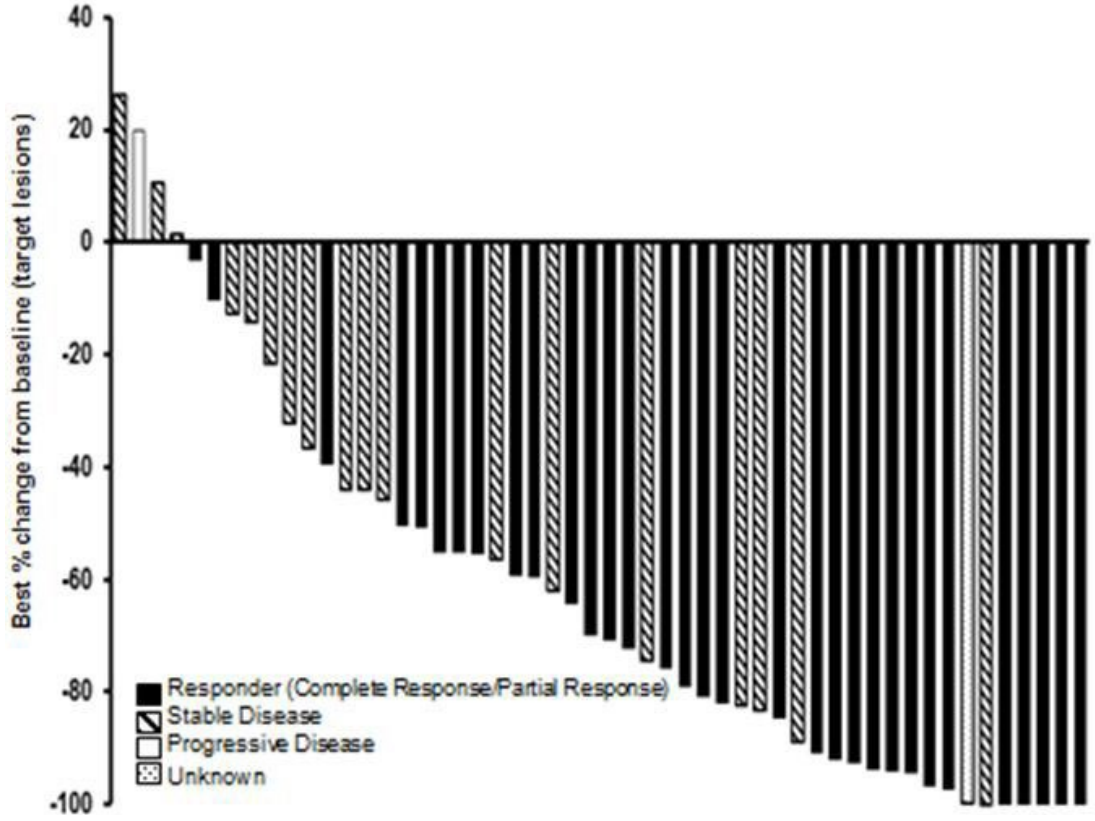
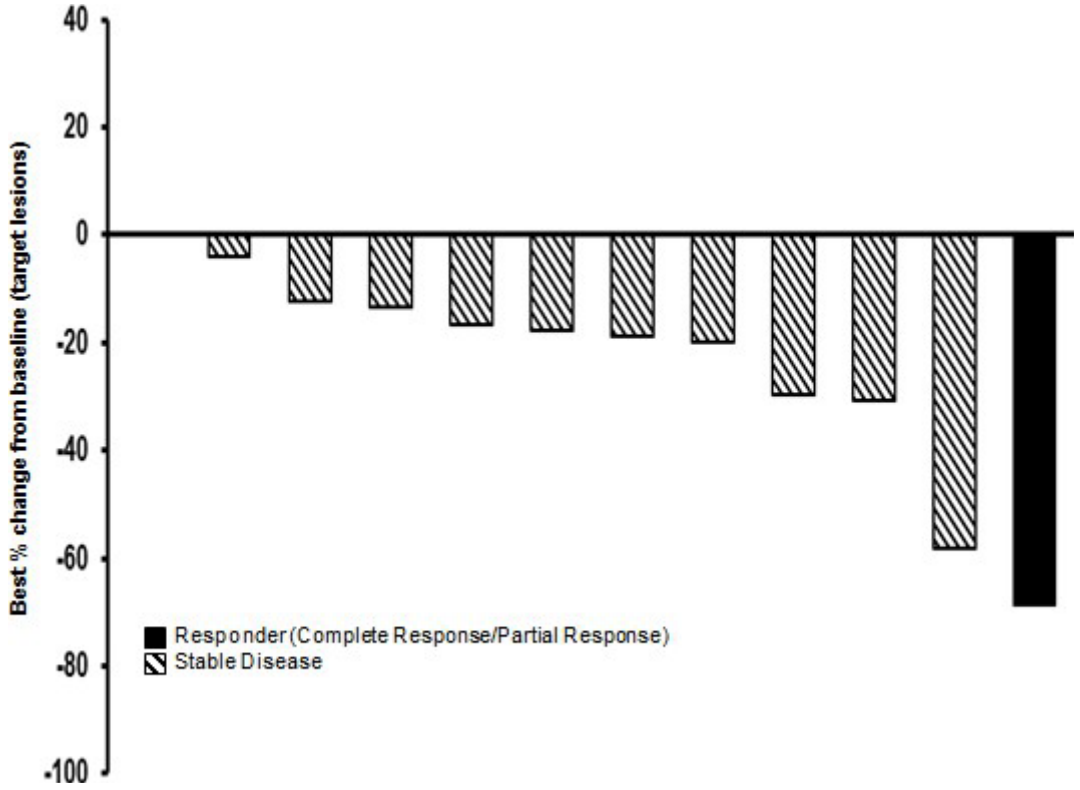
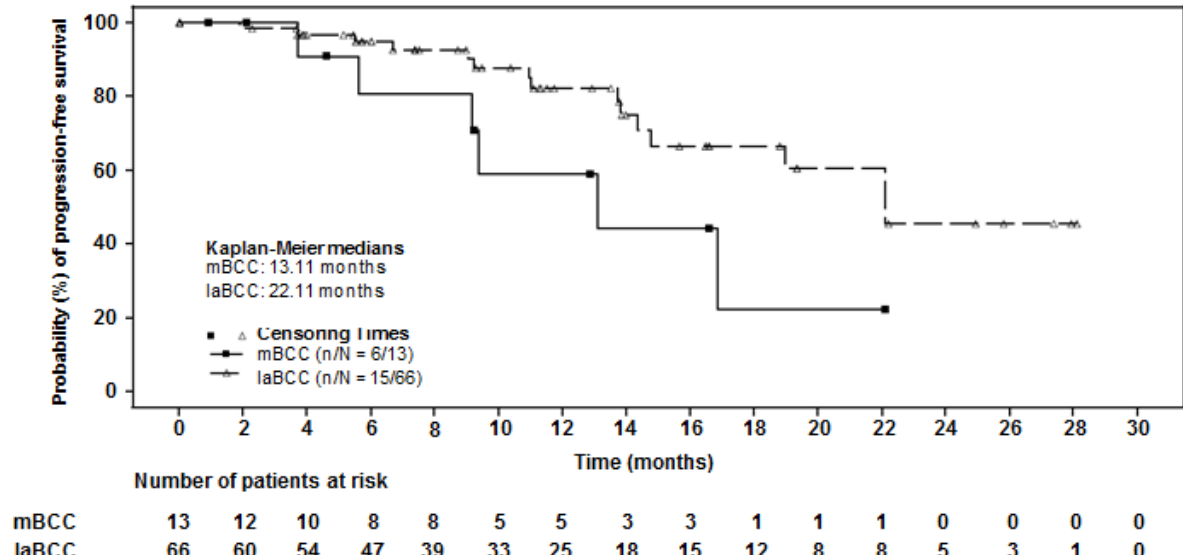


Figure 2: Best change from baseline in the target lesions of mBCC patients per central review by FAS



The estimated PFS rate at 12 months was 82% for laBCC and 59% for mBCC patients taking Odomzo200 mg based on central review (Figure 3).

Figure 3: Kaplan-Meier plot of PFS per central review by FAS



Patient-reported outcomes were evaluated as an exploratory endpoint to evaluate changes in disease-related symptoms (e.g. pain, fatigue, and weight loss), functioning (e.g. physical function, social function, trouble with social contact), and health status/quality of life (QoL)

using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and its associated head and neck cancer specific module (H&N35).

Results, from 18 months follow up data for all patients unless discontinued earlier, confirmed the consistency of the observed treatment effect in patients with laBCC or mBCC. The majority of patients experienced maintenance and/or improvement in their disease-related symptoms, functioning, and health status. Time to deterioration in the prespecified PRO scales (corresponding to >10-point worsenings without subsequent improvement) essentially mirrored the estimated PFS, reflecting durable clinical benefit.

5.2 Pharmacokinetic properties

Absorption:
Following the administration of a single dose of Odomzo (100 mg to 3000 mg) without food in patients with cancer, the median time-to-peak concentration (T_{max}) was 2-4 hours. Sonidegib is poorly absorbed following oral administration (6% to 7% of the administered dose at 800 mg in the fasting state. The oral absorption of sonidegib 200 mg is expected to be higher based on the nonlinear dose-exposure relationship, but is unlikely to exceed 14%. An absolute oral bioavailability study in humans has not been conducted due to the insolubility of sonidegib in a large number of potential vehicles. Sonidegib exhibited approximate dose-proportional increases in AUC and C_{max} over the dose range from 100 mg to 400 mg, but less than dose-proportional increases above 400 mg. There was no evidence of clearance change with repeated dosing based on the population PK analysis and estimated accumulation based on steady state AUC (0-24h) was 19-fold irrespective of dose (200 mg QD or 800 mg QD). Steady state was reached approximately 4 months after starting sonidegib. The average steady state C_{trough} for 200 mg was 810 ng/mL (range 182 to 2810 ng/mL) in cancer patients. Compared to the fasted state, the C_{max} and AUC of sonidegib 800 mg was increased 7.8- and 7.4-fold, respectively when the single dose of sonidegib was given with a high-fat meal in healthy subjects.

Distribution:
Based on a population pharmacokinetic analysis of 351 patients who received oral doses of Odomzo in the dose range of 100 mg to 3000 mg, the apparent steady-state volume of distribution (Vss/F) was 9170 L. Steady-state level of sonidegib in the skin was 6-fold higher than in plasma.

Sonidegib was highly bound to human plasma proteins (human serum albumin and alpha-1 acid glycoprotein) *in vitro* (>97%), and binding was not concentration-dependent from 1ng/mL to 2500 ng/mL.

Sonidegib is not a substrate of P-gp, BCRP or multi-resistance protein 2 (MRP2).

Metabolism:
Sonidegib is primarily metabolized by CYP3A4. Unchanged sonidegib represented 36% of circulating radioactivity. The major circulating metabolite (45% of parent exposure) identified in plasma is the hydrolysis product of sonidegib and is pharmacologically inactive. The metabolites tested were at least 4-fold less potent than sonidegib.

Elimination:
Sonidegib and its metabolites are eliminated primarily by the hepatic route with 93.4% of the administered dose recovered in the feces and 1.95% recovered in urine. Unchanged sonidegib in feces represented 88.7% of the administered dose and was not detectable in urine. The elimination half-life ($t_{1/2}$) of sonidegib estimated from population PK modeling was approximately 28 days.

Pharmacokinetics in special patient groups
Patients with 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. C_{max} of sonidegib after a single oral 800 mg dose was 20%, 21%, and 60% lower in mild, moderate, and severe hepatic impairment, respectively, compared to normal hepatic function. AUC_{inf} of sonidegib was 40%, 22%, and 8% lower, respectively. AUC_{last} was 35% lower in mild hepatic impairment, 14% higher in moderate hepatic impairment, and 23% lower in severe hepatic impairment. No dose adjustment is necessary in patients with hepatic impairment.

Patients with renal impairment
The effect of renal impairment on the systemic exposure of sonidegib has not been studied. Since sonidegib is not renally excreted, no change in systemic exposure is anticipated in patients with renal impairment. A population pharmacokinetic analysis did not find significant influence of renal function (creatinine clearance >27 mL/min) on the apparent clearance (CL/F) of sonidegib suggesting that dose adjustment is not necessary in patients with renal impairment.

Effect of age, weight and gender
Population PK analyses showed that there are no clinically relevant effects of age, body weight, gender, or creatinine clearance on the systemic exposure of sonidegib.

Effect of ethnicity
The C_{max} and AUC_{inf} of sonidegib in Japanese healthy subjects were 1.56 and 1.68-fold higher respectively of those seen in Western healthy subjects for a single dose of 200 mg.

5.3 Preclinical safety data
Genotoxicity
Sonidegib was not genotoxic in studies conducted *in vitro* in bacteria (gene mutation) and in human lymphocytes and lymphoblastoid cells (chromosome aberration) and *in vivo* in rats (chromosome aberration).

Carcinogenicity
Carcinogenicity studies were performed in mice and rats. No carcinogenic potential was identified in either species.

Other Toxicological Findings
Cardiovascular studies in dogs receiving a daily dose of sonidegib for 26 weeks showed only a mild increase (approx. 7%) in QTc interval at plasma concentrations at least 15 fold higher than those anticipated at steady-state in patients taking 200 mg daily. Other safety pharmacology studies indicate that sonidegib is unlikely to interfere with the vital functions of the respiratory and CNS systems.

The safety of sonidegib was evaluated on an oral daily dosing schedule for up to 6 months in rats and dogs. The majority of adverse effects of sonidegib observed in toxicity studies in rats and dogs can be attributed to its pharmacologic mechanism of action on developmental pathways and effects in rats and dogs were similar. The most significant effects were on growing bone and consisted of thinning or closure of growth plates in the sternum and femur and decreasing proliferating chondrocytes in the chostochondral junction of ribs. Effects on growing teeth in rats were also seen, including dentine dysplasia of the incisors and loss of incisors. Neither effects on bone or teeth are expected to occur in adult cancer patients due to the maturity of the dental and skeletal systems.

Other drug-related effects, likely associated with the pharmacology of sonidegib, included effects on the male and female reproductive tract (see Effects on Fertility). Atrophy of the hair

follicles and hair thinning is also a pharmacologic effect of sonidegib. Gastrointestinal (GI) toxicity with body weight loss was dose limiting in rats and dogs. In rats, distention of stomach and duodenum, haemorrhage in the stomach wall, loss of mucosa with inflammation, and ulcerations of the non-glandular mucosa occurred. Emesis and diarrhea with single cell necrosis of intestinal epithelium and thinning of the epithelium with erosion were also seen in dogs.

An additional target organ was the kidney with acute tubular necrosis and mineralization of tubular epithelium seen in rats. Lymphoid depletion in thymus and spleen and lymphocytolysis/lymphophagocytes in lymph nodes and gut associated lymphoid tissue (GALT) were also seen in both rats and dogs.

In a juvenile rat study effects were seen in bone, teeth, reproductive tissues, GI tract, and lymphoid tissues similar to the effects in adult rats. In addition, a minimal to slight degeneration of nerve fibers was found in the sciatic nerve and, less commonly, in the thoracic spinal cord, but not in the cervical or lumbar spinal cord or optic nerve. These effects might be secondary to spinal cord and nerve compression resulting from sonidegib induced cessation of bone growth, but a direct effect of sonidegib cannot be excluded. Effects on nerves were not seen in any of the toxicity studies on more mature rats or dogs.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Odomzo capsules contain the following excipients: crospovidone, lactose monohydrate, magnesium stearate, poloxamer (188), butylated hydroxytoluene, anhydrous colloidal silica and sodium lauryl sulfate (sodium lauryl sulfate).

Capsule shell: gelatin, iron oxide red (E172), and titanium dioxide (E171).

Opacode manogramming ink S-1-277002 Black: ammonium hydroxide, iron oxide black (E172), propylene glycol, and shellac.

6.2 Incompatibilities

None known.

6.3 Shelf life

Bottles: Shelf life is 48 months from manufacture.

6.4 Special precautions for storage

Store below 25°C.Protect from moisture. Store in the original package.

Odomzo capsules must be kept out of the reach and sight of children.

6.5 Nature and contents of container

Bottles containing 30 capsules.

6.6 Special precautions for disposal

No special precautions required.

7 MEDICINE SCHEDULE

Prescription Only Medicine (Schedule 4)

8 SPONSOR

CARSL Consulting
PO Box 766
Hastings 4156
Tel: 0275086002
www.carsl.co.nz

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Distributed in NZ:
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Auckland, 0753

9 DATE OF FIRST APPROVAL

5 December 2019

10 DATE OF REVISION OF THE TEXT

08 October 2026

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
8	Updated with current information