Attachment 1: Product information AusPAR Odomzo sonidegib Novartis Pharmaceuticals Australia Pty Ltd PM-2014-01865-1-4 - FINAL 27 November 2019. This Product information was approved at the time this AusPAR was published.

ODOMZO Ò

Sonidegib

NAME OF THE MEDICINE

Structural formula:

Chemical name (IUPAC):
N-{6-[(2*R*,6*S*)-2,6-Dimethylmorpholin-4-yl]pyridin-3-yl}-2-methyl-

DESCRIPTION

The compound is a white to off-white powder obtained by a standard synthetic organic chemistry synthesis. Sonidegib free base is practically insoluble, with <10µg/mL solubility across the pH range (pH 1-10). The diphosphate salt has a similar solubility profile to the free base, but shows increased solubility at pH 2 (0.018 mg/mL). The diphosphate salt also shows improved solubility in fed state simulated intestinal fluid (0.275 mg/mL). Dissolution profiles of the free base and diphosphate salt were similar in fed and fasted state simulated intestinal fluid.

Odomzo capsules contain 200 mg of sonidegib as the diphosphate salt.

Excipients

Odomzo capsules contain the following excipients: crospovidone, lactose, 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.

PHARMACOLOGY

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 Cmax 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.

Pharmacokinetics

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 1 ng/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 effect of hepatic impairment on the systemic exposure of sonidegib has not been studied. As sonidegib is primarily metabolized by the liver, it is anticipated that impaired hepatic function may impact sonidegib pharmacokinetics.

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.

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 mBC

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. LaBCC biopsies were taken 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): ndicular diameters (SPD) of lesions,

increase in the SPD of lesions].

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 18 months unless discontinued earlier. The key efficacy results per central review and local investigator assessment are presented in Table 1.

Table 1 Efficacy overview per central review and local investigator assessment by FAS[a]

	Odomzo 200 mg			
	Central		**Local Investigator**	
	laBCC	**mBCC**	**laBCC**	**mBCC**
	N=66	**N=13**	**N=66**	**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)

	Odomzo 200 mg							
	Central				**Local Investigator**			
	laBCC		**mBCC**		**laBCC**		**mBCC**	
	N=66		**N=13**		**N=66**		**N=13**	
Best overall response, n (%)								
Complete response	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)	14	(21.2)	8	(61.5)
Disease progression	1	(1.5)	0		1	(1.5)	2	(15.4)
Unknown	5	(7.6)	1	(7.7)	4	(6.1)	0	
Time to tumor response (months)								
Median	4.0		1.8		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*	10		0		21		1	
No. censored	27		1		26		2	
Median (months)	NE		NE		14.3		17.7	
95% CI	(NE)		(NE)		(12.0,20.2)		(NE)	
Event-free probability (%), (95% CI)								
6 months	86.9 (68.6,94.9)		100 (NE)		89.8 (74.8, 96.1)		100 (NE)	
9 months	75.8 (55.7,87.7)		100 (NE)		80.7 (63.5,90.4)		100 (NE)	
12 months	65.6 (43.2,81.0)		100 (NE)		70.9 (52.2,83.3)		100 (NE)	
Progression-free survival								
No. of events*	15		6		26		8	
No. censored	51		7		40		5	
Median (months)	22.1		13.1		19.4		13.1	
95% CI	(NE)		(NE)		(16.6, 22.6)		(NE)	
Progression-free survival probability (%), (95% CI)								
6 months	94.8 (84.6, 98.3)		80.8 (42.3, 94.9)		94.8 (84.7, 98.3)		84.6 (51.2, 95.9)	
12 months	82.2 (67.0, 90.8)		58.9 (23.4, 82.5)		76.0 (61.4, 85.7)		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

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

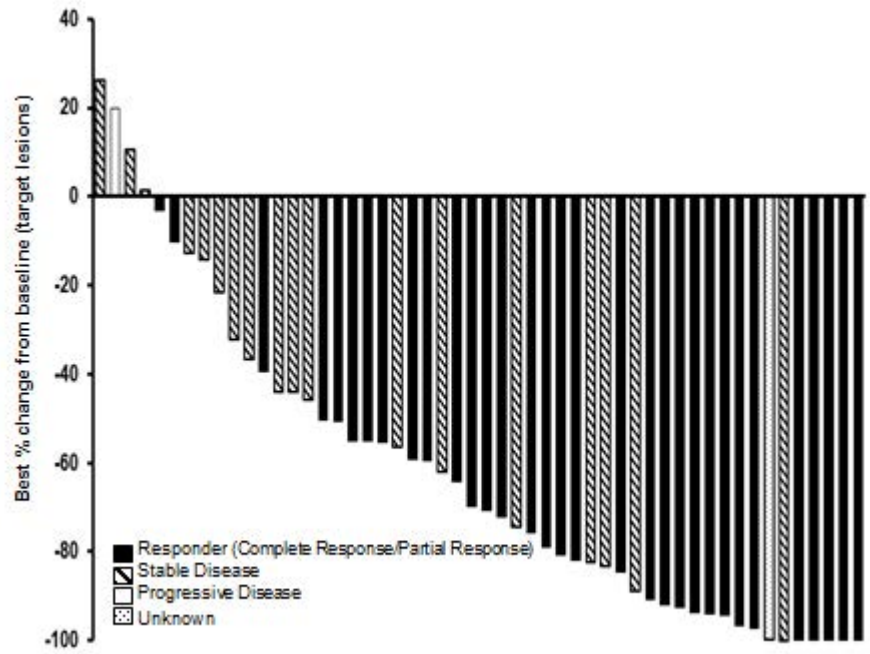
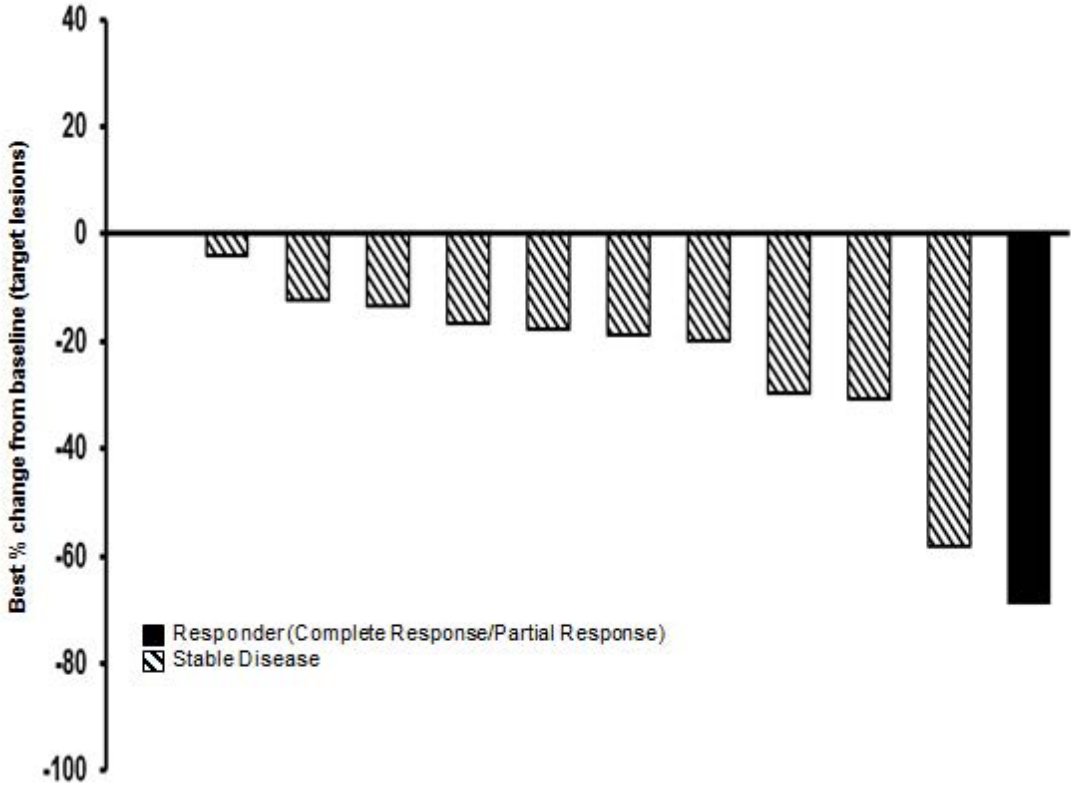
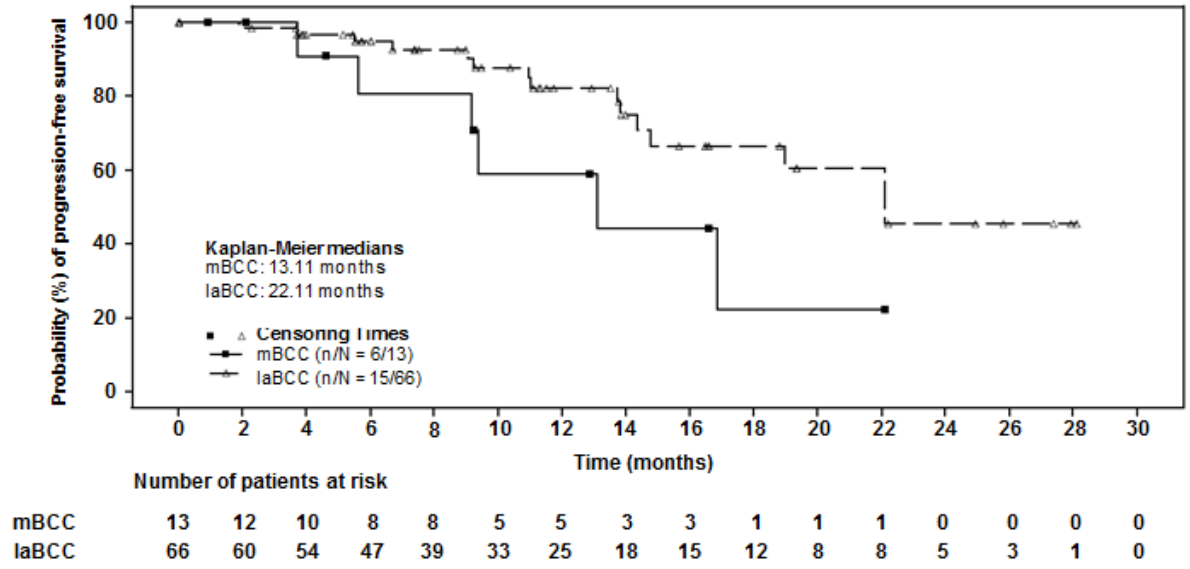


Figure 2: Best change from baseline in the target lesions of mBCC patients per central review by FAS



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.

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.

CONTRAINDICATIONS

Women who are pregnant or breast-feeding (see Precautions – 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 Precautions - Women of child-bearing potential and sexually active men).

PRECAUTIONS

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, eg if muscle related symptoms are reported. If clinically notable elevation of CK is detected, renal function should be assessed (see Dosage and administration).

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 Interactions with Other Medicines).

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.

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.

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 feto-toxic in rabbits as evidenced by abortion and/or complete resorption of fetuses an
(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. Feto-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.

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.

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 Pharmacology).

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 have not been performed with sonidegib.

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 15fold 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.

Blood donation

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

Advice to handler

Do not open capsules due to risk of teratogenicity.

INTERACTIONS WITH OTHER MEDICINES

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.

Medicinal products that increase the pH of the upper gastrointestinal tract, such as proton pump inhibitors (PPIs), may alter the solubility of sonidegib and potentially reduce its bioavailability. No formal clinical study has been conducted to evaluate the effect of PPIs on the systemic exposure of sonidegib. However, concomitant use of PPIs or H2 receptor antagonists was tested as a covariate in the population pharmacokinetic analysis. PPIs were estimated to decrease the bioavailability to 0.69 (95% CI: 0.60, 0.81), while H2 receptor antagonists were estimated to have no significant effect on bioavailability. The effect of PPIs or H2 receptor antagonists on efficacy of sonidegib is unknown.

Anticipated interactions to be considered

Sonidegib is a competitive inhibitor of CYP2B6 and CYP2C9 *in vitro*, potentially increasing the concentrations of drugs metabolized by these enzymes. Sonidegib is also a breast cancer resistance protein (BCRP) inhibitor. Monitor patients carefully for adverse drug reactions with concomitant use of substrates of CYP2B6 and CYP2C9 enzymes or 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 Pharmacology). Odomzo should be taken at least 1 hour before, or two hours after a meal.

ADVERSE EFFECTS

Summary of the safety profile

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 18 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 33.5 months). Thirteen (13) (16.5%) patients had a dose reduction and 22 (27.8%) 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.

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

; 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 200 mg 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	5 (6)	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	25 (32)	1 (1)	0	Very common
Myalgia	15 (19)	0	0	Very common
Myopathy [muscular fatigue and muscular weakness]	3 (4)	0	0	Common
General disorders and administration site conditions				
Fatigue	32 (41)	3 (4)	0	Very common
Pain	11 (14)	1 (1)	0	Very common
Investigations				
Weight decreased	24 (30)	2 (3)	0	Very common

Clinically relevant laboratory abnormalities

The most commonly reported Grade 3/4 laboratory abnormalities 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 200 mg all grades
Hematological parameters					
Hemoglobin decreased	19 (24)	6 (8)	0	0	Very common
Lymphocyte count decreased	14 (18)	6 (8)	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)	6 (8)	9 (11)	1 (1)	Very common
Alanine amino transaminase (ALT) increased	12 (15)	0	3 (4)	0	Very common
Aspartate amino transaminase (AST) increased	12 (15)	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 toxicity is the most clinically relevant side effect reported in patients receiving Odomzo therapy, and is believed to be 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.

DOSAGE AND 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 4 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 4: 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 Pharmacology).

Patients with Hepatic Impairment

Sonidegib has not been studied in patients with hepatic impairment. Based on the available data, sonidegib is primarily metabolized by the liver. It is anticipated that impaired hepatic function may impact sonidegib pharmacokinetics. Therefore, caution should be used in patients with hepatic impairment (see Pharmacology).

OVERDOSAGE

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 for advice on management.

PRESENTATION AND STORAGE CONDITIONS

200 mg hard gelatin capsule: 200 mg: 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.

Blisters containing 10, 30 capsules

Pack sizes: Not all pack sizes may be marketed.

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.

NAME AND ADDRESS OF THE SPONSOR

Novartis Pharmaceuticals Australia Pty Limited

ABN 18 004 244 160

54 Waterloo Road

Macquarie Park NSW 2113

Ò = Registered Trademark

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine (Schedule 4)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS

10 August 2015

For Internal Use Only

Odo100815i based on the CDS of 20 February 2015