ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Odomzo 200 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 200 mg sonidegib (as phosphate).

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

Hard capsule (capsule).

Opaque pink hard capsule containing white to almost white powder with granules, with “NVR” imprinted in black ink on the cap and “SONIDEGIB 200MG” imprinted in black ink on the body.

The size of the capsule is “Size #00” (dimensions 23.3 x 8.53 mm).

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.

4.2 Posology and method of administration

Odomzo should only be prescribed by or under the supervision of a specialist physician experienced in the management of the approved indication.

Posology

The recommended dose is 200 mg sonidegib taken orally once daily.

Treatment should be continued as long as clinical benefit is observed or until unacceptable toxicity develops.

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

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

Table 1 Recommended dose modifications and management for symptomatic CK elevations and muscle-related adverse reactions

Severity of CK elevation	Dose modifications* and management recommendations
Grade 1 [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 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 level. • 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 sonidegib 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 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 sonidegib 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.

* The above recommendations for dose modifications are based on the Common Terminology Criteria for Adverse Events (CTCAE) v4.03, developed by the National Cancer Institute (USA). The CTCAE is a standardised classification of adverse events used in assessing medicinal products for cancer therapy**.**

Cr: creatinine; ULN: upper limit of normal

Other dose modifications

Management of severe or intolerable adverse reactions may require temporary dose interruption (with or without a subsequent dose reduction) or discontinuation.

When dose interruption is required, consider resuming Odomzo at the same dose after resolution of the adverse reaction to ≤ grade 1.

If dose reduction is required, then the dose 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.

Due to the long half-life of sonidegib the full effect of a dose interruption or dose adjustment of sonidegib on several adverse reactions is expected to generally occur after a few weeks (see section 5.2).

Duration of treatment

In clinical studies, treatment with Odomzo was continued until disease progression or until unacceptable toxicity. Treatment interruptions of up to 3 weeks were allowed based on individual tolerability.

Benefit of continued treatment should be regularly assessed, with the optimal duration of therapy varying for each individual patient.

Special populations

Patients with renal impairment

Sonidegib has not been studied in a dedicated pharmacokinetic study in patients with renal impairment. Based on the available data, sonidegib 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 apparent clearance (CL/F) of sonidegib, suggesting that dose adjustment is not necessary in patients with renal impairment (see section 5.2). No efficacy and safety data are available in patients with severe renal impairment.

Patients with hepatic impairment

No dose adjustment is necessary in patients with hepatic impairment (see section 5.2).

Elderly (≥65 years)

Safety and efficacy data in patients aged 65 years and older do not suggest that a dose adjustment is required in these patients (see section 5.2).

Paediatric population
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.

Method of administration

Odomzo is for oral use. The capsules must be swallowed whole. They must not be chewed or crushed. The capsules must not be opened due to risk of teratogenicity (see section 5.3).

Odomzo must be taken at least two hours after a meal and at least one hour before the following meal to prevent increased risk of adverse reactions due to higher exposure of sonidegib when taken with a meal (see section 5.2). If vomiting occurs during the course of the treatment, then no re-dosing of the patient is allowed before the next scheduled dose.

If a dose is missed, it should be taken as soon as this is realised, unless more than six hours have passed since it was scheduled to be taken; in this case, the patient should wait and take the next scheduled dose.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Pregnancy and breast-feeding (see sections 4.4 and 4.6).

Women of childbearing potential who do not comply with the Odomzo Pregnancy Prevention Programme (see sections 4.4 and 4.6).

4.4 Special warnings and precautions for use

Muscle-related adverse reactions

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 management.

All patients starting therapy with Odomzo must be informed of the risk of muscle-related adverse reactions, including the possibility of rhabdomyolysis. They must be instructed to report promptly any unexplained muscle pain, tenderness or weakness occurring during treatment with Odomzo or if symptoms persist after discontinuing treatment.

CK levels should be checked 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).

Dose modification or interruption guidelines should be followed (see section 4.2). 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.

Patients should be closely monitored for muscle-related symptoms if Odomzo is used in combination with certain medicinal products that may increase the potential risk of developing muscle toxicity (e.g. CYP3A4 inhibitors, chloroquine, hydroxychloroquine, fibric acid derivatives, penicillamine, zidovudine, niacin and HMG-CoA reductase inhibitors) (see section 4.5).

Patients with neuromuscular disorders (e.g. inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis, spinal muscular atrophy) must be closely monitored due to an increased risk of muscle toxicity.

Embryofoetal death or severe birth defects

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. Women taking Odomzo must not be pregnant or become pregnant during treatment and for 20 months after ending treatment.

Criteria defining a woman of childbearing potential

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

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

Counselling

For women of childbearing potential
Odomzo is contraindicated in women of childbearing potential who do not comply with the Odomzo Pregnancy Prevention Programme. A woman of childbearing potential must understand that:

- Odomzo exposes a teratogenic risk to the unborn child.
- She must not take Odomzo if she is pregnant or plans to become pregnant.
- She must have a negative pregnancy test, conducted by a healthcare professional within 7 days before starting Odomzo treatment.
- She must have a negative pregnancy test monthly during treatment, even if she has become amenorrhoeic.
- She must not become pregnant while taking Odomzo and for 20 months after her final dose.
- She must be able to comply with effective contraceptive measures.
- She must use 2 methods of recommended contraception (see the "Contraception" section below and section 4.6) while she is taking Odomzo, unless she commits to not having sexual intercourse (abstinence).
- She must tell her healthcare provider 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.
- She must not breast-feed while taking Odomzo and for 20 months after the final dose.

For men
Sonidegib may pass into the semen. To avoid potential foetal exposure during pregnancy, a male patient must understand that:

- Odomzo exposes a teratogenic risk to the unborn child if he engages in unprotected sexual activity with a pregnant woman.
- He must always use the recommended contraception (see the "Contraception" section below and section 4.6).
- He will tell his healthcare provider if his female partner becomes pregnant while he is taking Odomzo or during the 6 months after his final dose.

For healthcare professionals
Healthcare professionals must educate patients so they understand and acknowledge all the conditions of the Odomzo Pregnancy Prevention Programme.

Contraception

Women of child-bearing potential
Women of child-bearing potential must use two methods of recommended contraception, including one highly effective method and a barrier method, while taking Odomzo and for 20 months after ending treatment (see section 4.6).

Men
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 and for 6 months after ending treatment (see sections 4.6 and 5.3).

Pregnancy testing

The pregnancy status of women of child-bearing potential must be established within 7 days prior to the initiation of Odomzo treatment and monthly during treatment by means of a test performed by a healthcare professional. Pregnancy tests should have a minimum sensitivity of 25 mIU/ml as per local availability. In the event of pregnancy, treatment must not be initiated. In case of pregnancy occurring during treatment, Odomzo must be stopped immediately (see section 5.3). Patients who present with amenorrhoea during treatment with Odomzo should continue monthly pregnancy testing while on treatment.

Prescribing and dispensing restrictions for women of childbearing potential

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

Educational material

In order to help healthcare providers and patients avoid embryonic and foetal exposure to Odomzo, the Marketing Authorisation Holder will provide educational materials (Odomzo Pregnancy Prevention Programme) to reinforce the potential risks associated with use of the medicinal product.

Blood donation

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

Semen donation

Male patients should not donate semen while taking Odomzo and for at least 6 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).

Interactions

Concomitant treatment with strong CYP inducers (e.g. rifampicin, carbamazepine or phenytoin) should be avoided, as a risk for decreased plasma concentrations and decreased efficacy of sonidegib cannot be excluded (see also section 4.5).

Cutaneous squamous cell carcinoma (cuSCC)

Patients with advanced BCC have an increased risk of developing 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.

Additional precautions

Patients should be instructed never to give this medicinal product to another person. Any capsules that remain unused at the end of treatment should immediately be disposed of by the patient in accordance with local requirements (e.g. by returning the capsules to their pharmacist or physician).

Excipients

Odomzo capsules contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products 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 sonidegib 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 C_{max}, respectively, compared with sonidegib alone. Longer duration of concomitant use of CYP3A4 strong inhibitors (e.g. more than 14 days) will lead to a larger fold change in sonidegib exposure based on simulation. If concomitant use of a strong CYP3A inhibitor is required, the sonidegib dose should be reduced to 200 mg every other day. Strong CYP3A inhibitors include, but are 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.

Agents that may decrease sonidegib plasma concentration

In healthy subjects, co-administration of a single dose of 800 mg sonidegib with rifampicin (600 mg daily for 14 days), a strong CYP3A inducer, resulted in 72% and 54% decreases in sonidegib AUC and C_{max} respectively, compared with when sonidegib was given alone. Co-administration of sonidegib with strong CYP3A inducers decreases sonidegib plasma concentration. Concomitant use of strong CYP3A inducers should be avoided; this includes, but is not limited to, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin and St John's Wort (*Hypericum perforatum*). If a strong CYP3A4 inducer must be used concomitantly with sonidegib, consideration should be given to increasing the daily dose of sonidegib to 400-800 mg. This dose of sonidegib is predicted to adjust the AUC to the range observed without inducers based on pharmacokinetic data when the concomitant treatment with the inducer is no longer than 14 days. Longer concomitant treatment with inducer is not recommended because sonidegib exposure will be decreased and this may compromise efficacy. The dose of sonidegib 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. This interaction is not expected to be clinically significant.

Effects of sonidegib on other medicinal products

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 (IC50 ~1.5μM). Patients concomitantly using substrates of BCRP transporters should be carefully monitored for adverse drug reactions. Substances that are BCRP substrates with narrow therapeutic range (e.g. methotrexate, mitoxantrone, irinotecan, topotecan) should be avoided.

Agents that may increase muscle-related adverse reactions

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

In the phase II pivotal trial, 12 (15.2%) patients treated with Odomzo 200 mg took concomitant HMG-CoA reductase inhibitors (9 took pravastatin, 3 took non-pravastatin HMG-CoA reductase inhibitors including rosuvastatin and simvastatin). Of these patients, 7 (58.3%) had up to grade 1 muscle symptoms while 43 (64.1%) 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.

Food interaction

The bioavailability of sonidegib is increased in the presence of food (see section 5.2). Odomzo must be taken at least two hours after a meal and at least one hour before the following meal.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Due to the risk of embryofoetal 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 4.4).

Odomzo is contraindicated in woman of childbearing potential who do not comply with the Odomzo Pregnancy Prevention Programme (see section 4.3).

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.

Contraception in males and females

Women of childbearing potential
Women of childbearing potential must be able to comply with effective contraceptive measures. They must use two methods of recommended contraception, including one highly effective method and a barrier method, during Odomzo therapy and for 20 months after the final dose. Women of childbearing potential whose periods are irregular or have stopped must follow all the advice on effective contraception.

Men
It is unknown whether sonidegib is contained in semen. Men should not father a child or donate semen while taking Odomzo and for at least 6 months after ending treatment. To avoid potential foetal exposure during pregnancy, 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 and for 6 months after the final dose.

The following are recommended forms of highly effective methods

- Tubal sterilisation
- Vasectomy
- Intrauterine device (IUD)

The following are recommended barrier methods

- Any male condom (with spermicide, if available)
- Diaphragm (with spermicide, if available)

Pregnancy

There are no data on the use of sonidegib in pregnant women. Studies in animals have shown teratogenicity and foetotoxicity (see section 5.3). Odomzo is contraindicated during pregnancy.

Breast-feeding

It is unknown whether sonidegib is excreted in human milk. Because of the potential for serious adverse drug reactions, such as serious developmental defects in breast-fed newborns/infants from sonidegib, women must not breast-feed while taking Odomzo or for 20 months after ending treatment (see section 5.3).

Fertility

Data from studies in rats and dogs indicate that male and female fertility may be irreversibly compromised by treatment with Odomzo (see section 5.3). Additionally, amenorrhoea has been observed in clinical studies in women of childbearing potential (see section 4.8). Fertility preservation strategies should be discussed with women of childbearing potential prior to starting treatment with Odomzo.

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

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 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). One death occurred while on treatment or within 30 days of the last dose taken in either metastatic BCC or locally advanced BCC patients taking Odomzo 200 mg.

The most common adverse drug reactions occurring in ≥10% of 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 (Table 2), the frequency was greater in patients taking Odomzo 800 mg than in patients taking Odomzo 200 mg except for musculoskeletal pain, diarrhoea, abdominal pain, headache and pruritus. This was also true for grade 3/4 adverse reactions, except fatigue.

Tabulated list of adverse drug reactions

Adverse drug reactions for the recommended dose from the phase II pivotal clinical study (Table 2) are listed by Medical Dictionary for Regulatory Activities (MedDRA) version 18 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	**Frequency all grades** 200 mg
Metabolism and nutrition disorders	
Decreased appetite	Very common
Dehydration	Common
Nervous system disorders	
Dysgeusia	Very common
Headache	Very common
Gastrointestinal disorders	
Nausea	Very common
Diarrhoea	Very common
Abdominal pain	Very common
Vomiting	Very common
Dyspepsia	Common
Constipation	Common
Gastro-oesophageal reflux disorder	Common
Skin and subcutaneous tissue disorders	
Alopecia	Very common
Pruritus	Very common
Rash	Common
Abnormal hair growth	Common
Musculoskeletal and connective tissue disorders	
Muscle spasms	Very common
Musculoskeletal pain	Very common
Myalgia	Very common
Myopathy [muscular fatigue and muscular weakness]	Common
Reproductive system and breast disorders	
Amenorrhoea*	Very common
General disorders and administration site conditions	
Fatigue	Very common
Pain	Very common
Investigations	
Weight decreased	Very common
* Of the 79 patients receiving Odomzo 200 mg, 5 were women of childbearing age. Among these women, amenorrhoea was observed in 1 patient (20%).	

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	Frequency all grades 200 mg
Haematological parameters	
Haemoglobin decreased	Very common
Lymphocyte count decreased	Very common
Biochemistry parameters	
Serum creatinine increased	Very common
Serum creatine phosphokinase (CK) increased	Very common
Blood glucose increased	Very common
Lipase increased	Very common
Alanine amino transaminase (ALT) increased	Very common
Aspartate amino transaminase (AST) increased	Very common
Amylase increased	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 reactions including CK elevation
Muscle toxicity is the most clinically relevant side effect reported in patients receiving sonidegib therapy and is believed to be a class effect of inhibitors of the Hedgehog (Hh) signalling pathway. In the phase II pivotal study muscle spasms were the most common "muscle-related" adverse reactions, 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 normalisation or grade 1) of 12 days (95% CI 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.

In the phase II pivotal study, no reported cases of rhabdomyolysis were confirmed (defined as CK levels >10-fold above the pre-treatment or baseline level or >10x ULN if no baseline level reported plus a 1.5-fold increase in serum creatinine from the pre-treatment or baseline level). However, one reported case in a patient treated with Odomzo 800 mg in a non-pivotal study was confirmed.

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

Paediatric population
The evaluation of safety in the paediatric population is based on data from 16 adult and 60 paediatric patients from Study CLDE225X2104 and 16 adult and 2 paediatric patients from Study CLDE225C2301. The median duration of exposure to sonidegib during Study X2104 was 97 days (range 34 to 511 days) for adult patients and 55 days (range 2 to 289 days) for paediatric patients. The median duration of exposure to sonidegib during Study C2301 was 2.8 months (range 0.4 to 33.2 months) for adult patients and 3.5 months (range 1.3 to 5.7 months) for paediatric patients.

The toxicity of sonidegib as observed in studies C2301 and X2104 in adults was in line with the already known treatment related toxicity reported in adult patients with basal cell carcinoma.
The sonidegib-related toxicity reported in paediatric patients was similar to the results reported in adults, with the exceptions of a reduced incidence of muscle toxicity (e.g. CK elevations observed in 16.7% of paediatric patients compared with 50% of adults in study X2104) and the observation of post-natal development effect particularly with prolonged exposure (reported as cases of epiphyseal plate of phalanx disorder, knee subchondral condensation of area of growth plate, physeal distal femur disorder, chondropathy, and chipped tooth).

Premature fusion of the 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 treated with sonidegib during clinical studies 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 should not be used in paediatric patients as safety and effectiveness is not established in this population.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In dose escalation studies, Odomzo was administered at doses 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, other antineoplastic agents, ATC code: L01XJ02

Mechanism of action

Sonidegib is an orally bioavailable inhibitor of the Hh signalling pathway. It binds to Smoothened (Smo), a G protein-coupled receptor-like molecule that positively regulates the Hh pathway and eventually activates and releases glioma-associated oncogene (GLI) transcription factors which induces the transcription of Hh target genes involved in proliferation, differentiation and survival. Aberrant Hh signalling has been linked to the pathogenesis of several types of cancer, including basal cell carcinoma (BCC). Sonidegib binding to Smo will inhibit Hh signalling and consequently block signal transduction.

Pharmacodynamic effects

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. Therefore, therapeutic doses of Odomzo are not expected to cause clinically significant QTc prolongation. Further, sonidegib plasma concentrations above those achieved with the therapeutic doses were not associated with life-threatening arrhythmias or torsades de pointes.

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

Clinical efficacy and safety

A phase II, randomised double-blind study of two dose levels (200 mg or 800 mg once daily) 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 (≥18 years of age) patients with laBCC or mBCC who were not candidates for radiotherapy, surgery or other local therapies, were randomised to receive Odomzo at either 200 mg or 800 mg daily until disease progression or unacceptable toxicity.

The primary efficacy endpoint of the study was objective response rate according to modified Response Evaluation Criteria in Solid Tumours (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, time to tumour response 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 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 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 a lesion; complete response (CR): disappearance of all lesions; progressive disease: ≥25% increase in the SPD of lesions]. For a composite Complete Response, all modalities used for assessment had to demonstrate absence of tumour.

Of the 230 patients randomised, 79 patients were assigned to Odomzo 200 mg. 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 key efficacy results per central review and local investigator assessment are presented in Table 4.

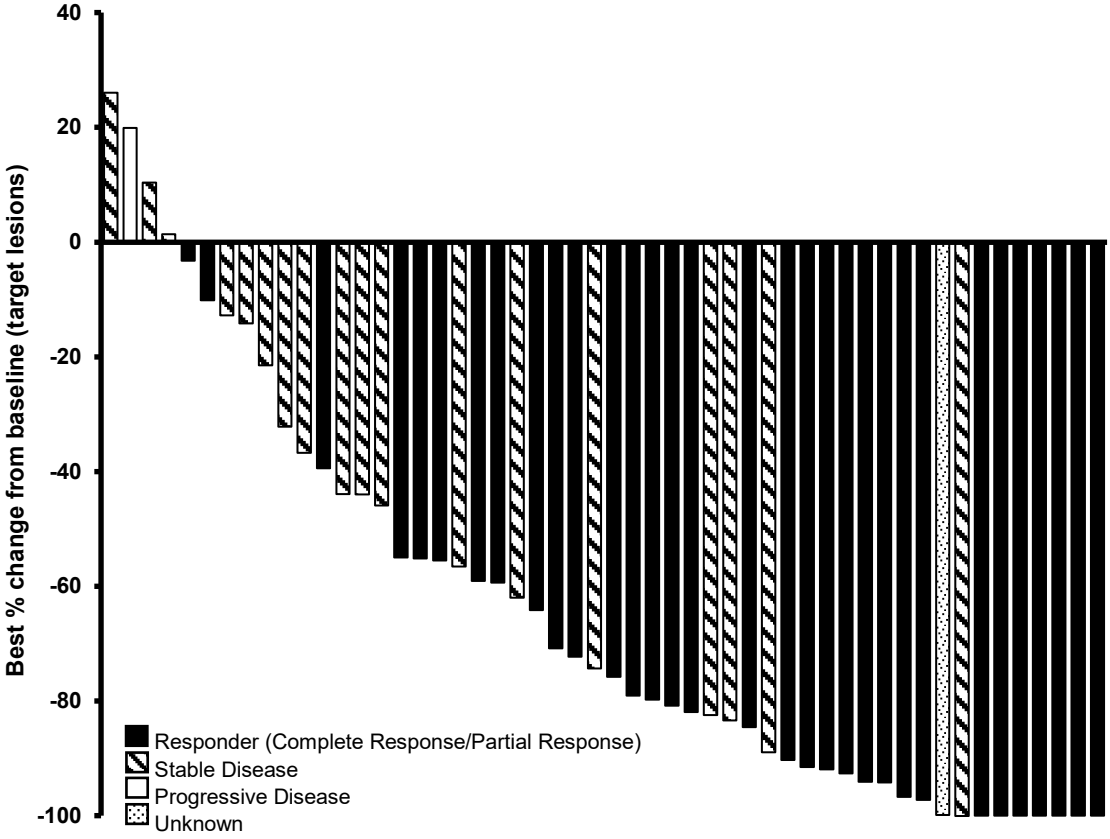
Table 4 Efficacy overview per central review and local investigator assessment by FAS[a]

	Odomzo 200 mg	
	Central laBCC N=66	**Local investigator laBCC N=66**
Objective response rate, n (%)	**37 (56.1)**	**47 (71.2)**
95% CI	(43.3, 68.3)	(58.7, 81.7)
Best overall response, n (%)		
Complete response	3 (4.5)[b]	6 (9.1)
Partial response	34 (51.5)	41 (62.1)
Disease stabilisation	23 (34.8)	13 (19.7)
Disease progression	1 (1.5)	1 (1.5)
Unknown	5 (7.6)	5 (7.6)
Time to tumour response (months)		
Median	4.0	2.5
95% CI	(3.8, 5.6)	(1.9, 3.7)
Duration of response		
No. of events*	11	22
No. censored	26	25
Median (months)	26.1	15.7
95% CI	(NE)	(12.0,20.2)
Event-free probability (%), (95% CI)		
6 months	86.4 (67.7, 94.7)	89.8 (74.8, 96.1)
9 months	74.9 (54.4, 87.2)	80.7 (63.5, 90.4)
12 months	64.9 (42.3,80.4)	71.4 (53.1, 83.6)
Progression-free survival		
No. of events*	16	28
No. censored	50	38
Median (months)	22.1	19.4
95% CI	(NE)	(16.6, 23.6)
Progression-free survival probability (%), (95% CI)		
6 months	94.8 (84.6, 98.3)	94.7 (84.5, 98.3)
12 months	82.0 (66.7, 90.7)	75.5 (60.7, 85.4)

[a] Full analysis set included all randomised patients (intent-to-treat population).
[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 CR rate of 21.2%.
*Event refers to disease progression or death due to any reason.
FAS: Full analysis set
CI: confidence interval
NE: not estimable

Figures 1 shows the best change in target lesion size for each patient with laBCC 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 assessment by FAS



Patient-reported outcomes were evaluated as an exploratory endpoint using the European Organisation 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).

The majority of patients experienced maintenance and/or improvement in their disease-related symptoms, functioning, and health status. Time to deterioration in the pre-specified PRO scales (corresponding to >10-point worsenings without subsequent improvement) essentially mirrored the estimated PFS.

In the pivotal study, 29.1% of patients discontinued due to adverse reactions, which were mostly mild or moderate (see section 4.8).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Odomzo in all subsets of the paediatric population in basal cell carcinoma (see section 4.2 for information on paediatric use).

Efficacy and safety of sonidegib have been studied in two clinical studies involving a total of 62 paediatric patients. Study CLDE225X2104 was a Phase I/II study of sonidegib in paediatric patients with recurrent or refractory medulloblastoma or other tumours potentially dependent on the Hedgehog (Hh) signalling pathway and adult patients with recurrent or refractory medulloblastoma. Study CLDE225C2301 was a Phase II, multi-centre, open-label, single-arm study of the efficacy and safety of oral sonidegib in patients with Hh-activated relapsed medulloblastoma. Results show a lack of significant efficacy despite the enrichment strategy focussed on Hh-activated medulloblastoma.

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 to 4 hours. Sonidegib exhibited 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 pharmacokinetic analysis and estimated accumulation at steady state was 19-fold irrespective of dose. Steady state was reached approximately 4 months after starting sonidegib. The average steady state C_{trough} for 200 mg was 830 ng/ml (range 200 to 2400 ng/ml) in cancer patients. Compared to the fasted state, the C_{max} and AUC of Odomzo 800 mg was increased 7.8- and 7.4-fold, respectively when the dose was given with a high-fat meal. Compared to the fasted state, the C_{max} and AUC of Odomzo 200 mg was increased 2.8- and 3.5-fold, respectively, when the dose was given with a light meal. Compared to the fasted state, the C_{max} and AUC of Odomzo 200 mg increased 1.8- and 1.6-fold, respectively, when a moderate meal was taken 2 hours before the administration. A moderate meal taken 1 hour after the administration of Odomzo 200 mg provided similar exposures compared to the fasted state.

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 litres. 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.

Based on *in vitro* data, sonidegib is not a substrate of P-gp, BCRP or multi-resistance protein 2 (MRP2). 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.

Biotransformation

Sonidegib is primarily metabolised by CYP3A4. Unchanged sonidegib represented 36% of circulating radioactivity and the major circulating metabolite (45% of parent exposure) identified in plasma is the hydrolysis product of sonidegib and is pharmacologically inactive. All the metabolites were deemed 4 to 90 times 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 faeces and 1.95% recovered in urine. Unchanged sonidegib in faeces 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 pharmacokinetic modeling was approximately 28 days.

Special populations

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 pharmacokinetic analyses showed that there are no clinically relevant effects of age (range tested from 20-93 years, mean 61 years), body weight (range tested 42-181 kg, mean 77 kg), gender, or creatinine clearance (range tested 27.3-290 ml/min, mean 92.9 ml/min) 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, than those seen in Western healthy subjects for a single dose of 200 mg.

5.3 Preclinical safety data

Sonidegib was evaluated in rats and dogs.

General toxicology

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, effects on the male and female reproductive tract, atrophy of the hair follicles with alopecia, gastrointestinal toxicity with body weight loss and effects on lymph nodes. At exposures well above the clinical exposure, an additional target organ was the kidney.

Carcinogenesis and mutagenesis

Sonidegib was not genotoxic in studies conducted *in vitro* and *in vivo*. No carcinogenic potential was identified in rat and mice carcinogenicity studies. However, exposure levels were far below clinical exposure levels in rats, and around clinical exposure levels in mice.

Reproductive and developmental toxicity

Sonidegib was shown to be foetotoxic in rabbits, as evidenced by abortion and/or complete resorption of foetuses and teratogenic resulting in severe malformations at very low exposure. Teratogenic effects included vertebral, distal limb and digit malformations, severe craniofacial malformations and other severe midline defects. Foetotoxicity in rabbits was also seen at very low maternal exposure. There was reduced fertility at low exposure in female rats. For sonidegib treated male rats, exposure at approx. 2-fold the clinical exposure did not impact male fertility.

Environmental risk assessment (ERA)

Environmental risk assessment studies have shown that sonidegib may pose a risk for surface water (see section 6.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Crospovidone Type A
Lactose monohydrate
Magnesium stearate
Poloxamer 188
Silica, colloidal anhydrous
Sodium laurilsulfate

Capsule shell

Gelatin
Iron oxide red (E172)
Titanium dioxide (E171)

Printing ink

Iron oxide black (E172)
Propylene glycol (E1520)
Shellac

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Do not store above 30°C.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

10 x 1 hard capsule in PCTFE/PVC/Alu perforated unit-dose blisters.

Each pack contains either 10 or 30 hard capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

This medicinal product may pose a risk to the environment (see section 5.3).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Sun Pharmaceutical Industries Europe B.V.
Polarisavenue 87
2132JH Hoofddorp
Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1030/001
EU/1/15/1030/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of initial authorisation: 14 August 2015
Date of latest renewal: 20 May 2020

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Sun Pharmaceutical Industries Europe B.V.
Polarisavenue 87
2132JH Hoofddorp
Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorization holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

Prior to launch in each Member State the Marketing Authorisation Holder (MAH) shall agree the following with the National Competent Authority:
- The national part of the DHPC
- Methodology to collect information on the use of Odomzo and the compliance with the pregnancy pharmacovigilance programme and its effectiveness
- The format and content of the Healthcare professional and patient material

The MAH shall distribute a Direct Healthcare Professional Communication letter at launch of the product, which should contain the following:
- A core text as agreed by the CHMP

- National specific requirements as agreed with the National Competent Authority regarding:
  - Distribution of the product
  - Measures to ensure that all appropriate actions have been performed prior to Odomzo being prescribed and dispensed

The MAH shall continuously ensure that all physicians who are expected to prescribe Odomzo are provided with the following:
- Product information
- Healthcare professional educational material
- Healthcare professional reminder card
- Patient educational material
- Patient reminder card

The healthcare professional educational material for Odomzo should contain the following key elements:
- Brief background on Odomzo, its licensed indication and posology
- A requirement to inform patients of the teratogenic risks associated with Odomzo and the need to avoid foetal exposure
- Description of the pregnancy prevention programme and categorisation of patients based on sex and childbearing potential
- Information on the recommended forms of contraception both for women and men
- Obligations of the health care professional in relation to the prescribing of Odomzo
- Safety advice for women of childbearing potential
- Safety advice for men
- Requirements in the event of pregnancy
- Inform patients that they should not donate blood during treatment with Odomzo and for at least 20 months after their final dose
- Check list for healthcare professional ensuring that patients receive the appropriate counselling
- The need to ensure all patients complete and sign the Odomzo Verification of Counselling Form which is to be present in the healthcare professional educational material
- Adverse event reporting

The patient educational material for Odomzo should contain the following key elements:
- Information for patients on the teratogenic risks associated with Odomzo and the need to avoid foetal exposure
- The need for adequate contraception and definition of adequate contraception
- National or other applicable specific arrangements for a prescription for Odomzo to be dispensed
- Not to give Odomzo to any other person as well as information on the disposal of unwanted medicinal product and the need to keep Odomzo capsules out of sight and reach of children
- That the patient should not donate blood during treatment and for at least 20 months after their final dose
- That the patient should not breastfeed during treatment and for 20 months after their final dose
- That the patient should tell the healthcare professional about any adverse event
- Information for women of childbearing potential
- Information for men

The healthcare professional's reminder card should contain the following key elements:
- Information for women of childbearing potential
- Information for men
- The need to tell patients to report immediately to the treating healthcare professional if pregnancy is suspected in a female patient, or in a female partner of a male patient
- Remind patients to return unused capsules at the end of the treatment (disposal will depend on local requirements)
- Remind patients not to donate blood during treatment and for at least 20 months after final dose

The patient reminder card should contain the following key elements:

- Information for patients of the teratogenic risks associated with Odomzo and the need to avoid foetal exposure
- Not to donate blood during treatment and for at least 20 months after the final dose
- Information for women of childbearing potential
- Information for men
- To return unused capsules at the end of the treatment (disposal will depend on local requirements)
- Emergency contact phone numbers

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Odomzo 200 mg hard capsules
sonidegib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 200 mg sonidegib (as phosphate).

3. LIST OF EXCIPIENTS

Contains lactose. Read the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsules

10 x 1 hard capsule
30 x 1 hard capsule

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.
Do not crush, open or chew the capsule.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Risk of severe birth defects.
Do not use while pregnant or breast-feeding.
You must follow the Odomzo Pregnancy Prevention Programme.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sun Pharmaceutical Industries Europe B.V.
Polarisavenue 87
2132JH Hoofddorp
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1030/001 10 hard capsules
EU/1/15/1030/002 30 hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Odomzo 200 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER –HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Odomzo 200 mg capsules
sonidegib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Sun Pharmaceutical Industries Europe B.V.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Odomzo 200 mg hard capsules
sonidegib

Odomzo may cause severe birth defects. It may lead to the death of a baby before it is born or shortly after being born. You must not become pregnant while taking this medicine. You must follow the contraception instructions contained in this leaflet.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Odomzo is and what it is used for

What Odomzo is

Odomzo contains the active substance sonidegib. It is an anti-cancer medicine.

What Odomzo is 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 locally and cannot be treated with surgery or radiation.

How Odomzo works

The normal growth of cells is controlled by various chemical signals. In patients with basal cell carcinoma, changes occur to genes controlling a part of this process known as the “hedgehog pathway”. This switches on signals that make the cancer cells grow out of control. Odomzo works by blocking this process, stopping cancer cells from growing and making new cells.

2. What you need to know before you take Odomzo

Read the specific instructions given to you by your doctor, particularly on the effects of Odomzo on unborn babies.

Read carefully and follow the instructions of the patient brochure and reminder card given to you by your doctor.

Do not take Odomzo
- if you are allergic to sonidegib or any of the other ingredients of this medicine (listed in section 6).
- if you are pregnant or think you may be pregnant. This is because Odomzo may cause harm or death to your unborn baby (see section "Pregnancy").
- if you are breast-feeding. This is because it is not known whether Odomzo can pass into your breast milk and cause harm to your baby (see section "Breast-feeding").
- if you are able to become pregnant but are unable or unwilling to follow the necessary pregnancy prevention measures that are listed in the Odomzo Pregnancy Prevention Programme.

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.

Additional information on the above points can be found in the sections "Pregnancy", "Breast-feeding", "Fertility" and "Contraception for women and men".

Warnings and precautions
- Odomzo may cause muscle problems. Tell your doctor before taking Odomzo if you have a history of muscle cramps or weakness or if you are taking other medicines. Some medicines (e.g. medicines used to treat high cholesterol) might increase the risk for muscle problems. Tell your doctor or pharmacist **immediately** if your muscles hurt or you have unexplained muscle cramps or weakness during treatment with Odomzo. Your doctor may need to change your dose, or stop your treatment temporarily or permanently.
- You should not donate blood while on treatment with Odomzo and for 20 months after ending your treatment.
- If you are male, you should not father a child or donate semen at any time during treatment and for 6 months after the final dose.
- Your doctor will check your skin regularly for another type of cancer called cutaneous squamous cell carcinoma (SCC). It is not known whether SCC can be related to treatment with Odomzo. Usually this type of cancer appears on sun-damaged skin, does not spread and can be cured. Tell your doctor if you notice any changes in your skin.
- Never give this medicine to anyone else. You should return unused capsules at the end of your treatment. Talk to your doctor or pharmacist regarding where to return the capsules.

Blood tests during treatment with Odomzo
Your doctor will perform blood tests before treatment, and possibly during treatment as well. These tests will check the health of your muscles by measuring the levels of an enzyme in your blood called creatine phosphokinase.

Children and adolescents (under 18 years of age)
Odomzo should not be used in children and adolescents below the age of 18. Problems with growing teeth and bones were seen with this medicine. Odomzo may cause bones to stop growing in children and adolescents. This can also happen after discontinuation of the treatment.

Other medicines and Odomzo
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription and herbal medicines. This is because Odomzo can affect the way some medicines work. Some other medicines can also affect how Odomzo works, or make it more likely that you will have side effects.

In particular tell your doctor or pharmacist if you are taking any of the following:
- medicines such as statins and fibric acid derivatives used to treat high cholesterol and lipids
- vitamin B3, also known as niacin
- medicines such as methotrexate, mitoxantrone, irinotecan, or topotecan used to treat certain types of cancers or other diseases such as severe joint problems (rheumatoid arthritis) and psoriasis
- medicines such as telithromycin, rifampicin or rifabutin used to treat bacterial infections
- medicines such as ketoconazole (not including shampoos and creams), itraconazole, posaconazole or voriconazole used to treat fungal infections

- medicines such as chloroquine and hydroxychloroquine used to treat parasitic infections as well as other diseases such as rheumatoid arthritis or lupus erythematosus
- medicines such as ritonavir, saquinavir or zidovudine used to treat AIDS or HIV
- medicines such as carbamazepine, phenytoin or phenobarbital used to treat acute seizures
- a medicine called nefazodone used to treat depression
- a medicine called penicillamine used to treat rheumatoid arthritis
- a herbal medicine called St. John's wort (also known as *Hypericum perforatum*) used to treat depression.

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

These medicines should be used with caution or may need to be avoided during your treatment with Odomzo. If you are taking any of these, your doctor might need to prescribe an alternative medicine for you.

During your treatment with Odomzo, you should also tell your doctor or pharmacist if you are prescribed another medicine that you were not taking before.

Pregnancy
Do not take Odomzo if you are pregnant, think you may be pregnant, or are planning to become pregnant during your treatment or during the 20 months after your treatment has finished. You must stop taking Odomzo and talk to your doctor immediately if you become pregnant or suspect you could be pregnant. Odomzo may cause your baby to have severe birth defects or lead to the death of your unborn baby. Specific instructions (the Odomzo Pregnancy Prevention Programme) given to you by your doctor contain information particularly on the effects of Odomzo on unborn babies.

Breast-feeding
Do not breast-feed during your treatment or during the 20 months after your treatment has finished. It is not known whether Odomzo can pass into your breast milk and cause harm to your baby.

Fertility
Odomzo may have an impact on fertility in men and women. Talk to your doctor if you plan to have children in the future.

Contraception for women and men
Women
Before starting Odomzo treatment, 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.

If you are able to become pregnant:
- you must take precautions so that you do not become pregnant while taking Odomzo,
- you must use 2 methods of contraception, one highly effective method and one barrier method (see the examples below) while you are taking Odomzo,
- you must keep using this contraception for 20 months after you have stopped taking Odomzo because traces of the medicine remain in the body for a long time.

Your doctor will discuss with you the best method of contraception for you.

You must use one highly effective method, such as:
- an intra-uterine device ("the coil" or IUD)
- surgical sterilisation.

You must also use one barrier method, such as:
- a condom (with spermicide, if available)
- a diaphragm (with spermicide, if available).

Your doctor will test you for pregnancy:
- at least 7 days before starting treatment – to make sure that you are not already pregnant

- every month during treatment.

During treatment and during the 20 months after your treatment has finished, tell your doctor straight away if:
- you think your contraception has not worked for any reason
- your periods stop
- you stop using contraception
- you need to change contraception

Men
While you are taking Odomzo, always use a condom (with spermicide, if available) when you have sex with a female partner, even if you have had a vasectomy. You must keep doing this for 6 months after your treatment has finished.

Tell your doctor straight away if your partner becomes pregnant while you are taking Odomzo and for 6 months after your treatment has finished.

You should not father a child or donate semen during your treatment and for 6 months after your treatment has finished.

Driving and using machines
Odomzo is not likely to affect your ability to drive or use any tools or machines. Talk to your doctor if you are unsure.

Odomzo contains lactose
Odomzo contains lactose (milk sugar). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take Odomzo

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Taking this medicine
The recommended dose is 200 mg (1 capsule) a day.
- Do not eat for 2 hours before taking Odomzo and for 1 hour afterwards.
- Take your capsule at about the same time each day. This will help you to remember when to take your medicine.
- Swallow the capsule whole. Do not open, chew or crush the capsule. Any contact with the content of the capsules should be avoided, as it may have harmful effects.

Do not change your dose without talking to your doctor. Do not exceed the recommended dose prescribed by your doctor. If you vomit after you swallow the capsule, do not take any more capsules until your next scheduled dose.

How long to take Odomzo
Keep taking Odomzo for as long as your doctor tells you. If you have questions about how long to take Odomzo, talk to your doctor or pharmacist.

If you take more Odomzo than you should
If you take more Odomzo than you should, or if someone else accidentally takes your medicine, talk to a doctor or go to a hospital straight away. Take the medicine and its packaging and leaflet with you.

If you forget to take Odomzo
If you forget to take a dose of Odomzo, take it as soon you realise. If more than six hours have passed since

the dose was due to be taken, skip the missed dose, then take the next dose at the scheduled time. Do not take a double dose to make up for a forgotten dose.

If you stop taking Odomzo
Do not stop taking Odomzo without talking to your doctor first.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Odomzo may cause severe birth defects, You must not become pregnant while taking this medicine (see "Pregnancy", "Breast-feeding", "Fertility" and "Contraception for women and men" in section 2 for more information).

Stop taking Odomzo and tell your doctor straight away if you notice any of the following as these could be signs of an allergic reaction:
- difficulty breathing or swallowing
- swelling of the face, lips, tongue or throat
- severe itching of the skin, with a red rash or raised bumps.

Some side effects could be serious
Tell your doctor or pharmacist straight away if you notice any of the following:
- severe muscle cramps, muscle pain or muscle weakness. These could be signs of a problem called rhabdomyolysis, which involves the breakdown of muscle tissue.
- dark urine, decreased urine output or no urine output. These could be signs that your muscle fibre is breaking down, which is harmful to your kidneys.

Other possible side effects
If any of these side effects become severe, tell your doctor or pharmacist.

Very common: may affect more than 1 in 10 people
- muscle cramps, muscle pain, pain in the bones, ligaments and tendons
- absence of menstrual periods
- diarrhoea or heartburn
- decreased appetite
- headache
- disturbed sense of taste or strange taste in the mouth
- pain in the belly
- feeling sick
- vomiting
- itching
- hair loss
- tiredness
- pain
- weight loss.

Common: may affect up to 1 in 10 people
- upset stomach or indigestion
- constipation
- rash
- abnormal hair growth
- thirst, not passing much urine, weight loss, dry flushed skin, irritability (possible symptoms of low

level of fluids in the body, known as dehydration).

During Odomzo treatment, you may also have some **abnormal blood test results**. These can alert your doctor to possible changes in the function of some parts of your body, for example:
- high levels of the following enzymes: creatine phosphokinase (muscle function), lipase and/or amylase (pancreas function), alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) (liver function)
- high level of creatinine (kidney function)
- high level of sugar in the blood (known as hyperglycaemia)
- low level of haemoglobin (needed to transport oxygen in the blood)
- low level of white blood cells.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Odomzo

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the pack and the blister after EXP. The expiry date refers to the last day of that month.
- Do not store above 30°C.
- Store in the original package in order to protect from moisture.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Odomzo contains
- The active substance is sonidegib (as phosphate). Each capsule contains 200 mg sonidegib.
- The other ingredients are:
- Capsule contents: crospovidone type A, lactose monohydrate (see section 2, ‘Odomzo contains lactose’), magnesium stearate, poloxamer 188, silica, colloidal anhydrous, sodium laurilsulfate.
- Capsule shell: gelatin, iron oxide red (E172), titanium dioxide (E171).
- Printing ink: iron oxide black (E172), propylene glycol (E1520), shellac.

What Odomzo looks like and contents of the pack

Odomzo 200 mg capsules are pink and opaque. They are imprinted with “SONIDEGIB 200MG” and “NVR”.

Odomzo is provided in perforated unit-dose blisters containing 10 x 1 capsule. It is available in pack sizes of 10 and 30 capsules.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

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Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

As part of the Odomzo Pregnancy Prevention Programme, all patients will receive a:
- Patient Brochure
- Patient Reminder Card

Please refer to these documents for further information.