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Summary of the risk management plan (RMP) for Odomzo (sonidegib)

This is a summary of the risk management plan (RMP) for Odomzo, which details the measures to be taken in order to ensure that Odomzo is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Odomzo, which can be found on Odomzo's EPAR page.

Overview of disease epidemiology

Odomzo (sonidegib) is a cancer medicine used to treat adults with basal cell carcinoma (a type of skin cancer). Basal cell carcinoma is the most common type of skin cancer but the number of people who get the cancer varies greatly between countries; during one year, as many as 1,800 people in 100,000 are expected to get basal cell carcinoma in Australia and as few as 77 people in 100,000 are expected to get it in Malta. The number of people who get the disease increases with age but basal cell carcinoma also occurs in young people. Basal cell carcinoma which has spread nearby (locally advanced basal cell carcinoma) may represent between 1 and 10 cases out of every 100 patients with the cancer. In 3 to 500 cases in every 100,000 patients with basal cell carcinoma, the cancer may have spread to other parts of the body (metastatic disease). About 5 out of 10 million women and 8 out of 10 million men are likely to die from basal cell carcinoma, most of whom will be over 65 years of age. The main factor that increases the risk of basal cell carcinoma is exposure to sun. The cancer usually grows slowly.

Summary of treatment benefits

Odomzo is used to treat adults with basal cell carcinoma which has spread nearby (locally advanced) and cannot be treated with surgery or radiation. It is available in capsules, each containing 200 mg sonidegib.

Odomzo was studied in one main study involving 230 patients with basal cell carcinoma which was either locally advanced or metastatic (spread to other parts of the body). Patients were started on two different doses of Odomzo: 200 or 800 mg once a day. The main measure of effectiveness was the response to treatment, based on a reduction in tumour size and improvement in other signs of cancer; treatment was considered sufficiently effective if the response rate was at least 30%.

Unknowns relating to treatment benefits

The main study enrolled adults with basal cell carcinoma, nearly all of whom were Caucasians. The effects and tolerability of Odomzo in other races and in patients with other types of cancer have not been established, and are being investigated. Safety and efficacy of Odomzo in children and adolescents aged below 18 years have not been established.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Muscle problems including pain and weakness (muscle-related events)	Odomzo can cause muscle disease (myopathy) or muscle pain (myalgia). Muscle symptoms may progress and become serious, sometimes leading to muscle breakdown (rhabdomyolysis) which is a serious condition that can cause kidney damage.	Patients should be advised to avoid medicines that cause muscle damage and increase a muscle enzyme called creatine kinase. They should tell their doctor of any muscle weakness or pain right away. If muscle disease is suspected it is recommended that the doctor review all of the patient's treatments and consider stopping Odomzo and other medicines that can cause muscle disease. Creatine kinase levels should be checked before starting Odomzo and then according to the patient's condition, for instance if muscle-related problems occur. The patient's kidney function should also be checked in case of muscle-related problems.
Abnormal development of unborn babies (teratogenicity)and harm from breastfeeding (reproductive toxicity)	Abnormalities occurred in baby animals whose parents were given sonidegib, the active ingredient of Odomzo. It is not known if Odomzo causes problems in unborn human babies but abnormal development is highly likely, based on findings from animal studies. Abnormalities have occurred in unborn baby animals of mothers taking a medicine similar to Odomzo. It is not known if the medicine is present in the milk of a breastfeeding mother.	Odomzo must not be used during pregnancy. Women who could possibly become pregnant must use highly effective contraception while taking Odomzo, and for 20 months after ending treatment. Men must not father a child or donate semen while taking Odomzo and for 6 months after ending treatment. Men, even those who have had a vasectomy (an operation that stops men from having children), must always use a condom when having sex with a female partner during treatment and for 6 months after ending treatment. Because many medicines are present in milk, and because of the potential for serious side effects in breastfed babies, women must not breastfeed while taking Odomzo or for 20 months after ending treatment.
Effect of food (food interactions)	Taking Odomzo with food may raise the blood level of sonidegib, the active ingredient; this may	The patient must not eat for two hours before taking Odomzo and for one hour

Risk	What is known	Preventability
	increase the risk of side effects.	after taking it.
Effect of taking some medicines while being treated with Odomzo (interactions with strong CYP3A4 inhibitors and CYP3A4 inducers)	Odomzo is broken down in the body by a liver enzyme called CYP3A4. Taking Odomzo with medicines which block this enzyme (also called inhibitors) can increase the level of sonidegib in the blood and therefore its side effects. Taking Odomzo with medicines which increase the activity of the enzyme CYP3A4 (also called inducers) can decrease the level of sonidegib in the blood and possibly make it less effective.	Medicines which strongly block CYP3A4 such as ketoconazole and ritonavir should be avoided during Odomzo treatment. Medicines which strongly increase the activity of CYP3A4 such as rifampicin or carbamazepine should be avoided during Odomzo treatment.

Important potential risks

Risk	What is known
Reduced ability to have children (impaired fertility)	Based on findings from animal studies, Odomzo may permanently affect the ability of men and women to have children.
New cancers in different sites (second primary malignancies)	Patients with advanced basal cell carcinoma have an increased risk of developing a different type of skin cancer called cutaneous squamous cell carcinoma. Cases of cutaneous squamous cell carcinoma have been reported in patients with advanced basal cell carcinoma treated with Odomzo. It has not been determined whether cutaneous squamous cell carcinoma is related to sonidegib treatment.
Post-natal developmental defects	Based on findings from animal studies, abnormal tooth and bone development is likely in infants and children exposed to Odomzo.
Fractures	Given Odomzo's effect on growing bone, the risk of fracture is highest in children and adolescents. The effect of Odomzo on mature bones is not known; fractures are not likely in adult cancer patients because their bones are no longer developing.
Effects of Odomzo on certain medicines that are acted on by the enzymes CYP2B6, CYP2C9, and the protein BCRP (interaction with sensitive CYP2B6, CYP2C9, and BCRP substrates with low therapeutic index)	Odomzo may raise the levels of certain medicines broken down in the body by enzymes whose function is reduced by Odomzo. Odomzo may also raise the levels of certain drugs that are transported in and out of cells by the protein BCRP, whose function is reduced by Odomzo.

Risk	What is known
Interaction with proton-pump inhibitors (medicines that reduce stomach acid)	Proton-pump inhibitors may alter solubility of Odomzo and potentially decrease Odomzo levels.
Interaction with medicines that can cause muscle disease (interaction with drugs with a known risk of myopathy)	Patients who are taking Odomzo with other medicines that increase the level of creatine kinase (a muscle enzyme), such as statins for reducing cholesterol, may be at higher risk of muscle problems and therefore these medicines should be avoided during treatment with Odomzo.
Effects on the heart: reduced oxygen supply to the heart, heart's inability to pump sufficient blood for the body's needs, and death because of heart problems (cardiac events: myocardial ischemia, cardiac failure and cardiac death)	Harmful effects on the heart occurred in patients taking Odomzo, but it is not known if Odomzo caused the effects.
Fainting (syncope)	Patients taking Odomzo suffered fainting, but it is not known if Odomzo caused the effect.
Damage to the transparent layer at the front of the eye (corneal disorders)	Corneal disorders occurred in patients taking Odomzo, but it is not known if Odomzo caused the effects.

Missing information

Risk	What is known
Occurrence of other cancers (carcinogenicity studies)	Animal studies lasting up to 6 months did not reveal abnormal cell growth or signs of cancer.
Patients with kidney function problems (patients with severe renal impairment)	Patients with severe kidney damage were not included in clinical studies so it is not known if the safety of Odomzo is altered in these patients. The kidneys are not involved in the removal of Odomzo from the body.
Patients with liver function problems (patients with severe hepatic impairment)	Odomzo is removed from the body mainly by the liver. Odomzo should be used with caution in patients with severe liver impairment.
Races other than Caucasians	The majority of patients in the main clinical studies on Odomzo were Caucasian. Therefore, the effects of Odomzo on patients of other races is not known.
Female patients of childbearing potential taking concomitant oral contraceptives	It is not known if Odomzo has an effect on the effectiveness of oral contraceptives (contraceptive 'pill').
Long-term safety in patients with locally advanced basal cell carcinoma	The safety of using Odomzo for a long time in patients with locally advanced basal cell carcinoma is not known.

Risk	What is known
Unapproved use of Odomzo in medulloblastoma (a cancer in the brain and spinal cord that mainly affects children), basal cell carcinoma that can be treated by surgery or radiotherapy, and other cancers (off-label use in patients with medulloblastoma, basal cell carcinoma appropriate for surgery or radiotherapy, and other cancers)	Inadequate evidence is available on the use of Odomzo for the treatment of cancer in children and of other cancers that depend on the activated Hedgehog pathway. Odomzo has not been studied in patients whose basal cell carcinoma can be treated by surgery or radiotherapy.
Patients with low red cell count (patients with anaemia—haemoglobin of less than 9 g/dL)	Patients with anaemia (haemoglobin of less than 9 g/dL) were not included in the main clinical study. Therefore, the safety profile of Odomzo in these patients is not known.
Patients with reduced oxygen supply to the heart or whose heart is not able to pump sufficient blood for the body's needs (patients with recent myocardial ischemia or cardiac failure)	There were few patients in the main clinical study who had previously suffered reduced oxygen supply to the heart or whose heart had not been able to pump sufficient blood for the body's needs. Therefore, the safety profile of Odomzo in these patients is not known.

Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides doctors, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in plain language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The SmPC and the package leaflet are part of the medicine's product information. The product information for Odomzo can be found on Odomzo's EPAR page.

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). Full details on these conditions and the key elements of any educational material can be found in Annex II of the product information which is published on Odomzo's EPAR page; how they are implemented in each country however will depend upon agreement between the marketing authorisation holder and the national authorities.

These additional risk minimisation measures are for the following risks:

Harm to the unborn baby (teratogenicity) and effect of ability to have children (impaired fertility)

Risk minimisation measure: Educational material
Objective and rationale: To avoid the risk of severe birth defects and to inform healthcare professionals and patients about the risk of infertility
Description: Distribution of educational material to prescribers and patients, including a reminder card and direct

Risk minimisation measure: Educational material
communication to healthcare professionals at product launch, that will include advice on: • Reproductive toxicity • Fertility

Planned post-authorisation development plan

List of studies in post-authorisation development plan

Study / activity (including study number)	**Objectives**	**Safety concerns / efficacy issue addressed**	**Status**	**Planned date for submission of (interim and) final results**
Measuring the effectiveness of the Odomzo pregnancy prevention programs on a country-specific level, in agreement with National Competent Authorities (3)	To assess health care professionals' knowledge of the risk of abnormal development of unborn babies associated with the use of Odomzo during pregnancy and of reduced ability to have children, after supplying educational materials to healthcare professionals.	Reproductive toxicity: (abnormal development of unborn babies) and reduced ability to have children	Planned start after product local launch	Regularly as part of every periodic safety update report

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
A relative bioavailability study to evaluate timing of meal relative to dose and fasting conditions and effect of light meal (low fat meal) (3)	To estimate the risks of too much or too little medicine in the body as a result of different amounts or compositions of food in the stomach and to potentially provide more guidance on how to take Odomzo.	Food interaction	Planned start after product launch (first quarter of 2016)	Fourth quarter of 2016
Study LDE225A2113 A phase I, open label, multi-center, single dose study to evaluate the pharmacokinetics of sonidegib in healthy subjects with normal hepatic function and subjects with impaired hepatic function (3)	To potentially provide better guidance on how Odomzo should be used in patients with reduced liver function.	Safety in patients with liver impairment	Ongoing	Interim report 3 November 2014 Final report: third quarter of 2016 (planned)
Study LDE225A2112 A Phase Ib, multi-center, two parallel group, open label, drug-drug interaction study to assess the effect of sonidegib on the PK of bupropion and warfarin in patients with advanced solid tumors (3)	To evaluate effect of Odomzo on the pharmacokinetics of warfarin and bupropion.	Interaction with CYP2B6 and CYP2C9 substrate	Ongoing	Final clinical study report: second quarter 2017

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
Analyses of AESI in the registration Study ongoing studies without a final CSR, including the registration Study A2201, C2301, X2114, X2116, X2203, and will be analyzed in the final CSRs for these studies. In addition, longer-term data using the 30-month and 42-month will be analyzed and reported. (3)	To analyse adverse events of special interest in order to better characterise and understand these risks.	Heart problems, second cancers, and fractures	LDE225A2201 Ongoing	Final clinical study report: October 2017
			LDE225C2301 Ongoing	Final clinical study report: fourth quarter 2015
			LDE225X2114 Data collection completed	Final clinical study report: fourth quarter 2015
			LDE225X2116 Ongoing	Final clinical study report: first quarter 2017
			LDE225X2203 Ongoing	Final clinical study report: fourth quarter 2016
Analyses of AESI in studies LDE225X2104 and LDE225C2301(3)	To analyse adverse events of special interest in order to better characterise and understand the risk.	Post-natal developmental defects	LDE225X2104 Data collection completed	Final clinical study report: second quarter 2015
			LDE225C2301 Ongoing	Final clinical study report:fourth quarter 2015
Analyses of long term safety data available from the registration Study A2201(3)	To analyse long term safety data from the registration Study A2201, and in the final clinical study report.	Long term safety in patient with locally	Ongoing	Final clinical study report: October 2017

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
A non-interventional post-authorization safety study (PASS) is being planned to further characterize long-term safety (3)	Non-interventional post-authorisation safety study to assess the long-term safety and tolerability of Odomzo, when given to patients with locally advanced basal cell carcinoma, as determined by the occurrence of adverse events and serious adverse events.	advanced basal cell carcinoma	Planned	Fourth quarter 2024 (after the completion of 3-year follow-up for each enrolled patient)
LDE225A2118 A phase I, single-center, parallel group, open label randomized study to investigate the effect of esomeprazole (proton-pump inhibitor)on the pharmacokinetics of sonidegib in healthy volunteers (3)	To determine the impact of proton-pump inhibitors on the pharmacokinetics of Odomzo.	Interaction of Odomzo with esomeprazole	Data collection completed	Final clinical study report:December 2015
A study to perform an evaluation of a subset of tissues from the 6-month rat study using KI-67 immunohistochemistry and to quantify cell proliferation (3)	To address missing information relating to carcinogenicity	Carcinogenicity	Planned	December 2016
Provision of the Study CLDE225A2201 interim analysis (1)	To provide the following: -updated efficacy and safety analyses. -an analysis of	Long term efficacy data	Interim analyses (30-month data)	30 October 2016

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
	response to treatment and levels of Gli1 (a key protein in the Hedgehog signalling pathway) at various times during the main clinical study for all patients -an updated analysis of outcomes by aggressive vs non-aggressive histological subtypes of basal cell carcinoma.			
Provision of the Final CSR for Study CLDE225A2201 (1)	To provide an updated analysis of outcomes by aggressive vs non-aggressive histological subtypes.	Long term efficacy data	Final clinical study report	30 October 2017
Provision of the Study CLDE225A2201 interim analysis (1)	To provide a molecular analysis in tumor material still available from patients treated in study A2201 whose disease worsened.	Long term efficacy data	Interim analyses (30-month data)	30 October 2016

Studies which are a condition of the marketing authorisation

Providing interim, final and molecular analysis of a Phase II study (CLDE225A2201)— a randomised double-blind study of effectiveness and safety of two dose levels of Odomzo in patients with locally advanced or metastatic basal cell carcinoma—is a condition of the marketing authorisation of Odomzo.

Summary of changes to the risk management plan over time

Not applicable

This summary was last updated in 07-2015.