FDA approves Novartis drug Odomzo® (sonidegib) for locally advanced basal cell carcinoma (laBCC), a form of skin cancer

- Approval is based on pivotal Phase II study in which objective response rate (ORR) in patients with laBCC was 58%; responses were durable
- Basal cell carcinoma, the most common form of skin cancer, can be highly disfiguring at advanced stages
- Odomzo adds to company’s expanding portfolio of targeted treatments for skin cancer

Basel, July 24, 2015 – Novartis today announced the US Food and Drug Administration (FDA) has approved Odomzo® (sonidegib, formerly LDE225) 200 mg capsules for the treatment of adult patients with locally advanced basal cell carcinoma (laBCC) that has recurred following surgery or radiation therapy, or those who are not candidates for surgery or radiation therapy.

“The FDA approval of Odomzo offers a new and non-invasive treatment option for a potentially devastating disease that is hard to treat and can be disfiguring," said Bruno Strigini, President, Novartis Oncology. “Odomzo is an important addition to our growing portfolio of targeted treatments for advanced skin cancers and underscores our commitment to developing and bringing to market new options for patients.”

The Odomzo approval was based on the demonstration of a durable objective response rate (ORR) in an international, multi-center, double-blind, randomized, two-arm, non-comparative trial in patients with laBCC not amenable to local therapy or metastatic basal cell carcinoma (mBCC).

Patients with laBCC treated with Odomzo 200 mg (n=66) were followed for at least 12 months unless discontinued earlier. The ORR was 58% (95% confidence interval: 45, 70), consisting of 5% (n=3) complete responses (CR) and 53% (n=35) partial responses (PR). A pre-specified sensitivity analysis using an alternative definition for CR, defined as at least a PR according to MRI and/or photography and no evidence of tumor on biopsy of residual lesion, yielded a CR rate of 20%. Among the 38 patients with an objective response, 31 patients (82%) have ongoing responses ranging from at least 1.9 to 18.6 months and the median duration of response has not been reached.

The most serious risks of Odomzo are embryofetal toxicity and musculoskeletal adverse reactions including rhabdomyolysis. Musculoskeletal adverse reactions, which may be accompanied by serum creatine kinase (CK) elevations, may occur with Odomzo and other drugs which inhibit the hedgehog pathway. The incidence of musculoskeletal adverse reactions in patients with laBCC treated with Odomzo 200 mg was 68%, with 9% reported as grade 3 or 4. Adverse reactions occurring in more than 10% of patients treated with Odomzo 200 mg were muscle spasms, alopecia, dysgeusia, fatigue, nausea, musculoskeletal pain, diarrhea, decreased weight, decreased appetite, myalgia, abdominal pain, headache, pruritus, and vomiting.
laboratory abnormalities occurring in at least 5% of patients were serum creatine kinase (CK) elevation and lipase elevation1.

About the BOLT Clinical Trial
Data from the Phase II, randomized, double-blind multicenter BOLT (Basal cell carcinoma Outcomes in LDE225 Trial) formed the basis of the FDA’s approval. The primary endpoint was ORR of patients treated with Odomzo 200 mg and 800 mg, defined as the proportion of patients with confirmed complete or partial tumor response, or shrinkage, as measured by a central review committee. There was no evidence of better ORR among patients with laBCC randomized to receive Odomzo 800 mg daily1.

The evaluation of tumor response was based on a composite assessment of modified Response Evaluation Criteria in Solid Tumors (mRECIST) that integrated tumor measurements obtained by radiographic assessments of target lesions (per RECIST 1.1), digital clinical photography (World Health Organization (WHO) adapted criteria), and histopathology assessments (via punch biopsies). All modalities used must have demonstrated absence of tumor to achieve a composite assessment of CR1.

About Basal Cell Carcinoma
BCC consists of abnormal, uncontrolled growths or lesions that arise in the skin’s basal cells, which line the deepest layer of the epidermis (the outermost layer of the skin)6 and accounts for more than 80% of non-melanoma skin cancers7. It occurs most frequently on the head and neck, with the nose being the most common site7. BCC that spreads from where it started to nearby tissue is called locally advanced3 and can be highly disfiguring2. Advanced BCC is thought to represent roughly 1–10% of all cases of BCC6-11. While BCC is generally diagnosed and treated early, it may recur in an estimated 3% of patients after five years12. Although BCC rarely becomes advanced, there have been few treatment options at this stage of the disease. Worldwide incidence of BCC is rising by 10% each year due to factors such as an aging population and increased ultraviolet exposure. Incidence rates are estimated to be between 0.003% and 0.55% worldwide13.

About Odomzo
Odomzo (sonidegib, formerly LDE225) is an oral, selective smoothened (SMO) inhibitor approved by the FDA for the treatment of adult patients with locally advanced basal cell carcinoma (laBCC) that has recurred following surgery or radiation therapy, or those who are not candidates for surgery or radiation therapy7. SMO is a molecule that regulates the hedgehog (Hh) signaling pathway, which plays a critical role in stem cell maintenance and tissue repair, as well as in advanced basal cell carcinoma3-5. Odomzo is currently in clinical development in other diseases.

Odomzo was approved in Switzerland for the treatment of advanced BCC that is not amenable to curative surgery or radiotherapy on June 30, 2015. The CHMP granted a positive opinion on June 25, 2015. Additional regulatory submissions are being reviewed by health authorities worldwide.

IMPORTANT SAFETY INFORMATION
Important note: Before prescribing, consult the full prescribing information.

Presentation: Hard gelatin capsules containing 200 mg sonidegib.

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.

Dosage and administration: Adults: One 200 mg dose taken orally once daily on an empty stomach, at the same time each day. Children: Safety and effectiveness has not been established in pediatric patients with BCC.
Patients with renal impairment: Sonidegib has not been studied in patients with renal impairment. Based on available data, sonidegib elimination via the kidney is negligible. A population pharmacokinetic analysis did not find significant influence of renal function on the apparent clearance (CL/F) of sonidegib suggesting that dose adjustment is not necessary in patients with renal impairment.

Patients with hepatic impairment: No dose adjustment necessary in patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment. Sonidegib has not been studied in patients with severe hepatic impairment (Child-Pugh class C). Caution should therefore be used in patients with severe hepatic impairment.

Contraindications: Women who are pregnant or breast-feeding.

Warnings and precautions:
Muscle related adverse events: Creatine phosphokinase (CK) levels should be checked prior to starting treatment and as clinically indicated thereafter, for example, if muscle related symptoms are reported. If clinically notable elevation of CK is detected, renal function should be assessed. Dose modification or interruption guidelines should be followed. Patients should be closely monitored for muscle related symptoms if Odomzo is used in combination with certain medications that may increase the potential risk of developing muscle toxicity (e.g. CYP3A4 inhibitors, chloroquine, hydroxychloroquine, fibric acid derivatives, penicillamine, zidovudine, niacin, HMG-CoA reductase inhibitors). Closely monitor patients with neuromuscular disorders (e.g. inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis and spinal muscular atrophy) due to an increased risk of muscle toxicity.

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

Women of child-bearing potential:
Women of childbearing potential must use a highly effective method of contraception while receiving Odomzo. Contraception must be continued for 20 months after ending treatment.

Pregnancy: Negative pregnancy status must be confirmed by a test performed by a health care provider prior to initiation of Odomzo treatment. Odomzo must not be used during pregnancy.

Breast-feeding: Women must not breast feed while taking Odomzo and for at least 20 months after ending treatment.

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

Fertility: Male and female fertility may be compromised with Odomzo. Fertility preservation strategies should be discussed prior to starting treatment with Odomzo.

Adverse drug reactions:
Very common (≥10%): amenorrhea, decreased appetite, dysgeusia, headache, nausea, diarrhea, vomiting, abdominal pain, alopecia, pruritus, muscle spasms, myalgia, musculoskeletal pain, fatigue, pain, weight decreased.
Common (between 1 to 10%): constipation, dyspepsia, gastroesophageal reflux disorder, rash, abnormal hair growth, myopathy (muscular fatigue and muscular weakness), dehydration.
Laboratory abnormalities: Very common (≥10%): hemoglobin decreased, lymphocyte count decreased, amylase increased, blood glucose increased, lipase increase, serum creatine phosphokinase increase, serum creatinine increased, alanine amino transaminase (ALT) increased, aspartate amino transaminase (AST) increased.

Interactions: Avoid concomitant use of strong CYP3A inhibitors, including but not limited to, ritonavir, saquinavir, telithromycin, ketoconazole, itraconazole, voriconazole, posaconazole and nefazodone.

Avoid concomitant use of strong CYP3A inducers, including but not limited to carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin and St John’s Wort (Hypericum perforatum). If a strong CYP3A inducer must be used concomitantly with sonidegib, consideration should be given to increasing the dose of sonidegib by 200 mg increments to a maximum daily dose of 800 mg.

Monitor patients carefully for adverse drug reactions with concomitant use of substrates of CYP2B6 and CYP2C9 enzymes or BCRP transporter, especially those with a narrow therapeutic range.

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

Disclaimer
The foregoing release contains forward-looking statements that can be identified by words such as “can,” “expanding,” “offers,” “potentially,” “growing,” “commitment,” “developing,” “bringing to market,” “in clinical development,” “positive opinion,” “are being reviewed,” or similar terms, or by express or implied discussions regarding potential additional marketing approvals or new indications or labeling for Odomzo, or regarding potential future revenues from Odomzo. You should not place undue reliance on these statements. Such forward-looking statements are based on the current beliefs and expectations of management regarding future events, and are subject to significant known and unknown risks and uncertainties. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those set forth in the forward-looking statements. There can be no guarantee that Odomzo will be submitted or approved for any additional indications or labeling in any market, or at any particular time. Neither can there be any guarantee that Odomzo will be submitted or approved for sale in any additional markets or at any particular time. Nor can there be any guarantee that Odomzo will be commercially successful in the future, or will achieve any particular level of revenue. In particular, management's expectations regarding Odomzo could be affected by, among other things, the uncertainties inherent in research and development, including unexpected clinical trial results and additional analysis of existing clinical data; unexpected regulatory actions or delays or government regulation generally; the company's ability to obtain or maintain proprietary intellectual property protection; general economic and industry conditions; global trends toward health care cost containment, including ongoing pricing pressures and reimbursement issues; unexpected safety issues; unexpected manufacturing issues, and other risks and factors referred to in Novartis AG's current Form 20-F on file with the US Securities and Exchange Commission. Novartis is providing the information in this press release as of this date and does not undertake any obligation to update any forward-looking statements contained in this press release as a result of new information, future events or otherwise.

About Novartis
Novartis provides innovative healthcare solutions that address the evolving needs of patients and societies. Headquartered in Basel, Switzerland, Novartis offers a diversified portfolio to best meet these needs: innovative medicines, eye care and cost-saving generic pharmaceuticals. Novartis is the only global company with leading positions in these areas. In 2014, the Group achieved net sales of USD 58.0 billion, while R&D throughout the Group amounted to approximately USD 9.9 billion (USD 9.6 billion excluding impairment and amortization charges). Novartis Group companies employ approximately 120,000 full-time-equivalent associates. Novartis products are available in more than 180 countries around the world. For more information, please visit http://www.novartis.com.
References

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