

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***

**203388Orig1s000**

**LABELING**

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ERIVEDGE safely and effectively. See full prescribing information for ERIVEDGE.

ERIVEDGE™ (vismodegib) capsule for oral use  
Initial U.S. Approval: 2012

### WARNING: EMBRYO-FETAL DEATH AND SEVERE BIRTH DEFECTS

*See full prescribing information for complete boxed warning.*  
ERIVEDGE can result in embryo-fetal death or severe birth defects. Verify pregnancy status prior to initiation of ERIVEDGE. Advise male and female patients of these risks. Advise females of the need for contraception and advise males of the potential risk of ERIVEDGE exposure through semen. (Boxed Warning, 5.1, 8.1, 8.6)

### INDICATIONS AND USAGE

ERIVEDGE™ (vismodegib) capsule is a hedgehog pathway inhibitor indicated for the treatment of adults with metastatic basal cell carcinoma, or with locally advanced basal cell carcinoma that has recurred following surgery or who are not candidates for surgery, and who are not candidates for radiation. (1)

### DOSAGE AND ADMINISTRATION

The recommended dose is 150 mg orally once daily. (2)

### DOSAGE FORMS AND STRENGTHS

150 mg capsules. (3)

### CONTRAINDICATIONS

None.

### WARNINGS AND PRECAUTIONS

- Embryo-fetal death and severe birth defects: ERIVEDGE can cause embryo-fetal death or severe birth defects. (5.1)
- Blood donation: Advise patients not to donate blood or blood products while receiving ERIVEDGE and for at least 7 months after the last dose of ERIVEDGE. (5.2)

### ADVERSE REACTIONS

- The most common adverse reactions (incidence of  $\geq 10\%$ ) are muscle spasms, alopecia, dysgeusia, weight loss, fatigue, nausea, diarrhea, decreased appetite, constipation, arthralgias, vomiting, and ageusia.

To report SUSPECTED ADVERSE REACTIONS, contact Genentech, Inc. at 1-888-835-2555 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### USE IN SPECIFIC POPULATIONS

- Pregnancy: Can cause fetal harm. Advise females of reproductive potential of potential risk to the fetus. (5.1, 8.1)
- Nursing Mothers: Discontinue drug or nursing taking into consideration importance of drug to mother. (8.3)
- Females of Reproductive Potential and Males: Counsel males and females on pregnancy prevention and planning. Report immediately exposure to ERIVEDGE during pregnancy to the Genentech Adverse Event Line at 1-888-835-2555. Encourage patient participation in the ERIVEDGE pregnancy pharmacovigilance program by contacting the Genentech Adverse Event Line at 1-888-835-2555. (8.6)

See Section 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling (Medication Guide).

Revised: 01/2012

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## FULL PRESCRIBING INFORMATION

### **WARNING: EMBRYO-FETAL DEATH AND SEVERE BIRTH DEFECTS**

**ERIVEDGE (vismodegib) capsule can result in embryo-fetal death or severe birth defects. ERIVEDGE is embryotoxic and teratogenic in animals. Teratogenic effects included severe midline defects, missing digits, and other irreversible malformations.**

**Verify pregnancy status prior to the initiation of ERIVEDGE. Advise male and female patients of these risks. Advise female patients of the need for contraception and advise male patients of the potential risk of ERIVEDGE exposure through semen [see *Warnings and Precautions* (5.1), *Use in Specific Populations* (8.1, 8.6)].**

### **1 INDICATIONS AND USAGE**

ERIVEDGE capsule is indicated for the treatment of adults with metastatic basal cell carcinoma, or with locally advanced basal cell carcinoma that has recurred following surgery or who are not candidates for surgery, and who are not candidates for radiation.

### **2 DOSAGE AND ADMINISTRATION**

The recommended dose of ERIVEDGE is 150 mg taken orally once daily until disease progression or until unacceptable toxicity [see *Clinical Studies* (14)].

ERIVEDGE may be taken with or without food. Swallow capsules whole. **Do not open or crush capsules.**

If a dose of ERIVEDGE is missed, do not make up that dose; resume dosing with the next scheduled dose.

### **3 DOSAGE FORMS AND STRENGTHS**

ERIVEDGE (vismodegib) capsules, 150 mg. The capsule has a pink opaque body and a grey opaque cap, with “150 mg” printed on the capsule body and “VISMO” printed on the capsule cap in black ink.

### **4 CONTRAINDICATIONS**

None.

## 32 **5 WARNINGS AND PRECAUTIONS**

### 33 **5.1 Embryo-Fetal Death and Severe Birth Defects**

34 ERIVEDGE capsules can cause fetal harm when administered to a pregnant woman based on its  
35 mechanism of action. Vismodegib is teratogenic, embryotoxic, and fetotoxic in rats at maternal  
36 exposures lower than the human exposures at the recommended dose of 150 mg/day. In rats,  
37 malformations included craniofacial anomalies, open perineum, and absent or fused digits. Fetal  
38 retardations and variations were also observed.

39 Verify pregnancy status prior to the initiation of ERIVEDGE. Advise male and female patients of  
40 the risks of embryo-fetal death and severe birth defects and the need for contraception during and  
41 after treatment. Advise patients to contact their healthcare provider immediately if they suspect they  
42 (or, for males, their female partner) may be pregnant. Female and male patients of reproductive  
43 potential should be counseled regarding pregnancy prevention and planning. If ERIVEDGE is used  
44 during pregnancy or if a patient becomes pregnant while taking (or for a male patient, if his female  
45 partner is exposed to) ERIVEDGE, the patient should be apprised of the potential hazard to the fetus.  
46 Report immediately exposure to ERIVEDGE during pregnancy to the Genentech Adverse Event  
47 Line at 1-888-835-2555. Encourage women who may have been exposed to ERIVEDGE during  
48 pregnancy, either directly or through seminal fluid, to participate in the ERIVEDGE pregnancy  
49 pharmacovigilance program by contacting the Genentech Adverse Event Line at 1-888-835-2555  
50 [see *Boxed Warning, Use in Specific Populations (8.1, 8.6)*].

### 51 **5.2 Blood Donation**

52 Advise patients not to donate blood or blood products while receiving ERIVEDGE and for at least  
53 7 months after the last dose of ERIVEDGE.

54

## 55 **6 ADVERSE REACTIONS**

### 56 **6.1 Clinical Trials Experience**

57 Because clinical trials are conducted under widely varying conditions, adverse reaction rates  
58 observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of  
59 another drug and may not reflect the rates observed in clinical practice.

60 ERIVEDGE capsule was administered as monotherapy at doses  $\geq$  150 mg orally daily in four  
61 open-label, uncontrolled, dose-ranging or fixed single dose clinical trials enrolling a total of  
62 138 patients with advanced basal cell carcinoma (BCC). The median age of these patients was  
63 61 years (range 21 to 101), 100% were White (including Hispanics), and 64% were male. The  
64 median duration of treatment was approximately 10 months (305 days; range 0.7 to 36 months);  
65 111 patients received ERIVEDGE for 6 months or longer.

66 The most common adverse reactions ( $\geq$  10%) were muscle spasms, alopecia, dysgeusia, weight loss,  
67 fatigue, nausea, diarrhea, decreased appetite, constipation, arthralgias, vomiting, and ageusia  
68 (Table 1).

69 **Table 1: Adverse Reactions Occurring in ≥ 10% of Advanced BCC Patients**

MedDRA Preferred Term <sup>2</sup>	All aBCC <sup>1</sup> Patients (N = 138)		
	All Grades <sup>3</sup> (%)	Grade 3 (%)	Grade 4 (%)
Gastrointestinal disorders			
Nausea	42 (30.4%)	1 (0.7%)	-
Diarrhea	40 (29.0%)	1 (0.7%)	-
Constipation	29 (21.0%)	-	-
Vomiting	19 (13.8%)	-	-
General disorders and administration site conditions			
Fatigue	55 (39.9%)	7 (5.1%)	1 (0.7%)
Investigations			
Weight loss	62 (44.9%)	10 (7.2%)	-
Metabolism and nutrition disorders			
Decreased appetite	35 (25.4%)	3 (2.2%)	-
Musculoskeletal and connective tissue disorders			
Muscle spasms	99 (71.7%)	5 (3.6%)	-
Arthralgias	22 (15.9%)	1 (0.7%)	-
Nervous system disorders			
Dysgeusia	76 (55.1%)	-	-
Ageusia	15 (10.9%)	-	-
Skin and subcutaneous tissue disorders			
Alopecia	88 (63.8%)	-	-

<sup>1</sup>aBCC = Advanced Basal Cell Carcinoma.  
<sup>2</sup>MedDRA = Medical Dictionary for Regulatory Activities.  
<sup>3</sup>Grading according to NCI-CTCAE v3.0.

70  
71 *Amenorrhea:*

72 In clinical trials, a total of 3 of 10 pre-menopausal women developed amenorrhea while receiving  
73 ERIVEDGE [see *Non-Clinical Toxicology (13.1)*].

74 *Laboratory Abnormalities:*

75 Treatment-emergent Grade 3 laboratory abnormalities observed in clinical trials were hyponatremia  
76 in 6 patients (4%), hypokalemia in 2 patients (1%), and azotemia in 3 patients (2%).

77  
78 **7 DRUG INTERACTIONS**

79 **7.1 Effects of Other Drugs on Vismodegib**

80 *Drugs that Inhibit or Induce Drug Metabolizing Enzymes*

81 Vismodegib elimination involves multiple pathways. Vismodegib is predominantly excreted as an  
82 unchanged drug. Several minor metabolites are produced by multiple CYP enzymes. Although  
83 vismodegib is a substrate of CYP2C9 and CYP3A4 *in vitro*, CYP inhibition is not predicted to alter  
5 of 17

84 vismodegib systemic exposure since similar steady-state plasma vismodegib concentrations were  
85 observed in patients in clinical trials concomitantly treated with CYP3A4 inducers  
86 (i.e., carbamazepine, modafinil, phenobarbital) and those concomitantly treated with CYP3A4  
87 inhibitors (i.e., erythromycin, fluconazole).

#### 88 *Drugs that Inhibit Drug Transport Systems*

89 *In vitro* studies indicate that vismodegib is a substrate of the efflux transporter P-glycoprotein  
90 (P-gp). When ERIVEDGE is coadministered with drugs that inhibit P-gp (e.g. clarithromycin,  
91 erythromycin, azithromycin), systemic exposure of vismodegib and incidence of adverse events of  
92 ERIVEDGE may be increased.

#### 93 *Drugs that Affect Gastric pH*

94 Drugs that alter the pH of the upper GI tract (e.g. proton pump inhibitors, H<sub>2</sub>-receptor antagonists,  
95 and antacids) may alter the solubility of vismodegib and reduce its bioavailability. However, no  
96 formal clinical study has been conducted to evaluate the effect of gastric pH altering agents on the  
97 systemic exposure of vismodegib. Increasing the dose of ERIVEDGE when coadministered with  
98 such agents is not likely to compensate for the loss of exposure. When ERIVEDGE is  
99 coadministered with a proton pump inhibitor, H<sub>2</sub>-receptor antagonist or antacid, systemic exposure  
100 of vismodegib may be decreased and the effect on efficacy of ERIVEDGE is unknown.

### 101 **7.2 Effects of Vismodegib on Other Drugs**

102 Results of a drug-drug interaction study conducted in cancer patients demonstrated that the systemic  
103 exposure of rosiglitazone (a CYP2C8 substrate) or oral contraceptives (ethinyl estradiol and  
104 norethindrone) is not altered when either drug is co-administered with vismodegib.

105 *In vitro* studies indicate that vismodegib is an inhibitor of CYP2C8, CYP2C9, CYP2C19 and the  
106 transporter BCRP. Vismodegib does not induce CYP1A2, CYP2B6, or CYP3A4/5 in human  
107 hepatocytes.

108

## 109 **8 USE IN SPECIFIC POPULATIONS**

### 110 **8.1 Pregnancy**

#### 111 Pregnancy Category D

112 ERIVEDGE capsule can cause fetal harm when administered to a pregnant female based on its  
113 mechanism of action. Vismodegib is teratogenic in rats at doses corresponding to an exposure of  
114 20% of the exposure at the recommended human dose (estimated AUC<sub>0-24hr</sub> steady-state exposure).  
115 In rats, malformations included craniofacial anomalies, open perineum, and absent or fused digits.  
116 Fetal retardations and variations were also observed. Vismodegib is embryolethal in rats at  
117 exposures within the range achieved at the recommended human dose. If ERIVEDGE is used during  
118 pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised  
119 of the potential hazard to the embryo or fetus. Report immediately exposure to ERIVEDGE during  
120 pregnancy to the Genentech Adverse Event Line at 1-888-835-2555. Encourage women who may  
121 have been exposed to ERIVEDGE during pregnancy, either directly or through seminal fluid, to  
122 participate in the ERIVEDGE pregnancy pharmacovigilance program by contacting the Genentech  
123 Adverse Event Line at 1-888-835-2555 [see *Boxed Warning*, *Warnings* and *Precautions* (5.1)].

124 In an embryo-fetal developmental toxicity study, pregnant rats were administered oral vismodegib at  
125 doses of 10, 60, or 300 mg/kg/day during the period of organogenesis. Pre- and post-implantation  
126 loss were increased at doses of ≥ 60 mg/kg/day (approximately ≥ 2 times the systemic exposure  
127 (AUC) in patients at the recommended human dose), which included early resorption of 100% of the  
128 fetuses. A dose of 10 mg/kg/day (approximately 0.2 times the AUC in patients at the recommended  
129 dose) resulted in malformations (including missing and/or fused digits, open perineum and

130 craniofacial anomalies) and retardations or variations (including dilated renal pelvis, dilated ureter,  
131 and incompletely or unossified sternal elements, centra of vertebrae, or proximal phalanges and  
132 claws).

### 133 **8.3 Nursing Mothers**

134 It is not known whether vismodegib is excreted in human breast milk. Because many drugs are  
135 excreted in human milk and because of the potential for serious adverse reactions in nursing infants  
136 from ERIVEDGE, a decision should be made whether to discontinue nursing or to discontinue the  
137 drug, taking into account the importance of the drug to the mother.

### 138 **8.4 Pediatric Use**

139 The safety and effectiveness of ERIVEDGE capsule have not been established in pediatric patients.

140 In repeat-dose toxicology studies in rats, administration of oral vismodegib resulted in toxicities in  
141 bone and teeth. Effects on bone consisted of closure of the epiphyseal growth plate when oral  
142 vismodegib was administered for 26 weeks at  $\geq 50$  mg/kg/day (approximately  $\geq 0.4$  times the  
143 systemic exposure (AUC) in patients at the recommended human dose). Abnormalities in growing  
144 incisor teeth (including degeneration/necrosis of odontoblasts, formation of fluid-filled cysts in the  
145 dental pulp, ossification of the root canal, and hemorrhage resulting in breakage or loss of teeth)  
146 were observed after administration of oral vismodegib at  $\geq 15$  mg/kg/day (approximately  $\geq 0.2$  times  
147 the AUC in patients at the recommended human dose).

### 148 **8.5 Geriatric Use**

149 Clinical studies of ERIVEDGE capsule did not include sufficient numbers of patients aged 65 and  
150 over to determine whether they respond differently from younger patients.

### 151 **8.6 Females of Reproductive Potential and Males**

152 ERIVEDGE capsule can cause harm to the embryo or fetus when administered during pregnancy.  
153 Counsel female and male patients regarding pregnancy prevention and planning. Advise patients to  
154 contact their healthcare provider immediately if they suspect they (or, for males, their female  
155 partner) may be pregnant [see *Boxed Warning, Warnings and Precautions (5.1), Use in Specific*  
156 *Populations (8.1)*].

#### 157 *Female patients*

158 Determine pregnancy status within 7 days prior to initiation of treatment in females of reproductive  
159 potential. For females with a negative pregnancy test, initiate a highly effective form of  
160 contraception (failure rate of less than 1%) prior to the first dose. Continue highly effective  
161 contraception during therapy and for 7 months after the last dose of ERIVEDGE. If a patient  
162 becomes pregnant while taking ERIVEDGE, or during the 7 months after the last dose of treatment,  
163 report the pregnancy to the Genentech Adverse Event Line at 1-888-835-2555. Encourage pregnant  
164 females to participate in the ERIVEDGE pregnancy pharmacovigilance program by calling the  
165 Genentech Adverse Event Line at 1-888-835-2555. Counsel pregnant females about the teratogenic  
166 risk to the fetus.

167 Amenorrhea has been observed in clinical trials in females of reproductive potential. Reversibility  
168 of amenorrhea is unknown [see *Adverse Reactions (6), Nonclinical Toxicology (13.1)*].

#### 169 *Male patients*

170 Male patients should use condoms with spermicide, even after a vasectomy, during sexual  
171 intercourse with female partners while being treated with ERIVEDGE capsule and for 2 months after  
172 the last dose to avoid exposing an embryo or fetus to vismodegib.

### 173 **8.7 Hepatic Impairment**



174 The safety and effectiveness of ERIVEDGE capsule have not been established in patients with  
175 hepatic impairment [see *Clinical Pharmacology (12.3)*].

176 **8.8 Renal Impairment**

177 The safety and effectiveness of ERIVEDGE capsule have not been established in patients with renal  
178 impairment [see *Clinical Pharmacology (12.3)*].

179

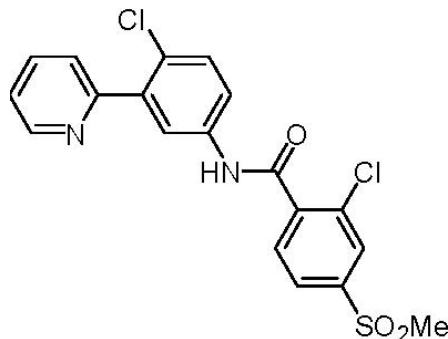
180 **10 OVERDOSAGE**

181 There is no information on overdosage in humans. In clinical trials, ERIVEDGE capsule was  
182 administered at 540 mg orally once daily; exposure did not increase between 150 mg and 540 mg  
183 daily.

184

## DESCRIPTION

Vismodegib is an inhibitor of the hedgehog (Hh) signaling pathway, which is described chemically as 2-Chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonyl)benzamide. The molecular formula is C<sub>19</sub>H<sub>14</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>3</sub>S. The molecular weight is 421.30 g/mol and the structural formula is:



Vismodegib is a crystalline free base with a pK<sub>a</sub> (pyridinium cation) of 3.8, appearing as a white to tan powder. The solubility of vismodegib is pH dependent with 0.1 µg/mL at pH 7 and 0.99 mg/mL at pH 1. The partition coefficient (log P) is 2.7.

Each ERIVEDGE (vismodegib) capsule for oral administration contains 150 mg vismodegib and the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, sodium lauryl sulfate, povidone, sodium starch glycolate, talc, and magnesium stearate (non-bovine). The capsule shell contains gelatin, titanium dioxide, red iron oxide, and black iron oxide. The black printing ink contains shellac and black iron oxide.

## CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Vismodegib is an inhibitor of the Hedgehog pathway. Vismodegib binds to and inhibits Smoothened, a transmembrane protein involved in Hedgehog signal transduction.

### 12.3 Pharmacokinetics

#### *Absorption*

Vismodegib is a highly permeable compound with low aqueous solubility (BCS Class 2). The single dose absolute bioavailability of vismodegib is 31.8%. Absorption is saturable as evidenced by the lack of dose proportional increase in exposure after a single dose of 270 mg or 540 mg vismodegib. ERIVEDGE capsule may be taken without regard to meals because the systemic exposure of vismodegib at steady state is not affected by food.

#### *Distribution*

The volume of distribution of vismodegib ranges from 16.4 to 26.6 L. Vismodegib plasma protein binding in patients is greater than 99%. Vismodegib binds to both human serum albumin and alpha-1-acid glycoprotein (AAG) and binding to AAG is saturable.

#### *Metabolism*

Greater than 98% of the total circulating drug-related components are the parent drug. Metabolic pathways of vismodegib in humans include oxidation, glucuronidation, and pyridine ring cleavage. The two most abundant oxidative metabolites recovered in feces are produced *in vitro* by recombinant CYP2C9 and CYP3A4/5.

220 *Elimination*

221 Vismodegib and its metabolites are eliminated primarily by the hepatic route with 82% of the

222 administered dose recovered in the feces and 4.4% recovered in urine. The estimated elimination

223 half-life ( $t_{1/2}$ ) of vismodegib is 4 days after continuous once-daily dosing and 12 days after a single

224 dose.

225 *Pharmacokinetics in Specific Populations*

226 Hepatic Impairment: The effect of hepatic impairment on the systemic exposure of vismodegib has

227 not been studied.

228 Renal Impairment: The effect of renal impairment on the systemic exposure of vismodegib has not

229 been studied.

230 Population pharmacokinetic analyses showed that weight (range: 41-140 kg), age

231 (range: 26-89 years), creatinine clearance (range: 30 to 80 mL/min), and sex do not have a clinically

232 meaningful influence on the systemic exposure of vismodegib.

233 **12.6 Cardiac Electrophysiology**

234 In a thorough QTc study in 60 healthy subjects, there was no effect of therapeutic doses of

235 ERIVEDGE on the QTc interval.

236

237 **13 NONCLINICAL TOXICOLOGY**

238 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

239 Carcinogenicity studies with vismodegib have not been conducted. Pilomatricoma (a benign

240 cutaneous neoplasm) was observed in rats administered oral vismodegib for 26 weeks at

241 100 mg/kg/day (approximately 0.8 times the systemic exposure (AUC) in patients at the

242 recommended human dose).

243 Vismodegib was not mutagenic in the *in vitro* bacterial reverse mutation (Ames) assay and was not

244 clastogenic in the *in vitro* human chromosomal aberration assay in human peripheral blood

245 lymphocytes or in the *in vivo* rat bone marrow micronucleus assay.

246 Studies to assess the potential of vismodegib to affect fertility have not been conducted; however,

247 data from repeat-dose toxicology studies in rats and dogs indicate that male and female reproductive

248 function and fertility may be impaired in patients receiving ERIVEDGE capsule. In a 26-week

249 toxicology study in rats, a relative decrease in percent motile sperm was observed at  $\geq 15$  mg/kg/day

250 (approximately  $\geq 0.3$  times the AUC in patients at the recommended human dose). In dogs,

251 increased numbers of degenerating germ cells and hypospermia were observed in young animals

252 administered oral vismodegib for 4 weeks at  $\geq 50$  mg/kg/day (approximately  $\geq 2$  times the AUC in

253 patients at the recommended human dose). No corresponding findings were observed in sexually

254 mature dogs at similar doses in 13-week and 26-week toxicology studies. A decrease in the number

255 of corpora lutea was observed in female rats administered oral vismodegib for 26 weeks at

256 100 mg/kg/day (approximately 0.8 times the AUC in patients at the recommended human dose).

257 **13.2 Animal Toxicology**

258 Neurologic effects characterized as limb or body tremors or twitching were observed in rats

259 administered oral vismodegib for 4 weeks or longer at  $\geq 50$  mg/kg/day (approximately  $\geq 0.4$  times

260 the AUC in patients at the recommended human dose). These observations resolved upon

261 discontinuation of dosing and were not associated with microscopic findings.

262

263 **14 CLINICAL STUDIES**

264 A single, international, single-arm, multi-center, open-label, 2-cohort trial was conducted in  
265 104 patients with either metastatic basal cell carcinoma (mBCC) (n = 33) or locally advanced BCC  
266 (laBCC) (n = 71). Patients with laBCC were required to have lesions that had recurred after  
267 radiotherapy, unless radiotherapy was contraindicated or inappropriate (e.g. Gorlin syndrome;  
268 limitations because of location of tumor or cumulative prior radiotherapy dose), and where the  
269 lesions were either unresectable or surgical resection would result in substantial deformity. Patients  
270 were to receive 150 mg vismodegib per day orally until disease progression or unacceptable toxicity.

271 The major efficacy outcome measure of the trial was objective response rate (ORR) as assessed by  
272 an independent review facility (IRF). In the mBCC cohort, tumor response was assessed according  
273 to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0. In the laBCC cohort,  
274 tumor response evaluation included measurement of externally assessable tumor (including scar) and  
275 assessment for ulceration in photographs, radiographic assessment of target lesions (if appropriate),  
276 and tumor biopsy. An objective response in laBCC required at least one of the following criteria and  
277 absence of any criterion for disease progression: (1)  $\geq 30\%$  reduction in lesion size [sum of the  
278 longest diameter (SLD)] from baseline in target lesions by radiographic assessment; (2)  $\geq 30\%$   
279 reduction in SLD from baseline in externally visible dimension of target lesions; (3) complete  
280 resolution of ulceration in all target lesions. Complete response was defined as objective response  
281 (as defined above) with no residual BCC on sampling tumor biopsy. Disease progression was  
282 defined as any of the following: (1)  $\geq 20\%$  increase in the SLD from nadir in target lesions (either by  
283 radiography or by externally visible dimension); (2) new ulceration of target lesions persisting  
284 without evidence of healing for at least 2 weeks; (3) new lesions by radiographic assessment or  
285 physical examination; (4) progression of non-target lesions by RECIST.

286 Of the 104 patients enrolled, 96 patients were evaluable for ORR. Twenty-one percent of patients  
287 carried a diagnosis of Gorlin syndrome. The median age of the efficacy evaluable population was  
288 62 years (46% were at least 65 years old), 61% male and 100% White. For the mBCC cohort  
289 (n = 33), 97% of patients had prior therapy including surgery (97%), radiotherapy (58%), and  
290 systemic therapies (30%). For the laBCC cohort (n = 63), 94% of patients had prior therapies  
291 including surgery (89%), radiotherapy (27%), and systemic/topical therapies (11%). The median  
292 duration of treatment was 10.2 months (range 0.7 to 18.7 months).

293 The key outcome measures are presented in Table 2, below.

294 **Table 2: Objective Response Rate: Efficacy-Evaluable Patients<sup>1</sup>**

295

	<b>mBCC (n = 33)</b>	<b>laBCC (n = 63)</b>
<b>IRF<sup>2</sup>-Confirmed ORR, n (%)</b>	10 (30.3)	27 (42.9)
<b>(95%CI)</b>	(15.6, 48.2)	(30.5, 56.0)
<b>Complete response<sup>3</sup></b>	0 (0.0)	13 (20.6)
<b>Partial response</b>	10 (30.3)	14 (22.2)
<b>Median Response Duration (months)</b>	7.6	7.6
<b>(95% CI<sup>5</sup>)</b>	(5.6, NE <sup>4</sup> )	(5.7, 9.7)

296 <sup>1</sup>Patients who received at least one dose of ERIVEDGE with independent pathologist-confirmed diagnosis of BCC

297 <sup>2</sup>IRF = Independent Review Facility

298 <sup>3</sup>For laBCC, complete response was defined as objective response with no residual BCC on sampling tumor biopsy.

299 <sup>4</sup>NE = Not estimable

300 <sup>5</sup>CI = Confidence Interval

301

302 **16 HOW SUPPLIED/STORAGE AND HANDLING**

303 Each ERIVEDGE (vismodegib) capsule has a pink opaque body and a grey opaque cap with  
304 “150 mg” printed on the capsule body and “VISMO” printed on the capsule cap in black ink.  
305 ERIVEDGE capsules are available in bottles of 28 capsules (NDC 50242-140-01).

306 Store at room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C  
307 (59°F to 86°F) [see USP Controlled Room Temperature].

308

309 **17 PATIENT COUNSELING INFORMATION**

310 **See *FDA-approved patient labeling (Medication Guide)*.**

- 311 • Advise patients that ERIVEDGE exposure during pregnancy can cause embryo-fetal death or  
312 severe birth defects.
- 313 • Instruct female patients of reproductive potential to use a highly effective form of contraception  
314 (failure rate of less than 1%) while taking ERIVEDGE and for at least 7 months after the last  
315 dose of ERIVEDGE.
- 316 • Instruct all male patients, even those with prior vasectomy, to use condoms with spermicide,  
317 during sexual intercourse with female partners while taking ERIVEDGE and for at least  
318 2 months after the last dose of ERIVEDGE.
- 319 • Instruct patients to immediately contact their healthcare provider if they (or, for males, their  
320 female partner) become pregnant or if pregnancy is suspected following exposure to  
321 ERIVEDGE.
- 322 • Instruct patients to immediately report any pregnancy exposure to ERIVEDGE and encourage  
323 participation in the ERIVEDGE pregnancy pharmacovigilance program by calling the Genentech  
324 Adverse Event Line at 1-888-835-2555.

- 325 • Inform female patients of the potential for serious adverse reactions in nursing infants from  
326 ERIVEDGE, taking into account the importance of the drug to the mother.
- 327 • Advise patients not to donate blood or blood products while taking ERIVEDGE and for at least  
328 7 months after the last dose of ERIVEDGE.
- 329 • Advise patients to swallow ERIVEDGE capsules whole and not to crush or open the capsules.

330

331

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ERIVEDGE™ [vismodegib] capsule

Manufactured by:

Patheon, Inc.

Mississauga, Canada

ERIVEDGE is a registered trademark of Genentech, Inc.

Distributed by:

**Genentech USA, Inc.**

A Member of the Roche Group

1 DNA Way

South San Francisco, CA 94080-4990

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332

**MEDICATION GUIDE**  
**ERIVEDGE™ (EH-rih-vej)**  
(vismodegib)  
capsule

Read this Medication Guide before you start taking ERIVEDGE and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your healthcare provider about your medical condition or your treatment.

**What is the most important information I should know about ERIVEDGE?**

**ERIVEDGE can cause your baby to die before it is born (be stillborn) or cause your baby to have severe birth defects.**

For females who can become pregnant:

- You should talk with your healthcare provider about the risks of ERIVEDGE to your unborn child.
- Your healthcare provider should do a pregnancy test within 7 days before you start taking ERIVEDGE to find out if you are pregnant.
- In order to avoid pregnancy, you should start using highly effective birth control before you start ERIVEDGE, and continue to use highly effective birth control during treatment, and for 7 months after your last dose of ERIVEDGE. Talk with your healthcare provider about what birth control method is right for you during this time.
- Talk to your healthcare provider right away if you have unprotected sex or if you think that your birth control has failed.
- Tell your healthcare provider right away if you become pregnant or think that you may be pregnant.

For males:

- You should always use a condom with a spermicide, even if you have had a vasectomy, during sex with female partners while you are taking ERIVEDGE and for 2 months after your last dose to protect your female partner from being exposed to ERIVEDGE.
- Tell your healthcare provider right away if your partner becomes pregnant or thinks she is pregnant while you are taking ERIVEDGE.

**Exposure to ERIVEDGE during pregnancy:**

If you think that you or your female partner may have been exposed to ERIVEDGE during pregnancy, talk to your healthcare provider right away. Pregnant women are encouraged to participate in a program that collects information about exposure to ERIVEDGE during pregnancy, and the effects on the mother and her unborn child. This program is called the ERIVEDGE pregnancy pharmacovigilance program. You may participate in this program by calling the Genentech Adverse Event Line at 1-888-835-2555.

366 **What is ERIVEDGE?**

367 ERIVEDGE is a prescription medicine used to treat adults with a type of skin cancer, called basal  
368 cell carcinoma, that has spread to other parts of the body or that has come back after surgery or that  
369 your healthcare provider decides cannot be treated with surgery or radiation.

370 It is not known if ERIVEDGE is safe and effective in children.

371  
372 **What should I tell my healthcare provider before taking ERIVEDGE?**

373 **Before taking ERIVEDGE, tell your healthcare provider if you:**

- 374 • **are pregnant or plan to become pregnant.** See “What is the most important  
375 **information I should know about ERIVEDGE?”**
- 376 • **are breastfeeding or plan to breastfeed.** It is not known if ERIVEDGE passes into your  
377 breast milk. You and your healthcare provider should decide if you will take ERIVEDGE or  
378 breastfeed. You should not do both.

379 **Tell your healthcare provider about all the medicines you take,** including prescription and  
380 non-prescription medicines, vitamins, and herbal supplements.

381 Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist  
382 when you get a new medicine.

383  
384 **How should I take ERIVEDGE?**

- 385 • Take ERIVEDGE exactly as your healthcare provider tells you.
- 386 • You can take ERIVEDGE with or without food.
- 387 • Swallow ERIVEDGE capsules whole. Do not open or crush the capsules.
- 388 • Take ERIVEDGE one time each day.
- 389 • If you miss a dose, skip the missed dose. Just take your next scheduled dose.

390  
391 **What should I avoid while taking ERIVEDGE?**

- 392 • Do not donate blood or blood products while you are taking ERIVEDGE and for 7 months  
393 after your last dose.

394  
395 **What are the possible side effects of ERIVEDGE?**

396 **ERIVEDGE can cause serious side effects, including:**

- 397 • See “What is the most important information I should know about ERIVEDGE?”

398 The most common side effects of ERIVEDGE are:

- 399 • muscle spasms
- 400 • hair loss
- 401 • change in how things taste or loss of taste
- 402 • weight loss
- 403 • tiredness
- 404 • nausea
- 405 • diarrhea



406       • decreased appetite  
407       • constipation  
408       • vomiting  
409       • joint aches

410 Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

411 These are not all the possible side effects of ERIVEDGE. For more information, ask your healthcare  
412 provider or pharmacist.

413 Call your doctor for medical advice about side effects. You may report side effects to FDA at  
414 1-800-FDA-1088.

415 You may also report side effects to Genentech, Inc. at 1-888-835-2555.

416

417 **How should I store ERIVEDGE?**

418       • Store ERIVEDGE at room temperature between 68°F to 77°F (20°C to 25°C).

419 **Keep ERIVEDGE and all medicines out of the reach of children.**

420

421 **General information about ERIVEDGE**

422 Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do  
423 not use ERIVEDGE for a condition for which it was not prescribed. Do not give ERIVEDGE to  
424 other people, even if they have the same symptoms that you have. It may harm them.

425 This Medication Guide summarizes the most important information about ERIVEDGE. If you  
426 would like more information, ask your health care provider. You can ask your healthcare provider  
427 or pharmacist for the FDA-approved information about ERIVEDGE that is written for healthcare  
428 professionals.

429 For more information, call 1-855-737-4833 or visit [www.erivedge.com](http://www.erivedge.com)

430

431 **What are the ingredients in ERIVEDGE?**

432 Active ingredient: vismodegib

433 Inactive ingredients: microcrystalline cellulose, lactose monohydrate, sodium lauryl sulfate,  
434 povidone, sodium starch glycolate, talc, magnesium stearate (non bovine). The capsule shell  
435 contains gelatin, titanium dioxide, red iron oxide, and black iron oxide. The black printing ink  
436 contains shellac and black iron oxide.

437 This Medication Guide has been approved by the U.S. Food and Drug Administration.

438 MG Issued: 01/2012

439 Manufactured by:  
440 Patheon, Inc.  
441 Mississauga, Canada

442 Distributed by:  
443 **Genentech USA, Inc.**  
444 A Member of the Roche Group  
445 1 DNA Way  
446 South San Francisco, CA 940804990

447 ERIVEDGE is a registered trademark of Genentech, Inc.



# PREPRESS - INFORMATION

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NDC 50242-2140-01

**Erivedge™**  
(vismodegib)  
capsules

**150 mg**

**Rx only**  
Attention Pharmacist:  
Dispense the accompanying  
Medication Guide to each  
patient.

**28 capsules**

**Genentech**

Made in Canada  
Manufactured by Fathion, Inc., Mississauga, Canada  
Distributed by:  
**Genentech USA, Inc.**  
A Member of the Roche Group  
South San Francisco, CA 94065-4090

(01) 103 5024-2140 01 7

Each capsule contains 150 mg of vismodegib.  
Usual dosage: see prescribing information.  
Store at room temperature 20°C–25°C (68°F–77°F);  
excursions permitted between 15°C and 30°C (59°F  
and 86°F).

US (cN) 1111 10135490

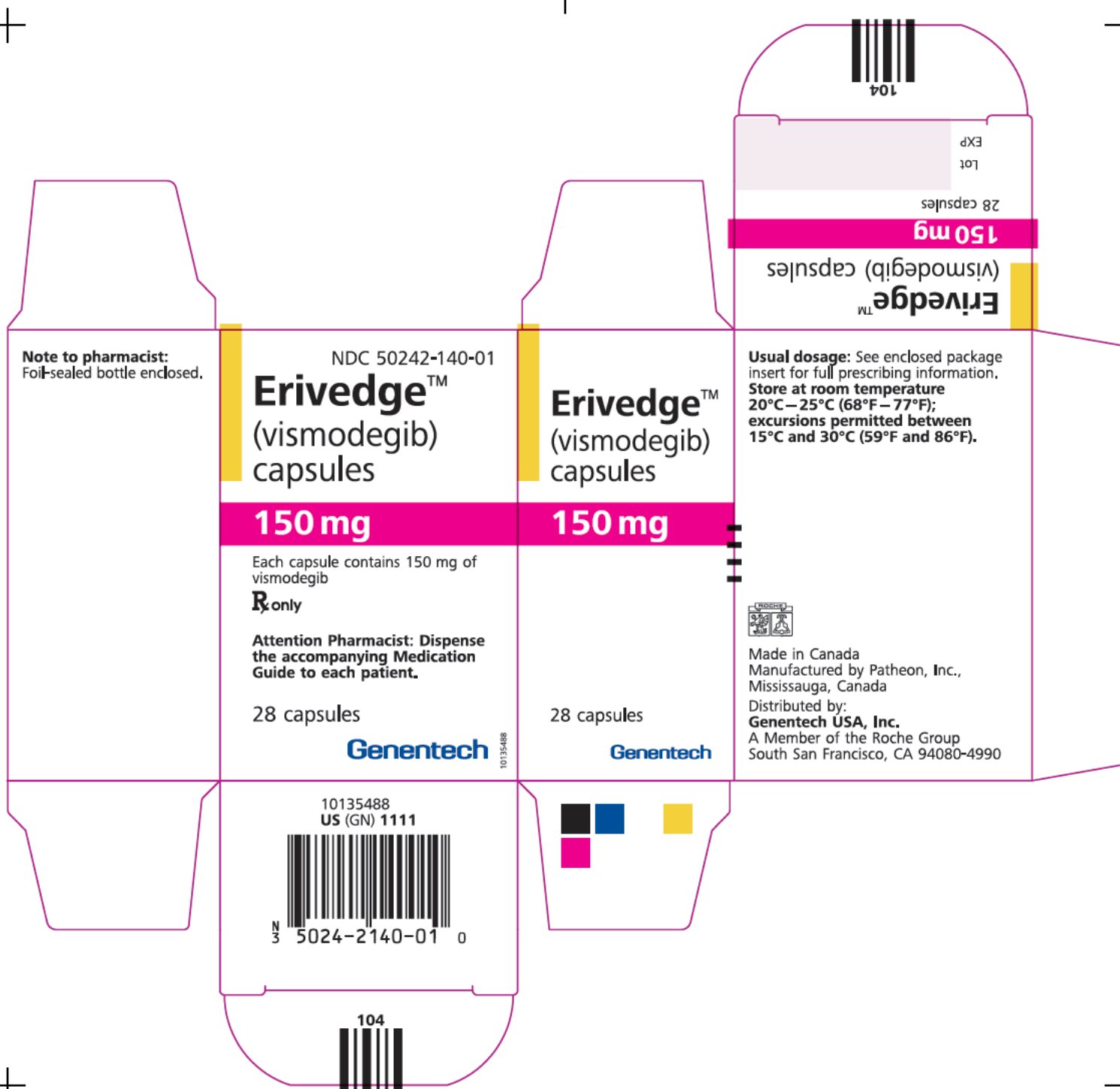
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PREPRESS - INFORMATION

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/s/  
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RICHARD PAZDUR  
01/30/2012