INTRODUCTION

Basal cell carcinoma (BCC), first described in 1827,1 is the most common form of skin cancer,2–4 accounting for approximately 80% of all skin malignancies.6 An estimated 2.8 million new cases of BCC are diagnosed each year in the U.S.7

As its name implies, BCC develops in the basal, or lowest, layer of the epidermis (Figure 1).5,6 Cells in this layer of the skin continually divide to form keratinocytes, the predominant cell type in the epidermis. Keratinocytes, in turn, produce the protein keratin, which helps the skin protect the rest of the body.8–10 Although BCC can occur anywhere, it most commonly develops on the head and neck.11 BCC is an indolent disease,11 but in rare cases the tumors can invade local tissue (stage III disease) or metastasize to other parts of the body (stage IV disease).6,12,13

BCC can be highly disfiguring, involving extensive areas of soft tissue, cartilage, and bone.7,8,12,13 The disease, however, is rarely fatal.6,7

The major risk factor for the development of any type of skin cancer is excessive exposure to ultraviolet radiation from the sun or indoor tanning.14,15 Additional risk factors for BCC include fair skin, light hair, a family history of skin cancer, and a weakened immune system (Table 1).6,14–16

The absolute incidence of BCC is difficult to determine because non-melanoma skin cancers are rarely reported to cancer registries.14 Nevertheless, available data indicate that BCC may have an annual incidence of 0.1% to 0.5% in the U.S.17,18 Incidence rates of BCC have steadily increased throughout the world during the past 30 years.17,19 During that period, the number of women younger than 40 years of age with BCC has more than doubled in the U.S.7 In 1994, it was estimated that Caucasian populations in North America had nearly a one-in-three (30%) risk of developing BCC over their lifetimes. In addition, age-standardized yearly rates in the U.S. were estimated at up to 407 cases of BCC per 100,000 Caucasian men and 212 cases per 100,000 Caucasian women.20 In South Wales, the United Kingdom, the age-standardized incidence of BCC was estimated at 114 per 100,000 population in 1998.21 The reported incidence of BCC in Australia was 726 per 100,000 in 1993,22 and Australia continues to have the highest rate of BCC in the world.17

Although BCC most commonly occurs in elderly men, patients with this disease are increasingly likely to be young women.23 BCC is rarely seen in individuals younger than 20 years of age19 or in dark-skinned races.16,19 Skin cancers affect only 1% to 2% of all African Americans.7 Approximately six or seven cases of BCC are diagnosed by primary care physicians in the U.S. each year.24

Because of its high incidence and significant morbidity, BCC imposes a...
substantial economic burden on health care systems. In 2004, the total direct cost associated with the treatment of non-melanoma skin cancer (i.e., BCC and squamous cell carcinoma) was $1.5 billion. Surgery and radiation therapy are the mainstays of treatment for localized BCC. Topical therapies, such as 5-fluorouracil, imiquimod (Aldara, 3M/Medicis), photodynamic therapy, and cryotherapy, may be used in patients for whom surgery or radiation is contraindicated or impractical, although these approaches are less effective than primary treatment. BCC is generally curable if it is restricted to a small area of skin. Advanced BCC, however, cannot be effectively treated with surgery or radiation. The median survival time for patients with metastatic BCC is 8 months.

In January 2012, the FDA approved vismodegib (Erivedge, Genentech), the first oral medication for adults with metastatic BCC or locally advanced BCC that has recurred after surgery or for patients who are not candidates for surgery or radiation.

### CHEMICAL AND PHYSICAL PROPERTIES

Vismodegib is a crystalline free base with a dissociation constant (pKa) acidity rating (pyridinium cation) of 3.8. Vismodegib appears as a white powder. Its solubility is pH-dependent, with 0.1 mcg/mL at pH 7 and 0.99 mg/mL at pH 1. The structural formula of vismodegib is shown in Figure 2.

Each capsule contains 150 mg of vismodegib and the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, sodium lauryl sulfate, povidone, sodium starch glycolate, talc, and magnesium stearate (non-bovine). The capsules have a pink opaque body and a gray opaque cap, with "150 mg" printed on the capsule body and "VISMO" printed on the capsule cap in black ink. The capsule shell contains gelatin, titanium dioxide, red iron oxide, and black iron oxide. The black printing ink contains shellac and black iron oxide.

### MECHANISM OF ACTION

Vismodegib is a small-molecule systemic inhibitor of the Hedgehog (Hh) intracellular signaling pathway. During embryogenesis, this pathway plays an important role in the growth and development of tissues, including the promotion of primitive hematopoietic, neural, and mammary stem cells. The Hh signaling pathway is initiated when the Hh protein binds to its cell-surface receptor ( Patched). Both the Hh and the Patched proteins then move inside the cell. Binding of the Patched protein liberates an intracellular protein (Smoothed), which moves to the cell surface. There, Smoothened activates the GLI protein family, leading to the activation of Hh target genes involved in cell growth. Normally, the Hh pathway is quiescent in adults. Reactivation of the Hh pathway has been implicated in several cancers, including BCC and medulloblastoma. Mutations in the Smoothed or Patched proteins, which encode the Hh pathway, are believed to lead to cancer cell growth in BCC. Vismodegib selectively binds to the Smoothened protein, thereby blocking intracellular signaling and deactivating the Hh pathway. This activity, in turn, interferes with tumor cell growth and survival.

Because of its mechanism of action, vismodegib can cause severe injury or death to an embryo or fetus, and the product labeling includes a boxed warning to that effect.

### PHARMACOKINETICS

Orally administered, vismodegib demonstrates nonlinear, time-dependent pharmacokinetics resulting from differential plasma protein binding, solubility-limited absorption, and slow metabolic elimination properties.

#### Absorption and Distribution

Vismodegib is a highly permeable compound with low aqueous solubility (Biopharmaceutics Classification System Class 2). The drug’s absolute bioavailability is low (32%) after a single dose. Absorption is saturable, as indicated by the absence of a dose-proportional increase in exposure after a single dose of 270 mg or 540 mg.

The systemic exposure of vismodegib at steady state is not affected by food; therefore, vismodegib capsules may be taken without regard to meals.

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

#### Metabolism and Elimination

The parent drug accounts for more than 98% of the total circulating drug-related components of vismodegib. The metabolic pathways in humans include oxidation, glucuronidation, and pyridine ring cleavage.
**Drug Forecast**

*In vitro*, the two most abundant oxidative metabolites recovered in feces are produced by recombinant cytochrome P450 (CYP) 2C9 and CYP3A4/5. Vismodegib and its metabolites are eliminated primarily by the liver; 82% of the administered dose is recovered in feces and 4.4% is recovered in urine. The estimated elimination half-life of vismodegib is 12 days after a single dose and 4 days after continuous once-daily administration.

**Specific Populations**

The effect of hepatic or renal impairment on the systemic exposure of vismodegib has not been studied. In pharmacokinetic analyses, weight (range, 41–140 kg), age (range, 26–89 years), creatinine clearance (range, 30–80 mL/minute), and the patient’s sex did not have clinically meaningful effects on the systemic exposure of vismodegib.

**SAFETY PROFILE**

**Boxed Warning**

The labeling for vismodegib includes a boxed warning regarding the potential for embryofetal death or severe birth defects. Both male and female patients must be advised of this risk. In addition, before initiating treatment with vismodegib, physicians must verify a female patient’s pregnancy status and must advise female patients of the need for contraception. Male patients must be informed of the potential risk of exposing their partners to vismodegib through semen.

**Warnings and Precautions**

As noted previously, vismodegib can cause fetal harm when administered to pregnant women, based on its mechanism of action. Vismodegib is teratogenic, embryotoxic, and fetotoxic in rats at maternal exposures lower than human exposures at the recommended dose of 150 mg/day. In rats, malformations including craniofacial anomalies, an open perineum, and absent or fused digits. Fetal retardations and variations were also noted. Patients should contact their health care provider immediately if pregnancy is suspected. Female and male patients of reproductive age should be counseled regarding pregnancy prevention and planning.

If vismodegib is used during pregnancy or if a female patient becomes pregnant while taking vismodegib, the patient should be informed of the potential hazard to the fetus. Patients should not donate blood or blood products during treatment and for at least 7 months after they receive the last dose of vismodegib.

**Common Adverse Reactions**

Four open-label clinical trials were conducted to evaluate vismodegib monotherapy at doses of 150 mg or greater once daily in 138 patients with advanced BCC. Patients’ median age was 61 years (range, 21–101 years). All patients were Caucasian (including Hispanic individuals), and most (64%) were men.

The median duration of treatment was approximately 10 months (range, 0.7–36 months). A total of 111 patients were treated with vismodegib for 6 months or longer.

Common adverse reactions (all grades) included muscle spasms (71.7%), alopecia (63.8%), dysgeusia (55.1%), and weight loss (44.9%) (Table 2). The most common serious adverse reactions (grade 3 or 4) included weight loss (7.2%), fatigue (5.8%), muscle spasms (3.6%), and decreased appetite (2.2%) (see Table 2).

In clinical trials, amenorrhea developed in three of 10 premenopausal women during vismodegib treatment. Serious (grade 3) treatment-emergent laboratory abnormalities included hypotension in six patients (4%), azotemia in three patients (2%), and hypokalemia in two patients (1%).

**Safety**

Vismodegib is a Pregnancy Category D drug, and it can cause fetal harm when administered to a pregnant woman, based on its mechanism of action. It is teratogenic in rats at doses corresponding to 20% of the exposure at the recommended human dose.

It is not known whether vismodegib is excreted in human breast milk. Because of the potential for serious adverse reactions in nursing infants from exposure to vismodegib, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

The safety and efficacy of vismodegib have not been established in pediatric patients or in patients with hepatic or renal impairment. Clinical studies of vismodegib did not include sufficient numbers of patients 65 years of age or older to determine whether they respond differently from younger patients.

**DRUG INTERACTIONS**

**Effects of Other Drugs on Vismodegib**

The metabolism of vismodegib involves multiple pathways (oxidation, glucuronidation, and pyridine ring cleavage). Vismodegib is excreted predominantly as an unchanged drug, and several minor metabolites are produced by multiple CYP enzymes.

Although vismodegib is a substrate of CYP2C9 and CYP3A4, CYP inhibition is not expected to affect systemic exposure, because similar steady-state plasma concentrations of vismodegib were observed in patients concomitantly treated with CYP3A4 inducers, such as carbamazepine (e.g., Carbafol, Shire), modafinil (Provigil, Cephalon/Teva), and phenobarbital or CYP3A4 inhibitors such as erythromycin and fluconazole (Diflucan, Pfizer) in clinical trials.

*In vitro* studies indicate that vismodegib is a substrate of the efflux transporter P-glycoprotein (P-gp). When vismodegib is given with a drug that inhibits P-gp, such as clarithromycin (Biaxin, Abbott), erythromycin, or azithromycin (Zithromax, Pfizer), the systemic exposure of vismodegib and the incidence of adverse events with vismodegib may be increased.

Drugs that alter the pH of the upper gastrointestinal tract (e.g., proton pump inhibitors, histamine H2-receptor antagonists, and antacids) may alter the solubility of vismodegib and may reduce its bioavailability. No clinical studies have evaluated the effect of gastric pH-altering drugs on the systemic exposure of vismodegib. When vismodegib is taken with such agents, increasing the vismodegib dose is not likely to compensate for the loss of exposure.

Coadministration of vismodegib with a proton pump inhibitor, an H2-receptor antagonist, or an antacid may reduce the systemic exposure of vismodegib. The effect on the efficacy of vismodegib in this situation is unknown.

**Effects of Vismodegib on Other Drugs**

Results of a drug–drug interaction study in cancer patients showed that the systemic exposure of rosiglitazone (Avandia, GlaxoSmithKline), a CYP2C8
substrate, or of an oral contraceptive (ethinyl estradiol or norethindrone) was not altered when either drug was administered with vismodegib.33,48

In vitro studies indicate that vismodegib inhibits the hepatic enzymes CYP-2C8, CYP2C9, and CYP2C19 and the drug efflux transporter Bcrp. Vismodegib does not induce CYP1A2, CYP2B6, or CYP3A4/5 in human hepatocytes.33

CLINICAL EFFICACY

A phase 1 study was conducted to evaluate vismodegib in patients with solid tumors that were refractory to current therapies or for which no standard treatment existed.39,49 The malignancies included BCC, pancreatic cancer, medulloblastoma, and 17 other types of cancer.

This was the first clinical trial that investigated the efficacy and safety of oral vismodegib, given at escalating doses (150, 270, and 540 mg/day), in patients with advanced solid malignancies. Of the 68 patients in this study, 33 had advanced BCC. Seventeen of these patients received vismodegib 150 mg/day; 15 patients received 270 mg/day; and one patient received 540 mg/day, for a median period of 9.8 months.

Of the 33 patients with BCC, 18 (54.5%) demonstrated an objective response to vismodegib: seven according to imaging assessments, and 11 on physical examination (one patient was rated on both). Two patients (6.0%) had a complete response, and 16 (48.5%) had a partial response.39

Eight grade 3 adverse events that were considered to be related to vismodegib occurred in six patients, including four patients with fatigue, two with hyponatremia, one with muscle spasms, and one with atrial fibrillation. One patient withdrew from the study because of adverse events.29

The results of this study established the recommended phase 2 dosage of vismodegib at 150 mg/day, because pharmacokinetic analyses indicated that higher doses did not result in higher steady-state plasma concentrations of vismodegib and because no dose-limiting toxic effects were observed.19

The investigators found evidence of Hh signaling in tumors that responded to vismodegib treatment as well as evidence of down-modulation of the GLI1 oncogene in non-involved skin, indicating inhibition of the Hh pathway.20,40

Subsequent FDA approval of vismodegib was based on results from a pivotal phase 2 single-arm, open-label, two-cohort clinical study (ERIVANCE BCC) that included 104 patients with locally advanced (n = 71) or metastatic (n = 33) BCC.22,33,50

In this pivotal trial, patients with locally advanced BCC had to have lesions that had recurred after radiotherapy unless radiotherapy was contraindicated or inappropriate; the lesions were unresectable; or surgical resection would result in substantial deformity. Patients received vismodegib 150 mg once daily until disease progression or unacceptable toxicity occurred.33,50

The primary efficacy measure was the objective response rate (ORR). In the cohort with metastatic BCC, tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0. In the cohort with locally advanced BCC, the evaluation of tumor response included measurement of externally assessable lesions (including scars), assessment of ulceration in photographs, radiographic assessment of target lesions (if appropriate), and tumor biopsy.33,50

An objective response in locally advanced BCC required at least one of the following criteria and the absence of any criterion for disease progression:33,50

- a reduction of 30% or more in lesion size (the sum of the longest diameter (SLD)) from baseline in target lesions on radiography
- a reduction of 30% or more in SLD from baseline in the externally visible dimension of target lesions
- complete resolution of ulceration in all target lesions

A complete response was defined as an objective response with no residual BCC on sampling tumor biopsy.
progression was defined as any of the following:33,50

- an increase of 20% or more in SLD from nadir in target lesions, determined either by radiography or by an increase in visible dimensions
- new ulceration of target lesions persisting without evidence of healing for at least 2 weeks
- new lesions detected by radiography or physical examination
- progression of non-target lesions, as defined by RECIST parameters

Of the 104 patients enrolled in this study, 96 were evaluable for ORR. Neviod basal cell carcinoma (Gorlin syndrome), a rare, inherited genetic disorder, had been diagnosed in 21% of the patients. The median age of the evaluable population was 62 years (46% were at least 65 years of age). Most of the patients (61%) were men, and all were Caucasian.

In the cohort with locally advanced BCC (n = 63), 94% of the patients had received prior therapy, including surgery (89%), radiotherapy (27%), and systemic or topical therapies (11%). In the cohort with metastatic disease (n = 33), 97% of the patients had received prior treatment, including surgery (97%), radiotherapy (58%), and systemic therapies (30%).33,50

The median duration of treatment was 10.2 months.33,50 Key results are presented in Table 3. Vismodegib shrank lesions (ORR) in 43% of patients (27/63) with locally advanced BCC and in 30% of patients (10/33) with metastatic disease.33,50

Genentech is continuing to investigate vismodegib in several ongoing studies of BCC (Table 4).

**DOSAGE AND ADMINISTRATION**

The recommended dose of vismodegib is one capsule (150 mg) once daily until disease progression or unacceptable toxicity occurs.33 Vismodegib may be taken with or without food. The capsules should be swallowed whole.33

**DRUG DEVELOPMENT AND APPROVAL**

Vismodegib was discovered by Genentech, a South San Francisco–based member of the Roche Group, and was jointly validated by Genentech and Curis, Inc., in a series of preclinical studies. Roche proceeded to develop vismodegib under a collaboration agreement with Curis. Through this collaboration, Genentech, Roche, and Chugai Pharmaceuticals, respectively, are responsible for the clinical development and commercialization of vismodegib inside the U.S., outside the U.S. (excluding Japan and Korea), and in...
Japan. Under the agreement with Roche, Curis is eligible to receive cash payments upon the successful achievement of specified clinical development and regulatory approval milestones as well as royalties upon commercialization of vismodegib.11

Genentech filed an Investigational New Drug (IND) application with the FDA in September 2006. In May 2011, a pre-submission meeting was held between representatives of the FDA and Genentech to reach an agreement on the content and format of a New Drug Application (NDA) for registration of vismodegib in advanced BCC. In September 2011, Genentech submitted the NDA for vismodegib for use in adults with advanced BCC for whom surgery was inappropriate, based on results from the pivotal phase 2 ERIVANCE BCC study.12

The FDA granted Genentech’s application priority review status in November and set the action date for March 8, 2012.53,54 On January 30, 2012—6 weeks ahead of the action date—the FDA approved oral vismodegib for the treatment of adults with metastatic BCC, or with locally advanced BCC that has recurred following surgery or who are not candidates for surgery, and who are not candidates for radiation.52,53 The FDA approval triggered a $10 million payment to Curis, Inc.55

COST AND AVAILABILITY

Genentech has set the price of vismodegib at $7,500 for a month’s supply of once-daily capsules—or approximately $250 per capsule. Although the duration of treatment with vismodegib can vary, patients are expected to be using the therapy for about 10 months, for an average cost of $75,000 for a total course of treatment.56 Financial analysts have predicted that sales of vismodegib, including sales in Europe (where the drug is expected to launch in 2013), will reach $401 million in 2015 and will peak at $533 million in 2022.55 Vismodegib is available only through specialty pharmacies.55,57

CONCLUSION

The Hh pathway inhibitor vismodegib (Erivedge), the first medication for advanced BCC, provides an important new therapy for this disfiguring and potentially life-threatening disease and offers new possibilities for long-term clinical management. The Roche Group is pursuing further development of vismodegib for BCC and other cancers.

REFERENCES

35. Miller RJ, Lucks CA, Nyland J. Drug Forecast.
continued from page 677

entech; January 2012. Available at: www.


48. LoRusso PM, Piha-Paul SA, Colevas AD, et al. Pharmacokinetic assessment of drug–drug interaction potential when rosiglitazone or combined oral contracep-
tive is coadministered with vismodegib in patients with locally advanced or meta-


51. FDA approves Erivedge (vismodegib) capsule, the first medicine for adults with advanced basal cell carcinoma. Roche, January 30, 2012. Available at: www.
roche.com/media/media_releases/med-


