CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203388Orig1s000

OFFICE DIRECTOR MEMO

Office Director Summary Review for Regulatory Action

Date	Electronic stamp date
From	Richard Pazdur, MD
Subject	Office Director Decisional Memo
NDA #	203388
Applicant Name	Genentech, Inc.
Date of Submission	September 8, 2011
PDUFA Goal Date	March 8, 2012
Proprietary Name / Established (USAN) Name	Erivedge/ vismodegib
Dosage Forms / Strength	Hard gelatin capsules/ 150 mg
Proposed Indication	Vismodegib as treatment for patients with advanced basal cell carcinoma for whom surgery is inappropriate.
Recommended Action for NME:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Division Director	Pat Keegan
Regulatory Project Manager Review	Mona Patel
Medical Officer Review	Michael Axelson
Statistical Review	Xiaoping Jiang
Pharmacology Toxicology Review	Dubravka Kufrin
CMC (DP) and Biopharmaceutics Review	Zedong Dong
CMC Review (DS)	Anne Marie Russell
Product Quality Microbiology Review	John Metcalfe
Facilities (EES) Review	Mahesh Ramanadham
Clinical Pharmacology Review	Jian Wang & Hong Zhao (TL)
Clinical Pharmacometrics Review	Bahru Habetemariam
Clinical Pharmacogenomics Review	Christian Grimstein
IRQT Consultant Review	Qianyu Dang; Joanne Zhang; Justin Earp
OPDP	Carole Broadnax (PI) Sharon Mills (Med Guide)
OSI	Lauren Iaconno-Conners
CDTL Review	Jeff Summers
OSE/DMEPA Review	Richard Abate
OSE/DRISK Review	Amarylis Vega
MHT Consult	Tammie Brent Howard

OND=Office of New Drugs
IRQT+
OPDP=Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OSI=Office of Scientific Investigations
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

1. Introduction

On September 8, 2011, Genentech Inc., submitted an NDA for a new molecular entity, vismodegib (ERIVEDGE capsules), with a novel mechanism of action (inhibition of hedgehog pathway signaling). Vismodegib was studied in patients with recurrent locally advanced or metastatic basal cell carcinoma (BCC) following surgery, with disease progression after radiation or in whom radiation is contraindicated. There is no FDA-approved treatment for patients with metastatic BCC; the most commonly unapproved systemic treatment cited in the published literature is platinum-based chemotherapy. FDA-approved topical therapies (5-FU and imiquimod creams) for localized lesions have been shown to be effective in patients with small lesions (i.e., < 2 cm in diameter) and their efficacy in patients with recurrent disease and large tumor burden is not known.

Basal cell carcinoma (BCC) is a non-melanocytic skin cancer that arises from basal cells, small round cells found in the lower layer of the epidermis. An estimated 1.5 million new cases of BCC were diagnosed in 2010 in the US, making it the most common form of cancer. The majority of BCCs occur on the face (70%), with 25% occurring on the trunk and extremities and 5% on the genitalia. There is a modest male predominance and most cases occur in patients 50 years of age or older. BCCs are typically slow growing and, if not resected at an early stage, locally invasive. Metastatic disease to bone, brain, or lungs is estimated to occur in less than ≤ 0.5% of patients. The disease-specific mortality is estimated at less than 0.1%. Recurrence following initial treatment occurs in ≤ 5% of patients; reported risk factors for recurrence are tumor stage (size & depth of invasion), tumor location (head/face), positive surgical margins, and use of poor technique in non-surgical modalities of treatment.

The etiologic role of sun exposure and sun- or UV-damaged skin in the development of BCC is supported by the location of most BCCs in sun-exposed areas, the higher incidence of BCCs in equatorial regions, and the higher incidence of BCC in light-skinned individuals. Other risk factors for BCC include prior irradiation, arsenic exposure, immunosuppression, and a variety of genetic disorders. The patched/hedgehog intracellular signaling pathway has been shown to be altered in both sporadic BCCs and nevoid BCC syndrome (Gorlin syndrome). Loss of inhibition of this pathway is correlated with an increased risk of cancer, including BCC.

2. CMC

Chemistry reviewers have recommended an overall acceptability of the manufacturing of the drug product and drug substance. Additionally, the Office of Compliance has recommended an overall acceptability regarding the manufacturing facility for the drug substance.

The commercial vismodegib drug product is a hard gelatin capsule formulation containing vismodegib 150 mg. Stability testing supports an expiry of 24 months for ERIVEDGE when stored at room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F).

3. Nonclinical Pharmacology/Toxicology

There are no outstanding pharm/tox issues that preclude approval.

Pharmacology, pharmacokinetic and toxicology studies were conducted as a part of the nonclinical evaluation of vismodegib. Single dose toxicology studies were conducted in mice, rats, and dogs. Repeat-dose toxicology studies were conducted in rats and dogs. In rats receiving multiple doses, treatment-related effects in bone (premature closure of epiphyseal growth plate), teeth (e.g., missing teeth, degeneration/necrosis of odontoblasts, formation of fluid-filled cysts in dental pulp, ossification of root canal, and hemorrhage resulting in breakage or loss of teeth), and taste buds (decreased number of taste buds on tongue) were observed. The effects on taste buds showed a trend of reversibility following an eight week recovery period.

Findings observed in repeat-dose toxicology studies that were also in human subjects are alopecia (observed in both rats and dogs) and muscle spasms (in rat). In contrast, elevations in total cholesterol, up to 3 and 5 fold, respectively, and increases in both HDL and LDL were observed in both rats and dogs but have not been observed human subjects. The effects on cholesterol levels were reversible in animals and were not correlated with histopathologic findings.

In an embryo-fetal developmental toxicity study, vismodegib was teratogenic at a dose corresponding to an exposure of 20% of the exposure at the recommended human dose, and was embryotoxic and fetotoxic at exposures in the range achieved in patients at the recommended dose.

> Note: *Vismodegib exhibits non-linear pharmacokinetics and saturable absorption. The concentrations of vismodegib achieved in non-clinical studies are substantially higher than was observed in human subjects.*

A standard battery of genetic toxicology studies was conducted with vismodegib. Vismodegib was not mutagenic in the *in vitro* bacterial reverse mutation (Ames) assay and was not clastogenic in the *in vitro* human chromosomal aberration assay in human peripheral blood lymphocytes or in the *in vivo* rat bone marrow micronucleus assay.

Carcinogenicity studies have not been conducted with vismodegib; these studies will be conducted under a post-marketing requirement.

4. Clinical Pharmacology

There are no outstanding clinical pharmacology issues that preclude approval.

Dose Selection

Dose selection is based on studies assessing the exposure in clinical trials of patients with cancer following vismodegib at doses of 150 mg, 270 mg, or 450 mg daily and comparisons of daily dosing of vismodegib 150 mg for 11 days followed by random allocation to continue 150 mg daily, 150 mg three times per week, and 150 mg weekly. There was no evidence of increased exposure at daily doses above 150 mg however there was a decrease in exposure following less frequent dosing schedules (e.g., 150 mg three times per week or weekly).

ADME

Pharmacokinetic (PK) data were obtained in eight trials in healthy subjects or patients with advanced cancers and the results of a population PK analysis that included PK sampling in the efficacy trial (SHH 4476g) were provided in the NDA. Based on these data, the absolute bioavailability of a single dose of vismodegib 150 mg is 31.8% and its absorption is saturable. Systemic exposure of vismodegib at steady state is not affected by food. Vismodegib 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. With daily dosing, the average unbound steady-state vismodegib concentrations were <1% of total vismodegib concentrations, regardless of dose (ranging from 150 mg-540 mg). The parent drug is the predominant component (> 98%) in the circulation. Vismodegib and its metabolites are eliminated primarily by the hepatic route. The estimated elimination half-life (t1/2) of vismodegib is 4 days after multiple daily doses.

Pharmacokinetics in Specific Populations

The effect of hepatic and renal impairment on the systemic exposure of vismodegib has not been studied. Similarly, the effects of drug interactions have not been adequately studied. However limited *in vivo* data do not suggest that there are significant interactions.

Population PK analyses suggest that weight (range: 41-140 kg), age (range: 26-89 years), creatinine clearance (range: 30 - 80 mL/min), and sex do not have a clinically meaningful influence on the systemic exposure of vismodegib.

Drug Interactions

The NDA contained an interim report for an *in vivo* drug interaction trial (SHH4593g) being conducted in patients with cancer. This DDI trial is assessing the interactions between vismodegib and rosiglitazone (vismodegib as a perpetrator of CYP2C8 inhibition) and between vismodegib and oral contraceptives (vismodegib as a perpetrator of CYP3A induction). The preliminary results indicate that vismodegib does not alter the AUC or Cmax of roxiglitazone or ethinyl estradiol. Modest effects on the Cmax (12% increase) and AUC (23% increase) were observed with norethindrone and vismodegib compared with norethindrone alone. These preliminary data suggest that the efficacy of oral contraceptives will not be compromised by concomitant administration of vismodegib.

Effects on QTc

In a thorough QTc study in 60 healthy subjects, no QTc interval prolongation was observed at vismodegib concentrations achieved in therapeutic trials.

5. Clinical Microbiology

No clinical microbiology review was required for this product.

6. Clinical/Statistical-Efficacy

Efficacy was demonstrated in a single-arm, parallel cohort trial enrolling 104 patients. Patients received 150 mg of vismodegib daily. Central pathologic review of archival or baseline tissue confirmed the diagnosis of basal cell carcinoma (BCC) in 96 patients: 33 patients with metastatic basal cell carcinoma (mBCC) and 63 patients with locally advanced basal cell carcinoma (laBCC).

Efficacy was evaluated in these 96 patients with confirmed BCC. The median age of this population was 62 years, 61% were male, and 97% had an ECOG performance status of 0 or 1. Twenty-one percent of patients carried a diagnosis of Gorlin syndrome. Sixty-six percent had locally advanced disease; 34% had metastatic disease. Among those with mBCC, 97% were previously treated. Prior therapy included surgery (97%), radiotherapy (58%), and systemic therapies (30%). Among laBCC patients, 94% were previously treated. Prior therapies included surgery (89%), radiotherapy (27%), and systemic/topical therapies (11%).

The trial's primary endpoint was objective response rate (ORR) assessed by an independent review facility. Tumor response criteria for laBCC included assessment of tumor size, the presence or absence of ulceration, and biopsy of local disease sites. The criteria for complete response in localized disease required tumor biopsy (ies) demonstrating no pathologic evidence of BCC. RECIST version 1.0 criteria were used to assess responses in the mBCC population.

The ORRs were 30.3% (95% CI: 15.6, 48.2) and 42.9% (95% CI: 30.5, 56.0) in patients with mBCC and laBCC, respectively. All responses in the mBCC cohort were partial responses. For the 63 evaluable patients with laBCC, 13 (20.6%) patients had complete responses and 14 (22.2%) had partial responses. The median

response duration was 7.6 months (95% CI: 5.6, not estimable) and 7.6 months (95% CI: 5.6, 9.7) for patients with mBCC and laBCC, respectively.

The primary and key secondary efficacy endpoints are summarized in the following table.

Efficacy Results

Efficacy Endpoints	Metastatic BCC	Locally Advanced BCC
	(n = 33)	(n = 63)
Primary Endpoint		
Objective response rate by IRF (%) (95% CI)	30.3% (15.6%, 48.2%)	42.9% (30.5%, 56.0%)
Complete response	0	13
Partial response	10	14
Secondary endpoints		
Objective response rate by investigator (%) (95% CI)	45.5% (28, 62)	60.3% (47.2%, 71.7%)
Complete response	0	20
Partial response	15	18
Duration of response (IRF) Median (95% CI)	 7.6 mos (5.6, NE)	 7.6 mos (5.6, 9.7)
Duration of response (investigator) Median (95% CI)	 12.9 mos (5.6, 12.9)	 7.6 mos (7.4, NE)

7. Safety

Safety was evaluated in 138 patients who received vismodegib as monotherapy for laBCC or mBCC. Adverse reactions occurring in more than 10% of patients were muscle spasms, alopecia, dysgeusia, weight loss, fatigue, nausea, diarrhea, decreased appetite, constipation, arthralgias, vomiting, and ageusia. In clinical trials, a total of 3 of 10 pre-menopausal women developed amenorrhea. Grade 3 adverse reactions occurring in more than 1% of patients were weight loss, fatigue, muscle spasms, and decreased appetite.

Teratogenicity Risk

There are no human data on the effects of vismodegib on fetal development, however, the extent of the nonclinical data, consistency of findings across the class (e.g., cyclopamine), the well-established mechanism for vismodegib, and the established role of this pathway in embryofetal development are sufficient to establish this risk.

In a pilot embryo-fetal developmental toxicity study, pregnant rats were administered oral vismodegib at doses of 10, 60 or 300 mg/kg/day during the period of organogenesis. Pre- and post-implantation loss were increased at doses of ≥ 60 mg/kg/day (approximately ≥ 2 times the systemic exposure (AUC) in patients at the recommended human dose), which included early resorption of 100% of the fetuses. Malformations were observed in pregnant rats at a dose of 10 mg/kg/day (approximately 0.2 times the AUC in patients at the recommended dose) administered during organogenesis. This included an increased incidence above the background rate in control animals within the same pilot study of missing and/or fused digits, incompletely or unossified sternal elements, centra of vertebrae or proximal phalanges and claws (30% of the 70 vismodegib-exposed fetuses). Additional findings included multiple fetuses with retardations or variations (including dilated renal pelvis, dilated ureter)

occurring only in the vismodegib-exposed fetuses, one fetus with an open perineum and an additional fetus with craniofacial anomalies among the 70 vismodegib-exposed fetuses in rats receiving doses of 10 mg/kg/day.

(b) (4)

the Division did not request nor recommend that a REMS be submitted.

(b) (4)

Following internal discussion and teleconferences with Genentech, a revised risk management plan was submitted consisting of revised product labeling (Pregnancy Category D; (b) (4) (b) (4) revised Medication Guide, a voluntary communication plan, and an enhanced pharmacovigilance plan. (b) (4)

The DOP2, DRISK, and MHT reviewers agreed that the revised plan was sufficient to mitigate risks through risk communication to patients and healthcare providers while minimizing burden and limitations on access to ERIVEDGE. Genentech's proposed pregnancy pharmacovigilance plan is designed to collect prospective and retrospective reports of pregnancy exposures to vismodegib. While not a formal pregnancy registry, it contains key elements described in the current Guidance for Industry Establishing Pregnancy Exposure Registries. Under this post-marketing requirement, Genentech will analyze the information submitted and provide descriptive statistics in a stand-alone annual report (separate from the PSUR).

8. Advisory Committee Meeting

ERIVEDGE was not referred for review to the Oncologics Drugs Advisory Committee because there were no controversial issues that would benefit from advisory committee discussion.

9. Pediatrics

The Pediatric Review Committee (PeRC) recommended that a full waiver be granted for vismodegib for studies required under PREA (Pediatric Research Equity Act) because the disease (BCC) does not exist in children.

(b) (4)

10. Other Relevant Regulatory Issues

There are no other relevant unresolved regulatory issues.

11. Labeling

- Proprietary name: DMEPA, OPDP and OHOP have found the proprietary name, ERIVEDGE, to be acceptable.

- Physician labeling/Medication Guide/Carton and immediate container labels: There are no outstanding issues that would preclude approval.

12. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Approval.
- Risk Benefit Assessment

  The benefits of ERIVEDGE outweigh its risks in this patient population, for whom there is no FDA-approved treatment for metastatic disease or where FDA-approved local therapy (imiquimod or 5FU cream) has not been adequately studied. Regular approval should be granted for this application based on the long duration of responses, which provide both cosmetic improvement as well as the potential for symptomatic relief, in a population with a serious and potentially life-threatening disease.

  The toxicity profile of this product is dominated by mild to moderate muscle spasms, fatigue, and weight loss, as well as alopecia in most patients, however these toxicities led to termination of treatment in a small fraction of the patients, primarily those with localized disease. The major risk is to the fetus of a woman exposed to ERIVEDGE during pregnancy. As discussed below, this risk can be minimized through contraception (females) and barriers (males); this risk is common to other antineoplastic agents has been generally well-managed by medical oncology community through education of patients and contraceptive use. These risks do not outweigh the benefits of durable tumor shrinkage in the indicated patient population.

  The risk-benefit profile was also assessed in the Division Director, CDTL and clinical review, and I concur with their assessment as well as their (and review team's) recommendation to approve this application.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
  Despite the seriousness of teratogenic risk, a REMS should not be required for the following reasons:

  - There are no effective alternative therapies
  - Treatment is administered for a limited duration of treatment (median 10 months)
  - The number of individuals potentially affected by these risks (estimated at 230 women of child-bearing potential per year) is small
  - The standard of medical care in the medical oncology community prescribing this drug provides adequate safeguards through familiarity with the risks, risk communication, and patient monitoring.

- Recommendation for other Postmarketing Requirements
  See action letter.

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/s/

TAMY E KIM
01/30/2012

RICHARD PAZDUR
01/30/2012