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APPLICATION NUMBER:

203388Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Risk Evaluation and Mitigation Strategy (REMS) Options Review

Date: January 9, 2012

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Drug Name(s): Vismodegib (Erivedge)

Therapeutic Class: Hedgehog Pathway Inhibitor

Dosage and Route: 150 mg once a day, oral (capsule)

Application Type/Number: NDA 203388

Applicant/sponsor: Genentech

OSE RCM #: 2011-3452

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EXECUTIVE SUMMARY

This review from the Division of Risk Management (DRISK), Office of Surveillance and Epidemiology (OSE), evaluates management options for the risk of teratogenicity associated to vismodegib, New Drug Application (NDA) 203388. Vismodegib is a first-in-class small-molecule Hedgehog (Hh) pathway inhibitor developed for the treatment of adults with advanced basal cell carcinoma (aBCC) that has recurred following surgery or who are not candidates for surgery, and (b) (4) who are not candidates for radiation. Efficacy data demonstrated vismodegib is an effective therapy for aBCC. The intended prescriber population for vismodegib is likely oncologists and specialized dermatologists. The estimated size of the patient population expected to receive treatment with vismodegib for this indication is (b) (4) new patients/year, of which approximately 10% are females of childbearing potential.

Vismodegib's mechanism of action, nonclinical findings, and published literature on the teratogenic effects of other Hh pathway inhibitors indicate, with high level of certainty, that vismodegib is a likely human teratogen and a developmental toxicant. (b) (4)

(b) (4) The FDA raised concerns regarding access to drug and the burden to patients and healthcare providers imposed (b) (4) and requested the sponsor to reevaluate (b) (4) and the tools employed to achieve these goals. The sponsor (b) (4) proposed mitigating the risk of teratogenicity through professional labeling, routine pharmacovigilance, and a communication plan implemented voluntarily by the company.

A Regulatory Briefing panel was convened on 9 December 2011 to solicit guidance from CDER senior management. Panel members believed that a REMS was not necessary to mitigate the risk for teratogenicity for the following reasons: (1) the risk of teratogenicity for most oncology drugs is managed through professional labeling only; (2) de facto restricted distribution programs exist in oncology for cancer drugs; (3) concerns regarding the burden to the healthcare system imposed by a REMS; and (4) the premise that the standard of medical care in oncology provides adequate safeguards for risk communication and patient monitoring. The panel acknowledged that a regulatory decision for vismodegib requiring a REMS could set a precedent for future approvals of other antineoplastic drugs and raise the question if drugs approved prior to vismodegib should be re-evaluated for a REMS program.

Conclusion and Recommendations

DRISK believes that the risk of teratogenicity associated with vismodegib should be communicated to prescribers and patients through a communication plan and prescriber education program under a REMS. While not in full agreement, DRISK aligns with the advice provided by the Regulatory Briefing panel and the decision the Division of Oncology Products 2 has made to approve vismodegib without a REMS based upon the conclusions reached by the FDA pharmacology and toxicology review team and on the existing regulatory precedent for managing the risk for teratogenicity in oncology drugs. However, DRISK has a low threshold for re-evaluating the need for a REMS for vismodegib, particularly if the treated patient population expands or if new safety data become available indicating that product labeling alone is not effective at managing vismodegib's risk of teratogenicity. DRISK recommends strong labeling regarding the teratogenic risk and requiring postmarketing pregnancy exposure data collection and analysis under a postmarketing requirement (PMR).

1 INTRODUCTION

This review from the Division of Risk Management (DRISK), Office of Surveillance and Epidemiology (OSE), evaluates management options for the risk of teratogenicity associated to vismodegib, New Drug Application (NDA) 203388.

1.1 BACKGROUND

Non-melanoma skin cancers (NMSCs) include basal cell carcinoma and squamous cell skin cancers. There were approximately 2.1 million new patients treated for NMSC in 2006 in the US.

¹ Basal cell carcinoma (BCC) is the most common malignancy in the United States; approximately 80% of NMSCs are BCC.¹ Only a very small proportion of BCCs progress to an advanced disease state. Advanced basal cell carcinoma (aBCC) includes locally advanced lesions and metastatic disease. Locally advanced, inoperable lesions may cause deep ulceration, chronic pain, bacterial infections, bleeding, compromise of the function of the affected anatomical site (e.g., ear, nose, eye, bone, brain, blood vessel), and may result in death. Currently, there are no available treatment options for patients with tumors that have not responded to surgery or radiation or for whom surgery or radiation is not recommended.

Vismodegib is a first-in-class small-molecule Hedgehog (Hh) pathway inhibitor developed as an antineoplastic agent for aBCC. The proposed indication is for the treatment of adults with BCC that has recurred following surgery or who are not candidates for surgery, and (b) (4) who are not candidates for radiation. The proposed dose is 150 mg daily administered orally.

Vismodegib is a likely human teratogen and a developmental toxicant based on its mechanism of action, nonclinical findings, and published literature on the teratogenic effects of other Hh pathway inhibitors. The Hh pathway is essential in the regulation of embryonic development and remains active in some tissues in mature animals and humans. Dysregulation of the pathway has been implicated in the development of cancer including BCC.²

1.2 REGULATORY HISTORY

Following are pertinent regulatory milestones for vismodegib:

- **8 September 2011** – FDA received the original NDA 203388 for Vismodegib (GDC-0449) for the treatment of adult patients with aBCC for whom surgery is inappropriate. (b) (4)
- **11 October 2011** – Genentech provided an application orientation presentation to FDA. (b) (4)

¹ Genentech Vismodegib Common Technical Document Summary, Introduction, 8 September 2011.

² Vismodegib, NDA 203388, Toxicology written summary, page 3, 8 September 2011.

(b) (4)

FDA encouraged Genentech to design a risk management plan that will not limit access to patients of non-childbearing potential.

(b) (4)

- **4 November 2011** – Genentech submitted a proposal for a risk management plan (b) (4)
- **9 December 2011** – Regulatory Briefing held to solicit guidance from CDER senior management regarding the management of the risk of teratogenicity with vismodegib. The Panel did not support requiring a REMS for vismodegib.

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

DRISK reviewed the following materials:

(b) (4)

- Amended risk management plan for vismodegib, submitted on 4 November 2011, sequence number 0013.
- Revised labeling submitted by the sponsor on December 21, 2011, sequence number 0021.
- CDER Regulatory Briefing Meeting Minutes: Risk Mitigation Strategies for Teratogenicity for vismodegib, a Hedgehog Pathway Inhibitor, 9 December 2011.
- Dubravka Kufirin, Pharmacology and Toxicology NDA Review and Evaluation, entered in DARRTS³ 13 January 2012

³ DARRTS: Document Archiving, Reporting & Regulatory Tracking System.

- Michael Axelson, Clinical and Statistical Review, dated 6 January 2012, entered in DARRTS 13 January 2012.

3 RESULTS OF REVIEW

3.1 CLINICAL DEVELOPMENT PROGRAM: EFFICACY

The pivotal trial that demonstrated efficacy for this NDA was a Phase II study (SHH4476g). Efficacy was also supported by data from a Phase I study (SHH3925g). There are no ongoing Phase III studies with vismodegib.

See Table 1 below.

Table 1: Primary Studies in Support of Efficacy of Vismodegib in Patients with Advanced BCC⁴

Study No., FPI - LPI Data Cutoff Date	Title	# of Patients	Dose Regimen	Primary Endpoints
SHH4476g 2/10/2009 - 2/26/2010 Study ongoing CSR Database Cutoff: 11/26/2010	Pivotal, confirmatory, Phase II, Multicenter, Single-Arm, Two-Cohort Trial Evaluating the Efficacy and Safety of GDC-0449 in Patients with Advanced Basal Cell Carcinoma	104	150 mg daily by mouth	ORR per IRF ^a
SHH3925g 1/23/2007 - 11/3/2009 Study completion: 11/12/2010	Open-Label, Phase I Study of Systemic Hh Antagonist, GDC-0449, in Patients with Locally Advanced or Metastatic Solid Tumors That are Refractory to Standard Therapy or for Whom No Standard Therapy Exists	68 (33 aBCC)	150, 270, or 540 mg daily by mouth	Safety PK Determination of MTD ^b

aBCC = advanced basal cell carcinoma; **CSR**=Clinical Study Report; **FPI** = first patient in; **IRF** = independent review facility; **LPI** = last patient in; **MTD** = maximal tolerated dose; **ORR** = objective response rate; **PK** = pharmacokinetics.

^a Secondary endpoints included ORR per investigator assessment, duration of response and progression-free survival per IRF and investigator assessment, overall survival, histopathological response, and SF36 patient-reported outcomes. ^b Tumor response per investigator assessment was a secondary endpoint.

The study population for SHH4476g (n=104) consisted of patients ≥ 18 years with histologically confirmed aBCC. The median age was 62 years (range 21-101), 61.5% males and 38.5% females. The study population for SHH3925g (n=33 with aBCC) consisted of patients ≥ 18 years with histologically confirmed, incurable, locally advanced or metastatic solid malignancy that had progressed after first-line and second-line therapy. The median age was 53 years (range 38-84), 75.8% males and 24.2% females. The race of all patients included in both studies was identified as “White”.

Efficacy Findings - SHH4476g

The Objective Response Rate (ORR) by Independent Review Facility (IRF) for SHH4476g was 30.3% (95% CI 15.6%, 48.2%) for metastatic BCC and 42.9% (95% CI 30.5%, 56.0%) for locally aBCC. The median duration of response per IRF was 7.6 months (95% CI 5.62, Not Estimable)

⁴ Genentech Vismodegib, Clinical Overview, page 8, 8 September 2011.

for locally advanced and 7.6 months (95% CI 5.65, 9.66) for metastatic BCC. Median progression-free survival in months by IRF was 9.5 months (95% CI 7.36, Not Estimable) for metastatic BCC and 9.5 months (95% CI 7.39, 11.93) for locally advanced BCC. The median duration of response for locally advanced BCC patients was 7.6 months and 12.9 months for metastatic BCC patients. The study was not designed to estimate overall survival.

Efficacy Findings – SHH3925g

The overall ORR by investigator assessment was 54.5% (95 CI 37.8%, 71.9%) and the median duration of response was 9.2 months (95 CI 5.72, Not Estimable).

In summary, vismodegib showed clinically meaningful anti-tumor activity in patients with locally advanced BCC and metastatic BCC.

3.2 CLINICAL DEVELOPMENT PROGRAM: SAFETY

3.2.1 Overall Adverse Event Profile

Safety data was pooled from Phase I and II studies in patients with aBCC or other solid tumors, and clinical pharmacology studies. A total of 138 aBCC patients were pooled to evaluate the safety of vismodegib (pooled safety population). In addition, data from 52 patients treated for ovarian cancer (Study SHH4489g) were included in the safety analysis (expanded pooled safety population).

One hundred percent (n=138) of the patients experienced treatment-emergent adverse events of any grade. Most patients (n=76) experienced only adverse events of Grade 1-2 in severity.

The most common adverse events, occurring in > 30% of patients, were muscle spasms (71.7%), alopecia (63.8%), dysgeusia (55.1%), weight decreased (44.9%), fatigue (39.9%), and nausea (30.4%). Grade ≥ 3 adverse events occurring in five or more patients were weight decreased (7.2%), fatigue (5.8%), and muscle spasms (3.6%).

Thirty-six patients (26.1%) in the pooled safety population experienced a serious adverse event. Serious adverse events reported in ≥ 2 patients were death (n= 3), pneumonia (n= 3), cardiac failure (n= 2), gastrointestinal hemorrhage (n= 2), pulmonary embolism (n = 2), deep vein thrombosis (n= 2), and hemorrhage (n= 2).

There were 17 (12.3%) deaths in the pooled safety population. See Table 2. Patients with deaths of unknown cause and deaths due to cardiovascular adverse events had risk factors or comorbidities associated with increased risk of death or concomitant medications associated with sudden death.

Table 2: On-Study Deaths and Cause of Death (Pooled Safety Population)

	Pooled Safety Population (n= 138)
All deaths	17 (12.3%)
Cause of death	
Progressive disease	7 (5.1%)
Adverse event	8 (5.8%)
Other ^a	2 (1.4%)
Occurrence of death	
≤ 30 days from last study drug administration	7 (5.1%)
> 30 days from last study drug administration	10 (7.2%)

^a Two patients in Study SHH4476g died with the cause of death as "Other"; the cause of death for these patients was reported as "other: unknown" (b) (4) after the last study treatment, respectively.

Source: Table 14, Summary of Clinical Safety.

3.2.2 Teratogenicity

Mechanism of Action

Vismodegib is a Hh pathway inhibitor. The Hh signaling pathway is a major regulator for cell differentiation, tissue polarity and cell proliferation.⁵ The general signaling mechanisms of the Hh pathway is conserved from fly to the humans.⁶ Vismodegib binds and inhibits Smoothed (SMO), which serves as the key player for signal transduction of this pathway. The Hh signaling pathway regulates epithelial and mesenchymal interactions during mammalian embryogenesis and remains active in some tissues in adult animals and humans (e.g., taste buds, hair follicles, reproductive organs, growing bones, and teeth). Dysregulation of the pathway has been implicated in the development of cancer including BCC.² **Error! Bookmark not defined.**

Nonclinical

Nonclinical data demonstrated vismodegib is embryotoxic and teratogenic at clinically relevant doses.⁷ In addition, vismodegib is expected to be a developmental toxicant based on its irreversible effects on growing teeth and bones observed in rats.⁷

Animal Studies²

A pilot embryo-fetal developmental toxicity study in rats showed vismodegib was 100% embryotoxic at doses 2.8-fold (60 mg/kg/day) and 4.6-fold (300 mg/kg/day) greater than that typically observed in patients at steady state. Exposure in rats given approximately 20% (10 mg/kg/day) of that typically observed in patients at steady resulted in:

- malformations of absent and/or fused digits in 21/70 fetuses (30%) and 4/5 litters (open perineum in 1 fetus and multiple craniofacial anomalies in 1 fetus)

⁵ Yang L, Xie G, Fan Q, Xie J.: Activation of the hedgehog-signaling pathway in human cancer and the clinical implications. *Oncogene*. 2010 Jan 28;29(4):469-81. Epub 2009 Nov 23.

⁶ Ingham PW, Placzek M.: Orchestrating ontogenesis: variations on a theme by sonic hedgehog. *Nat Rev Genet* 7: 841–850. 2006.

⁷ Dubravka Kufirin, Pharmacology and Toxicology NDA Review and Evaluation, 13 January 2012.

- increase in retardations or variations (dilated renal pelvis, dilated ureter) and incompletely or unossified sternal elements, centra of vertebrae or proximal phalanges and claws

FDA pharmacology and toxicology reviewers concluded that the teratogenicity findings described above were not substantially different from nonclinical findings with other approved oncology drugs.⁸

Literature on Hg Signaling Pathway Inhibitors

There is a body of literature documenting the teratogenic potential of Hh pathway inhibitors. Following are selected relevant publications:

- Binns et al. 1963⁹ and 1965¹⁰ – identified cyclopamine, a Hh pathway antagonist, as the causal agent of an outbreak of cyclopia in sheep feeding on the cyclopamine-containing plant *Veratrum californicum*.
- Binns et al. 1972¹¹ and Keeler 1990¹² – demonstrated that ingestion of *Veratrum californicum* in the first trimester resulted in early embryonic death, prolonged gestation, and congenital defects including cyclopia, hare lip, cleft palate, and hypoplasia of metacarpal and metatarsal bones in lambs, calves, or goats.
- Chiang et al. 1996¹³ – documented that mice deficient in Sonic hedgehog (Shh) expression exhibited reduced growth and severe craniofacial defects.
- St-Jacques et al. 1998¹⁴ – documented severe defects in bone growth in Indian hedgehog-deficient mice.
- Lipinski et al. 2008,¹⁵ 2010¹⁶ – observed craniofacial defects, including cleft lip and palate or holoprosencephaly, in mice exposed to cyclopamine or a cyclopamine analog in utero.
- Kimura et al. 2008¹⁷ – observed irreversible defects in bone development in young mice treated with as few as two PO doses of a synthetic, structurally unrelated small-molecule Hh antagonist.

⁸ CDER Regulatory Briefing Meeting Minutes: Risk Mitigation Strategies for Teratogenicity for Vismodegib, a Hedgehog Pathway Inhibitor, slide #31, 9 December 2011.

⁹ Binns W, James LF, Shupe JL, et al. A congenital cyclopiatype malformation in lambs induced by maternal ingestion of a range plant, *Veratrum californicum*. *Am J Vet Res* 1963;24 (103):1164–1175.

¹⁰ Binns W, Shupe JL, Keeler RF, et al. Chronologic evaluation of teratogenicity in sheep fed *veratrum californicum*. *J Am Vet Med Assoc* 1965;147 (8):839–842.

¹¹ Binns W, Keeler RF, Balls LD. Congenital deformities in lambs, calves, and goats resulting from maternal ingestion of *Veratrum californicum*: hare lip, cleft palate, ataxia, and hypoplasia of metacarpal and metatarsal bones. *Clin Toxicol* 1972; 5:245–61.

¹² Keeler RF. Early embryonic death in lambs induced by *Veratrum californicum*. *Cornell Vet* 1990; 80:203–7.

¹³ Chiang C, Litingtung Y, Lee E, et al. Cyclopia and defective axial patterning in mice lacking Sonic hedgehog gene function. *Nature* 1996;383:407–13.

¹⁴ St-Jacques B, Dassule HR, Karavanova I, et al. Sonic hedgehog signaling is essential for hair development. *Curr Biol* 1998;24:1058–68.

¹⁵ Lipinski RJ, Hutson PR, Hannam PW, et al. Dose- and route-dependent teratogenicity, toxicity, and pharmacokinetic profiles of the hedgehog signaling antagonist cyclopamine in the mouse. *Toxicol Sci* 2008;104:189–97.

¹⁶ Lipinski RJ, Song C, Sulik KK, et al. Cleft lip and palate results from Hedgehog signaling antagonism in the mouse: Phenotypic characterization and clinical implications. *Birth Defects Res A Clin Mol Teratol* 2010;88:232–40.

¹⁷ Kimura H, Ng JM, Curran T. Transient inhibition of the Hedgehog pathway in young mice causes permanent defects in bone structure. *Cancer Cell* 2008;13:249–60.

3.3 APPLICANT'S PROPOSED

(b) (4)

(b) (4)

of enrolled prescribers by specialty and the Periodic Safety Update Report (PSUR) will serve as the safety assessment.

3.3.1.8 Proposed Pregnancy Prevention Program

(b) (4) on 8 September 2011 with the original NDA, Genentech submitted to FDA a proposed Pregnancy Prevention Program (PPP), which was also included as part of all marketing applications related to vismodegib worldwide. The objectives of the vismodegib PPP included the following:

- Prevent pregnant women and women who are lactating from exposure to vismodegib.
- Ensure that all patients and Healthcare Professionals (HCPs) understand the teratogenic risks to the fetus that are associated with vismodegib use.
- Provide a centralized database of all vismodegib pregnancy reports.
- Determine the vismodegib exposure status for each reported pregnancy.
- Document the outcome of each vismodegib pregnancy.
- Document abnormal fetal outcomes for vismodegib pregnancy reports.
- Provide pregnancy documentation to assist in the Root Cause Analysis of each pregnancy.
- Provide pregnancy data to worldwide Regulatory Authorities where the product is marketed or investigated as per local regulations and guidelines.

Through this program, Genentech planned to: (1) collect and analyze data for all pregnancies reported in association with exposure to vismodegib by female patients and female partners of male patients treated with vismodegib, (2) follow up reported pregnancies periodically until delivery and infants exposed in utero for the first year, and (3) perform Root Cause Analysis for each exposed pregnancy.

During the first 2 years of the initial program, Genentech will send biannual pregnancy safety reports including descriptive statistics summarizing data from the pregnancy pharmacovigilance plan. In addition, all pregnancy exposure-related data will be included in the PSUR document.

3.3.2 Sponsor's Revised Proposal for a Risk Management Plan

On 20 October 2011, a teleconference was held with the FDA and the sponsor (b) (4). The FDA expressed concern about restricting drug access to female patients of childbearing potential given the seriousness of the disease and the lack of alternative therapies (b) (4). FDA encouraged the sponsor to (b) (4) submit a revised proposal. (b) (4). On 4 November 2011, the sponsor submitted a proposed risk management plan; (b) (4). Below is a summary of the revised proposal.

The goals of the revised risk management plan included the following:

- To inform HCPs and patients about the serious risks associated with vismodegib, including the risk of embryo-fetal and postnatal developmental toxicity.
- To inform HCPs and patients about the importance of pregnancy prevention.
- To allow treatment of patients with severe and life-threatening disease for whom the benefits of therapy would outweigh the potential risks to a developing embryo/fetus.

4 DISCUSSION

Efficacy data from a single trial demonstrates that vismodegib offers clinical benefit in the treatment of adults with aBCC. There is a high level of certainty vismodegib is a human teratogen and a developmental toxicant based on its mechanism of action, nonclinical findings, and published literature on the teratogenic effects of other Hh signaling pathway inhibitors. Malformations described in rats exposed in utero to vismodegib included craniofacial anomalies, open perineum, and absent or fused digits. Fetal retardations and variations were also observed. Ongoing research evaluating the use of vismodegib for other indications (e.g., medulloblastoma) may result in expansion of the patient population.

Given the extent of the evidence establishing vismodegib as a likely human teratogen, DRISK believes the risk of teratogenicity should be communicated to prescribers and patients through a REMS with a communication plan and a prescriber education program that is not linked to the prescribers' ability to prescribe the drug. This approach will provide prescribers access to FDA-approved, product-specific risk information to enhance their understanding of vismodegib's high teratogenic potential, facilitate patient counseling, and emphasize the importance of compliance with pregnancy testing. Requiring this strategy as part of a REMS will also allow FDA to monitor the content of the risk message and communication of specific requirements for safe use; enforce the continuity of prescriber training long after initial product approval; and allow for systematic assessments of program effectiveness.

With the exception of thalidomide and lenalidomide, the risk of teratogenicity associated to oncology drugs has generally been managed through professional labeling only. A Regulatory Briefing panel convened on 9 December 2011 did not support the implementation of a REMS for vismodegib.⁸ Panel members and DOP2 believe that a REMS is not necessary to mitigate the risk for teratogenicity of vismodegib for the following reasons: (1) the risk of teratogenicity for most oncology drugs is managed through professional labeling only; (2) de facto restricted distribution programs exist in oncology for cancer drugs; (3) concerns regarding the burden to the healthcare system imposed by REMS¹⁸; and (4) the premise that the standard of medical care in oncology

¹⁸ It is worth noting that a REMS with a communication plan and a prescriber education program (as described above) would not add burden to prescribers or patients or limit patient access to the drug. On the contrary, this strategy would provide prescribers with FDA-approved tools to learn about vismodegib's risks of teratogenicity and facilitate patient counseling.

provides adequate safeguards for risk communication and patient monitoring.^{8,19} In addition, panel members were concerned that if a REMS is mandated for vismodegib, this decision would set a precedent that could affect future drug approvals and raise the question if drugs approved prior to this should be re-evaluated for a REMS program.⁸

DRISK acknowledges there is a regulatory precedent for not requiring a REMS for most oncology drugs demonstrating a risk for teratogenicity. While this has been the standard approach for oncology products, it is unclear this is the most appropriate approach for all oncology drugs. We urge further discussion regarding the development of a consistent regulatory approach for the management of the risk of teratogenicity for oncology drugs that demonstrate a risk of teratogenicity. Points to consider in this discussion should include whether an oncology drug with a teratogenic risk would ever require a REMS to mitigate the risk, and if so what factors would be most important in making that determination (e.g., nature of the disease, patient population, prescriber population, characteristics of the drug, and expected benefits). In addition, FDA should engage professional organizations (e.g. ASCO) to develop guidances and educational programs to assist oncology prescribers in counseling females of childbearing potential on how to mitigating the risk of teratogenicity.

5 CONCLUSION AND RECOMMENDATIONS

DRISK believes that the risk of teratogenicity associated with vismodegib should be communicated to prescribers and patients through a communication plan and prescriber education program under a REMS. While not in full agreement, DRISK aligns with the advice provided by the Regulatory Briefing panel and the decision DOP2 has made to approve vismodegib without a REMS based upon the conclusions reached by the FDA pharmacology and toxicology review team and on the existing regulatory precedent for managing the risk for teratogenicity in oncology drugs. However, DRISK has a low threshold for re-evaluating the need for a REMS for vismodegib, particularly if the treated patient population expands or if new safety data become available indicating that product labeling alone is not effective at managing vismodegib's risk of teratogenicity. DRISK recommends strong labeling regarding the teratogenic risk and requiring postmarketing pregnancy exposure data collection and analysis under a postmarketing requirement (PMR). The pharmacovigilance plan section of the Pregnancy Prevention Program included in Genentech's original risk management proposal provides a reasonable framework for the development of a PMR.

¹⁹ There is a general assumption that oncologists routinely perform pregnancy testing and provide contraceptive counseling to female patients of childbearing potential. While this is a logical premise, we were not able to find published practice standards or guidelines in the National Guidelines Clearinghouse or PubMed, U.S. National Library of Medicine, National Institutes of Health that provide recommendations or guidance for pregnancy testing and contraceptive counseling for female patients of childbearing potential undergoing treatment for cancer (search terms included: cancer, oncology, teratogen, teratogenicity, fetal exposure, contraception, counseling, women, females of child bearing potential, risk mitigation, and guidelines; searched on 6 January 2012).

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