

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202324Orig1s000

**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**

Final Risk Evaluation and Mitigation Strategy (REMS) Review

Date: December 15, 2011

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Drug Name(s): Axitinib (Inlyta)

Therapeutic Class: Kinase inhibitor

Dosage and Route: 5mg twice daily, orally

Application Type/Number: NDA 202324

Submission Number: 1

Applicant/sponsor: Pfizer

OSE RCM #: 2011-1289

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1 INTRODUCTION

An application for axitinib (Inlyta) was submitted April 14, 2011 with a proposed indication of treatment of patients with advanced renal cell carcinoma (RCC). The Oncologic Drugs Advisory Committee (ODAC) convened December 7, 2011 to consider the application. The committee advised unanimously that the application should be approved. Risk management was not discussed at the meeting.

2 MATERIALS REVIEWED

Risk Management Plan submitted with application April 14, 2011

3 RESULTS OF REVIEW OF PROPOSED INLYTA RISK EVALUATION AND MITIGATION STRATEGY

3.1 OVERVIEW OF CLINICAL PROGRAM OR POSTMARKETING EXPOSURE

The data supporting the indication comprised a single, randomized study in patients with RCC. Patients had failed one prior regimen. Patients in the axitinib arm had a median progression-free survival (PFS) of 6.7 months compared with 4.7 months in the comparator (sorafenib) arm.

3.2 SAFETY CONCERNS

The FDA-edited draft labeling for axitinib lists the following safety concerns, listed in order of level of concern:

- Hypertension including hypertensive crisis
- Hypothyroidism requiring thyroid hormone replacement
- Arterial and venous thrombotic events
- Hemorrhagic events, including fatal events
- Gastrointestinal perforation and fistula, including death
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS)
- Proteinuria
- Fetal harm

The adverse events observed in the clinical trial are largely known events for the class of kinase inhibitors. Compared with sorafenib, the axitinib arm had a higher incidence of gastrointestinal effects, fatigue, asthenia, hypertension, dysphonia, and hypothyroidism. The sorafenib arm had a higher incidence of palmar-plantar erythrodysesthesia, rash, pruritis, alopecia, erythema, and anemia. Evaluating the side effect profile of axitinib, ODAC indicated that they judged the degree of toxicity to be similar to other agents in the class.

3.3 RISK MANAGEMENT PROPOSED BY APPLICANT

The applicant proposes routine measures (labeling and routine pharmacovigilance) to manage the risks of axitinib.

4 DISCUSSION

The safety concerns for axitinib are similar to other approved kinase inhibitors used to treat renal cell carcinoma, sorafenib and sunitinib. Sorafenib and sunitinib do not have REMS in place to manage the risks.

Based on the mechanism of action, all three drugs are expected to cause fetal harm if used by a pregnant woman. The Surveillance Epidemiology and End Results cancer data estimates that about 23,800 women are diagnosed with renal cancer yearly, with 25% of the women being under the age of 54 years. Nine percent of the women diagnosed are younger than 45 years of age. Based on this, it is possible that fetal exposure might occur with axitinib. Based on recent guidance from senior management within CDER, it is expected that the oncology community manages the risk of fetal harm from agents used to treat cancer without additional FDA-imposed risk management measures in place. Fetal toxicity occurs with many oncology agents, and it is reasonable for drugs likely to cause fetal harm to be used within the oncology community without a REMS.

5 CONCLUSION

The applicant's proposal for labeling and routine pharmacovigilance is reasonable, and is consistent with other agents in the class used for the same indication.

6 RECOMMENDATIONS

Axitinib (Inlyta) can be approved without a REMS.

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/s/

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12/15/2011

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