IND SAFETY REPORT: INITIAL WRITTEN REPORT

TO: *Division of Drug Oncology Products, Center for Drug Evaluation and Research, FDA*

FAX: *301-796-9845*

1. IND NUMBER
77782
63383

2. AGENT NAME
AZD6244 Hydrogen sulfate
OSI-774 (erlotinib, Tarceva®)

3. DATE
October 12, 2011

4. SPONSOR
Division of Cancer Treatment and Diagnosis, National Cancer Institute

5. REPORTER'S NAME, TITLE, AND INSTITUTION
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6. PHONE NUMBER
301-496-1196

7. EMAIL ADDRESS
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8a. PROTOCOL NUMBER (AE #)
8444 (AE# 1745420)

8b. AE GRADE: AE
Grade 4: CPK increased

9. PATIENT IDENTIFICATION
1010020

10. AGE
64 years

11. SEX
Female

12. PROTOCOL SPECIFIED
Cycle = 28 Days
AZD6244 Hydrogen sulfate: 150 mg PO QAM
Erlotinib: 100 mg PO QPM

13. TREATMENT RECEIVED AND DATES
The patient began the investigational therapy on June 15, 2011, and received her last doses of AZD6244 Hydrogen sulfate and OSI-774 on August 8, 2011 (Cycle 2, Day 28).

14. DESCRIPTION OF ADVERSE EVENT
The patient is a 64-year-old female with poorly differentiated KRAS mutant non-small cell lung cancer who experienced a grade 4 increased creatine phosphokinase (CPK) while on a phase 2 trial utilizing the investigational agents AZD6244 Hydrogen sulfate and OSI-774. On August 9, 2011, the patient presented to the clinic for pre-cycle 3 evaluation, and had a creatine kinase (CK) of 2610 U/L (reference range: 38-252 U/L) as compared to a CK of 334 U/L on July 12, 2011 (Cycle 2, Day 1). She had no clinical symptoms. The patient was given 1 liter of normal saline, and the study drugs were held with plans for a re-evaluation in one week. By August 16, 2011, the patient's CK had recovered to 230 U/L. She resumed the investigational treatments that day. Additional information has been requested from the investigational site. There is a reasonable possibility that the experience may have been caused by the drug.

15. ACCRUAL AND IND EXPERIENCE
Number of patients enrolled in NCI-sponsored clinical trials using AZD6244 Hydrogen sulfate = 529, AZD6244 = 183, and OSI-774 = 3,670.
There have been 6 other cases of increased CPK reported to the NCI through AdEERS as serious adverse events for the AZD6244 Hydrogen sulfate NSC and/or IND and 1 other case of increased CPK reported to the NCI through AdEERS as a serious adverse event for the AZD6244 NSC and/or IND as shown in the table below. There have been no other cases of increased CPK reported to the NCI through AdEERS as serious adverse events for the OSI-774 NSC and/or IND.

Adverse Event	Grade	Attribution
AZD6244 Hydrogen sulfate		
CPK increased (n=6)	3 2	2 Possible, 1 Definite 1 Unlikely, 1 Possible, 1 Probable
AZD6244		
CPK increased (n=1)	4	1 Unlikely

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16. ASSESSMENT

In this case, it is thought that a possible causal relationship between the event and AZD6244 Hydrogen sulfate cannot be excluded.

	CPK increased
AZD6244 Hydrogen sulfate	Possible
OSI-774	Unlikely
Lung adenocarcinoma	Unlikely

17. COMMENTS

Medications taken at the time of the event included Zofran®, loperamide, and clindamycin topical solution.

AT THIS TIME, NO OTHER INFORMATION IS AVAILABLE. IF UPON FURTHER INVESTIGATION RELEVANT INFORMATION BECOMES AVAILABLE, THEN A FOLLOW-UP REPORT WILL BE SUBMITTED IN ACCORDANCE WITH 21CFR 312.32(d) (2).

DISCLAIMER per 21 CFR 312.32(e): THIS SAFETY REPORT DOES NOT NECESSARILY REFLECT A CONCLUSION OR ADMISSION BY THE CTEP IDB SENIOR INVESTIGATOR/SPONSOR THAT THE INVESTIGATIONAL AGENT/THERAPY CAUSED OR CONTRIBUTED TO THE ADVERSE EXPERIENCE BEING REPORTED.