



DATE: OCT 28 2011

FROM: L. Austin Doyle, M.D., Investigational Drug Branch, CTEP, DCTD, NCI
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SUBJECT: AZD6244 Hydrogen sulfate and OSI-774 (erlotinib) NCI IND Safety Report, AE # 1745420

TO: Investigators Using AZD6244 Hydrogen sulfate (NSC 748727) and OSI-774 (NSC 718781)

The U.S. Food and Drug Administration (FDA) regulations require sponsors of clinical studies conducted under a U.S. IND to notify the FDA and all participating investigators of any serious and unexpected adverse experiences that are possibly related to the investigational agent. Please find attached a copy of an IND Safety Report recently submitted to the FDA for the CTEP-sponsored investigational agents AZD6244 Hydrogen sulfate and OSI-774.

The following must be completed by all investigators using AZD6244 Hydrogen sulfate under NCI IND 77782 and OSI-774 under NCI IND 63383:

- Send a copy of this letter to your Institutional Review Board (IRB) of record according to your policies and procedures.
- File a copy of this letter in your protocol file.

If your study is not covered under INDs 77782 and/or 63383, it is strongly recommended that you follow the instructions above.

Please note that for Cooperative Group studies, the Cooperative Group Operations Office will provide instructions for IRB submissions, any patient notifications, etc.

Based on CTEP's assessment of the current information in light of previous experience with AZD6244 Hydrogen sulfate and OSI-774, there does not appear to be a change in the risk-benefit ratio for AZD6244 Hydrogen sulfate and OSI-774 studies; therefore, CTEP is not requiring a protocol amendment at this time.

Please continue to report events according to the adverse event reporting guidelines in your protocol(s).

The attached Adverse Events Assessment describes the adverse event(s) (synopsis provided below), relevant previous experience under these INDs and/or NSCs, and the total number of patients enrolled in trials under these INDs and/or NSCs.

A 64-year-old female with poorly differentiated KRAS mutant non-small cell lung cancer experienced a grade 4 increased creatine phosphokinase (CPK) while on a phase 2 trial utilizing the investigational agents AZD6244 Hydrogen sulfate and OSI-774.

IND SAFETY REPORT: FOLLOW-UP #1TO: *Division of Drug Oncology Products, Center for Drug Evaluation and Research, FDA*

FAX: 301-796-9845

1. IND NUMBER
77782
633832. AGENT NAME
AZD6244 Hydrogen sulfate
OSI-774 (erlotinib, Tarceva[®])3. DATE
October 24, 20114. SPONSOR
Division of Cancer Treatment and Diagnosis, National Cancer Institute5. REPORTER'S NAME, TITLE, AND INSTITUTION
L. Austin Doyle, MD - Senior Investigator for Investigational Therapeutics 2,
Investigational Drug Branch, CTEP, DCTD, NCI6. PHONE NUMBER
301-496-1196Helen Chen, MD - Associate Branch Chief for Investigational Therapeutics 3,
Investigational Drug Branch, CTEP, DCTD, NCI7. EMAIL ADDRESS
ctepsupportae@tech-res.com8a. PROTOCOL NUMBER (AE #)
8444 (AE# 1745420)8b. AE GRADE: AE
Grade 4: CPK increased9. PATIENT IDENTIFICATION
101002010. AGE
64 years11. SEX
Female12. PROTOCOL SPECIFIED
Cycle = 28 Days
AZD6244 Hydrogen sulfate: 150 mg PO QAM
Erlotinib: 100 mg PO QPM13. 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.**Follow-up #1: Additional information was received from the investigator on 10/13/2011.****On August 9, 2011, the patient's creatinine was 1.42 mg/dL (reference range: 0.56-1.16 mg/dL) and her blood urea nitrogen (BUN) was 28 mg/dL (reference range: 8-22 mg/dL), as compared to a baseline creatinine of 1.24 mg/dL and a BUN of 22 mg/dL on June 13, 2011. On August 31, 2011, her CK increased to 498 U/L, creatinine reduced slightly to 1.32 mg/dL, and her BUN rose again to 28 mg/dL. At a follow-up visit on September 13, 2011, the patient's CK increased to 836 U/L, her creatinine was 1.33 mg/dL, and her BUN decreased to 23 mg/dL. An increase in her fluid intake was recommended, and she continued the investigational therapies at reduced dose levels.**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.

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IND SAFETY REPORT: FOLLOW-UP #1

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

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).