Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pediatric Postmarketing Pharmacovigilance Review

Date: November 14, 2018

Safety Reviewers: Shital Patel, PharmD, BCPS
Safety Evaluator
Division of Pharmacovigilance II (DPV II)

Ivone Kim, MD, FAAP
Medical Officer
Division of Pharmacovigilance I (DPV I)

Peter Waldron, MD
Medical Officer
DPV II

Team Leader: Afrouz Nayernama, PharmD
DPV II

Deputy Division Director: Ida-Lina Diak, PharmD, MS
DPV II

Product Names/Application Types/Numbers/Sponsors:

Tarceva™ (erlotinib)	NDA 021743	OSI Pharms
Erlotinib	ANDA 091002	Mylan Pharms Inc.
Erlotinib	ANDA 091059	Teva Pharms

Pediatric Labeling Approval Date: April 27, 2015

OSE RCM #: 2018-1417

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Tarceva® (erlotinib) in pediatric patients through age 16 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA). This review focuses on the U.S. serious, unlabeled adverse events associated with erlotinib in pediatric patients.

FDA approved erlotinib on November 18, 2004, and it is indicated for non-small cell lung cancer and pancreatic cancer in the adult population. Erlotinib is not approved for use in pediatric patients because no clinical benefit was demonstrated in the clinical trials conducted in 2010-2012.

Of the pediatric FAERS reports reviewed, there were no new safety signals, no increased severity or frequency of any labeled adverse events and no deaths directly associated with erlotinib. We reviewed all serious U.S. FAERS reports with erlotinib in the pediatric population (ages 0 to <17 years) from November 18, 2004 to July 6, 2018, and eight cases were included in our case series. The eight cases described unlabeled adverse events but lacked sufficient details such as dechallenge or rechallenge to determine causality, were labeled events of concomitant medications, or were attributable to underlying diseases.

DPV did not identify any pediatric safety concerns for erlotinib at this time. DPV recommends no regulatory action and will continue to monitor all adverse events associated with the use of erlotinib.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Tarceva® (erlotinib) in pediatric patients through age 16 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA). This review focuses on the U.S. serious, unlabeled adverse events associated with erlotinib in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

FDA approved erlotinib on November 18, 2004, and it is indicated for the following in the adult population[1]:

- *Metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations*
- *In combination with gemcitabine for first-line treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer*

Erlotinib is not approved for use in pediatric patients. On March 23, 2015, FDA granted the Tarceva® sponsor pediatric exclusivity after the sponsor satisfied all elements in FDA's Pediatric Written Request, dated May 10, 2010, in accordance with the BPCA.[2,3] Consequently, on April 27, 2015, the Tarceva® U.S. prescribing information (USPI) underwent a pediatric labeling change to reflect the new information generated from a pharmacokinetic (PK) study in pediatric cancer patients and two open-label multicenter trials in pediatric patients with recurrent or refractory ependymoma (NCT 01032070, NCT 01247922).[4,5] The latter trials did not establish safety or efficacy and were terminated prematurely. Additionally, the adverse event profile of erlotinib was consistent with the known adverse event profile in adults.[6] This review was triggered by the pediatric labeling change.

1.2 RELEVANT LABELED SAFETY INFORMATION

The Tarceva® USPI contains the following information under the Highlights of Prescribing Information[1]:

HIGHLIGHTS OF PRESCRIBING INFORMATION

----------WARNINGS AND PRECAUTIONS----------

- Interstitial lung disease (ILD): Occurs in 1.1% of patients. Withhold TARCEVA for acute onset of new or progressive unexplained pulmonary symptoms, such as dyspnea, cough and fever. Discontinue TARCEVA if ILD is diagnosed. (5.1)
- Renal failure: Monitor renal function and electrolytes, particularly in patients at risk of dehydration. Withhold TARCEVA for severe renal toxicity. (5.2)
- Hepatotoxicity: Occurs with or without hepatic impairment, including hepatic failure and hepatorenal syndrome: Monitor periodic liver testing. Withhold or discontinue TARCEVA for severe or worsening liver tests. (5.3)
- Gastrointestinal perforations: Discontinue TARCEVA. (5.4)
- Bullous and exfoliative skin disorders: Discontinue TARCEVA. (5.5)
- Cerebrovascular accident (CVA): The risk of CVA is increased in patients with pancreatic cancer. (5.6)
- Microangiopathic hemolytic anemia (MAHA): The risk of MAHA is increased in patients with pancreatic cancer. (5.7)

- Ocular disorders: Discontinue TARCEVA for corneal perforation, ulceration or persistent severe keratitis. (5.8)
  Hemorrhage in patients taking warfarin: Regularly monitor INR in patients taking warfarin or other coumarin-derivative anticoagulants. (5.9)
- Embryo-fetal toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to the fetus and to use effective contraception. (5.10, 8.1, 8.3)

----------ADVERSE REACTIONS----------

The most common adverse reactions (≥ 20%) with TARCEVA from a pooled analysis in patients with NSCLC across all approved lines of therapy, with and without EGFR mutations, and in patients with pancreatic cancer were rash, diarrhea, anorexia, fatigue, dyspnea, cough, nausea, and vomiting. (6.1)

Under section 8 USE IN SPECIFIC POPULATIONS, the *Pediatric Use* subsection includes the following information[1]:

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

The safety and effectiveness of TARCEVA in pediatric patients have not been established.

In an open-label, multicenter trial, 25 pediatric patients (median age 14 years, range 3-20 years) with recurrent or refractory ependymoma were randomized (1:1) to TARCEVA or etoposide. Thirteen patients received TARCEVA at a dose of 85 mg/m2/day orally until disease progression, death, patient request, investigator decision to discontinue study drug, or intolerable toxicity. Four patients randomized to etoposide also received TARCEVA following disease progression. The trial was terminated prematurely for lack of efficacy; there were no objective responses observed in these 17 TARCEVA-treated patients.

No new adverse events were identified in the pediatric population.

Based on the population pharmacokinetics analysis conducted in 105 pediatric patients (2 to 21 years old) with cancer, the geometric mean estimates of CL/F/BSA (apparent clearance normalized to body surface area) were comparable across the three age groups: 2-6 years (n = 29), 7-16 years (n = 59), and 17-21 years (n = 17).

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in **Table 1**.

Table 1. FAERS Search Strategy*	
Date of Search	July 13, 2018
Time Period of Search	November 18, 2004† - July 6, 2018
Search Type	FBIS – Product-Manufacturing Reporting Summary FBIS – Quick Query
Product Terms	erlotinib, erlotinib hydrochloride
MedDRA Search Terms (Version 21.0)	All Preferred Terms (PTs)
* See **Appendix A** for a description of the FAERS database. † U.S. product approval date	

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

Table 2 presents the number of adult and pediatric FAERS reports from November 18, 2004 to July 6, 2018 with erlotinib.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA from November 18, 2004 to July 6, 2018 with erlotinib

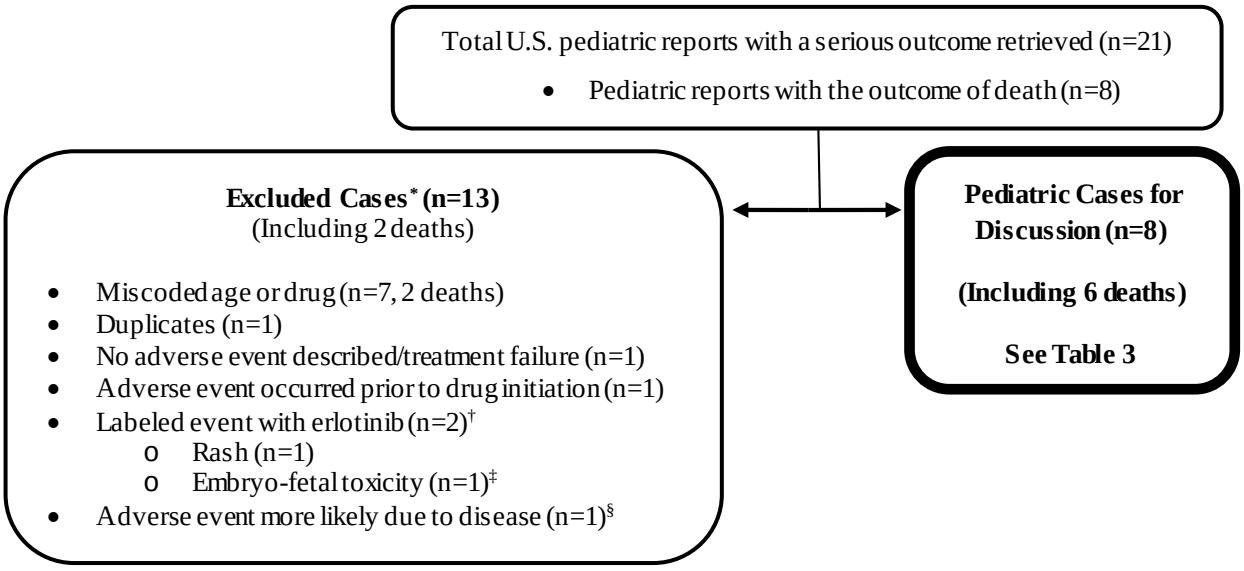
	All reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 17 years)	18131 (12298)	15410 (9620)	7576 (5073)
Pediatrics (0 - <17 years)	40 (24)	37 **(21)**	13 **(8)**

* May include duplicates and transplacental exposures, and have not been assessed for causality
† For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.

3.1.2 Selection of U.S. Serious Pediatric Cases in FAERS

Our FAERS search retrieved 21 U.S., serious pediatric reports (See Table 3). See **Figure 1.** below for the selection of cases to be summarized in **Sections 3.1.4** and **3.1.5**.

Figure 1. Selection of Serious U.S. Pediatric Cases with Erlotinib



* DPV reviewed these cases, but they were excluded from further discussion for the reasons listed above.
† All cases with labeled events were reviewed, but we did not identify patterns indicating worsening severity of these adverse events.
‡ This case described a neonate born with adactyly. The mother became pregnant while the father was receiving erlotinib and bevacizumab for NSCLC. Notably, embryo-fetal toxicity is labeled for erlotinib under *Warnings and Precautions*.[1]
§ This case described a patient with an unspecified brain malignancy who experienced a rash, hallucinations, aggression, and abnormal behavior. Rash is a labeled event for erlotinib; however hallucinations, aggression, and abnormal behavior are not.[1] The case lacked additional information on time to onset, concomitant medications, medical history and a clinical work-up. However, the reporter stated that the oncology team attributed the hallucinations, aggression, and abnormal behavior to the brain tumor.

3.1.3 Characteristics of Pediatric Cases

Appendix B contains a line listing of the eight pediatric cases.

Table 3 summarizes the characteristics of the eight FAERS cases in U.S. pediatric patients with erlotinib reporting a serious outcome that are included in the case series.

Table 3. Characteristics of the FAERS U.S. Serious Pediatric Cases with Erlotinib Received by FDA from November 18, 2004 to July 6, 2018 (N=8)		
Age	6- <12 years	4
	12- < 17 years	4
Sex	Male	3
	Female	5
Reported Reason for Use	Astrocytoma	2
	Glioblastoma multiforme (GBM)	1
	Unspecified brain tumor	2
	NSCLC	2
	Unknown	1
Serious Outcome*	Death	6
	Life-threatening	1
	Hospitalization	2
	Required Intervention	1
	Other Serious	2
Reported Causes of Death (n=6)	Intracranial hemorrhage	1
	Tumor progression	1
	Unknown	4
* For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events. Reports may have more than one outcome.		

3.1.4 Summary of Fatal Pediatric U.S. Cases (N=6)

We identified six FAERS cases with erlotinib in the U.S pediatric population reporting death as an outcome in our case series for discussion. The reported age range was 7 to 15 years, including three males and three females. Four of the six cases did not contain sufficient information to determine the patients' causes of death; none of these cases provided case level detail regarding adverse event development, disease status, cause of death, or autopsy results. Additionally, one case reported death due to tumor progression. The remaining case reported death due to an intracranial hemorrhage and is described below:

Vascular disorders: *intracranial hemorrhage* (n=1)

An 8-year-old female was enrolled in a clinical trial for erlotinib with concomitant radiation therapy for newly diagnosed anaplastic astrocytoma. On diagnosis, the brain magnetic resonance imaging (MRI) revealed a right thalamic tumor extending into the right midbrain. The patient underwent unspecified "medical device implantation", assumed to be ventriculo-peritoneal (VP) shunt placement, followed by treatment with erlotinib and radiation therapy. Ten months later, she developed new neurological deficits. A computed tomography (CT) scan showed changes consistent with new areas of hemorrhage associated with the thalamic mass, and an MRI was not determinative whether there was tumor progression. The patient underwent tumor resection at that time. The narrative stated uncertainty whether erlotinib therapy was continued after the surgery. However, erlotinib was listed as a concomitant medication in a statement two

months later, at which time it was discontinued. Three months following the tumor resection and one month after erlotinib discontinuation, a CT scan revealed tumor progression and hydrocephalus. VP shunt revision was conducted, and postoperatively, she developed seizures and diabetes insipidus. A repeat CT scan showed hemorrhage into the tumor bed, ventricles and brain parenchyma. Brain perfusion scan revealed brain death; the patient subsequently expired. The reporter acknowledged the cause of death as intracranial hemorrhage; however, "possible relation to the study drug cannot be ruled out."

Reviewer's comments: *Brain tumors and tumor progression are risk factors for intratumoral hemorrhage.[7] It is noteworthy that in this case, hemorrhage occurred at the tumor site during and after erlotinib therapy at times of suspected or confirmed tumor progression. Intracranial hemorrhage is a well-known complication of brain surgery and VP shunt placement due to potential trauma.[7,8] Furthermore, hemorrhage from radiation-induced vasculopathy may occur years after radiotherapy.[7] There was almost a one year interval from the first erlotinib dose to the first episode of intracranial hemorrhage. The second episode of intracranial hemorrhage occurred a month after erlotinib discontinuation. Therefore, the event is unlikely related to erlotinib. The cause of death is multifactorial including procedures, tumor progression, concomitant cranial radiation, and erlotinib.[8-10] Therefore, it is difficult to attribute the cause of death to a single factor of therapy.*

3.1.5 Summary of Non-Fatal Pediatric U.S. Serious Cases (N=2)

Of the two non-fatal cases in U.S. pediatric patients included in our case series, there were no new safety signals identified. A summary of these cases reporting serious, unlabeled events of interest, organized by System Organ Class (SOC), is provided below.

Metabolism and nutrition disorders: ***hypokalemia, hypophosphatemia (n=1)***

An 8-year-old female initiated erlotinib with radiation therapy for newly diagnosed GBM in a clinical trial. Past medical history was not reported. Concomitant medications included dexamethasone. Eleven days later, the patient presented with asymptomatic hypokalemia with serum potassium 3.3 mmol/L (baseline 3.7 mmol/L) and hypophosphatemia with serum phosphorus 1.8 mg/dL (baseline 3.8 mg/dL). Erlotinib was continued; treatment included potassium and phosphate supplementation. Over the next two weeks, serum potassium and phosphorus improved to 4 mmol/L and 4 mg/dL, respectively.

Reviewer's comments: *This case demonstrates a close temporal relationship between erlotinib and hypokalemia and hypophosphatemia; however, the patient received concomitant dexamethasone and cranial radiation. Dexamethasone is labeled for "increased excretion of potassium" under Warnings. Additionally, the report lacked information on past medical history and underlying risk factors that may contribute to electrolyte abnormalities, such as inadequate dietary intake, glycemic status, or medications and conditions that may cause potassium- or phosphate-wasting.[11,12] The lack of dechallenge and rechallenge information make it difficult to attribute the adverse events to a single medication.*

Vascular disorders: ***hemoptysis (n=1)***

A 13-year-old female with refractory NSCLC was started on erlotinib and experienced hemoptysis a few days (unspecified date) later. The patient had small blood streaks in her

sputum and later developed frank blood in the sputum. She was hospitalized for embolization to control the bleeding. No other information was provided.

Reviewer's comments: *Hemoptysis is an associated symptom of lung malignancies and may not always be the first symptom to present.[13] In this case, the patient was started on erlotinib for progression of her lung malignancy. The lack of dechallenge and rechallenge information makes it difficult to determine whether the hemoptysis was due to erlotinib or underlying lung malignancy. Additionally, the lack of other clinical information prevents us from ruling out other etiologies or risk factors, such as infection or coagulopathy as well as the possibility of an erroneous report of age in view of the rarity of NSCLC in early adolescence.[14,15]*

4 DISCUSSION

Of the eight serious and unlabeled event cases included in this series, no specific pattern or trend of unlabeled adverse events was noted. These cases described adverse events that can be attributed to concomitant therapies/procedures or the cases had limited information, which precluded a meaningful causality assessment. Therefore, we identified no new safety signals, no increased severity of labeled adverse events, and no deaths that were solely attributed to erlotinib. The most commonly reported indication was a brain malignancy, either GBM, astrocytoma, or unspecified. The treatment regimen typically consisted of erlotinib monotherapy or combination erlotinib and radiation therapy.

5 CONCLUSION

DPV did not identify any pediatric safety concerns for erlotinib that warrant regulatory action.

6 RECOMMENDATION

DPV recommends no regulatory action at this time and will continue to monitor all adverse events associated with the use of erlotinib.

7 REFERENCES

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8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

Data Mining of FAERS Using Empirica Signal

Empirica Signal refers to the software that OSE uses to perform data mining analyses while using the Multi-item Gamma Poisson Shrinker (MGPS) data mining algorithm. "Data mining" refers to the use of computer algorithms to identify patterns of associations or unexpected occurrences (i.e., "potential signals") in large databases. These potential signals can then be evaluated for intervention as appropriate. In OSE, the FDA Adverse Event Reporting System (FAERS) database is utilized for data mining. MGPS analyzes the records in FAERS and then quantifies reported drug-event associations by producing a set of values or scores that indicate varying strengths of reporting relationships between drugs and events. These scores, denoted as Empirical Bayes Geometric Mean (EBGM) values, provide a stable estimate of the relative reporting of an event for a particular drug relative to all other drugs and events in FAERS. MGPS also calculates lower and upper 90% confidence limits for EBGM values, denoted EB05 and EB95, respectively. Because EBGM scores are based on FAERS data, limitations relating to FAERS data also apply to data mining-derived data. Further, drug and event causality cannot be inferred from EBGM scores.

8.2 APPENDIX B. FAERS LINE LISTING OF THE PEDIATRIC CASE SERIES (N=8)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcomes*
1	8/27/2014	10412038	1	US-ASTELLAS-2014US010986	Expedited	13	FEMALE	USA	DE
2	10/7/2015	11607957	1	US-ASTELLAS-2015US036530	Expedited	8	MALE	USA	DE
3	11/11/2015	11722831	1	US-ASTELLAS-2015US042026	Expedited	15	MALE	USA	DE
4	4/29/2016	12318362	1	US-ASTELLAS-2016US016207	Expedited	15	FEMALE	USA	DE, OT
5	5/11/2018	14967907	1		Direct	10	MALE	USA	DE, LT
6	7/25/2005	5850327	2	2005001277	Expedited	8	FEMALE	USA	OT, RI
7	2/12/2007	6248802	1		Direct	13	FEMALE	USA	HO
8	4/9/2009	6973054	1	2008000810	Expedited	9	FEMALE	USA	DE, HO

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect, and other serious important medical events. This outcome should not be confused with the clinical outcome of the reported adverse drug experience. Those which are blank were not marked as serious (per the previous definition) by the reporter and are coded as non-serious. A report may have more than one serious outcome.
Abbreviations: DE=Death, HO=Hospitalization, LT = Life-threatening, OT =Other medically significant, RI=Required intervention

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/s/

SHITAL H PATEL
11/14/2018

IVONE E KIM
11/14/2018

PETER E WALDRON
11/14/2018

AFROUZ R NAYERNAMA
11/14/2018

IDA-LINA DIAK
11/15/2018