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Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review

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Product Name(s): Kepivance[®] (palifermin)

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EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA), the Office of Surveillance and Epidemiology (OSE) evaluated postmarketing adverse event reports with a serious outcome and drug utilization data for Kepivance[®] (palifermin) in pediatric patients.

Kepivance was first approved on December 15, 2004, to decrease the incidence and duration of severe oral mucositis in patients with hematologic malignancies receiving myelotoxic therapy requiring hematopoietic stem cell support. Kepivance is indicated as supportive care for preparative regimens predicted to result in greater than or equal to WHO Grade 3 mucositis in the majority of patients. Use of Kepivance for the treatment of the same indication in pediatric patients ages 1 to 16 years is supported by adequate and well-controlled studies of Kepivance in adults and a phase 1 study that included 27 pediatric patients with acute leukemia undergoing hematopoietic stem cell transplant.

Drug utilization patterns were assessed in order to capture pediatric use of Kepivance and to provide context for the adverse event reports submitted to the FDA Adverse Event Reporting System (FAERS) database for Kepivance. From May 2013 through December 2015, a total of 1,375 patients had a hospital discharge billing for Kepivance from U.S. non-federal hospitals; of which, the pediatric population aged 0-16 years accounted for 16.6% (228 patients). Among the pediatric patients, Kepivance use was only captured in patients aged 1-16 years for the examined time period.

Between January 1, 1969, and March 28, 2016, DPV identified three FAERS pediatric cases with serious outcomes, including one death. Though unlikely related to Kepivance use, the fatal pediatric case describes an off-label use (progressive lung disease) of Kepivance based on its potential pharmacologic effect. A clinical trial for similar off-label use in adult human subjects with acute lung injury had actually shown a statistically significant increased ICU and 28-day mortality in the Kepivance group compared to placebo. The risks associated with using Kepivance off-label should be discouraged until further studied with evidence of a positive risk benefit profile.

Two additional FAERS reports with serious, non-fatal outcomes are associated with adverse events which are labeled for Kepivance (rash) or can be attributed to concomitant medication (cardiotoxicity with doxorubicin). The remaining unlabeled adverse event reports of hepatic failure and seizure do not have enough information to allow for further causality assessment.

DPV plans to continue routine postmarketing surveillance of all adverse events with the use of Kepivance.

1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY

Kepivance[®] (palifermin) is a mucocutaneous epithelial human growth factor indicated to decrease the incidence and duration of severe oral mucositis in patients with hematologic malignancies receiving myelotoxic therapy in the setting of autologous hematopoietic stem cell support and as supportive care for preparative regimen predicted to result in greater than or equal to WHO Grade 3 mucositis. Kepivance is available as lyophilized powder, requiring reconstitution in sterile water for injection, USP, and given as intravenous bolus injection.¹

Upon approval in December 15, 2004, the Sponsor of Kepivance was required to conduct a deferred pediatric study under section 2 of the Pediatric Research Equity Act (PREA).

Postmarketing requirement (PMR) 38-1 stated for the Sponsor:²

To conduct a deferred pediatric study under PREA to determine well-tolerated and pharmacologically active doses of palifermin in three patient cohorts defined by age (1-2, 3-11, and 12-16 years) with hematologic malignancies treated with myelotoxic therapy and undergoing hematologic stem cell transplant. In study 20010133, "A Phase 1 Dose escalation Study to Evaluate the Safety and Pharmacokinetics (PK) of Palifermin in Pediatric Subjects with Acute Leukemia Undergoing Myeloablative Therapy and Allogeneic Hematopoietic Stem Cell Transplant (HSCT)," that will be conducted at approximately seven sites registered with the Pediatric Blood and Marrow Transplant Consortium (PBMTc), 18 to 54 subjects will be treated in the specified age groups. The study will evaluate the safety and pharmacokinetics of palifermin in patients with acute leukemias receiving myelotoxic therapy followed by hematologic stem cell transplant. Three doses (40/μg/kg/day, 60/μg/kg/day, 80/μg/kg/day) will be evaluated in each age cohort in a dose-escalation manner. Age cohorts will be treated simultaneously with the objective to identify a safe, well-tolerated, efficacious dose in each age cohort.

On May 30, 2013, the clinical reviewers with the Office of Clinical Pharmacology/Division of Clinical Pharmacology V determined that the Sponsor had fulfilled PMR 38-1 and noted the following regarding the PREA-mandated studies:³

On December 21, 2011, the sponsor submitted the final clinical study report (20010133) entitled, "A Phase 1 Dose-Escalation Study to Evaluate the Safety and PK of Palifermin in Pediatric Subjects with Acute Leukemias Undergoing Myeloablative Therapy and Allogeneic Hematopoietic Stem Cell Transplant". The objective of the study was to determine the well tolerated and pharmacologically active doses (40, 60 and 80 μg/kg/day) of palifermin in 3 patient cohorts (n=9/cohort) defined by age (1-2, 3-11, and 12-16 years old). The primary endpoint was the development of dose limiting toxicities. The results of this study suggest that age did not influence the pharmacokinetics of palifermin following IV administration of Kepivance 40, 60, and 80 μg/kg/day.

Exposure did not appear to increase with increasing doses. No accumulation was observed following three consecutive daily doses of Kepivance.

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES¹

-----**CONTRAINDICATIONS**-----
None

-----**WARNINGS AND PRECAUTIONS**-----
Potential for stimulation of tumor growth — Kepivance is not indicated for non-hematologic tumors. The effects of Kepivance on stimulation of keratinocyte growth factor (KGF) receptor-expressing, non-hematopoietic tumors in patients are not known (1, 5.1)

-----**ADVERSE REACTIONS**-----
Most common adverse reactions (incidence $\geq 20\%$ and $5\% \geq$ placebo) are rash, fever, elevated serum amylase (Grade 3/4), pruritus, erythema, and edema (6)

To report SUSPECTED ADVERSE REACTIONS, contact Swedish Orphan Biovitrum at 1-866-773-5274 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----**DRUG INTERACTIONS**-----

- Heparin increases systemic exposure (7)
- Myelotoxic chemotherapy (7, 14)

2 DRUG UTILIZATION DATA

2.1 METHODS AND MATERIALS

We used proprietary drug utilization databases available to the Agency to conduct this analysis. **Appendix A** includes detailed descriptions and limitations of the databases.

2.1.1 Determining Settings of Care

The IMS Health, IMS National Sales Perspectives™ database was used to determine the various settings of care where Kepivance (palifermin) is distributed by the manufacturer. Sales data from May 2013 through December 2015 showed that approximately 99.3% of Kepivance packages/vials were sold to U.S. non-retail settings (primarily non-federal hospitals) and less than 1% to mail order/specialty and outpatient retail pharmacy settings.⁴ Based on these results, we examined the drug utilization data for only the U.S. non-federal hospitals. Data from mail-order/specialty and outpatient retail pharmacy settings were not included in this analysis.

2.1.2 Data Sources Used

The IMS Inpatient Healthcare Utilization System (IHCARUS) database was used to obtain the nationally estimated number of patients with a hospital discharge billing for Kepivance (palifermin) from inpatient and outpatient settings of U.S. non-federal hospitals, stratified by

patient age groups (0-11 months, 1-16, and 17 years and older) from May 2013 through December 2015, aggregated.

2.2 DRUG UTILIZATION DATA RESULTS

Table 2.2: Nationally estimated number of patients with an inpatient or outpatient hospital discharge billing for Kepivance® (palifermin) from U.S. non-federal hospitals[†], stratified by patient age*, May 2013 to December 2015, aggregated

	May 2013 - December 2015	
	Patient Count [‡] N	Share %
Palifermin Total Patients	1,375	100.0%
0-16 years	228	16.6%
0 - 11 months	--	--
1-16 years	228	100.0%
17 years and older	1,147	83.4%

Source: IMS Health, Inpatient HealthCare Utilization System. May 2013 - December 2015. Data extracted July 2016. File: IHCARUS 2016-745 Kepivance by age groups, 7-6-2016

[†]Data from standalone pediatric and other specialty hospitals are not available.

*Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0-16 years include patients less than 17 years of age (16 years and 11 months).

[‡]Unique patient counts may not be added due to the possibility of double counting those patients aging during the study, and may be counted more than once in the individual categories.

3 POSTMARKET ADVERSE EVENT REPORTS

3.1 METHODS AND MATERIALS

3.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy

DPV searched the FAERS database with the strategy described in Table 3.1.1. See Appendix B for a description of the FAERS database.

Table 3.1.1 FAERS Search Strategy

Date of Search	March 28, 2016
Time Period of Search	January 1, 1969* - March 28, 2016
Search Type	Product/Manufacturer Adverse Event Reporting Summary
Product Name(s)	Kepivance Palifermin
Search Parameters	All ages, all outcomes, worldwide

*Date of the start of FAERS data collection is used as the initial search date.

3.2 RESULTS

3.2.1 Total Number of FAERS Reports by Age

Table 3.2.1 Total adult and pediatric FAERS reports* January 1, 1969, to March 28, 2016 with Kepivance

	All reports (US)	Serious [†] (US)	Death (US)
Adults (≥ 17 years)	176 (36)	166 (27)	20 (5)
Pediatrics (0 - <17 years)	8 (1)	7 [‡] (0)	1 (0)

* May include duplicates and transplacental exposures, and have not been assessed for causality

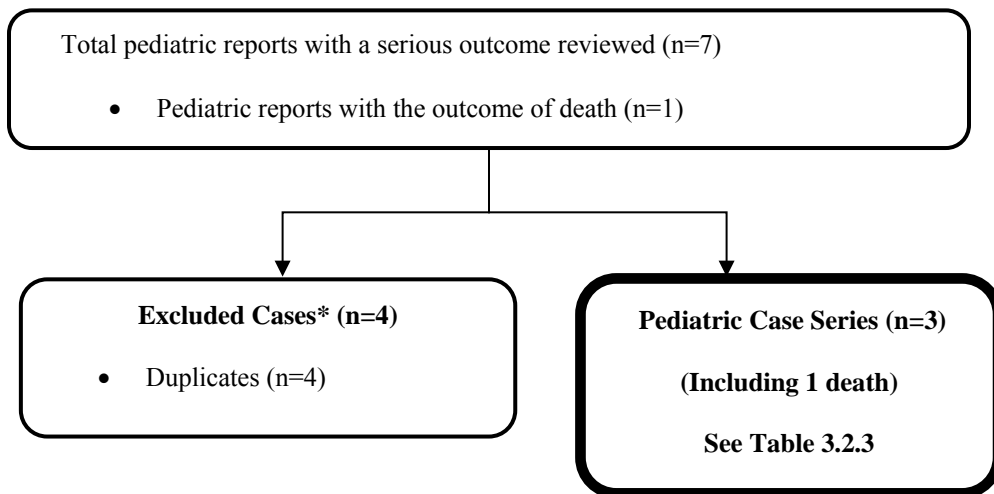
† For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.

‡ See Figure 3.2.2

3.2.2 Selection of Serious Pediatric Cases in FAERS

We identified seven pediatric reports with a serious outcome (See Table 3.2.1). See **Figure 3.2.2** below for the specific selection of cases to be summarized in **Sections 3.3 and 3.4**.

Figure 3.2.2 Selection of Serious Pediatric Cases with Kepivance



* DPV reviewed these cases, but they were excluded from the case series for the reasons listed above

3.2.3 Characteristics of Pediatric Case Series

Appendix C lists all the FAERS case numbers, FAERS version numbers and Manufacturer Control Numbers for the Pediatric Case Series

**Table 3.2.3 Characteristics of Pediatric Case Series with
Kepivance
(N=3)**

Age	1 month- < 2 years	2
	2- < 6 years	0
	6- <12 years	0
	12- < 17 years	1
Sex	Male	0
	Female	3
Country	United States	0
	Foreign	3
Reported Reason for Use	Autoimmune disorder	1
	Lung disease	1
	Mucosal inflammation	1
Serious Outcome*	Death	1
	Life-threatening	2
	Hospitalized	0
	Disability	0
	Congenital anomaly	0
	Required Intervention	0
	Other serious	2

* 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.

3.3 SUMMARY OF FATAL PEDIATRIC ADVERSE EVENT CASES (N=1)

Case # 9012281, Denmark, 2012:

A six month old female with a severe and progressive respiratory issue since birth died three weeks after being treated with Kepivance from respiratory insufficiency and pulmonary hypertension resulting in right ventricular failure. Incidental findings of multifocal hepatoblastoma and cardiac fibrosis were noted at autopsy.

Patient was reportedly small for gestational age at birth. Patient had a medical history significant for a patent ductus arteriosus failing medical therapy with need for ligation, left-to-right shunting via ventricular septal defect and atrial septal defect, recurrent pulmonary and systemic infections, and an episode of pulmonary hemorrhage. Patient received systemic dexamethasone for the treatment of respiratory issue in hopes of weaning her off of the ventilator, but without improvement.

The reporter noted: “An ultimate treatment option with rhKGF [Kepivance] was sought after extensive discussions with the parents, because KGF may result in improved epithelial stability

in lungs, resulting in less capillary and epithelial water, protein leakage and ultimately shorter alveolo-capillary diffusion distance.”

Reviewer Comment: This report describes an off-label use based on a potential pharmacologic effect of Kepivance. The reported fatality is related to the patient’s multiple, pre-existing medical issues and is unlikely associated with Kepivance use.

3.4 SUMMARY OF NON-FATAL PEDIATRIC SERIOUS ADVERSE EVENT CASES (N=2)

3.4.1 Cardiac Failure, Hepatic failure (n=1)

Case #6275676, France, 2007:

Approximately 10 months after starting Kepivance and eight months after the last dose, a 13 year old female patient with clear cell renal sarcoma experienced acute decompensations of cardiac function and hepatic failure requiring extracorporeal circulation, dialysis, and ventilation. The patient was also treated with doxorubicin.

Reviewer comment: Event of cardiac failure is confounded by the concomitant use of doxorubicin, which has a Boxed Warning for cardiotoxicity. Hepatic failure is not a labeled event for either medications, but there is insufficient information for further assessment (no laboratory results reported). DPV plans to continue routine pharmacovigilance of hepatic failure.

3.4.2 Rash, Seizure (n=1)

Case # 7114642, Great Britain, 2009:

A four month old female with Omenn syndrome developed a moderate rash two days after Kepivance therapy was started and three days after cyclophosphamide therapy. The following two days, the patient experienced severe seizures and was admitted to the intensive care unit. Therapy with Kepivance was withheld. No history of seizure or signs of infection was reported. Other concurrent medications include amphotericin B, cetirizine, codeine, co-trimoxazole, cyclosporine, immunoglobulin, meropenem, mesna, nifedipine, nystatin, ondansetron, teicoplanin, and treosulfan.

Reviewer comment: Skin rash is a labeled event in the Kepivance label. Seizure is confounded by concomitant medications. DPV plans to continue routine pharmacovigilance of seizures.

4 CLINICAL TRIALS EXPERIENCE

The FDA has received two reports of off-label use of Kepivance that suggest an increased risk of mortality and infection.

The applicant informed FDA regarding the results of an investigator sponsored study in Ireland, called the Keratinocyte growth factor in Acute lung injury to Reduce pulmonary dysfunction – (KARE) study. This was a randomized trial of Kepivance 60 µg/kg IV daily x 6 days in patients with acute lung injury. The study results showed a statistically significant increased ICU and 28-day mortality in the Kepivance group compared to placebo.

Reviewer comment:

This is an off-label indication, and the dosing was not consistent with approved schedule. These results do not change the risk benefit for the approved indication.

The applicant informed FDA regarding the preliminary results of an investigator sponsored preclinical study in mice to determine if Kepivance augments innate pulmonary defense against bacterial and viral pathogens. Prophylactic intranasal Kepivance administration was given to mice that were thereafter inoculated with a lethal dose of different influenza virus strains. The results of the study show that death from virus infection was accelerated with approximately three days in KGF-treated animals. Accelerated spread of the virus infection and accelerated time to death was documented.

Reviewer comment:

This is a preclinical study in an off-label indication. Kepivance was administered via an intranasal route at doses much higher than the approved doses for the transplant indication.

Evaluation of Increased Risk of Infection

There were four prospective randomized studies of Kepivance in the transplant population. The incidence of infection was not increased in the Kepivance-treated patients compared to placebo-treated in any of these studies.

There was a randomized prospective trial of a chemotherapy-only preparative regimen in patients with multiple myeloma. This was a negative study regarding mucositis, and resulted in a limitation of use in the label. In this study, there was an increased risk of infection in Kepivance-treated patients. It was noted the timing of pre-preparative regimen Kepivance and the post preparative regimen Kepivance was much shorter than in the two studies that supported approval.

In the fourth study, patients undergoing allogeneic transplant were evaluated, and the primary endpoint was graft-versus-host disease (GVHD) prophylaxis. This study was negative regarding GVHD prevention, but was reported as an abridged report. FDA requested the applicant to submit a full study report with data sets, in order to more fully evaluate risk of infection. There was no increased risk of infection. Although the study was not powered to evaluate mucositis, it was noted that there was non-significant increased incidence of worse mucositis in the Kepivance treated patients. This was likely due to the post-transplant prophylactic methotrexate.

Action

Based on this evaluation the following changes were made to the Kepivance label effective July 1, 2016.

- The dosing schedule was revised from at least four days between pre and post dosing to seven days between pre and post doses.
- Information regarding the increased risk of infection observed in the melphalan study was added to Section 6.1 Clinical Trial Experience.
- A limitation of use in allogeneic transplant was added to the indication.
- Discussion of lack of efficacy in decreasing severe mucositis in the allogeneic transplant setting was added to Section 14 Clinical Studies.

5 DISCUSSION

Analysis of drug utilization data showed that pediatric patients aged 0-16 years old accounted for 16.6% (228 patients) of total patients with a hospital discharge billing for Kepivance (palifermin) from U.S. non-federal hospitals from May 2013 through December 2015. Among the pediatric patients, Kepivance use was only captured in patients aged 1-16 years; no Kepivance use was captured in patients aged 0-11 months for the examined time period. Although there appears to be some use of Kepivance in pediatric patients, the data cannot be validated due to the lack of access to patient medical records. Of note, our analyses focused on only the inpatient and outpatient emergency department (ED) non-federal hospital settings where the largest proportion of Kepivance sales was distributed. Our analyses do not include data from federal hospitals (including VA facilities) and other specialty hospitals (including children's hospitals and other standalone specialty oncology hospitals). Therefore, the overall use of Kepivance in pediatric patients in our hospital data may be underestimated as we suspect that some pediatric patients using Kepivance are treated in standalone pediatric and specialty oncology hospitals.

Between Jan 1, 1969, and March 28, 2016, DPV identified three FAERS pediatric cases with serious outcomes, including one death. Though unlikely related to Kepivance use, the fatal pediatric case describes an off-label use (progressive lung disease) of Kepivance based on its potential pharmacologic effect. A clinical trial for similar off-label use in adult human subjects with acute lung injury had actually shown a statistically significant increased ICU and 28-day mortality in the Kepivance group compared to placebo.

The two FAERS reports with serious, non-fatal outcomes are associated with adverse events which are labeled for Kepivance (rash) or can be attributed to concomitant medication (cardiotoxicity with doxorubicin). The remaining unlabeled adverse event reports of hepatic failure and seizure do not have enough information to allow for further causality assessment.

6 CONCLUSION

Based on the small number of pediatric reports identified, there is no new safety issue (signal, increased severity or frequency of labeled adverse events) noted with Kepivance at this time. Nevertheless, the fatal pediatric case draws attention to the risks of using Kepivance off-label; such practice is discouraged until further studied with evidence of a positive risk benefit profile.

7 RECOMMENDATIONS

DPV plans to continue routine postmarketing surveillance of all adverse events with the use of Kepivance.

8 REFERENCES

1. Kepivance® [package insert]. Stockholm, Sweden: Swedish Orphan Biovitrium AB; 2016.
2. Weiss KD. Correspondence Letter: BLA approval (BLA 125103). FDA Office of Drug Evaluation VI. December 2004.
3. Lubin RM, Bullock J. Clinical Pharmacology Review. FDA Division of Clinical Pharmacology V, Division of Hematology Products. 2013.
4. IMS Health, IMS National Sales Perspectives™. May 2013 – December 2015. Extracted July 2016. File: NSP 2016-745 Kepivance by Sup Ch, 7-6-2016.xlsx.

9 APPENDICES

9.1 APPENDIX A. DRUG UTILIZATION DATABASE DESCRIPTIONS/LIMITATIONS

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

IMS, Inpatient HealthCare Utilization System (IHCareUS)

IMS longitudinally tracks patient-level diagnoses, procedures, and drug utilization within hospitals (inpatients and outpatients). CDM is a collection of data streams that is large, well distributed, and geographically representative. IMS collects and maintains patient-level hospital inpatient and hospital outpatient (including all ED) setting data from more than 630 hospitals, covering each census region of the United States (US), including all inpatient hospital and outpatient (including ED) hospital patient level records. The hospital data is collected electronically on a weekly and monthly basis from hospital CDM patient level records. Data fields collected include diagnoses, procedures, drugs (i.e., ingredient name, brand name, strength, and daily administrations), and location of each service and room type (e.g. Pediatric ICU) by day of stay. The hospital inpatient and outpatient patient records are linked longitudinally through unique patient-level IDs. The lag time between the hospital encounter date and availability of IMS' hospital inpatient and hospital outpatient raw and projected hospital data and reporting is 25-30 days.

All IMS data is third-party verified HIPAA-compliant with patients being assigned a unique anonymized patient ID, which allows IMS to track patients anonymously and longitudinally over time. IMS also has the ability to match their anonymized patient ID's and records to government and commercial patient registries utilizing anonymized patient IDs. IMS datasets are geographically representative and well characterized, providing a high degree of accuracy in projections to the US population.

The IMS Hospital CDM sample does not include Federal hospitals, including VA facilities, and some other specialty hospitals (including children's hospitals and other standalone specialty hospitals), and does not necessarily represent all acute care hospitals in the U.S. in all markets. Caveats of the IMS CDM data source are common to this type of hospital charge information, but are mostly limited to limitations of charge descriptions and what is actually entered by the sample hospitals. However, validations of IMS' Hospital CDM data using both the National Hospital Discharge Survey (NHDS) and the AHRQ HCUP data have shown IMS' patient level data to be representative and accurate across multiple therapeutic areas.

9.2 APPENDIX B FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

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.

9.3 APPENDIX C. FAERS CASE NUMBERS, FAERS VERSION NUMBERS AND MANUFACTURER CONTROL NUMBERS FOR THE PEDIATRIC CASES WITH KEPIVANCE (N=7)

Case Number	Version Number	Manufacturer Control Number
6275676	1	FR-AMGEN-UK215698
6793931	2	GB-AMGEN-UK313213
6812482	1	GB-BAXTER-2008BH012001
6848989	1	AEGBR200800273
6851484	1	HAPL-003-08-GB
7114642	2	UK313213
9012281	2	2012DE0454

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/s/

SAHARAT PATANAVANICH
09/20/2016

KUSUM S MISTRY
09/20/2016

The drug use data in this review has been cleared by the database vendors.

PATRICIA A DINNDORF
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LYNDA V MCCULLEY
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JUSTIN A MATHEW
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ALBERT B DEISSEROTH
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