

# **Pediatric Focused Safety Review: Kepivance (palifermin)**

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## Background Drug Information: Kepivance (palifermin)

- **Therapeutic Category:** mucocutaneous epithelial human growth factor
- **Sponsor:** Swedish Orphan Biovitrum AB
- **Indication:** In adults:
  - 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. Kepivance is indicated as supportive care for preparative regimens predicted to result in  $\geq$  WHO Grade 3 mucositis in the majority of patients.
- **Formulation:** 6.25 mg lyophilized powder in single-dose vials
- **Dosage and Administration:** intravenous (IV) bolus injection
  - 60 mcg/kg/day for 3 consecutive days before and 3 consecutive days after myelotoxic therapy for a total of 6 doses



## Background Drug Information (cont'd): Kepivance (palifermin)

- **Original Market approval:** December 15, 2004
- **Pediatric labeling changes:** May 30, 2013
  - Data supporting use in patients 1 to 16 years of age added to labeling.
  - One current pending pediatric postmarketing study in hematopoietic stem cell transplant recipients to evaluate survival, incidence of secondary malignancies, cancer relapse rate and hospitalization days, and comparison to matched controls regarding engraftment, acute and chronic graft versus host disease, and other treatment related complications. Study report due on March 31, 2020.



## **Pediatric Pharmacokinetic and Safety Study: Kepivance (palifermin)**

- Use in patients 1 to 16 years of age was supported by adequate and well-controlled studies of Kepivance in adults and a phase 1 dose-escalation pharmacokinetic (PK) and safety study that included 27 pediatric patients with acute leukemia undergoing myeloablative therapy and hematopoietic stem cell transplant.

# Pediatric Labeling Changes: Kepivance (palifermin)

- **8.4 Use in Specific Populations, Pediatric Use**
  - Information on the dosing and safety of Kepivance in the pediatric population is limited. However, use of Kepivance in pediatric patients ages 1 to 16 years is supported by evidence from 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 transplantation.



# Additional Relevant Safety Labeling Changes: Kepivance (palifermin)

- Risk of infection evaluated in 2 pre-approval and 2 post-approval randomized studies of Kepivance in the adult transplant population.
  - **Autologous transplantation preparative regimens that include total body irradiation (2 studies; n=212 and n=169)**
    - No increased incidence of infection in the Kepivance-treated patients compared to placebo.
  - **Autologous transplantation with chemotherapy-only preparative regimen using high dose melphalan in patients with multiple myeloma (n=281)**
    - Incidence of treatment-emergent infections was significantly greater in patients treated with Kepivance compared to placebo associated with shorter timing between pre-preparative and post-preparative Kepivance regimens compared to the two studies that supported approval.
  - **Allogeneic Transplantation (n=155)**
    - Lack of efficacy in decreasing the incidence of severe acute graft versus host disease (aGVHD) in patients with hematologic malignancies undergoing allogeneic transplantation.
    - No increased risk of infection.
    - The incidence of WHO grade 3 and 4 mucositis was nominally higher in patients treated with Kepivance compared to placebo.

## **Additional Relevant Safety Labeling Changes (cont'd): Kepivance (palifermin)**

- Resulting labeling changes:
  - 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 the increased incidence of severe mucositis in the allogeneic transplant setting was added to Section 14 Clinical Studies.

# Kepivance Drug Utilization

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

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

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

<sup>†</sup>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).

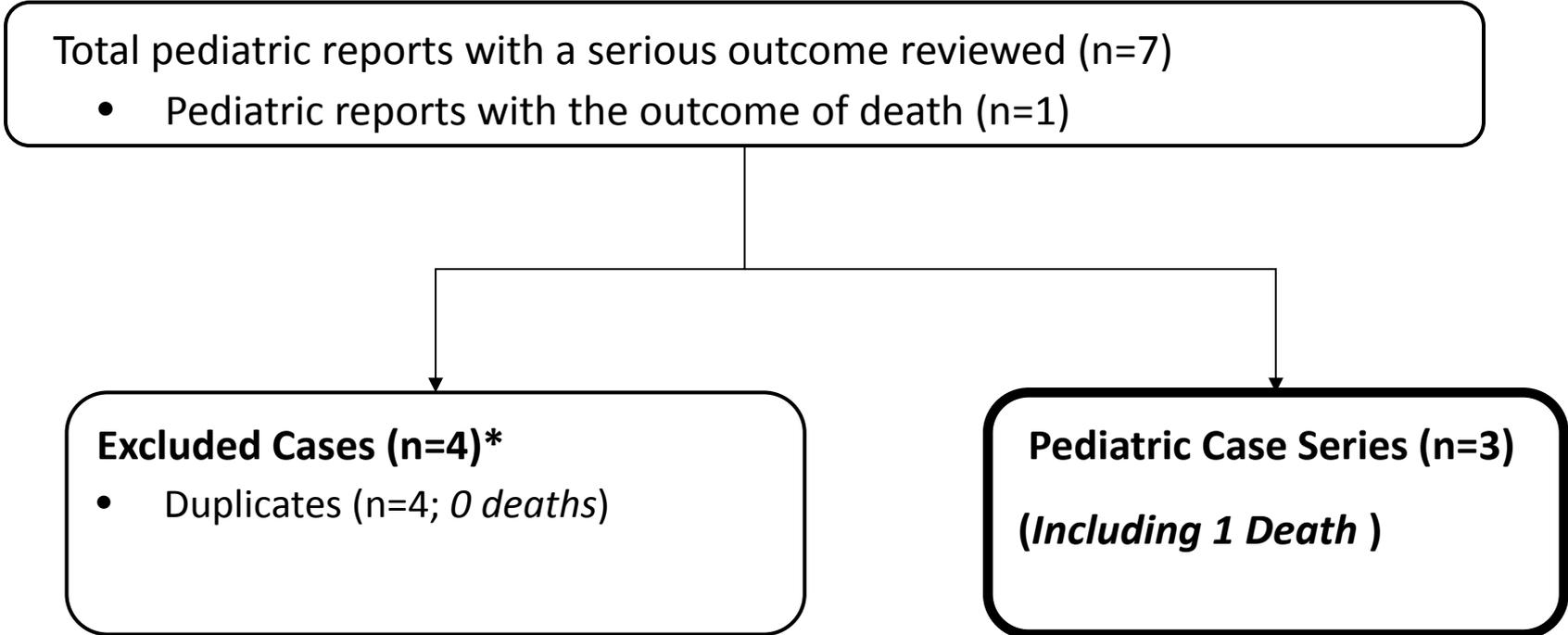
<sup>‡</sup>Unique patient counts may not be added due to the possibility of double counting those patients aging during the study, and may be counted more than once in the individual categories.

## Total Number\* of Kepivance Adverse Event Reports (January 1, 1969\*\* - March 28, 2016)

	All reports (US)	Serious (US) <sup>†</sup>	Death (US)
<b>Adults (≥ 17 yrs.)</b>	176 (36)	166 (27)	20 (5)
<b>Pediatrics (0-&lt;17 yrs.)</b>	8 (1)	<b>7 (0)</b>	<b>1 (0)</b>

\*May include duplicates and transplacental exposures, and have not been assessed for causality  
 \*\*Date of the start of FAERS data collection is used as the initial search date  
 †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.

# Selection of Serious Pediatric FAERS Cases



\*Reviewed and deleted for stated reasons.



## Summary of Serious Adverse Events (n=3): Kepivance (palifermin)

- Fatal Adverse Events (n=1)
- Nonfatal Serious Adverse Events (n=2)
  - Cardiac Failure, Hepatic failure (n=1)
  - Rash, Seizure (n=1)

Unlabeled events are underlined.

## Fatal Adverse Events (n=1): Kepivance (palifermin)

- A 6-month-old female with a complicated cardio-pulmonary pathology, including L → R intra-cardiac shunt across a VSD and ASD, intrapulmonary hemorrhage, and severe and progressive respiratory issues since birth was treated with Kepivance for severe lung disease. She died three weeks later from respiratory insufficiency and pulmonary hypertension resulting in right ventricular failure. She was previously treated with dexamethasone for lung disease, but failed to improve. Multifocal hepatoblastoma and cardiac fibrosis were noted at autopsy.
- *Reviewer Comment: Off-label use of Kepivance for respiratory indication was based on a potential pharmacologic effect. The fatality is related to the patient's multiple, pre-existing medical issues and is unlikely associated with Kepivance use.*

## Serious Non-Fatal Adverse Events (n=2): Kepivance (palifermin)

- Cardiac Failure, Hepatic failure (n=1)
- 13-year-old- female with clear cell renal sarcoma and concomitant exposure to doxorubicin experienced acute decompensation of cardiac function and hepatic failure requiring extracorporeal circulation, dialysis, and ventilation approximately 10 months after starting Kepivance and eight months after the last dose.

*Reviewer comment: Event of cardiac failure is confounded by the concomitant use of doxorubicin, which has a Black Box 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).*

## Serious Non-Fatal Adverse Events (n=2): Kepivance (palifermin)

- Rash, Seizure (n=1)
- A 4-month-old female with Omenn syndrome and no history of seizure or signs of infection developed a moderate rash and subsequent severe seizures two days after Kepivance therapy was started and three days after cyclophosphamide therapy was initiated prior to a stem cell transplant.
  - Kepivance was withheld.
  - Concurrent medications: 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.*

## Postmarketing Experience: Kepivance (palifermin)

- Randomized trial in Ireland in patients with acute lung injury to reduce pulmonary dysfunction\*
  - Administered Kepivance 60 µg/kg IV daily for 6 days.
  - Showed a statistically increased ICU stay and 28-day mortality compared to placebo.
- Preclinical study in mice to determine if Kepivance augments innate pulmonary defense against bacterial and viral pathogens\*\*
  - Administered prophylactic intranasal Kepivance followed by inoculation with lethal dose of different influenza virus strains.
  - Showed accelerated spread of the virus infection and time to death.

*Reviewer Comment: Two reports of off-label use for respiratory indications using dosing and/or a route of administration different from approved recommendations. Findings suggest an increased risk of mortality and infection in this setting.*

\*Presentation at Critical Care Canada Forum, October 2015,  
[http://www.criticalcarecanada.com/presentations/2015/drugs\\_are\\_best.pdf](http://www.criticalcarecanada.com/presentations/2015/drugs_are_best.pdf)

\*\*N. M. Nikolaidis, L. B. Pitstick, J. C. Gardner, K. E. Lewnard, M. R. White, K. L. Hartshorn, F. X. McCormack. Kgf Enhances Influenza-A Infectivity And Mortality In Mice. Am J Respir Crit Care Med 187;2013  
[http://www.atsjournals.org/doi/abs/10.1164/ajrccm-conference.2013.187.1\\_MeetingAbstracts.A4550](http://www.atsjournals.org/doi/abs/10.1164/ajrccm-conference.2013.187.1_MeetingAbstracts.A4550)

## Summary Pediatric Focused Safety Review: Kepivance (palifermin)

- This concludes the pediatric focused safety review.
- Overall the cases were related to patient's underlying medical conditions, and were confounded by concomitant medications or had limited information to assess causality.
- The safety review identified no new safety signals. However, the review highlights the risks of Kepivance off-label use for pulmonary indications and such practice is discouraged unless further study shows a positive risk benefit profile.
- FDA recommends continuing ongoing surveillance.
- Does the Committee concur?



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