CLINICAL REVIEW

Application Type	BLA
Application Number(s)	125164/S-078
Priority or Standard	Priority
Submit Date(s)	December 14, 2018
Received Date(s)	December 14, 2018
PDUFA Goal Date	June 14, 2018
Division/Office	Division of Hematology Products/Office of Hematology and Oncology Products
Reviewer Name(s)	Alexandria Schwarsin, MD
Review Completion Date	May 31, 2018
Established/Proper Name	methoxy polyethylene glycol-epoetin beta
(Proposed) Trade Name	Mircera®
Applicant	Vifor International
Dosage Form(s)	Injection: 30 mcg, 50 mcg, 75 mcg, 100 mcg, 120 mcg, 150 mcg, 200 mcg, or 250 mcg in 0.3 mL; and 360 mcg in 0.6 mL
Applicant Proposed Dosing Regimen(s)	Refer to prescribing information for recommended intravenous dosing regimen
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of anemia associated with chronic kidney disease (CKD) in pediatric patients 5 to 17 years of age on hemodialysis who are converting from another ESA (erythropoiesis stimulating agent) after their hemoglobin level was stabilized with an ESA

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Glossary

ALT	alanine aminotransferase
AST	aspartate aminotransferase
BLA	biologics license application
CKD	chronic kidney disease
CI	confidence interval
CRP	C-reactive protein
ESA	erythropoiesis-stimulating agents
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
SAE	serious adverse event
TEAE	treatment emergent adverse event
TIBC	total iron binding capacity
URR	urea reduction ratio

1. Executive Summary

1.1. Product Introduction

The following was taken from the Mircera Prescribing Information:

> Mircera is an erythropoietin receptor activator with greater activity in vivo as well as increased half-life, in contrast to erythropoietin. A primary growth factor for erythroid development, erythropoietin is produced in the kidney and relapsed into the bloodstream in response to hypoxia. In responding to hypoxia, erythropoietin interacts with erythroid progenitor cells to increase red cell production. Production of endogenous erythropoietin is impaired in patients in patients with chronic kidney disease and erythropoietin deficiency is the primary cause of their anemia.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant has provided evidence of effectiveness and safety in the pediatric population, age 5 to 17, on hemodialysis who are converting from another ESA (erythropoiesis-stimulating agent) after their hemoglobin level was stabilized. This approval is based on a single trial which evaluated two conversion factors, an intermediate conversion factor for group 1 and a high conversion factor for group 2. Based on evaluation of the mean change in hemoglobin and the percentage of patients in each group that had a stable hemoglobin within ±1 g/dL of baseline, the higher conversion factor was recommended. Substantial evidence of effectiveness was also established based on extrapolation of effectiveness from adequate and well-controlled studies of Mircera in adults with chronic kidney disease.

This supplement will also fulfill a PMR (post marketing requirement), discussed in section 3.1 of this review.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Methoxy polyethylene glycol-epoetin beta, Mircera®, is an erythropoietin receptor activator. This trial evaluated the use of Mircera to treat anemia associated with chronic kidney disease in the pediatric population on hemodialysis. The trial evaluated two conversion factors in the pediatric population, age 5-17, when converting from another ESA. Based on the evaluation of the two conversion factors tested, intermediate dose in group 1 and high dose in group 2, the higher dose conversion factor was recommended. This was based on evaluation of the mean change in hemoglobin and the percentage of patients in each group that had a stable hemoglobin within ±1 g/dL. The mean change in hemoglobin for group 1 was 0.7764 (95% confidence interval -1.56, 0001) and for group 2 was -0.1452 (95% confidence interval -0.49, 0.2). The percentage of patients in each group that maintained a stable hemoglobin within ±1 g/dL for each group was 58% for group 1 and 75% for group 2. Based on these results group 2 or the high conversion factor, was the recommended conversion factor.

For the safety evaluation, a total of 4 patients (25.0%) in group 1 and 17 patients (35.4%) in group 2 had a SAE (serious adverse event). The more common SAEs that occurred in 3 patients each are arteriovenous fistula thrombosis, device related infection, hypertension, and thrombosis. One patient died during the trial secondary to intracranial subdural hematoma which, based on reviewer assessment, was unrelated to the trial medication. The more common (>5%) TEAE (treatment emergent adverse events) were headache, nasopharyngitis, hypertension, vomiting, bronchitis, abdominal pain, arteriovenous fistula thrombosis, cough, device related infection, hyperkalemia, pharyngitis, pyrexia, thrombocytopenia, and thrombosis in device.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Patients with chronic kidney disease have anemia associated with their chronic kidney disease. • Anemia in kidney disease is associated with a risk of death and has been shown to increase the risk of death from other diseases	Anemia associated with chronic kidney disease is a serious condition.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• Current treatment options for anemia associated with kidney disease are ESAs. • Approved erythropoiesis stimulating agent in the U.S. include epoetin alfa, epoetin alfa-epbx, darbepoetin alfa, and methoxy polyethylene glycol-epoetin beta (Mircera®)	Methoxy polyethylene glycol-epoetin beta is one of several currently approved ESAs.
Benefit	• Analysis of two conversion factors showed that more patients who used the higher conversion factor maintain their hemoglobin within ±1 g/dL of baseline. This was 75% in group 2 (high conversion factor) compared to 58% in group 1 (intermediate conversion factor). An analysis of the change in the mean hemoglobin showed less variation in group 2. In group 2 (high conversion factor) the mean change was -0.1452 (95% confidence interval -0.49, 0.2) compared to -0.7764 (95% confidence interval -1.56,001) for group 1 (intermediate conversion factor).	The pediatric population ages 5-17 on this trial, currently on hemodialysis with a stable hemoglobin who switched from another erythropoietin stimulating agent, who utilized a high conversion factor had a less of a change in their hemoglobin compared to baseline.
Risk and Risk Management	• The more common SAEs that occurred in 3 patients each are arteriovenous fistula thrombosis, device related infection, hypertension, and thrombosis. • The more common (>5%) TEAEs are headache, nasopharyngitis, hypertension, vomiting, bronchitis, abdominal pain, arteriovenous fistula thrombosis, cough, device related infection, hyperkalemia, pharyngitis, pyrexia, thrombocytopenia, and thrombosis in device	The adverse events in the pediatric population are similar to the adult population.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
	□ Clinical outcome assessment (COA) data, such as	[e.g., Sec 6.1 Study endpoints]
	□ Patient reported outcome (PRO)	
	□ Observer reported outcome (ObsRO)	
	□ Clinician reported outcome (ClinRO)	
	□ Performance outcome (PerfO)	
	□ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Sec 2.1 Analysis of Condition]
	□ Observational survey studies designed to capture patient experience data	
	□ Natural history studies	
	□ Patient preference studies (e.g., submitted studies or scientific publications)	
	□ Other: (Please specify)	
□	Patient experience data that were not submitted in the application, but were considered in this review:	
	□ Input informed from participation in meetings with patient stakeholders	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
	□ Observational survey studies designed to capture patient experience data	
	□ Other: (Please specify)	
X	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

Patients with chronic kidney disease, including patients on dialysis and patients not yet on dialysis, have anemia associated with their chronic kidney disease. Symptoms of anemia include lethargy, easy fatigue, dizziness, increase in heart rate, headache and pallor. Anemia in kidney disease is associated with a risk of death and has been shown to increase the risk of death from other diseases [1].

2.2. Analysis of Current Treatment Options

Current treatment options for anemia associated with kidney disease are other erythropoiesis stimulating agents shown in Table 1.

Table 1 Current treatment options

Drug	Indication	Year of initial U.S. approval
Epogen® (epoetin alfa)	Treatment of anemia due to chronic kidney disease in patients on dialysis and not on dialysis	1989
Aranesp® (darbepoetin alfa)	Aranesp is indicated for the treatment of anemia due to Chronic Kidney Disease in patients on dialysis and not on dialysis.	2001
Retacrit (epoetin alfa-epbx)	Treatment of anemia due to chronic kidney disease in patients on dialysis and not on dialysis	2018

The epoetin alfa (Epogen®) Prescribing Information contains the following information regarding pediatric patients with CKD (chronic kidney disease) in section 8.4:

> Epogen is indicated in pediatric patients, ages 1 month to 16 years of age, for the treatment of anemia associated with CKD requiring dialysis. Safety and effectiveness in pediatric patients less than 1 month old have not been established.
>
> Use of Epogen in pediatric patients with CKD not requiring dialysis is supported by efficacy in pediatric patients requiring dialysis. The mechanism of action of Epogen is the same for these two populations. Published literature also has reported the use of Epogen in pediatric patients with CKD not requiring dialysis. Dose-dependent increases

> in hemoglobin and hematocrit were observed with reductions in transfusion requirements.
>
> The safety data from the pediatric studies and postmarketing reports are similar to those obtained from the studies of Epogen in adult patients with CKD. Postmarketing reports do not indicate a difference in safety profiles in pediatric patients with CKD requiring dialysis and not requiring dialysis.

The darbepoetin alfa (Aranesp®) Prescribing Information contains the following information regarding pediatric patients with CKD in section 8.4:

> Aranesp safety and efficacy were similar between adults and pediatric patients with CKD when Aranesp was use for initial treatment of anemia or patients were transitioned from treatment with epoetin alfa to Aranesp.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Mircera was approved in 2007 for use in adult patients with chronic kidney disease on dialysis or not on dialysis to correct and maintain hemoglobin levels. The pediatric PREA PMRs are:

1. To conduct a multi-center, dose-finding study to determine the optimum starting dose of intravenously administered methoxy polyethylene glycol-epoetin beta when used for the maintenance treatment of anemia in pediatric patients ages 5 to 17 years who have chronic kidney disease and are undergoing dialysis.

2. To conduct a multi-center, randomized, controlled, parallel-group study to confirm the optimal methoxy polyethylene glycol-epoetin beta dosage when used for the maintenance treatment of anemia in pediatric patients ages 5 to 17 years who have chronic kidney disease, inclusive of patients undergoing dialysis as well as patients who are not undergoing dialysis.

This submission is intended to fulfill the first pediatric PREA PMR. The final report submission was to be submitted by October 30, 2009. An extension was granted for the final report submission to December 31, 2017.

3.2. Summary of Presubmission/Submission Regulatory Activity

On December 8, 2016, a Type C meeting was held with Vifor (International) Inc. The purpose of this meeting was to discuss the completed phase 2 trial to address one of the PMRs as well as

information from population PK and PK/PD modeling and simulation, along with a proposed new phase 2 trial that would demonstrate an optimal Mircera maintenance dose for pediatric patients with CKD associated anemia.

During this meeting, it was discussed that safety information cannot be extrapolated from adults. The Agency recommended submission of safety information from at least 100 pediatric patients with CKD including patients on dialysis and not on dialysis. The Agency recommended the sponsor submit PMR proposals for a new phase 2 trial and a registry to substitute for the agreed upon randomized phase 3 trial. During this meeting, the sponsor agreed with the submission of an efficacy supplement based on trial NH19707, the trial submitted with this supplement.

3.3. Foreign Regulatory Actions and Marketing History

Mircera is currently approved for the treatment of anemia associated with CKD in adult patients, including those on dialysis and those not on dialysis, in 115 countries worldwide.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

A consult and inspection by the Office of Scientific Investigations was not requested.

4.2. Product Quality

Refer to previous reviews.

4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

Refer to previous reviews.

4.5. Clinical Pharmacology

Refer to previous and current clinical pharmacology reviews.

4.6. Devices and Companion Diagnostic Issues

Not applicable.

4.7. Consumer Study Reviews

None

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

This submission was based on a single trial for both safety and efficacy in the pediatric population. Trial NH19707 was entitled "An Open-Label, Multi-center, Multiple Dose Study to Determine the Optimum Starting Dose of Intravenous Mircera for Maintenance Treatment of Anemia in Pediatric Patients with Chronic Kidney Disease on Hemodialysis".

Table 2 Trials Submitted to Support Submission

Trial Number	Design	Regimen	Efficacy population	Safety Population
NH19707	Phase 2 trial evaluating conversion factors for patients converting from another ESA	Mircera was administered one every 4 week intravenously for 20 weeks with an optional safety extension period	Group 1: 12 patients Group 2: 36 patients	64 patients

5.2. Review Strategy

The review of the clinical data was done by the primary clinical reviewer. The trial NH19707 served as the primary trial for both safety and efficacy. For this trial, the clinical study report and datasets were reviewed. Unless otherwise stated, calculations were done by the Agency reviewers. Tools used to reproduce analysis include JMP and MAED.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. An Open-Label, Multi-Center, Multiple Dose Study to Determine the Optimum Starting Dose of Intravenous Mircera for Maintenance Treatment of Anemia in Pediatric Patients with Chronic Kidney Disease on Hemodialysis.

6.1.1. Study Design

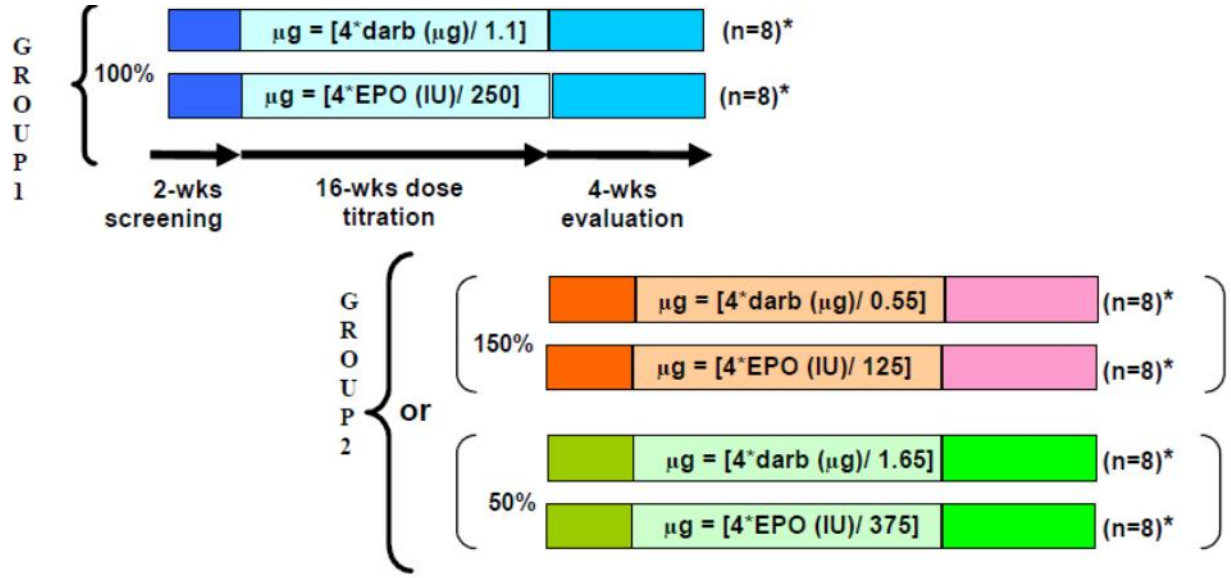
This is an open-label, multi-center, multiple dose trial of Mircera given every 4 weeks intravenously in pediatric patients with CKD receiving hemodialysis. The patients on this trial were previously on a stable maintenance dose of weekly epoetin or darbepoetin alfa. The starting Mircera dose was determined based on a conversion factor. Three possible Mircera doses were to be used, a low dose, an intermediate dose and a high dose. The first group was to receive the intermediate dose.

The first group of patients used the intermediate conversion factor. Once 16 patients have completed 16 weeks of dose titration a preliminary assessment of safety and efficacy was performed. The 90% CI (confidence interval) for the average hemoglobin change from baseline to weeks 14-16 was to be calculated. If the lower limit of the CI is ≥-1 g/dL, the upper limit ≤1 d/dL and the number of dose increases and decreases is balanced, no other conversion factor will be tested. Another 20 patients will be enrolled to the same conversion factor. If this criteria was not met, another higher or lower conversion factor will be tested. If the response criteria was met for this group, another 20 patients were to be enrolled. If the response criteria was not met, a third dose group may have been considered.

Dose adjustments were to be performed every 4 weeks. Patients completing the 20 weeks of treatment with a hemoglobin within a ±1 d/dL of baseline and within the target range of 10-12 g/dL, will be eligible to enter an optional safety extension period.

The scheme for the core trial period is shown in Figure 1, and the schema for the optional safety extension period is shown in Figure 2.

Figure 1 Trial Schema for core trial period



[Taken from sponsor submission, NH19707 Clinical Study Report No. 1035312 page 578]

Figure 2 Trial Schema for optional safety extension

[Taken from sponsor submission, NH19707 Clinical Study Report No. 1035312 page 578]

The primary objective was to determine the starting dose of Mircera in pediatric patients on hemodialysis when switching from a stable maintenance treatment with epoetin alfa, epoetin beta or darbepoetin alfa and to demonstrate changes in hemoglobin over time in response to different intravenous doses of Mircera.

Secondary objectives include:

- To study the pharmacokinetics of Mircera in pediatric patients
- To explore Mircera exposure-response relationship
- To assess the safety and tolerability of multiple doses of Mircera in pediatric patients

- To document long-term safety and efficacy of Mircera administration in pediatric patients with anemia associated with chronic kidney disease.

The conversion factors to determine the starting dose of Mircera when patients where switched from epoetin alfa or beta and darbepoetin alfa are displayed in Figure 3 and Figure 4 respectively.

Figure 3 Mircera starting dose conversion factors when switching from epoetin alfa or beta

	MIRCERA® dose (µg)	Injection frequency
Low dose*	4 x previous weekly EPO dose (IU)/375	Once every 4 weeks
Intermediate dose	4 x previous weekly EPO dose (IU)/250	Once every 4 weeks
High dose*	4 x previous weekly EPO dose (IU)/125	Once every 4 weeks

[Taken from Sponsor submission NH19797 Clinical Study Report No. 1035312 page 575]

Figure 4 Mircera starting dose conversion factors when switching from darbepoetin alfa

	MIRCERA® dose (µg)	Injection frequency
Low dose*	4 x previous weekly darbepoetin alfa dose (µg)/1.65	Once every 4 weeks
Intermediate dose	4 x previous weekly darbepoetin alfa dose (µg)/1.1	Once every 4 weeks
High dose*	4 x previous weekly darbepoetin alfa dose (µg)/0.55	Once every 4 weeks

[Taken from Sponsor submission NH19797 Clinical Study Report No. 1035312 page 575]

Patient population
Inclusion criteria (summarized)

- Informed consent
- Patients 5-17 years of age with stable chronic renal anemia
- Hemodialysis for at least 8 weeks
- Body weight ≥10 kg
- Adequate hemodialysis defined as URR (urea reduction ratio) of ≥ 65% or Kt/V ≥1.2 for

patients on three times a week hemodialysis. Patients with fewer or with more hemodialysis sessions per week should have a weekly Kt/V ≥3.6.

- Baseline pre-dialysis hemoglobin of 10.0-12.0 g/dL based on average weekly hemoglobin measured between -2 and -1 weeks.
- Intravenous maintenance epoetin alfa or beta, or darbepoetin alfa with same dosing interval for at least 8 weeks before screening.
- Adequate iron stores defined as ferritin ≥100 ng/mL or TSAT ≥20% (or percent of hypochromic red cells < 10%)

Exclusion criteria (summarized)

- Overt gastrointestinal bleed within 8 weeks
- Red blood cell transfusions within 8 weeks
- Hemoglobinopathies
- Hemolysis
- Active malignant disease
- Chronic, uncontrolled or symptomatic inflammatory disease
- Uncontrolled hypertension determined by the investigator
- Epileptic seizures within 3 months
- Any investigation drug within 4 weeks
- Severe hyperparathyroidism or biopsy proven bone marrow fibrosis
- Known hypersensitivity to recombinant erythropoietin
- Pure red cell aplasia or history of pure red cell aplasia
- High likelihood of early withdrawal or interruption of the study (such as planned kidney transplant within 16 weeks)
- Planned elective surgery during the trial (except hemodialysis access surgery)

Dose adjustments

The dose of Mircera was to be adjusted to maintain the hemoglobin within ±1 g/dL of their baseline and between 10.0 to 12.0 g/dL. Dose adjustments were to be done once every 4 weeks. Dose adjustments based on hemoglobin assessments are described in Figure 5.

Figure 5 Dose adjustments for Mircera based on hemoglobin level

Hb assessment:	Compared to the previous MIRCERA® dose:
Hb decreases by more than 1.0 g/dL compared to baseline Hb	- Increase dose by 25%
Hb is less than 10 g/dL and greater than or equal to 9 g/dL (Hb <10.0 and ≥9.0 g/dL)	- Increase dose by 25%
Hb is less than 9 g/dL (Hb <9.0 g/dL)	- Increase dose by 50%
Hb increases by more than 1.0 g/dL compared to the baseline Hb OR Hb is approaching 12 g/dL	- Decrease dose by 25%
Hb continues to increase, i.e. Hb exceeds 12 g/dL following dose reduction	- Stop doses until Hb is less than 12.0 g/dL - Resume dose at 25% below previous dose

[Taken from sponsor submission, NH19707 Clinical Study Report No. 1035312 page 593]

Statistical Analysis Plan

Refer to Statistical Analysis Review.

Protocol Amendments

The protocol was amended several times. The amendments were reviewed and did not affect the overall quality of the trial.

6.1.2. Study Results

Compliance with Good Clinical Practices

The Clinical Study for NH19707 contained the following statement:

> The study was conducted in accordance with the principles and the "Declaration of Helsinki" and Good Clinical Practice according the regulations and procedures described in the following sections of the protocol.

Financial Disclosure

The Applicant submitted the financial disclosure requirements for NH19707. See Appendix for Clinical Investigator Financial Disclosure Review.

Efficacy Results – Primary Endpoint

This trial was exploratory without a powered statistical group comparison. The primary endpoint was the change in hemoglobin concentration between the baseline period and the evaluation period. The evaluation period was defined as all assessments between visit 8 and visit 10, weeks 17 and 21, inclusive. The statistical reviewer calculated the 95% confidence intervals on means separately for each group. Results are shown in Table 3.

Table 3 Statistical Analysis of Primary Endpoint

Descriptive statistics	Group 1 (n=12)	Group 2 (n=36)
Mean	-0.7764	-0.1452
Median	-0.7292	-0.1083
Standard deviation	1.2366	1.0143
95% confidence interval on mean	(-1.56, 001)	(-0.49, 0.2)

[Taken from statistical review, Statistical Review and Evaluation by Dr. Kallappa M. Koti, page 6]

Efficacy Results – Secondary and other relevant endpoints

A secondary endpoint was the percentage of patients with average hemoglobin within ±1 g/dL of baseline hemoglobin. The statistical reviewer notes that analysis showed that in group 2, 75% of patients maintained hemoglobin values within ±1 g/dL of baseline and 81% maintained hemoglobin values within 10-12 g/dL during the evaluation period. This is shown is Table 4.

Table 4 Statistical Evaluation of secondary endpoints

Endpoint	Group 1	Group 2
Stable hemoglobin within ±1 g/dL	7/12=58%	27/36=75%
Hemoglobin within 10-12 g/dL	9/12=75%	29/26=81%
Hemoglobin within 10-12 g/dL and ±1 g/dL of baseline	7/12=58%	35/36=69%

[Taken from Statistical review, Statistical Review and Evaluation by Dr. Kallappa M. Koti, page 6]

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

A single trial was submitted and an integrated review of effectiveness was not done.

7.2. Additional Efficacy Considerations

None

7.3. Integrated Assessment of Effectiveness

Efficacy of Mircera for the indication was established based on extrapolation of efficacy from adequate and well-controlled studies of Mircera in adults and a dose-finding study in pediatric patients 5 to 17 years of age with CKD on hemodialysis. Extrapolation of efficacy from clinical trials in adults is supported by same pathophysiology and mechanism of action for efficacy in the adult and pediatric populations.

8. Review of Safety

8.1. Safety Review Approach

The safety review focused on trial NH19707 entitled "An Open-Label, Multi-Center Multiple Dose Study to Determine the Optimum Starting Dose of Intravenous Mircera for Maintenance Treatment of Anemia in Pediatric Patients with Chronic Kidney Disease on Hemodialysis". The safety population was defined as all patients with received at least one dose of the trial medication and had a safety follow-up.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The mean overall exposure for the 64 patients in the safety population was 7.7 months. The median overall exposure was 6.0 months with a minimum of 0 months and a maximum of 16.6 months.

8.2.2. Relevant characteristics of the safety population:

The demographics of the safety population are shown in Table 5. As shown, approximately 47% of the population was female and 53% were male. Based on age, approximately 39% were 5 to 11 years of age and approximately 61% were ≥12 years of age.

Table 5 Demographics of Safety Population

	Group 1 N=16		Group 2 N=48		Overall N=64	
	n	%	n	%	n	%
Sex						
Female	5	31.3	25	52.1	30	46.9
Male	11	68.8	23	47.9	34	53.1
Age group						
5-11	9	56.3	16	33.3	25	39.1
≥12	7	43.8	32	66.7	39	60.9
Previous Erythropoietic Agent						
Darbepoetin Alfa	8	50.0	26	54.2	34	53.1
Epoetin Alfa	0	0.0	4	8.3	4	6.3
Epoetin Beta	8	50.0	18	37.5	26	40.6

8.2.3. Adequacy of the safety database:

The safety database was adequate in support of the application.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The overall quality and integrity of the application was acceptable.

8.3.2. Categorization of Adverse Events

Adverse events were classified per the Medical Dictionary for Regulatory Activities 18.1. The intensity of the adverse events was classified as mild, moderate, severe and life threatening.

8.3.3. Routine Clinical Tests

Routine clinical testing was appropriate. Vital signs and weight was done weekly during the core period. Hemoglobin, hematocrit, PBC, and absolute reticulocyte count was done weekly during the core period, platelets were done at screening, and weeks 4, 7, 10, 13, 17 and 21, safety laboratory studies which included leukocytes and differential, AST (aspartate aminotransferase), ALT (alanine aminotransferase), serum albumin, alkaline phosphatase, CPR (C-reactive protein), potassium, phosphorus, calcium and blood glucose were done at screening, weeks 7, 13 and 21 during the core period. Iron parameters which included serum iron, serum ferritin, serum transferrin or TIBC (total iron binding capacity) were done at

screening, weeks 7, 13 and 21 during the core period.

8.4. Safety Results

8.4.1. Deaths

There was 1 death (b) (6)) during the core trial period. The patient was a 9-year-old man who on day 85 had vomiting and a seizure after dialysis. The patient was administered heparin with dialysis. The same day a CT scan showed a severe intracranial subdural hematoma. The patient's mother recalled two days earlier the patient had head trauma, but there were no symptoms and the patient did not receive medical attention. The hematoma was evacuated. On day 87 he developed left hemiparesis. His condition continued to worsen and the patient received transfusions. On day 105 the patient was admitted to the intensive care unit and stopped breathing. The last dose of study medication was on day 83. His hemoglobin prior to the event was 10 g/dL on day 76.

8.4.2. Serious Adverse Events

Overall a total of 21 patients (32.8%) reported at least 1 SAE during either the core study period or safety extension period. By treatment group, this included a total of 4 patients (25.0%) in group 1 and 17 patients (35.4%) in group 2. SAEs that occurred in either the core study period or safety extension period that occurred in 2 or more patients are listed in Table 6. As shown in the table, arteriovenous fistula thrombosis, device related infection, hypertension, and thrombosis in device each occurred in 3 patients.

Table 6 Serious Adverse Events

	N N=64	%
Arteriovenous fistula thrombosis	3	4.7
Device related infection	3	4.7
Hypertension	3	4.7
Thrombosis in device	3	4.7
Bronchitis	2	3.1
Fluid overload	2	3.1
Procedural Hemorrhage	2	3.1

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

One patient died during the core study period. No patients were withdrawn from treatment due to an adverse event.

8.4.4. Significant Adverse Events

Refer to section 8.4.5.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

TEAE that occurred, limited to 1 per patient, at worst level per patient, that occurred in 4 or more patients overall, during the trial including the safety extension study are displayed in Table 7. For the TEAE shown, the majority were increased on group 2, except vomiting and bronchitis which were increased in group 1. The TEAE with a >10% increase in group 2 are nasopharyngitis, headache and hypertension.

Table 7 TEAE by treatment group

	Group 1 N=16				Group 2 N=48			
	All		Severe and life threatening		All		Severe & life threatening	
	n	%	n	%	n	%	n	%
Blood and Lymphatic System Disorders								
Thrombocytopenia	0	0	0	0	4	8.33	0	0
Gastrointestinal Disorders								
Abdominal pain	1	6.25	0	0	4	8.33	0	0
Vomiting	2	12.5	0	0	5	10.4	1	2.08
General disorders and Administrative Site Conditions								
Pyrexia	1	6.25	0	0	3	6.25	0	0
Thrombosis in device	0	0	0	0	4	8.33	1	2.08
Infections and Infestations								
Bronchitis	2	12.5	0	0	4	8.33	0	0
Device related infection	0	0	0	0	4	8.33	0	0
Nasopharyngitis	0	0	0	0	14	29.2	0	0
Pharyngitis	0	0	0	0	4	8.33	1	2.08
Injury, Poisoning and Procedural Complications								
AV fistula thrombosis	1	6.25	1	6.25	3	6.25	2	4.17
Metabolism and Nutritional Disorders								
Hyperkalemia	1	6.25	0	0	3	6.25	1	2.08
Nervous System Disorders								
Headache	1	6.25	0	0	13	27.1	0	0
Respiratory, Thoracic and Mediastinal Disorders								
Cough	0	0	0	0	4	8.33	0	0
Vascular Disorders								

	Group 1 N=16				Group 2 N=48			
	All		Severe and life threatening		All		Severe & life threatening	
	n	%	n	%	n	%	n	%
Hypertension	1	6.25	0	0	11	22.9	1	2.08

Treatment emergent adverse events, that occurred in >5% of patients overall, irrespective of treatment group limited to 1 per patient, are displayed in Table 8.

Table 8 TEAE overall safety population

	N N=64	%
Headache	14	21.9
Nasopharyngitis	14	21.9
Hypertension	12	18.8
Vomiting	7	10.9
Bronchitis	6	9.4
Abdominal pain	5	7.8
Arteriovenous fistula thrombosis	4	6.3
Cough	4	6.3
Device related infection	4	6.3
Hyperkalaemia	4	6.3
Pharyngitis	4	6.3
Pyrexia	4	6.3
Thrombocytopenia	4	6.3
Thrombosis in device	4	6.3

8.4.6. Laboratory Finding

The sponsor's laboratory analysis was reviewed. Below is a summary of the sponsor's laboratory analysis (Taken from Clinical Study Report).

- Median platelet count remained within 16% and 20% of baseline for group 1 and group 2, respectively.
- Median changes from baseline for AST, ALT, serum albumin, calcium, blood glucose parameters were minor.
- In Group 2, the largest median changes from baseline were observed at week 13 for iron (+6.75 µM/L from 12.00 µM/L at baseline), at week 61 for ferritin (245.38 µg/L from

328.00 µg/L for ferritin) and week 53 for transferrin saturation (13.11% from 26.82% at baseline). A similar pattern was observed in Group 1.

Reviewer Comments: Patients were given iron during screening and during the trial to maintain adequate iron stores.

8.4.7. Vital Signs

Based on the Sponsor's analysis, "during the core period plots of pre-dialysis Z scores for systemic blood pressure and diastolic blood pressure showed no clear trend throughout the study".

8.4.8. Electrocardiograms (ECGs)

Routine ECGs were not done during the trial.

8.4.9. QT

Not applicable.

8.4.10. Immunogenicity

Refer to Clinical Pharmacology Review.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Hypertension

Hypertension was reported at baseline in 32 patients (50%). During the core trial period, 8 patients (13%) had an increase in antihypertension treatment. Of the 8 patients with arterial hypertension reported as an AE during the core study period, 7 had pre-existing hypertension at enrollment or within 12 weeks prior to enrollment, and 1 had previously received antihypertensive therapy although this patient was not reported to have hypertension at enrollment or within 12 weeks of enrollment. [Taken from Applicant submission, Clinical Study Report: NH19707 page 110].

Reviewer Comments: Uncontrolled hypertension is a contraindication is Mircera in the current Prescribing Information. Hypertension is also a Warning and Precaution. As this trial was without a control arm, it is difficult to discern the contribution of Mircera to the development of hypertension.

8.5.2. Thrombosis

An Standardized MedDRA Query analysis of embolic and thrombotic events demonstrated a total of 10 events in 7 patients occurred (10.9%). The TEAE included in this Standardized MedDRA Query are arteriovenous fistula thrombosis and thrombosis in device.

Reviewer Comments: As the trial is without a control arm, it is difficult to discern the contribution of Mircera to the development of embolic and thrombotic events.

8.6. Safety Analyses by Demographic Subgroups

An analysis by age demographic was done. TEAEs that occurred in >5% of patients in either age group is shown in Table 9. Given the small numbers of patients in each age group, a strong conclusion based on this analysis is difficult. An analysis of TEAE at the System Organ Class level, based on age group, is shown in Table 10. TEAE at the System Organ Class level that occurred in >10% are shown. As demonstrated in the table, at the System Organ Class level, the more frequent System Organ Classes are relatively balanced between the two age groups.

Table 9 Treatment emergent AE by age demographic

	Age group 5-11 N=25		Age group ≥12 N=39	
	n	%	n	%
Headache	4	16.0	10	25.6
Hypertension	4	16.0	8	20.5
Nasopharyngitis	4	16.0	10	25.6
Vomiting	4	16.0	3	7.7
Device related infection	3	12.0	1	2.6
Thrombosis in device	3	12.0	1	2.6
Abdominal pain	2	8.0	3	7.7
Bronchitis	2	8.0	4	10.3
Cough	2	8.0	2	5.1
H1N1 influenza	2	8.0	0	0.0
Hypotension	2	8.0	1	2.6
Pharyngitis	2	8.0	2	5.1
Pyrexia	2	8.0	2	5.1
Thrombocytopenia	2	8.0	2	5.1
Arteriovenous fistula thrombosis	1	4.0	3	7.7
Hyperkalemia	1	4.0	3	7.7
Ear pain	0	0.0	3	7.7

	Age group 5-11 N=25		Age group ≥12 N=39	
	n	%	n	%
Hyperphosphataemia	0	0.0	3	7.7
Nausea	0	0.0	3	7.7
Urinary tract infection	0	0.0	3	7.7
Oropharyngeal pain	1	4.0	2	5.1
Viral infection	1	4.0	2	5.1
Abdominal pain upper	0	0.0	2	5.1
Arteriovenous fistula site complication	0	0.0	2	5.1
Back pain	0	0.0	2	5.1
Dental caries	0	0.0	2	5.1
Ear infection	0	0.0	2	5.1
Eczema	0	0.0	2	5.1
Fluid overload	0	0.0	2	5.1
Haematoma	0	0.0	2	5.1
Hyperparathyroidism secondary	0	0.0	2	5.1
Non-cardiac chest pain	0	0.0	2	5.1
Pain	0	0.0	2	5.1
Procedural hypotension	0	0.0	2	5.1
Rhinitis	0	0.0	2	5.1
Toothache	0	0.0	2	5.1

Table 10 TEAE by age group at the System Organ Class level

	Age group 5-11 N=25		Age group ≥12 N=39	
	n	%	n	%
Infections and infestations	15	60.0	23	59.0
Gastrointestinal disorders	6	24.0	13	33.3
Nervous system disorders	6	24.0	11	28.2
General disorders and administration site conditions	5	20.0	10	25.6
Vascular disorders	5	20.0	9	23.1
Metabolism and nutrition disorders	4	16.0	8	20.5
Respiratory, thoracic and mediastinal disorders	4	16.0	4	10.3

	Age group 5-11 N=25		Age group ≥12 N=39	
	n	%	n	%
Blood and lymphatic system disorders	3	12.0	3	7.7
Injury, poisoning and procedural complications	3	12.0	11	28.2
Ear and labyrinth disorders	0	0.0	6	15.4
Skin and subcutaneous tissue disorder	1	4.0	5	12.8

8.7. Specific Safety Studies/Clinical Trials

Not applicable.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Mircera, in the current Prescribing Information, has the following boxed warning regarding cancer:

- Mircera is not indicated and is not recommended for the treatment of anemia due to cancer chemotherapy. A dose-Ranging study of Mircera was terminated early because of more deaths among patients receiving Mircera than another ESA
- ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in clinical studies in patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers.

In this trial, there were no reports of the development of malignancy noted by the reviewer. The patient population on this trial was not patients with cancer, rather it was patients with renal disease and the trial had a limited duration of follow up.

8.8.2. Human Reproduction and Pregnancy

There is no data available from adequate, controlled trials of Mircera in pregnant women. Thus, this trial excluded females who were pregnant, lactating, or intend to become pregnant during the trial and in addition sexually active females of childbearing potential and sexually active males were to use contraception. [Taken from Mircera Prescribing Information]

8.8.3. Pediatrics and Assessment of Effects on Growth

A total of 23 patients (35.9%) of the patient population had a history of growth retardation. Based on Application analysis, during the core-study period, the median z-score for height showed little variation. [Below is taken from Applicant Clinical Study Report: Protocol NH19707 page 116.]

> During the core-study period, the median z-score for height showed little variation (the biggest median change from baseline was -0.09 in Group 1 [median at baseline, -1.06] and +0.14 in Group 2 [median at baseline, -1.67]) and no clear trends. Likewise, during the safety extension period, median changes from baseline were also small (largest change was +0.14 at week 61 in Group 2).

Refer to CDTL review for discussion of pediatric assessment for Mircera.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Mircera is an approved drug. The Applicant continues to submit postmarketing safety reports. These reports are reviewed and safety issues that arise are addressed with labeling changes if needed.

8.9.2. Expectations on Safety in the Postmarket Setting

The Applicant will continue with routine pharmacovigilance and submit postmarketing safety reports as required.

8.9.3. Additional Safety Issues From Other Disciplines

Refer to previous reviews.

8.10. Integrated Assessment of Safety

As one pediatric trial was submitted, an integrated assessment of safety was not done.

9. Advisory Committee Meeting and Other External Consultations

Not applicable.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

The final approved indication, to address the pediatric patient population, is Mircera is an erythropoiesis-stimulating agent (ESA) indicated for the treatment of anemia associated with chronic kidney disease in pediatric patients 5 to 17 years of age on hemodialysis who are converting from another ESA after their hemoglobin level was stabilized.

In section 2.2 Patients with Chronic Kidney Disease of the Prescribing Information a table addressing the Mircera starting doses for pediatric patients currently receiving another ESA was added along with administration information.

In section 6.1 Clinical Trial Experience of the Prescribing Information under the subsection of Pediatric Patients the trial design is briefly discussed along with exposure and treatment emergent adverse events overall regardless of causality.

In section 14.2 Pediatric Patients on Hemodialysis the trial is described further along with then mean change in hemoglobin concentration from baseline to the evaluation period for the 36 patients who used the recommended conversion factor.

10.2. Nonprescription Drug Labeling

Not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

A REMS was not considered necessary.

12. Postmarketing Requirements and Commitments

Refer to Cross Discipline Team Leader review for issuance of new PMRs.

13. Appendices

13.1. References

1. Nakhoul, G. and J.F. Simon, Anemia of chronic kidney disease: Treat it, but not too aggressively. Cleve Clin J Med, 2016. 83(8): p. 613-24.

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): NH19707

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 32		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No (Request explanation from Applicant)

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/s/

ALEXANDRIA N SCHWARSIN
05/31/2018

ROMEO A DE CLARO
05/31/2018