Clinical and Cross-Discipline Team Leader Review

Date	October 30, 2020
From	Andreas Pikis, Medical Officer, Division of Antivirals Mary Singer, Medical Team Leader, Division of Antivirals
Subject	Clinical Review Cross-Discipline Team Leader Review
NDA/Supplement#	NDA 208984/Supplement-2 NDA 22128/Supplement-19
Applicant	ViiV Healthcare/GlaxoSmithKline
Date of Submission	May 1, 2020
PDUFA Goal Date	November 1, 2020
Proprietary Name / Established (USAN) names	SELZENTRY/maraviroc (MVC)
Dosage forms / Strength	Tablets: 25 mg, 75 mg, 150 mg and 300 mg Oral solution: 20 mg/mL
Proposed Indication(s)	Treatment of HIV-1 infection in children from birth to 2 years of age
Recommended:	Approval with labeling modifications

1. Introduction

In these supplemental New Drug Applications (sNDAs), sNDA 208984/S-02 and sNDA 22128/S-19, the Applicant seeks to:

- Expand the Indications and Usage of maraviroc (MVC) to include treatment of HIV-1 infected pediatric patients weighing at least 2 kg
- To provide dosing recommendations for HIV-1 infected pediatric patients weighing 10 kg to less than 30 kg when Selzentry (maraviroc) is used with noninteracting concomitant medications
- Add a 3-mL syringe to the convenience kit
- Fulfill the requirements of the Pediatric Written Request (PWR), together with the previously submitted Trial A4001031 which supported the MVC indication for treatment of HIV-1-infected children 2 to less than 18 years of age (NDA 208984 and sNDA 22128/S-17, approved November 4, 2006)

The Applicant's request is based on the following studies and provided data:

- Clinical Study IMPAACT 2007 (b) (4), a phase I, multicenter, open-label, intensive pharmacokinetic study designed to evaluate the pharmacokinetics and safety of MVC solution when administered with a single ARV drug (nevirapine or zidovudine) or a combination ARV regimen for prevention of perinatal HIV transmission to infants exposed to HIV-1.

- PMAR-2007, a neonatal population pharmacokinetic modeling and simulation analysis of MVC in neonates from the IMPAACT 2007 study
- PMAR-1030, a population pharmacokinetic and modeling and simulation analysis designed to predict exposures for dose selection for pediatric patients 6 weeks to 2 years of age
- Chemistry and manufacturing data for the new 3 mL syringe

2. Background

Although highly active antiretroviral (HAART) regimens have virtually transformed HIV infection to a chronic disease in developed countries, the management of HIV infection continues to challenge clinicians who care for patients with this infection. Currently available HIV drugs include 7 different antiretroviral drug classes, more than 25 individual antiretroviral drugs, and two pharmacokinetic enhancers, not including fixed- dose combinations. The drug classes include nucleoside reverse transcript inhibitors (NRTIs), non-nucleoside reverse transcript inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors, CCR5 receptor antagonists, integrase inhibitors, attachment inhibitors, and post-attachment inhibitors. Table 1 below summarizes the FDA-approved drugs for HIV-1 infection by drug class (does not include pharmacokinetic enhancers and combination HIV medicines)

Table 1. Treatment armamentarium for HIV-1 infection

Drug Class	**Generic Name**	**Trade Name**	**Pediatric Ages Approved**
NRTIs	Zidovudine	Retrovir	≥ 4 weeks
	Didanosine	Videx	≥ 15 days
	Stavudine	Zerit	From birth
	Lamivudine	Epivir	≥ 3 months
	Abacavir	Ziagen	≥ 3 months
	Tenofovir	Viread	≥ 2 years
	Emtricitabine	Emtriva	From birth
NNRTIs	Nevirapine	Virammune	≥ 15 days
	Efavirenz	Sustiva	≥ 3 months
	Etravirine	Intelence	≥ 2 years
	Rilpivirine	Edurant	≥ 12 years
	Doravirine	Pifeltro	Not approved in children
PIs	Ritonavir	Norvir	> 1 month
	Nelfinavir	Viracept	≥ 2 years
	Fosamprenavir	Lexiva	≥ 4 weeks
	Lopinavir/ritonavir	Kaletra	≥ 14 days
	Atazanavir	Reyataz	≥ 3 months
	Darunavir	Prezista	≥ 3 years
	Tipranavir	Aptivus	≥ 2 years
	Saquinavir	Invirase	Not approved in children
Fusion Inhibitors	Enfuvirtide (T-20)	Fuzeon	≥ 5 years
Integrase Inhibitors	Raltegravir	Isentress	From birth

	Dolutegravir	Tivicay	≥ 4 weeks
	Elvitegravir	Vitekta	Discontinued*
Attachment Inhibitors	Fostemsavir	Rukobia	Not approved in children
Post-Attachment Inhibitors	Ibalizumab-uiyk	Trogarzo	Not approved in children

*Elvitegravir is available as a fixed-drug combination (Genvoya and Stribild)

Children have fewer treatment options than adults due to lack of pediatric formulations and information to guide clinicians in dosing HIV-infected children. While most ARVs have dosing recommendations in at least one subset of the pediatric age range, almost 40 percent of the approved drugs have no indication for children less than 2 years of age. These limitations, coupled with other challenges such as poor tolerance, poor adherence, emergence of resistance, demonstrate the need for more HIV drugs for young children.

MVC, the first CCR5 co-receptor antagonist, received an FDA approval in 2007. It is currently indicated in combination with other antiretroviral agents for the treatment of only CCR5-tropic HIV-1 infection in patients 2 years of age and older weighing at least 10 kg. To obtain needed pediatric information on MVC, the Agency issued a formal Pediatric Written Request (PWR) in 2006. The Sponsor was asked to conduct two studies:

- A multiple-dose pharmacokinetic, safety and activity study of MVC in combination with other antiretroviral agents in HIV-infected pediatric patients 1 month of age to adolescence; and
- A multiple-dose pharmacokinetic and safety study of MVC in HIV-exposed neonates (born to HIV-infected mothers)

Due to the difficulty in enrolling subjects for the treatment of HIV-1 infection for pediatric patients aged more than 6 weeks to less than 2 years, the Agency and the Sponsor agreed to use modeling and simulation (M&S) to determine dosing recommendations for this age group. Thus, the PWR was amended and currently asks for:

- A multiple-dose pharmacokinetic, safety and activity study of MVC in combination with other antiretroviral agents in HIV-infected pediatric patients 2 years to adolescence; and
- A multiple-dose pharmacokinetic and safety study of MVC in HIV-exposed neonates (born to HIV-infected mothers) from birth to 6 weeks of age

The study in HIV-infected pediatric patients 2 years to adolescence was addressed by reports submitted previously to NDA 208984 and sNDA 22128/S-017 (approved November 4, 2016). In the current submissions, the Applicant provides a complete clinical study report for IMPAACT 2007, a Phase I, multi-center, open-label intensive pharmacokinetic study designed to evaluate the pharmacokinetics and safety of MVC solution when administered with a single ARV drug (nevirapine or zidovudine) or combination ARV regimen for the prevention of perinatal HIV transmission to infants exposed to HIV-1 infected mothers. Further, the Applicant provides dosing recommendations of MVC for children between 6 weeks to 2 years of age based on M&S studies.

3. CMC/Device

MVC is available in the following dosage forms and strengths:

- Tablets: 25 mg, 75 mg, 150 mg, and 300 mg
- Oral solution: 20 mg/mL

MVC for oral solution is supplied as a clear, colorless, strawberry-flavored liquid. It is available to the patient in a 230 mL plastic bottle co-packaged with one press-in bottle adapter and one 10 mL oral dosing syringe (oral dispenser) with 0.5 mL gradation.

In these submissions, the Applicant seeks extension of the indication to include pediatric patients aged from birth (weighing at least 2 kg) to less than 2 years with an age appropriate dosage form. To more accurately delivering doses of 2.5 mL or less, the Applicant seeks the addition of a 3 mL oral dispenser (with 0.5 mL gradations) to the convenience kit for oral solution. The new 3 mL oral dispenser is made of the same materials, same design, and by the same manufacturer as the current 10 mL oral dispenser in the existing convenience kit. As a result, these sNDAs contain revisions to Section 16 of the Package Insert to include the proposed 3 mL oral dispenser and revisions to the carton and container.

For more details regarding the chemistry and manufacturing of the 3 mL dispenser please refer to the review by Libaniel Rodriguez, Ph.D., the CMC reviewer. Dr. Rodriguez concurs with the addition of the 3 mL oral dispenser to the convenience kit and the corresponding changes in the Package Insert and the Carton and container.

4. Nonclinical Pharmacology/Toxicology

No new animal pharmacology and toxicology data were submitted with these sNDAs. Please refer to the original NDA 22128 reviews for background information.

5. Clinical Pharmacology/Biopharmaceutics

In these sNDAs, (sNDA 208984/S-02 and sNDA 22128/S-19), the Applicant seeks to expand the maraviroc (MVC) indication to include treatment of HIV-1-infection in pediatric patients weighing at least 2 kg. In addition, the Applicant provides dosage recommendations for HIV-1-infected children weighing 10 kg to less than 30 kg when MVC is used with non-interacting concomitant medications. The currently approved dosage recommendations for MVC in pediatric patients and those proposed in these submissions by the Applicant are summarized in Table 2.

Table 2: Approved dosage recommendations and the Applicant's proposed dosage recommendations for MVC in pediatric patients (blue font highlights the proposed changes)

	Current		**Proposed**	
Weight	With strong CYP3A inhibitors	With no interacting drugs	With strong CYP3A inhibitors	With no interacting drugs
2 to <4 kg	Not approved		(b) (4)	30 mg BID
4 to <6 kg				40 mg BID
6 to <10 kg				100 mg BID
10 to < 14 kg	50 mg BID	Not recommended	50 mg BID	150 mg BID
14 to <20 kg	50 mg BID	Not recommended	50 mg BID	200 mg BID
20 to < 30 kg	75 mg (tablet)or 80 mg (oral solution) BID	Not recommended	75 mg (tablet)or 80 mg (oral solution) BID	200 mg BID
30 to <40 kg	100 mg BID	300 mg BID	100 mg BID	300 mg BID
≥ 40 kg*	150 mg BID*	300 mg BID*	150 mg BID*	300 mg BID*

*Approved dose in adults
* In adults, 600 mg BID is approved when MCV is co-administered with a strong CYP3A inducer. However, the use of MCV with a strong inducer is not recommended in pediatric patients due to the lack of the supporting data.
Source: Clinical Pharmacology Review

The Applicant's proposed dosage recommendations are based on the following reports:

- Study IMPAACT 2007, a Phase I, multi-center, open-label, intensive pharmacokinetic study designed to evaluate safety and pharmacokinetics of MVC solution when administered with a single or combination ARV regimen for prevention of perinatal HIV transmission to infants exposed to HIV-1 infection;
- A population pharmacokinetic and modeling and simulation analysis of MVC in neonates from the IMPAACT 2007 study (PMAR-2007);
- A modeling and simulation report (PMAR-1030) evaluating dosing for pediatric subjects from birth to less than 2 years of age

It is important to note that:

- There are no pharmacokinetic data for children older than 6 weeks to less than 2 years of age.
- None of the enrolled subjects from birth to 6 weeks of age received MVC with concomitant CYP3A inhibitors

- The majority of pharmacokinetic data from children 2 years to adolescence and from adults were obtained from patients who received MVC with concomitant CY3A inhibitors.

Study IMPAACT 2007:
The study design is described in more details in Section 6. Briefly, this was a phase 1 PK study, open-label, intensive PK study of MVC solution in full-term neonates up to 3 days of life and weighing at least 2 kg. A total of 47 neonates from 4 countries (USA 20, South Africa 22, Kenya 2, Thailand 3) were enrolled in 1 of 2 sequential dosing cohorts stratified by efavirenz exposure:

Cohort 1:
Stratum 1A: Infants without *in utero* exposure to maternal EFV (no EFV exposure during the eight weeks immediately prior to delivery) (enrolled 8)

Stratum 1B: Infants with in utero exposure to maternal EFV (EFV exposure for a minimum of two weeks immediately prior to delivery) (enrolled 7)

Treatment assignment: Cohort 1 participants received 2 single doses of MVC ~8 mg/kg as an initial starting dose. The first dose was administered within 3 days after birth and the second dose at Week 1 (Day 7 to 14) of life.

Cohort 2:
Stratum 2A: Infants without any exposure to maternal EFV either in utero (no EFV exposure during the eight weeks immediately prior to delivery) and if breastfeeding while breastfeeding (enrolled 16)

Stratum 2B: Breastfeeding infants with exposure to maternal EFV both in utero and after birth while breastfeeding. (EFV exposure for a minimum of two weeks immediately prior to delivery and while breastfeeding) (enrolled 16)

Treatment assignment: Cohort 2 participants received doses of MVC BID at a dose ~8 mg/kg. MVC was administered within 3 days after birth and continued for up to 42 days of life.

Primary PK endpoint: Failure to achieve $C_{avg} \geq 75$ ng/mL. The selection of this target was based on the multivariate analysis of predictors of response evaluation at 48 weeks from the adult study in HIV-1 treatment-naïve subjects (A4001026) where MVC was dosed at 300 mg twice daily.

MVC exposures in neonates enrolled in IMPAACT 2007 study are summarized in Table 3.

Table 3. Summary of MVC exposures in neonates following single and multiple (BID) doses of MVC ~8 mg/kg (IMPAACT 2007)

Analysis Set	Median weight (range) (kg)	GM Cavg (95% CI) (ng/mL)	GM Cmax (95% CI) (ng/mL)	GM Ctau (95% CI) (ng/mL)	PK target met[a] n/N(%)
Entry/Day 1 (single-dose, Cohort 1)					
Cohort 1 (N=13)	3.30 (2.48-3.97)	292.46 (179.71, 475.95)	380.05 (195.94, 737.14)	N/A	13/13 (100)
Stratum 1A (n=6)	3.23 (2.48-3.84)	227.76 (81.9, 633.35)	225.59 (53.9, 944.1)	N/A	6/6 (100)
Stratum 1B (n=7)	3.44 (2.80-3.97)	362.36 (203.18, 646.23)	594.29 (344.43, 1025.39)	N/A	7/7 (100)
Week 1 (multiple-dose, Cohort 2)					
Cohort 2 (N=25)	3.10 (2.40-3.94)	101.37 (68.02, 151.07)	261.58 (165.48, 413.48)	22.71 (12.15, 42.44)	18/25 (72)
Stratum 2A (n=13)	2.97 (2.64-3.84)	102.32 (57.05, 183.52)	278.68 (141.35, 549.43)	22.7 (10.3, 50.04)	10/13 (77)
Stratum 2B (n=12)	3.25 (2.40-3.94)	100.34 (52.84, 190.53)	244.23 (118.42, 503.71)	22.72 (7.37, 70.03)	8/12 (67)
Week 4 (multiple-dose, Cohort 2)					
Cohort 2 (N=25)	3.73 (2.27-4.54)	115.42 (82.33, 161.81)	295.45 (218.96, 398.65)	42.67 (24.85, 73.29)	16/25 (64)
Stratum 2A (n=13)	3.50 (3.17-4.18)	128.75 (74.07, 223.79)	357.3 (234.7, 543.92)	40.19 (15.68, 103.03)	9/13 (69)
Stratum 2B (n=12)	3.87 (2.27-4.54)	102.53 (64.88, 162.04)	240.47 (151.23, 382.36)	45.54 (23.46, 88.38)	7/12 (58)

a. Number of participants to achieve PK target Cavg ≥ 75 ng/mL
Source: Applicant's clinical overview

Comments: The target C_{avg} was achieved in all subjects in Cohort 1 at Entry/Day 1 and in most participants in Cohort 2 (72% (18/25) at Week 1 and 64% (16/25) at Week 4).

MVC exposures were comparable between with and without maternal exposure to efavirenz

There has been a great variability in all strata and cohorts, a phenomenon observed in neonates with other ARVs

MVC exposures after a single or repeated BID dose of ~8 mg/kg were similar with those observed in adult studies and the pediatric study in children aged 2 years to adolescence (minimum weight > 10 kg)

Population pharmacokinetic modeling and simulation studies

The modeling and simulation studies were conducted to address different case scenarios:

- To identify more accurate dosage recommendations based on weight-bands for children from birth to 6 weeks of age using the pharmacokinetic data obtained from the IMPAACT 2007 study

- Propose dosing recommendations for the age group > 6 weeks to < 2 years of age where no pharmacokinetic data are available
- Proposed dosing recommendations, if feasible, for the age group birth to less than 2 years of age when maraviroc is co-administered with potent CYP3A inhibitors

A semi-physiological model which included maturation functions for hepatic (e.g., CYP3A ontogeny) and renal elimination was developed for MVC. This model was built with adult and all available pediatric data (from the IMPAACT 2007 study and the A4001031 study in children 2 years to adolescence). The model was initially built with adult and limited pediatric data from A4001031 without the neonatal data from IMPAACT 2007 to check how well the neonatal data were predicted under the initial assumptions regarding hepatic maturation. When it was shown that the neonatal data were not well predicted, the neonatal data (from IMPAACT 2007) were included in the dataset and the hepatic maturation factor was adjusted.

Neonates from birth to 6 weeks of age – Non-interacting drugs

Simulations have been performed to support dosing recommendations for neonates from birth to ≤ 6 weeks of age based on the pharmacokinetic data from the IMPAACT 2007 study. The developed semi-physiological model was updated for MVC with non-interacting drugs for this analysis. Table 4 below summarizes the predicted MVC exposures with non-interacting drugs for proposed doses of 30 mg for 2 to <4 kg and 40 mg for 4 to <6 kg.

Table 4. Predicted MVC exposures at steady-state with noninteracting drugs based on the final model with IMPAACT 2007 data (b) (4)

Dose (mg)	Adult	2 to <3 kg	3 to <4 kg	4 to <5 kg	5 to <6 kg
	300	30	30	40	40
Cavg (ng/mL)					
GM (CV%)	95 (53)	161 (65)	127 (65)	147 (65)	114 (62)
Median (90%PI)	98 (40-208)	163 (58-415)	128 (46-326)	149 (53-373)	116 (43-287)
% >75 ng/mL	69	89	82	87	77
Ratio to Adult		1.66	1.31	1.52	1.18
Cmax (ng/mL)					
GM (CV%)	188 (84)	275 (83)	218 (82)	256 (81)	201 (81)
Median (90%PI)	178 (61-671)	270 (86-920)	220 (67-705)	252 (80-852)	196 (64-650)
Ratio to Adult		1.52	1.24	1.42	1.10
Cmin (ng/mL)					
GM (CV%)	55 (64)	102 (74)	80 (74)	92 (76)	70 (73)
Median (90%PI)	57 (20-140)	105 (33-287)	82 (26-231)	94 (29-265)	72 (23-199)
Ratio to Adult		1.84	1.44	1.65	1.26

Source: Applicant's clinical overview

The results indicate that the ratio of the median C_{avg} and C_{max} are less than 2-fold compared to the adult exposures with non-interacting drugs. In general, these exposures appear to be similar to those observed with the adults (300 mg BID), to those with non-interacting drugs from the A4001031 pediatric trial in children 2 years old to adolescence and the IMPAACT 2007 study. These results also indicate that the target Cavg ≥ 75 ng/mL is achieved by ≥ 77% of the

simulated infants. It is relatively lower (77%) in the 5 to < 6 kg group and higher (89%) in the 2 to <3 kg group. These results indicate that the proposed dosage by the Applicant is acceptable.

Infants ≥ 6 weeks to < 2 years of age – Non-interacting drugs

Table 5 shows the simulated MVC steady-state exposures with non-interacting drugs (b) (4) for infants aged 6 weeks to less than 2 years by weight bands. The developed semi-physiological model was updated for MVC with non-interacting drugs for this analysis.

Table 5: Predicted MVC exposures at steady-state with noninteracting drugs based on the final model with IMPAACT 2007 data (b) (4) for infants ≥ 6 weeks to <2 years by weight bands vs. adults

Dose (mg)	Adult	3 to <6 kg	6 to <10 kg	10 to <14 kg	14 to <20 kg
	300	40	100	150	200
Cavg (ng/mL)					
GM (CV%)	95 (53)	97 (68)	147 (69)	152 (57)	181 (52)
Median(90%PI)	98 (40-208)	98 (34-260)	148 (52-403)	157 (61-341)	186 (78-384)
% >75 ng/mL	69	66	86	90	96
Ratio to Adult		1.00	1.51	1.60	1.90
Cmax (ng/mL)					
GM (CV%)	188 (84)	178 (87)	290 (91)	312 (86)	371 (82)
Median (90%PI)	178 (61-671)	176 (53-628)	285 (82-1095)	302 (96-1120)	356 (121-1302)
Ratio to Adult		0.99	1.60	1.70	2.00
Cmin (ng/mL)					
GM (CV%)	55 (64)	58 (80)	83 (83)	84 (71)	101 (66)
Median (90%PI)	57 (20-140)	59 (17-179)	84 (24-264)	87 (28-225)	104 (36-259)
Ratio to Adult		1.04	1.47	1.53	1.82

Source: Applicant's clinical overview

The predictions indicate that the ratio of the median C_{avg} and C_{max} for (b) (4) doses in pediatric patients compared to adult predictions for the solution formulation taken with food and receiving non-interaction drugs ranged from 1.00 to 1.90 for C_{avg} and from 0.99 to 2.00 for C_{max} across the 4 weight-bands. These results also indicate that the target Cavg ≥ 75 ng/mL is achieved by ≥ 66% of the simulated infants. It is relatively lower (66%) in the 3 to < 6 kg group and higher (96%) in the 14 to <40 kg. (b) (4)

(b) (4) For a more accurate assessment, the clinical pharmaclogy/ pharmacometric review team conducted their analysis using the Applicant's final semi-physiological model. The results are shown in Table 6.

Table 6: Predicted MVC exposures at steady-state with non-interacting drugs (b) (4) The simulations were performed by the Agency with the Applicant's final PPK model.

Dose (mg)	Adult	3 - <4kg	4 - <6kg
	300	30	40
Cavg (ng/mL)			
GM (CV)	95 (53)	90 (68)	95 (66)
Median	98	93	96
Ratio to Adult		0.95	0.98
Cmax (ng/mL)			
GM (CV)	188 (84)	166 (89)	174 (86)
Median	178	159	172
Ratio to Adult		0.89	0.97
Cmin(ng/mL)			
GM (CV)	55 (64)	55 (75)	57 (77)
Median	57	58	58
Ratio to Adult		1.01	1.01

Source: Clinical Pharmacology Review

These results demonstrate that the dosage of 30 mg/kg in the 3 to <4 kg group provides similar exposures with the dosage of 40 mg/kg in the 4 to <6 kg group. These findings support the Applicant's recommendations for those weight band groups when MVC is administered with no interacting drugs.

Infants from birth to < 2 years of age – When co-administered with potent CYP3A inhibitors

The clinical pharmacology/pharmacometrics review team does not agree with the Applicant's proposed dosage recommendations for the weight bands 2 to <4 kg, 4 to <6 kg, and 6 to <10 kg when MVC is co-administered with potent CYP3A inhibitors. Currently there are no pharmacokinetic data available for pediatric subjects less than 2 years of age, less than 10 kg, who received MVC with concomitant administration of potent CYP3A inhibitors.

Separate models were used to describe data with and without potent CYP3A inhibitors because the original model that accounts for drug-drug interaction (DDI) could not predict exposures in the noninteracting scenario, which results in challenges for utilizing noninteracting data for neonates to predict MVC exposure for subjects receiving concomitant CYP3A inhibitors. This is further complicated by the CYP3A maturation that takes place in children <1 year of age because it is not known whether the magnitude of the drug-drug interaction effect is changing with the maturation of the CYP3A expression. Therefore, the clinical pharmacology/pharmacometrics review team does not recommend the use of MVC in

pediatric subjects who are < 2 years of age, <10 kg, and are receiving concomitant potent CYP3A inhibitors.

- Table 7 below summarizes the Division's MVC dosage recommendations for pediatric patients weighing at least 2 kg based on the input and analysis by the clinical pharmacology/pharmacometrics review team. In summary, MVC is recommended for children weighing at least 2 kg when maraviroc is used with non-interacting concomitant medications. However, MVC is not recommended for approval for children < 10 kg when is co-administered with potent CYP3A inhibitors.

Table 7. MVC Dosage Recommended by the Agency in Pediatric Patients at least 2 kg (blue font shows the new recommended dosage, underline shows the difference between the Division's recommended dosage and the Applicant's proposed dosage)

Concomitant Medications	**Dosage (Volume of Solution) of SELZENTRY Based on Weight**							
	2 kg to <4 kg	**4 kg to <6 kg**	**6 kg to <10 kg**	**10 kg to <14 kg**	**14 kg to <20 kg**	**20 kg to <30 kg**	**30 kg to <40 kg**	**≥40 kg**
Potent CYP3A inhibitors (with or without a CYP3A inducer)	Not recommended			50 mg BID	50 mg BID	75 mg (tablet) or 80 mg (oral solution) BID	100 mg BID	150 mg BID
Noninteracting concomitant medications	30 mg BID	40 mg BID	100 mg BID	150 mg BID	200 mg BID	200 mg BID	300 mg BID	300 mg BID

The Division's recommendations were discussed and agreed upon by the Sponsor and will be included in the updated Package Insert.

For more details, please see the Clinical pharmacology/pharmacometrics review by Dr. Jenny Zheng, Dr. Justin Earp, and Dr. Su-Young Choi.

6. Clinical Microbiology

No clinical microbiology data were included in this submission.

7. Clinical/Statistical- Efficacy

The following clinical study was included in these submissions:

Study No	**Objectives of the study**	**Number of subjects**
IMPAACT 2007 (b) (4)	A phase I, multicenter, open-label, intensive pharmacokinetic study designed to evaluate the	47

	pharmacokinetics and safety of MVC solution when administered with a single or combination ARV regimen for prevention of perinatal HIV transmission to infants exposed to HIV-1.	

Study IMPAACT 2007

Study design: This was a Phase 1, multi-center, open-label intensive pharmacokinetic study designed to evaluate the pharmacokinetics and safety of MVC solution when administered with a single or combination ARV regimen for the prevention of perinatal HIV transmission to infants exposed to HIV-1 infected mothers. The study was conducted in full-term neonates (weighing at least 2 kg) up to 3 days old born to HIV-1 mothers. Infants were enrolled in 2 sequential dosing cohorts stratified by efavirenz (EFV) exposure. Cohort 1 was stratified by in utero exposure to maternal EFV and Cohort 2 was stratified by exposure to maternal EFV during breastfeeding. A total of 47 infants fulfilling the entry criteria were enrolled in the following cohorts and strata:

Cohort 1:

Stratum 1A: Infants without *in utero* exposure to maternal EFV (no EFV exposure during the eight weeks immediately prior to delivery) (enrolled 8)

Stratum 1B: Infants with in utero exposure to maternal EFV (EFV exposure for a minimum of two weeks immediately prior to delivery) (enrolled 7).

Treatment assignment: Cohort 1 participants received 2 single doses of MVC ~8 mg/kg as an initial starting dose. The first dose was administered within 3 days after birth and the second dose at Week 1 (Day 7 to 14) of life.

Cohort 2:

Stratum 2A: Infants without any exposure to maternal EFV either in utero (no EFV exposure during the eight weeks immediately prior to delivery) and if breastfeeding while breastfeeding (enrolled 16).

Stratum 2B: Breastfeeding infants with exposure to maternal EFV both in utero and after birth while breastfeeding. (EFV exposure for a minimum of two weeks immediately prior to delivery and while breastfeeding) (enrolled 16).

Treatment assignment: Cohort 2 participants received doses of MVC ~8 mg/kg b.i.d. MVC was administered within 3 days after birth and continued for up to 42 days of life.

Blood samples for pharmacokinetic analysis were obtained as follows:

Cohort 1: On Day 1 before and up to 24 hours (± 2 hours) post-dose. Additional sparse blood samples were collected at Week 1 (pre-dose, 1-2 hours and 22-26 hours post-dose

Cohort 2: Pre-dose and up to 12 hours (± 1 hour) at Week 1 and Week 4. Additional sparse blood samples were collected at Week 6 (single random sample)

Treatment assignment

This was an open-label study. Cohort 1 participants received 2 single doses of MVC ~8 mg/kg as an initial starting dose. The first dose was administered within 3 days after birth and the second dose at Week 1 (Day 7 to 14) of life. Cohort 2 participants received doses of MVC BID at a dose ~8 mg/kg. MVC was administered within 3 days after birth and continued for up to 42 days of life.

MVC was administered by oral syringe (oral dispenser) using weight-band based dosing as shown in Table 8. Infants were weighted at each visit to determine the dose.

Table 8. Weight-based dosing for infant participants (~ 8 mg/kg)

Weight band (kg)	Dose (mg)	Volume to administer (mL)
2.00 to 2.54	20	1
2.55 to 3.14	25	1.25
3.15 to 3.84	30	1.5
3.85 to 5.04	40	2
5.05 to 6.00	50	2.5

Inclusion criteria

Key inclusion criteria for mother-infant pairs were as follows:

- Criteria for participant mothers: participant mother was of legal age to provide independent informed consent for research participation and was willing and able to provide written informed consent for her and her infant's participation in the study; participant mother was confirmed to be living with HIV-1 infection based on testing of 2 samples (whole blood, serum, or plasma) collected at different time points
- Criteria at birth for infant participants: estimated gestational age was at least 37 weeks; weight was at least 2 kg, born after singleton delivery (not after multiple birth)
- Criteria at entry for infant participants: ≤ 3 days old; Grade 0 ALT (normal); ≤ Grade 1 AST and total bilirubin; ≤ Grade 2 hemoglobin, white blood cell counts, and platelet counts; had initiated ARV prophylaxis that did not include a potent CYP3A inhibitor or inducer; is generally healthy
- EFV exposure requirements for infant participants at entry:
  - Cohort 1, Stratum 1A: Born to a mother who did not receive EFV during the 8 weeks immediately prior to delivery. Breastfeeding and formula feeding infant participants were eligible
  - Cohort 1, Stratum 1B: Born to a mother who received EFV for a minimum of 2 weeks immediately prior to delivery. Breastfeeding and formula feeding infant participants were eligible.
  - Cohort 2, Stratum 2A: Born to a mother who did not receive EFV during the 8 weeks immediately prior to delivery and if breastfeeding, mother was not receiving maternal EFV. Breastfeeding and formula feeding infant participants were eligible.

- Cohort 2, Stratum 2B: Breastfed and born to a mother who received EFV for a minimum of 2 weeks immediately prior to delivery, intended to breastfeed for a minimum of 6 weeks and would continue to receive maternal EFV while breastfeeding. Only breastfeeding infant participants were eligible.

Exclusion criteria

Key exclusion criteria for mother-infant participant pairs were as follows:

- Infant had any other condition that may cause participation in the study to be unsafe or interfere with study outcome or interpretation
- Positive infant HIV nucleic acid test (NAT) result at entry
- Infant or breastfeeding mother was receiving any disallowed medication at entry
- Mother received MVC during pregnancy

Safety monitoring: Infants were followed for 16 weeks of life, including clinical and laboratory assessments. Mothers had evaluations performed only at screening and entry.

Primary endpoints: Safety and pharmacokinetic parameters were the primary endpoints of the study. The key primary pharmacokinetic endpoint for dose-finding purposes was the failure to achieve $C_{avg} \geq 75$ ng/mL (see Section 5, Clinical Pharmacology/Biopharmaceutics).

Disposition of Subjects and Baseline Characteristics

Study populations: A total of 47 mother-infant pairs from four countries (USA 20, South Africa 22, Thailand 3, and Kenya 2) and 9 different study sites were enrolled in the study. The study populations and patient disposition are summarized in Table 9.

Table 9. Study populations and patient disposition

Populations	Cohort 1			Cohort 2		
	Stratum 1A (N=8)	Stratum 1B (N=7)	Total (N=15)	Stratum 2A (N=16)	Stratum 2B (N=16)	Total (N=32)
All treated	8	7	15	16	16	32
Safety evaluable for dose-finding purposes	6	7	13	12	12	24
PK-evaluable for dose-finding purposes	6	7	13	13	12	25
Early treatment discontinuation	2	0	2	4	3	7
Early study discontinuation	0	0	0	3	3	6

Overall key baseline characteristics

Mothers

- Median age (years): Stratum 1A: 29.5; Stratum 1B: 26.0; Stratum 2A: 32.0; Stratum 2B: 32.0
- Race (Black): Stratum 1A: 62.5%; Stratum 1B: 100%; Stratum 2A: 62.5%; Stratum 2B: 100%

Infants

- Sex (Female): Stratum 1A: 62.5%; Stratum 1B: 57.1%; Stratum 2A: 43.8%; Stratum 2B: 43.8%

- Race (Black): Stratum 1A: 62.5%; Stratum 1B: 100%; Stratum 2A: 62.5%; Stratum 2B: 100%

Twenty-four (51%) of the enrolled neonates were male and 23 (49%) were female. The majority of the neonates were black (38/47, 81%), 6 (13%) were white, and 3 (6%) were Asian. The ethnicity breakdown was 42 (89%) subjects were not Hispanic or Latino and 5 (11%) subjects were Hispanic or Latino.

In addition to treatment with MVC, most infants received nevirapine (19), zidovudine (18), or nevirapine/zidovudine (6).

Pharmacokinetic results: Please see Section 5, Clinical pharmacology/Biopharmaceutics.

Efficacy outcome: Although this was not an efficacy study, none of the enrolled infants became HIV-1 infected during treatment and through the end of the follow-up period (16 week of life).

8. Safety

The adverse event profile associated with MVC is well established (see approved Selzentry Package Insert). No new safety signals were identified on review of this small pharmacokinetic and safety study. Based on study design, MVC treatment ended after Week 1 of life in Cohort 1 and after Week 6 of life in Cohort 2. All participants were followed for safety through 16 weeks. The median extent of exposure to MVC in Cohort 1 was 2 days (2 doses), while the median MVC exposure in Cohort 2 was 37.5 days (ranging from 1 to 42 days). A brief description of the safety findings in Study IMPAACT 2007 is presented below:

Adverse events: The majority of the subjects in both cohorts and within each stratum experienced at least one adverse event. More participants experienced an adverse event during the first 6 weeks of life compared to the follow-up period. The majority of the adverse events were of Grade 1 or Grade 2 in severity and none of the events was considered related to MVC.

The most common adverse events through Week 6 were:

AES observed in more than one infant:
Cohort 1: Decreased hemoglobin (5), nasal congestion (3), dermatitis diaper (3), eye discharge (2), elevated bilirubin (2), underweight (2), papule (2), rash (2), rash neonatal (2).

Cohort 2: Decreased hemoglobin (14), elevated bilirubin (13), decreased neutrophil count (8), cough (4), rash neonatal (4), increased AST (3), eye discharge (3), ophthalmia neonatorum (3), rash (3), underweight (3), hyperbilirubinemia (2), Failure to thrive (2), nasal congestion (2), feeling hot (2), jaundice neonatal (2), and miliaria (2).

Grade 3+ adverse events:
Cohort 1: Only one participant from Cohort 1 experienced 2 Grade 3 AEs: staphylococcal sepsis (serious) and ophthalmia neonatorum (non-serious). For additional information about this patient see “Withdrawals due to adverse events.”

Cohort 2: Twelve participants experienced at least 1 Grade 3+ AEs. Eight of the subjects experienced at least 1 Grade 3+ AE during the first 6 weeks and 12 subjects through Week 16. Most of the grade 3+ AEs were in the Investigations SOC which is not uncommon for this age group. None of the Grade 3+ AEs were considered related to study drug. Table 10 summarizes the Grade 3+ AEs observed in Cohort 2 during the study.

Table 10. Summary of Grade 3+ adverse events observed in Cohort 2.

System organ class – Preferred term	**Cohort 2 (N=32)**	
	6 weeks	**16 weeks**
Total participants with ≥ Grade 3+ AE	8 (25)	12(37.5)
Blood and lymphatic system disorders	0	1(3.1)
Hemolytic anemia	0	1
Hepatobiliary disorders	1(3.1)	2(6.3)
Hyperbilirubinemia	1(3.1)	1(3.1)
Jaundice	0	1(3.1)
Infections and Infestations	0	1(3.1)
Bacterial pneumonia	0	1(3.1)
Investigations*	7(21.9)	9(28.1)
Blood bilirubin increased	4(12.5)	4(12.5)
Hemoglobin decreased	1(3.1)	1(3.1)
Neutrophil count decreased	1(3.1)	4(12.5)
Weight decreased	2(6.3)	2(6.3)
Metabolism and nutrition disorders	2(6.3)	2(6.3)
Failure to thrive	2(6.3)	2(6.3)
Respiratory, thoracic and mediastinal disorders	0	1(3.1)
Hypoxia	0	1(3.1)

*Laboratory abnormalities were included under the definition of an AE and were captured under the Investigations SOC

Deaths: No deaths were reported during the study.

Serious adverse events: Five participants (2 participants in Cohort 1 and 3 in Cohort 2) experienced a total of 9 serious adverse events through week 6 of life. By Week 16, a total of 8 participants experienced a total of 14 SAEs (2 subjects in Cohort 1 and 6 subjects in Cohort 2). The SAEs observed during the first 6 weeks were one each of cyanosis, slow response to stimuli, tremor, staphylococcal sepsis, neonatal sepsis, decreased weight, and 2 events of failure to thrive. The additional SAEs observed after Week 6 were: hemolytic anemia, jaundice, *E. coli* urinary tract infection, bacterial pneumonia, and decreased neutrophil count).

Serious adverse events related to study drug: None of the serious adverse events was considered related to study drug.

Withdrawals due to adverse events: There was one subject who discontinued the study due to an adverse event. This was a 9-day-old female who was born at home with a birthweight of 2.2 kg. The participant developed staphylococcal sepsis 5 days after the first dose of MVC. The subject was discontinued from the study and did not receive the second dose of MVC. During

her Week 1 visit she was referred to the hospital for admission where she was diagnosed with staphylococcal sepsis, neonatal jaundice, and severe ophthalmia neonatorum. The events were resolved after treatment with antibiotics. The investigator considered the event of staphylococcal sepsis as not related to MVC.

Laboratory Abnormalities

Hematologic abnormalities (decreased hemoglobin, decreased neutrophil count) were the most common laboratory abnormalities seen in Study IMPAACT 2007. A total of 6 subjects (all of them in Cohort 2) experienced Grade 3 (5 subjects) or Grade 4 (1 subject) through 16 weeks of life. The subjects with Grade 3+ laboratory abnormalities were: hemolytic anemia 1, decrease hemoglobin 1, decreased neutrophil count 4 (3 subjects with Grade 3 and 1 subject with Grade 4). None of the events was considered related to study drug. The 6 participants with Grade 3+ laboratory abnormalities are described below:

Subject (b) (6): A 12-week-old female who developed Grade 4 decreased neutrophil count (serious) 60 days after the last dose of MVC. The infant was noted to have a neutrophil count of 360 cells/mm^3 and marked lymphocyte predominance during the 12-week visit. It was attributed to a viral infection (diarrhea for 3 days). Five weeks later the neutrophil count increased to 1500 cells/mm^3.

Subject (b) (6): A 23-day-old female who developed Grade 3 decreased hemoglobin (8.3 g/dL) (serious) 20 days after the first dose of MVC. The infant was also receiving lamivudine (from birth to 3 weeks), nevirapine at birth, and zidovudine (from birth, ongoing) MVC was continued and the event resolved by Week 16. Zidovudine was considered as the most likely cause of decreased hemoglobin.

Subject (b) (6): A 16-week-old female who developed Grade 3 neutrophil count decreased (non-serious) 71 days after the last dose of MVC. Other AEs for this participant included cough, feeling hot, neonatal rash, and rhinorrhea. Concomitant medications included zidovudine/nevirapine routine vaccinations, trimethoprim/sulfamethoxazole, paracetamol and chlorphenamine. All AEs resolved.

Subject (b) (6): A 12-week-old male who developed Grade 3 neutrophil count decreased (non-serious) 44 days after the last dose of MVC. They had previously experienced a Grade 1 decrease in neutrophil count at Week 4 (for which treatment continued, uninterrupted) and a Grade 2 decrease in neutrophil count at Week 6; at Week 16, a further Grade 2 decrease in neutrophil count occurred. No other AEs for this participant were noted and all AEs resolved. The participant was also receiving nevirapine and had also received concomitant routine vaccinations.

Subject (b) (6): A 6-week-old male who developed Grade 3 neutrophil count decreased (non-serious) 1 day after the last dose of MVC and then again at 12 weeks of age (48 days after the last dose of MVC). The participant experienced other non-serious AEs, including Grade 1 abdominal distension and Grade 1 decreased hemoglobin at Week 1, Grade 1 miliaria at Week 4, Grade 2 decreased neutrophil count and Grade 1 rash at Week

16. The participant was receiving concomitant nevirapine and had also receive routine vaccinations. With the exception of rash at Week 16, all other AEs resolved.

Participant (b) (6): A 10-week-old male who experienced a Grade 3 hemolytic anemia (Hgb 5.7 g/dL (serious) at Week 12. Additional Grade 3 SAEs of jaundice, and *E. coli* related UTI were also reported at Week 12 (for all SAEs, the relative onset day to first dose of MVC was 67 days). Grade 2 and Grade 1 AST increased were reported at Week 1 and Week 4, respectively. Grade 2 increased bilirubin was reported at Week 6. MVC dosing was not changed or interrupted. At his 12-week visit all laboratory tests including Hgb, bilirubin, transaminases were within normal range. The investigator considered these AEs not related to MVC.

Comment: Evaluation of the safety data from the IMPAACT 2007 study showed that MVC treatment in combination with other antiretroviral drugs is generally well tolerated. No new safety concerns were identified compared to the known profile of MVC.

9. Advisory Committee Meeting

No Advisory Committee Meeting was held to discuss these sNDAs.

10. Pediatrics

These sNDAs contain pharmacokinetic and safety data for subjects from birth to 6 weeks of age enrolled in Study IMPAACT 2007 (b) (4). These submissions also provide dosage recommendations for children aged 6 weeks to less than 2 years based on population pharmacokinetic and modeling and simulation studies. These reports are in response to the Pediatric Written Request for MVC. The Applicant supports that these submissions together the previously submitted study in HIV-infected pediatric patients 2 years to adolescence (NDA 208984 and sNDA 22128/S-17; approved November 4, 2016) fulfill the requirements of the Pediatric Written Request. In fact, all data in response to the Pediatric Written Request were presented to the Pediatric Exclusivity Board on July 22, 2020. The Board determined that the submitted data fulfilled the intent and requirements of the Pediatric Written Request and exclusivity was granted.

These data were also presented to the Pediatric Review Committee on October 6, 2020. The Committee agreed with the Division's assessment and proposed plans for labeling.

11. Other Relevant Regulatory Issues

Financial disclosures

In compliance with the rule of Financial Disclosure by Clinical Investigators, the Applicant provided financial interest information for clinical investigators and sub-investigators participating in Study IMPAACT 2007. Based on the available financial data, the $25,000

threshold was exceeded by two sub-investigators (b) (6) participating in the study.

(b) (6) served as a sub-investigator for the study center (b) (6) . During the conduct of this study she received payments exceeding the $25,000 threshold from ViiV towards her services as investigator for Study 205860 (A phase I/II study of the pharmacokinetics, safety, and tolerability of abacavir/ dolutegravir/lamivudine dispersible and immediate release tablets in HIV-1-infected children less than 12 years of age).

(b) (6) also served as a sub-investigator for the study center (b) (6) During the conduct of this study, (b) (6) received payments exceeding the threshold of $25,000 from ViiV for services as investigator for Study 208580 (A phase I/II study of the safety, acceptability, tolerability and pharmacokinetics of oral and long-acting injectable cabotegravir and long-acting injectable rilpivirine in virologically suppressed HIV-infected children and adolescents).

Center (b) (6) recruited (b) (6) subjects from the total of 47 subjects which accounts for (b) (6)% of the total enrollment. The study statisticians were consulted, and a review was performed which determined no impact on the study.

Other Good Clinical Practice (GCP) issues

Study IMPAACT 2007 was conducted in collaboration with the IMPAACT Network on behalf of ViiV Healthcare. IMPAACT is sponsored by NAID, NICHD, and NIMH. The Applicant states the study was conducted according to accepted ethical standards based on the precepts established by the declaration of Helsinki. The study was conducted with the approval of Ethics Committees or Institutional Review Boards and Informed Consent form was signed by the mothers of all subjects.

Office of Study Integrity and Surveillance (OSIS) audits

At the request of the Division of Antivirals, the OSIS audited two sites from the IMPAACT 2007 study; one site in the United States (Site #5083, Rush University Medical Center, Chicago, IL) and one site in South Africa (Site #8052, Soweto, South Africa). These sites were selected based on enrollment. Due to the global COVID-19 pandemic, inspection for Study site #8052 was conducted remotely. Based on the inspections of the two clinical sites, the study appears to have been conducted adequately and the inspectional findings support the validity and acceptability of the data as reported by the Applicant under these two sNDAs. Please refer to OSIS Consult Review for additional details.

Of note, OSIS determined that an inspection of the Analytical site at the University of Alabama, Birmingham, AL, was not warranted at this time. The OSIS inspected this site in February 2020 which falls within the surveillance interval. The final classification for the inspection was No Action Indicated.

12. Labeling

Key labeling changes included the following sections:

- INDICATIONS AND USAGE: This section was modified to include the indication of MVC in combination with other antiretroviral agents for the treatment of only CCR5-tropic HIV-1-infection in pediatric patients from birth to less than 2 years of age weighing at least 2kg.
- DOSAGE AND ADMINISTRATION: This section was modified to include recommended dosage for patients weighing 2 kg up to less than 10 kg. In addition, a new dosing recommendation was added for patients weighing 10 kg to less than 30 kg when MVC is used with no interacting concomitant medications.
- ADVERSE REACTIONS: The subsection "Clinical Trials Experience" was modified to add information on the adverse reactions observed in Trial IMPAACT 2007.
- USE IN SPECIFIC POPULATIONS: The subsection "Pediatric Use" was modified to add information on the use of MVC for the treatment HIV-1-infected neonates aged from birth to 6 weeks and HIV-1-infected pediatric patients aged older than 6 weeks to less than 2 years.
- CLINICAL PHARMACOLOGY: The subsection "Pharmacokinetics" was modified to add information on the pharmacokinetics of MVC for pediatric patients aged from birth to less than 6 weeks. For pediatric patients aged older than 6 weeks to less than 2 years of age, this subsection includes a statement that dosing recommendation dosing recommendation is based on population pharmacokinetic modeling and simulation.
- HOW SUPPLIED/STORAGE AND HANDLING: This section was modified to add a 3-mL syringe to the convenience kit for the oral solution formulation to more accurately measure doses of 2.5 mL or less.

Modifications of the proposed label have been discussed and agreed upon by the Applicant. It is noteworthy that the proposed labels were also reviewed and agreed upon by the Division of Medical Policy Programs, the Division of Medication Error Prevention and Analysis, and the Office of Prescription Drug Promotion. Please see the Regulatory Project Manager Labeling Review for labeling changes.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action
  Based on the totality of the data presented and the input from the clinical pharmacology/pharmacometrics review team, the clinical review team recommends the following:
  - Approval for pediatric patients 2 kg to less than 30 kg when maraviroc is used with non-interacting concomitant medications
  - MCV is not recommended for pediatric patients less than 10 kg who are receiving concomitant potent CYP3A inhibitors because there are no available pharmacokinetic data and modeling and simulation studies are unable to reliably predict the

pharmacokinetics of maraviroc in this population when it is used with concomitant potent CYP3A inhibitors
- Approval of the addition of the 3-mL syringe to the convenience kit

- Risk Benefit Assessment
  The safety and efficacy of MVC for the treatment of HIV-1 infection have been previously established in adult patients and pediatric patients aged 2 years to adolescence. The IMPAACT 2007 study was an open-label study in which 47 full-term HIV-1 exposed neonates (born to HIV-infected mothers) received MVC in combination with other antiretrovirals, mostly zidovudine and/or nevirapine. Cohort 1 (15 subjects) received 2 single doses of MVC. The first within 3 days of birth and the second at 7-14 days of life. Cohort 2 (32 subjects) received MVC twice daily for the first 6 weeks of life. The safety profile observed in neonates was similar with that observed in adults and older children (2 to 18 years of age). MVC was generally safe and well tolerated in this small study. No deaths were reported and there were no serious adverse events related to the study drug.

  Clearly, the size of Study IMPAACT 2007 is very small and the study was not designed to provide efficacy data. Similarly, there are no safety and efficacy data from pediatric patients 6 weeks to less than 2 years of age. However, considering that the disease is similar between adults and pediatric patients of all age groups, efficacy for children less than 2 years of age could be extrapolated from adult studies and the A4001031 study in pediatric patients aged 2 years to adolescence. Similarly, safety for pediatric patients aged more than 6 weeks to less than 2 years could be interpolated from the safety data available from the IMPAACT 2007 and the study in children older than 2 years of age (A4001031). The review team believes that the risk/benefit of this drug for children from birth to less than 2 years of age is overall favorable.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies:
  A new Postmarketing Risk Evaluation and Management Strategy (REMS) is not recommended.

- Recommendation for other Postmarketing Requirements and Commitments: No post-marketing requirements or commitments are recommended.

- Recommended Comments to Applicant: None

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ANDREAS PIKIS
10/30/2020 10:09:06 PM

MARY E SINGER
10/30/2020 10:11:38 PM
I agree with Dr. Pikis' review and recommendation for approval of this pediatric supplement