CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215413Orig1s000

CLINICAL MICROBIOLOGY/VIROLOGY REVIEW(S)

DIVISION OF ANTIVIRALS (HFD-530)
VIROLOGY REVIEW
NDA: 215413 **SDN**: 000 **NDA**: 205551 S-028 **SDN:** 964 **DATE REVIEWED:** 11/01/2021
Virology Reviewer: Anamaris M. Colberg-Poley, Ph.D.

Reviewer: Anamaris M. Colberg-Poley, Ph.D.

Sponsor: **ViiV Healthcare Company**
c/o GlaxoSmithKline
PO Box 13398
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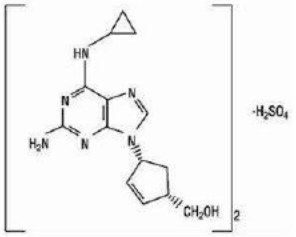
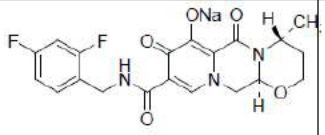
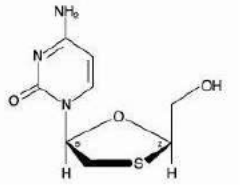
Submissions Reviewed:

SDN	Date Received	Date Assigned	PDUFA Date	Review Complete
N215413.000	09/30/2021	10/05/2021	03/30/2022	02/17/2022
N205551.S-028.964	09/30/2021	10/01/2021	03/30/2022	02/17/2022

Product Name(s)
Proprietary: Triumeq; Triumeq PD (dispersible tablet, DT, formulation), Triumeq DT
Non-Proprietary/USAN: abacavir, dolutegravir, lamivudine
Code Name/Number: GSK1349572A

Product Name	Abacavir, ABC	Dolutegravir, DTG, TIVICAY®	Lamivudine, 3TC
Chemical Structure			
Chemical Name	1S,cis)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol sulfate (salt) (2:1)	Sodium (4R,12aS)-9-{[(2,4-difluorophenyl)methyl]carbamoyl}-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido[1',2':4,5] pyrazino[2,1-b][1,3]oxazin-7-olate	(2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one
Molecular formula	$(C_{14}H_{18}N_6O)_2 \cdot H_2SO_4$	$C_{20}H_{18}F_2N_3NaO_5$	$C_8H_{11}N_3O_3S$
Molecular weight	670.76	441.36	229.26

Drug category: Antiretroviral
Indication: Triumeq and Triumeq PD are indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and in pediatric patients weighing at least 14 kg.
Dosage Form/Route of administration: tablet or dispersible tablet/oral

Supporting Documents: IND 075382 (dolutegravir); IND 114820 (abacavir, dolutegravir, lamivudine); NDA 020564 and 020596 (lamivudine), NDA 020977 (abacavir sulfate); and NDA 204790 (dolutegravir)

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Abbreviations
3TC, lamivudine; ABC, abacavir; ART, antiretroviral therapy; BL, baseline; DT, dispersible tablet; DTG, dolutegravir; Env, envelope; FDC, fixed dose combination; FTC, emtricitabine; HIV-1, human immunodeficiency virus type 1; IN, integrase; INSTI, integrase strand transfer inhibitor; ITT-E, Intent-to-Treat Exposed; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleos(t)ide analogue reverse transcriptase inhibitor; PMR, post-marketing requirements; PMS, post-marketing surveillance; RAS, resistance-associated substitution; RT, reverse transcriptase; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; VL, viral load; WB, weight bands

Background
Approvals of the individual components of Triumeq:
A tablet formulation of dolutegravir (DTG), an integrase strand transfer inhibitor (INSTI), tablets (Tivicay®) was originally approved (August 12, 2013, NDA 204790.S000lbl) in combination with other antiretroviral agents for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and children ≥12 years, weighing ≥40 kg. More recently, DTG tablets for oral suspension (Tivicay PD®) were approved (June 12, 2020, NDA 213983.S000lbl) in combination with other antiretrovirals for the treatment of HIV-1 infection in adults (treatment-naïve or -experienced) and in pediatric patients (treatment-naïve or -experienced but INSTI-naïve) aged ≥4 weeks and weighing ≥3 kg. The dispersible tablet (DT) formulation of DTG (+ 2 nucleos(t)ide analogue reverse transcriptase inhibitors, NRTIs) is now the recommended first-line treatment regimen for use in children in the U.S. aged ≥4 weeks and weighing at least 3 kg (DHHS Guidelines for the use of antiretroviral agents in pediatric HIV infection, 2021). The fixed dose combination (FDC) of two NRTIs, abacavir (ABC) and lamivudine (3TC) (Epzicom®), was originally approved on August 2, 2004 for the treatment of HIV-1 infection (NDA 021652s000lbl) and is currently approved to treat HIV-1 infection in adults and pediatric patients weighing ≥25 kg (NDA 021652s028lbl, approved February 17, 2021).

Approval of Triumeq:
Triumeq® is a FDC of DTG in combination with abacavir (ABC) + lamivudine (3TC) and was initially approved as a complete regimen for the treatment of HIV-1 infection in adults with no antiretroviral therapy (ART) history and with no known substitutions associated with resistance to the individual components of Triumeq on August 22, 2014 (NDA 205551s000lbl). The FDC of ABC+DTG+3TC is currently indicated for the treatment of HIV-1 infection in adults and in pediatric patients weighing ≥40 kg (NDA 205551s026lbl, approved on March 23, 2021). For details of the Clinical Virology review of Clinical Study data (ING113086, ING111762, ING114467 (ART naïve adults), and ING114915 (ART naïve adults)) of Triumeq treated adult and children ≥12 years, weighing ≥40 kg, see Dr. Lisa K. Naeger's review of NDA 205551.000 and review of NDA 205551.S-005.139.

The use of Triumeq PD (DTs for oral suspension of ABC 60 mg/DTG 5 mg/3TC 30 mg) for the treatment of HIV-1 infection in children weighing ≥14 kg has not yet been approved. This original NDA 215413 proposes dosing with Triumeq PD for the treatment of HIV-1 infected pediatric patients weighing ≥14 kg to <25 kg. In addition, the supplemental NDA 205551.S-028 proposes Triumeq tablet dosing to treat HIV-1 infected pediatric patients weighing ≥25 kg to <40 kg. The applications were also submitted in response to Post-Marketing Requirements (PMRs): 2768-1, 2768-2, and 2768-3 (below). On November 21, 2017, Triumeq (ABC 600 mg, DTG 50 mg, 3TC 300 mg) tablets were approved for use in pediatric patients weighing at least 40 kg and PMR 2768-3 was fulfilled. These two submissions are intended to fulfill PMR 2768-2. According to the sponsor, an additional application to fulfill PMR 2768-1 will be submitted at a later date when results from the IMPAACT P2019 study are available.

Triumeq NDA 205551 PMRs:
- **2768-1:** Conduct a pediatric trial to evaluate the pharmacokinetics, safety and antiviral activity (efficacy) of abacavir/dolutegravir/lamivudine FDC tablets in HIV infected pediatric participants 2 years to less than 6 years of age. The safety and antiviral activity (efficacy) of abacavir/dolutegravir/lamivudine FDC tablets in pediatric participants should be evaluated for a minimum of 24 weeks.

- **2768-2:** Conduct a pediatric trial to evaluate the pharmacokinetics, safety and antiviral activity (efficacy) of abacavir/dolutegravir/lamivudine FDC tablets in HIV infected pediatric participants 6 years to less than 12 years of age and in children older than 12 years of age who weigh less than 40 kg. The safety and antiviral activity (efficacy) of abacavir/dolutegravir/lamivudine FDC tablets in pediatric participants should be evaluated for a minimum of 24 weeks.

- **2768-3** [Fulfilled]: Evaluate the pharmacokinetics, safety and antiviral activity (efficacy) of abacavir/dolutegravir/lamivudine FDC tablets in HIV infected pediatric participants 12 years to less than 18 years of age and weighing at least 40 kg. The safety and antiviral activity (efficacy) of abacavir/dolutegravir/lamivudine FDC tablets in pediatric participants should be evaluated for a minimum of 24 weeks. A clinical trial in children 12 to less than 18 years of age and weighing at least 40 kg may not be required if dosing recommendation for the FDC tablets can be supported by pediatric trials already conducted with the individual drug products.

In the current submissions, the sponsor provided three biopharmaceutics studies (Study 205894, Study 2000402, Study 216149) and two clinical pharmacology reports (Clin Pharm reports 1 and 2) as well as post-marketing experience for DTG in combination with ABC+3TC and relevant literature in support of the proposed indication. Based upon the Agency's agreement (NDA 205551, PK 4746482, February 12, 2021), nonclinical and virology datasets, which supported the approvals of the ABC, DTG, and 3TC (Tivicay, Tivicay PD, Epivir and Ziagen) were not required for the current applications. Thus, the sponsor did not provide efficacy or safety data in these submissions but cross-referenced the approved single entity applications (below). Some of the cross-referenced applications were submitted from 1995 through 2003 (Epivir (3TC): NDA 020564, NDA 020597; Ziagen (ABC): NDA 020977, NDA 020978; Epzicom (ABC+3TC): NDA 021652) and their efficacy data were not accessible for review. Therefore, our review is focused on the cross-referenced pediatric clinical studies with efficacy data (ARROW Randomization 3, NDA 020977.S-027 and IMPAACT P1093, NDA 204790.S025) in the more recent submissions, which were accessible for review.

Dolutegravir treatment of pediatric subjects (IMPAACT P1093 Study (Clinical Study ING112578); NDA 204790.S-025 and NDA 213983.000)

We previously reviewed IMPAACT P1093 efficacy data, which included pediatric subjects treated with DTG in combination with ABC+3TC tablets and DTs used in support of approval of DTG treatment of HIV-1 infection in combination with other antiretroviral agents in adults and in pediatric patients aged at least 4 weeks and weighing at least 3 kg (Dr. Colberg Poley's review of NDA 204790.S-025 and NDA 213983.000).

The IMPAACT P1093 Study is an ongoing phase I/II multi-center, open-label, non-comparative study of pharmacokinetic (PK) parameters, safety, tolerability, and efficacy of DTG in pediatric populations (NCT01302847). Most pediatric subjects were treatment experienced and nonetheless, most were virologic responders during DTG treatment. At Week 24 (<50 copies/mL: 36/58, 62.1%; <400 copies/mL: 50/58, 86.2%) and Week 48 (<50 copies/mL: 29/42, 69.0%; <400 copies/mL: 33/42, 78.6%) were virologic responders. However, FDA analyses identified 11 evaluable virologic failures (19%) of the 58 pediatric subjects through Week 48. We concluded that known HIV-1 integrase (IN) resistance-associated substitutions (RASs: G118R E138T, S147S/G, S153S/A/F/V, R263K) emerged in three virologic failure subjects during DTG treatment (Clinical Virology analyses). The sponsor recently published their analyses of emergence of IN resistance in the IMPAACT P1093 study (Vavro et al., 2021), with similar findings to ours. Nonetheless, the underlying causes of virologic failure for some pediatric subjects with no emergence of known IN RAS were less clear. Based upon subject reported nonadherence and intensive PK data and sparse PK data, suboptimal adherence appears to have contributed to virologic failure in some pediatric subjects of the IMPAACT P1093 Study.

Formulations are being evaluated in P1093 in age-specific cohorts as shown below (Table 1 with relevant weight bands, WBs). DTG treatment of HIV-1 infected pediatric patients in the Weight Bands were comparable except in Weight Band III DT (14 to <20 kg), which only had one subject, at Week 48 (Table 1).

Table 1. Efficacy Outcomes in Clinical Study P1093 (ING112578) by Cohorts and Weight Bands through Week 48 (Source: extracted from Table 4, Dr. Colberg Poley's review of NDA 204790.S-025 and NDA 213983.000).

		Week 24		Week 48	
Cohort	**WB**	<50 copies/mL	<400 copies/mL	<50 copies/mL	<400 copies/mL
I (≥12 to <18 years old)	≥35 kg	14/19 (73.7%)	16/19 (84.2%)	12/19 (63.2%)	14/19 (73.7%)
IIA (≥6 to <12 years old)	≥35 kg	4/5 (80%)	5/5 (100%)	4/5 (80%)	4/5 (80%)
III DT (≥2 to <6 years old)	14-<20 kg	2/4 (50%)	3/4 (75%)	0/1 (0%)	0/1 (0%)
III DT (≥2 to <6 years old)	10-<14 kg	3/3 (100%)	3/3 (100%)	2/2 (100%)	2/2 (100%)
		Week 24		**Week 48**	
		<50 copies/mL	<400 copies/mL	<50 copies/mL	<400 copies/mL
WB	≥35 kg	18/24 (75%)	21/24 (87.5%)	16/24 (66.7%)	18/24 (75%)
WB	14 to <20 kg	2/4 (50%)	3/4 (75%)	0/1 (0%)	0/1 (0%)
WB	10 to <14 kg	3/3 (100%)	3/3 (100%)	2/2 (100%)	2/2 (100%)

Abbreviations: DT, dispersible tablet; WB, weight band

ABC+3TC treatment of pediatric patients ages 3 months to 17 years (Pivotal Efficacy Study: ARROW Randomization 3, Dr. Mishra's review of NDA 020977.S-027; N20978.S-031; N20564.S-033; N20596.S-032) ARROW was an open-label clinical study, sponsored and conducted by the Medical Research Council Clinical Trials Unit (London, UK) in Uganda and Zimbabwe using ABC, 3TC, Combivir, Epzicom tablets (n = 1,206 subjects).

In Pivotal Efficacy ARROW Randomization 3 Study (Virology Substudy Protocol Part C, ABC+3TC, n = 669 subjects), viral loads were determined at the time of randomization to either once- (n = 336 subjects) or twice- (n = 333 subjects) daily ABC+3TC dosing (Baseline, Week 0), and at Weeks 48 and 96 after randomization as primary and secondary efficacy outcomes, respectively. The ARROW study included subjects in the following weight bands: 5 to <7 kg, 7 to <10 kg, 10 to <12 kg, 12 to <14 kg, 14 to <20 kg, 20 to <25 kg, and ≥25 kg. The subjects were mostly in the younger age groups: 6 months to 2 years (n = 10.7%), 3 to 6 years (n = 48.7%), 7-11 (n = 36.4%) years, at Week 0.

At Week 0 (randomization) a slightly lower proportion of subjects with viral loads of <80 copies/mL in the once-daily dosing arm relative to the twice-daily arm (71% versus 76%, viral load measured retrospectively) (Table 2). The proportion of subjects with viral loads of <80 copies/mL remained similar for the 2 dosing frequencies at Weeks 48 and 96 after randomization to once- versus twice- daily ABC+3TC. The sponsor concluded that these results demonstrated the non-inferiority of once- compared to twice-daily ABC+3TC dosing.

Table 2: ARROW Virology Substudy Part C: Number and Percentage of Subjects with Viral Load of <80 Copies/mL at Randomization to Twice- and Once-Daily Dosing (Week 0) and after 48 and 96 Weeks of Twice- and Once-Daily Dosing of Abacavir and Lamivudine (Missing Data Points Excluded) (Source: Table 3, summary-clinical-efficacy, page 17)

Time Point Viral Load (Copies/mL)	Twice-Daily Dosing n (%)	Once-Daily Dosing n (%)	Total n (%)
Week 0[a]	331 (100)	335 (100)	666 (100)
<80	250 (76)	237 (71)	487 (73)
≥80	81 (24)	98 (29)	179 (27)
Risk difference (95% CI)	-4.8% (-11.5 – 1.9)		
Week 48[b]	331 (100)	330 (100)	661 (100)
<80	242 (73)	236 (72)	478 (72)
≥80	89 (27)	94 (28)	183 (28)
Risk difference (95% CI)	-1.6% (-8.4 – 5.2)		
Week 96[c]	326 (100)	331 (100)	657 (100)
<80	234 (72)	230 (69)	464 (71)
≥80	92 (28)	101 (31)	193 (29)
Risk difference (95% CI)	-2.3% (-9.3 – 4.7)		

Source data: ARROW Virology Statistical Report May 2013, Section 3.1 and Section 3.3, located in the appendix of ARROW Randomization 3 clinical study report.
Note: The n value for each week is for the number of subjects with available data. Subjects with missing data at each time point are excluded.
ARROW = AntiRetroviral Research fOr Watoto; CI = confidence interval.
a. Three subjects did not have viral load data at Week 0. One subject had a sample tested, and an error was noted. Two other subjects had samples tested, and discrepant results were noted.
b. Eight subjects did not have viral load data at Week 48. Three subjects had samples tested, and errors were noted. Three other subjects had samples tested, and discrepant results were noted. Samples from 2 additional subjects were not tested.
c. Twelve subjects did not have viral load data at Week 96. Four subjects died prior to this time point. Five subjects were lost to follow-up. Samples from 2 subjects were not tested. One subject had a sample tested, and an error was noted.

Post-marketing experience

In support of the proposed indication, the sponsor searched the GSK safety database (on April 30, 2021) for spontaneous reports and post-marketing surveillance (PMS) reports involving Triumeq. A total of 9,146 cases were retrieved cumulatively, 4 of which were identified in children <12 years of age (excluding cases where exposure to Triumeq was *in utero* or via breastmilk). All 4 cases were non-serious. The sponsor concluded that no new safety concerns are evident from review of the small number of cases identified involving Triumeq use in children.

The sponsor also searched the GSK Safety database (on April 30, 2021) for spontaneous reports and PMS reports involving Tivicay as the suspect drug. Cases were reviewed to identify those reported in children <12 years of age and where both ABC and 3TC (either as single entities or as FDC) were reported as co-suspect drugs. According to the sponsor, all 6 cases were non-serious.

The sponsor did not identify any articles containing specific safety information on the use of Triumeq FDC in children <12 years age. A recent abstract (Turkova et al., 2021, CROI Abstract 174), evaluated the ongoing Odyssey trial using DTG in combination with 2 NRTIs in comparison with standard of care (SOC) which consisted of 707 children who were ≥14 kg and randomized to either DTG plus 2 NRTIs (n=350) or SOC (n=357). The authors concluded that DTG-based ART was superior to SOC based on treatment failure by 96 weeks in children/adolescents starting first- or second-line ART. There were no safety concerns for DTG treatment. Further, the authors state that these results support the WHO guidelines, which recommend DTG-based regimens as preferred ART for children ≥14kg starting first- or second-line ART, allowing harmonization with adult treatment programs.

The sponsor concluded that no new safety concerns have been identified from the limited post-marketing safety data available for use of Triumeq in children <12 years of age. As Triumeq is not yet authorized for use in children the lack of data in this population is not unexpected. Although limited post-marketing safety data are available for use of Triumeq in children, all 3 components of Triumeq (DTG, ABC and 3TC) are approved individually for once daily dosing in children ≥14 kg. Furthermore, the safety of ABC and 3TC use in children is well established based on many years of post-marketing experience.

SUMMARY and CONCLUSION

Triumeq is a FDC of an INSTI (DTG) and two NRTIs (ABC+3TC), which is currently approved for the treatment of HIV-1 infection in adult and in children aged 12 years and older weighing ≥40 kg. The original NDA 215413 proposes dosing with Triumeq PD (DTs) for the treatment of HIV-1 infected pediatric patients weighing ≥14 kg to <25 kg and NDA 205551.S-028 proposes Triumeq treatment of HIV-1 infected pediatric patients weighing ≥25 kg to <40 kg. These two submissions are intended to fulfill NDA 205551 PMR 2768-2. Based upon the Agency's agreement, nonclinical and virology datasets, which supported the approvals of the single entity products were not required for the current applications. In support of the proposed indication, the sponsor cross-referenced applications, which supported the prior approval of Triumeq single entities. We focused on the cross-referenced pediatric clinical studies with efficacy data (ARROW Randomization 3, NDA 020977.S-027 and IMPAACT P1093, NDA 204790.S025) which were accessible for review of their efficacy data.

Although most pediatric subjects in the IMPAACT P1093 pediatric study were treatment experienced, most were virologic responders at <50 copies/mL (Week 24: 62% and Week 48: 69%). Nonetheless, FDA analyses identified the emergence of known HIV-1 IN RASs (G118R E138T, S147S/G, S153S/A/F/V, R263K) in three virologic failure subjects during DTG treatment. Based upon subject reported nonadherence and intensive PK data and sparse PK data, suboptimal adherence appears to have contributed to virologic failure in some pediatric subjects of the IMPAACT P1093 Study. In the pediatric ARROW Randomization 3 Study (Virology Substudy Protocol Part C), the proportion of pediatric subjects with viral loads of <80 copies/mL after randomization to once- versus twice- daily ABC+3TC remained similar at Week 48 (73% versus 72%, respectively) and Week 96 (72% versus 69%, respectively). The sponsor concluded that these results demonstrated the non-inferiority of once- compared to twice-daily ABC+3TC dosing. We agree with the sponsor's conclusion and have no recommendations for the sponsor at this time. There were minor changes to the virology section of the label shown in the Appendix.

Reviewer's Signature

Anamaris M. Colberg Poley, Ph.D.
Clinical Virology Reviewer

Concurrence

Clin.Virol.TL/J. O'Rear, Ph.D.
CC: HFD-530/N215413.000 and N205551.S-028
HFD-530/Division File
HFD-530/PM/Allen

FDC (NDA 215413.000 and NDA 205551.S-028) Package Insert

The sponsor's proposed edits are in yellow highlighted, red font and the FDA changes are indicated by blue highlighted text.

(b) (4)

[redacted]

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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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/

ANAMARIS M COLBERG POLEY
02/17/2022 10:32:54 AM

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02/17/2022 11:22:07 AM