Elvitegravir (EVG) (Last updated April 7, 2021; last reviewed April 7, 2021)

Formulations

Tablet: Discontinued by the manufacturer. Elvitegravir is available only in fixed-dose combination (FDC) tablets.

Fixed-Dose Combination Tablets:

- [Genvoya] Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide 10 mg
- [Stribild] Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg

When using fixed dose combination (FDC) tablets, refer to other sections of the Drug Appendix for information about the individual components of the FDC. See also Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents.

For additional information, see Drugs@FDA or DailyMed.

Dosing Recommendations

[Genvoya] Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (TAF)

Child (Weighing <14 kg) Dose:

- No data exist on the dosing of EVG/c/F/TAF for children weighing <14 kg.

Child (Weighing ≥14 to <25 kg)

- Data are currently limited on the dosing of a pediatric EVG/c/FTC/TAF formulation in children ≥14 kg to <25 kg. Studies are currently being conducted to assess the safety and efficacy of a fixed low-dose combination tablet.

Child and Adolescent (Weighing ≥25 kg) and Adult Dose:

- One tablet once daily with food in antiretroviral therapy (ART)-naive patients. This dose of Genvoya also can be used to replace the current antiretroviral (ARV) regimen in patients who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable ART regimen for at least 6 months with no history of treatment failure and no known mutations associated with resistance to the individual components of Genvoya.

[Stribild] Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate (TDF)

Child and Adolescent (Weighing <35 kg) Dose:

- There are no data on the appropriate dose of Stribild for children or adolescents weighing <35 kg.

Selected Adverse Events

Genvoya- and Stribild-Associated Adverse Events:

- Nausea
- Diarrhea
- Fatigue
- Headache

Elvitegravir-Associated Adverse Events:

- Diarrhea

TAF-Specific Adverse Events:

- Increased levels of low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, and total cholesterol

TDF-Specific Adverse Events:

- Glomerular and proximal renal tubular dysfunction
- Decreased bone mineral density
- Flatulence

Cobicistat-Specific Adverse Events:

- Benign increases in serum creatinine levels (reductions in estimated glomerular filtration) due to inhibition of tubular secretion of creatinine

Special Instructions

- Administer both Genvoya and Stribild with food.
- Genvoya and Stribild should be administered at least 4 hours before or after antacids and supplements or multivitamins that contain iron, calcium, aluminum, and/or magnesium.
- When using Stribild, which contains TDF,

Adolescent (Weighing ≥35 kg and Sexual Maturity Rating [SMR] 4 or 5) and Adult Dose:

- One tablet once daily with food in ART-naive patients. This dose of Stribild can also be used to replace the current ARV regimen in patients who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable ART regimen for at least 6 months with no history of treatment failure and no known mutations associated with resistance to the individual components of Stribild.

monitor estimated creatinine clearance (CrCl), urine glucose, and urine protein at baseline and every 3 to 6 months while on therapy. In patients who are at risk of renal impairment, also monitor serum phosphate. Patients with an increase in serum creatinine levels >0.4 mg/dL should be closely monitored for renal safety.

- Screen patients for hepatitis B virus (HBV) infection before using emtricitabine (FTC), TDF, or TAF. Severe acute exacerbation of HBV can occur when FTC, TDF, or TAF are discontinued; therefore, monitor hepatic function for several months after stopping therapy with FTC, TDF, or TAF.
- For information on crushing and cutting tablets, please see this table from Toronto General Hospital.

Metabolism/Elimination

- EVG is metabolized by cytochrome P450 (CYP) 3A4 and is a modest inducer of CYP2C9.
- EVG is available only in combination with the pharmacokinetic enhancer (boosting agent) cobicistat in Stribild or Genvoya. Refer to the TDF and TAF sections for further details on these components.

Elvitegravir Dosing in Patients with Hepatic Impairment:

- Stribild and Genvoya **should not be used** in patients with severe hepatic impairment.

Elvitegravir Dosing in Patients with Renal Impairment:

- Stribild **should not be initiated** in patients with estimated CrCl <70 mL/min, and it should be discontinued in patients with estimated CrCl <50 mL/min. FTC and TDF require dose adjustments in these patients, and these adjustments cannot be achieved with an FDC tablet.
- Genvoya **should not be initiated** in patients with estimated CrCl <30 mL/min.

Drug Interactions (see also the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker)

- *Absorption:* Elvitegravir (EVG) plasma concentrations are lower with concurrent administration of divalent cations because of the formation of complexes in the gastrointestinal tract and not due to changes in gastric pH. Therefore, Stribild and Genvoya should be administered at least 4 hours before or after administering antacids and supplements or multivitamins that contain iron, calcium, aluminum, and/or magnesium.[1]

- *Metabolism:* Stribild and Genvoya contain EVG and cobicistat (COBI). EVG is metabolized predominantly by cytochrome P450 (CYP) 3A4, secondarily by uridine diphosphate glucuronyl transferase 1A1/3, and by oxidative metabolism pathways. EVG is a moderate inducer of CYP2C9. COBI is a strong inhibitor of CYP3A4 and a weak inhibitor of CYP2D6. In addition, COBI inhibits the adenosine triphosphate-dependent transporters P-glycoprotein and the breast cancer resistance protein and the organic anion-transporting, polypeptides, OATP1B1 and OATP1B3. See the Cobicistat section for a more detailed summary of drug interactions. Multiple drug interactions are possible when using both EVG and COBI. Neither Stribild nor Genvoya should be administered concurrently with products or regimens that contain ritonavir (RTV), due to the similar effects of COBI and RTV on CYP3A4 metabolism.
- *Renal elimination:* Drugs that decrease renal function or compete for active tubular secretion could reduce clearance of tenofovir, in the form of tenofovir disoproxil fumarate (TDF), or emtricitabine (FTC). Concomitant use of nephrotoxic drugs should be avoided when using Stribild. COBI inhibits MATE1, which increases serum creatinine levels up to 0.4 mg/dL from baseline in adults. Creatinine-based calculations of estimated glomerular filtration rate (GFR) will be altered, but the actual GFR might be only minimally changed.[2] Significant increases in serum creatinine levels >0.4 mg/dL from baseline may represent renal toxicity and should be evaluated. People who experience a confirmed increase in serum creatinine levels should be closely monitored for renal toxicity; clinicians should monitor creatinine levels for further increases and perform a urinalysis to look for evidence of proteinuria or glycosuria.[3]

Major Toxicities

- *More common:* Nausea, diarrhea, fatigue, headache, flatulence.
- *Less common (more severe):* Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported in patients receiving nucleoside reverse transcriptase inhibitors, including TDF and FTC. TDF caused bone toxicity (osteomalacia and reduced bone mineral density [BMD]) in animals when given in high doses. Decreases in BMD have been reported in both adults and children who were taking TDF; the clinical significance of these changes is not yet known. Evidence of renal toxicity has been observed in patients taking TDF, including a higher incidence of glycosuria, proteinuria, phosphaturia, and/or calciuria; increases in the levels of serum creatinine and blood urea nitrogen; and decreases in serum phosphate levels. Numerous case reports of renal tubular dysfunction have been reported in patients receiving TDF; patients at increased risk of renal dysfunction should be closely monitored if they are being treated with Stribild. This nephrotoxicity may be more pronounced in patients with preexisting renal disease.[3] Genvoya, which contains tenofovir alafenamide (TAF), has an improved bone and renal safety profile when compared to Stribild, which contains TDF, in children and adults.[4,5] However, Genvoya is associated with greater increases in lipid levels than Stribild, according to findings from large-scale clinical trials in adults.[6]

Resistance

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation. There is phenotypic cross-resistance between EVG and raltegravir.[7]

Pediatric Use

Approval

Genvoya (EVG/c/FTC/TAF) is approved by the Food and Drug Administration (FDA) for use in antiretroviral (ARV)-naive children and adolescents with HIV weighing ≥25 kg with any sexual maturity rating (SMR). It also can be used to replace the current ARV regimen in those who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable ARV regimen for at least 6 months with no history of treatment failure and no known mutations associated with resistance to the individual components of Genvoya.[6]

Stribild (EVG/c/FTC/TDF) is approved by the FDA as a complete regimen for use in children and adolescents aged ≥12 years and weighing ≥35 kg. However, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) recommends limiting the use of Stribild to adolescents with SMRs of 4 or 5 due to concerns about decreased BMD in pre-pubertal patients. It can also be used to replace the current ARV regimen in those who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable ARV regimen for at least 6 months with no history of treatment failure and no known mutations associated with resistance to the individual components of Stribild.[3]

Efficacy in Clinical Trials in Adults

EVG/c/FTC/TDF was found to be noninferior to a regimen of efavirenz/emtricitabine/TDF (EFV/FTC/TDF)[8–10] and noninferior to a regimen of atazanavir/ritonavir (ATV/r) plus FTC/TDF in adults through 144 weeks of treatment.[11–13] In two studies, 1,733 adults were randomly assigned to receive either EVG/c/FTC/TDF or EVG/c/FTC/TAF.[5] After 48 weeks, those receiving EVG/c/FTC/TAF had significantly smaller mean serum creatinine increases (0.08 vs. 0.12 mg/dL; $P < 0.0001$), significantly less proteinuria (median percent change in protein −3% vs. +20%; $P < 0.0001$), and a significantly smaller decrease in BMD at the spine (mean percent change −1.30% vs. −2.86%; $P < 0.0001$) and hip (−0.66% vs. −2.95%; $P < 0.0001$). Larger increases in fasting lipid levels were observed with EVG/c/FTC/TAF than with EVG/c/FTC/TDF; the median increases in levels of total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides were all higher in patients who received EVG/c/FTC/TAF.

Use of Elvitegravir as Stribild or Genvoya in Adolescents Aged 12 to 18 Years and Weighing ≥35 kg

Studies of the use of Stribild and Genvoya in children with HIV aged ≥12 years and weighing ≥35 kg have demonstrated safety and efficacy similar to that seen in adults through 24 weeks and 48 weeks of study, respectively; these formulations are approved by the FDA for use in this age/weight group.[14,15] Genvoya is preferred over Stribild when treating children with SMRs 1 to 3, as Genvoya carries a lower risk of renal and bone toxicity than Stribild.[6] Stribild is not approved to treat children weighing <35 kg.

Use of Elvitegravir as Genvoya in Children Weighing ≥25 kg

Genvoya is approved by the FDA to treat children with any SMR who weigh ≥25 kg; this approval was based on 24 weeks of data in 23 children.[16] In this study, children who had been virologically suppressed (HIV RNA <50 copies/mL) for at least 6 months were switched from their current regimens to Genvoya. There were no study discontinuations due to medication toxicity, but a concerning decline in CD4 T lymphocyte (CD4) cell counts was observed in all 23 children over the first 24 weeks of Genvoya treatment. CD4 counts declined by a median of 130 cells/mm^3 (with a range of −472 cells/mm^3 to 266 cells/mm^3) from baseline. However, after enrolling additional children (for a total of 52 participants), the median CD4 count decline at 48 weeks[17] was 25 cells/mm^3. The mechanism for the reduction in CD4 count is unclear, and this reduction has only been reported in this study. Plasma exposures of all four drugs were higher in these children than the plasma exposures seen in historical data from adults, but no association was identified between plasma exposures of the four components of Genvoya and CD4 counts.[18]

Use of Elvitegravir as Genvoya in Children Weighing <25 kg

EVG/c/FTC/TAF is not approved to treat children weighing <25 kg.[3,6] A pharmacokinetic (PK), safety, and efficacy study with a low-dose tablet in children aged ≥2 years and weighing ≥14 kg to <25 kg is ongoing.[19] In this study, children had to be virologically suppressed (HIV RNA <50 copies/mL) for at least 6 months prior to entry. Virologic suppression was maintained in 27 (100%) of 27 children at Week 16, and 16 (94%) of 17 children at Week 24. No participant discontinued the study drug because of adverse events or met criteria for resistance analyses through Week 24. CD4 counts decreased by a mean (standard deviation [SD]) of 137 (278) cells/mm³ between baseline and Week 24, although the CD4 percentage did not differ (mean [SD] change of 0.0 [4.4]). At least 90% of children reported that swallowing the tablet was "easy" or "super easy" and perceived the tablet size when swallowing as "okay" at baseline, Week 4, and Week 24.

Pharmacokinetics

EVG/c/FTC/TDF (Stribild)

The PKs of EVG 150 mg, COBI 150 mg, FTC 200 mg, and TDF 300 mg as a fixed-dose combination (FDC) tablet were evaluated in 14 treatment-naive adolescents with HIV between 12 and <18 years of age and weighing ≥35 kg.[14] EVG area under the plasma concentration versus time curve over the dosing interval (AUC_{tau}) and peak concentrations (C_{max}) were 30% higher (90% confidence interval [CI], 105%, 162%) and 42% higher (90% CI, 116%, 173%), respectively, in comparison to historical data in adults. EVG concentrations at the end of the dosing interval (C_{tau}) were 6% higher (90% CI, 70%, 160%) than adults, and approximately ninefold higher than the protein-adjusted IC_{95} ($PA\text{-}IC_{95}$) of 44.5 ng/mL for EVG. COBI, FTC, and TFV exposures were comparable to those measured in adults.

Table A: Pharmacokinetics of EVG, COBI, FTC, and TFV from TDF (Stribild) in Adolescents with HIV Aged 12 to <18 Years and Weighing ≥35 kg

Component	Parameter	Adolescents Aged 12 to <18 Years and Weighing ≥35 kg[14]		Adults[a14]		% GLSM Ratio (90% CI)[14]
		n	GLSM	n	GLSM	
EVG	AUC_{tau} (ng·h/mL)	14	28,500	419	21,900	130 (105, 162)
	C_{max} (ng/mL)	14	2,390	419	1,690	142 (116, 173)
	C_{tau} (ng/mL)	14	410	419	387	106 (70, 160)
COBI	AUC_{tau} (ng·h/mL)	14	9,200	483	8,729	105 (78, 142)
	C_{max} (ng/mL)	14	1,275	483	1,179	108 (84, 139)
	C_{tau} (ng/mL)	14	19	483	18	107 (66, 173)
FTC	AUC_{tau} (ng·h/mL)	14	14,509	61	12,106	120 (103, 139)
	C_{max} ((ng/mL)	14	2,124	61	1,814	117 (101, 136)
	C_{tau} (ng/mL)	14	98	61	104	94 (79, 113)
TFV	AUC_{tau} (ng·h/mL)	14	4,281	419	3,114	137 (121, 156)
	C_{max} (ng/mL)	14	409	419	313	131 (110, 155)
	C_{tau}(ng/mL)	14	84	419	68	123 (109, 138)

AUC_{tau} = area under the plasma concentration versus time curve over the dosing interval; C_{max} = maximum observed plasma concentration of drug; C_{tau} = observed drug concentration at the end of the dosing interval; COBI = cobicistat; EVG = elvitegravir; FTC = emtricitabine; GLSM = geometric least squares mean; SD = standard deviation; TFV = tenofovir

[a] Results from Phases 2 and 3 studies in adults with HIV receiving EVG/c/FTC/TDF

EVG/c/FTC/TAF (Genvoya)

The PKs of EVG 150 mg, COBI 150 mg, FTC 200 mg, and TAF 10 mg as an FDC tablet have been evaluated in adolescents 12 to <18 years of age weighing ≥35 kg[14] and children 6 to <12 years of age weighing ≥25 kg.[16] AUC_{tau}, C_{max}, and Ctau for EVG, COBI, FTC, TAF, and TFV were comparable to or higher than those measured in adults with HIV in both cohorts (see Tables B and C below).

The PKs of a low-dose FDC tablet containing EVG 90 mg, COBI 90 mg, FTC 120 mg, and TAF 6 mg were evaluated in 27 children with HIV weighing ≥14 kg and <25 kg.[19] EVG and TAF AUC_{tau} were higher in comparison to historical data in adults receiving full-strength Genvoya (see Tables B and C). EVG C_{tau} was 21% lower (90% CI, 53.1%, 117%) in children versus adults but was approximately 4.4-fold higher and ninefold higher than the $PA\text{-}IC_{95}$ and $PA\text{-}IC_{50}$ for wild-type virus, respectively. However, EVG C_{tau} measured in this cohort was lower than those previously measured in children and adolescents weighing ≥25 kg with EVG at the 150 mg dose. COBI, FTC, and TFV exposures were all comparable to or higher than historical data in adults.

Table B. Pharmacokinetics of EVG, COBI, FTC, TAF, and TFV (Genvoya) in Children and Adolescents with HIV between 2 to <18 Years of Age and Weighing ≥14 kg

Component	Parameter	Children Aged ≥2 Years and Weighing ≥14 to <25 kg[19]		Children Aged 6 to <12 Years and Weighing ≥25 Kg[16]		Adolescents Aged 12 to <18 Years and Weighing ≥35 kg[15]		Adults[a15,16]	
		n	GLSM	n	Mean (%CV)	n	Mean (%CV)	n	Mean (%CV)
EVG	AUC_{tau} (ng·h/mL)	27	29,900	22	33,814 (58%)	24	23,840 (26%)	19	22,800 (35%)
	C_{max} (ng/mL)	27	2,850	23	3,055 (39%)	24	2,230 (19%)	19	2,100 (34%)
	C_{tau} (ng/mL)	27	195	23	370 (119%)	24	301 (81%)	19	290 (62%)
COBI	AUC_{tau} (ng·h/mL)	27	12,300	20	15,891 (52%)	23	8,241 (36%)	19	9,500 (34%)
	C_{max} (ng/mL)	27	1,270	23	2,079 (47%)	24	1,202 (35%)	19	1,500 (28%)
	C_{tau} (ng/mL)	27	16.6	23	96 (169%)	15	25 (180%)	19	20 (85%)
FTC	AUC_{tau} (ng·h/mL)	27	18,600	22	20,629 (19%)	24	14,424 (24%)	19	11,714 (17%)
	C_{max} (ng/mL)	27	2,810	23	3,397 (27%)	24	2,265 (23%)	19	2,056 (20%)
	C_{tau} (ng/mL)	27	77.4	23	115 (24%)	23	102 (39%)	19	95 (47%)
TAF	AUC_{tau} (ng·h/mL)	27	344	23	333 (45%)	24	189 (56%)	539	206 (72%)
	C_{max} (ng/mL)	27	218	23	313 (61%)	24	167 (64%)	539	162 (51%)
TFV	AUC_{tau} (ng·h/mL)	27	327	23	440 (21%)	23	288 (19%)	841	293 (27%)
	C_{max} (ng/mL)	27	19.1	23	26 (21%)	23	18 (24%)	841	15 (26%)
	C_{tau} (ng/mL)	27	11.1	23	15 (25%)	23	10 (21%)	841	11 (29%)
TFV-DP in PBMCS	C_{0h} (fmol/10^6 cells)	—	—	—	—	12	222 (94%)	21	121 (91%)

AUC_{tau} = area under the plasma concentration versus time curve over the dosing interval; C_{0h} = concentration at time 0 (pre-dose); C_{max} = maximum observed plasma concentration of drug; C_{tau} = observed drug concentration at the end of the dosing interval; COBI = cobicistat; CV = coefficient of variation; EVG = elvitegravir; FTC = emtricitabine; GLSM = geometric least squares mean; PBMCs = peripheral blood mononuclear cells; TAF = tenofovir alafenamide; TFV = tenofovir; TFV-DP = tenofovir-diphosphate

[a] Adult pharmacokinetic parameters for elvitegravir, cobicistat, and emtricitabine were derived from intensive pharmacokinetic analysis from Phase 2 study 102; data for tenofovir alafenamide and tenofovir were from population pharmacokinetic analyses in Phase 3 studies 104 and 111.

Table C. Comparisons of EVG, COBI, FTC, TAF, and TFV (Genvoya) Pharmacokinetics in Children and Adolescents with HIV between 2 and <18 Years of Age and Weighing ≥14 kg to Adult Values

Component	Parameter	% GLSM (90% CI) Compared with Adult Values[a]			
		Dose (mg)	Children Aged ≥2 Years and Weighing ≥14 to <25 kg[16]	Dose (mg)	Children Aged 6 to <12 Years and Weighing ≥25 kg[19]
EVG	AUC_{tau} (ng·h/mL)	90	139 (112, 172)	150	134 (104, 173)
	Cmax (ng/mL)		143 (113, 180)		141 (115, 173)
	C_{tau} (ng/mL)		79 (53, 117)		86 (55, 133)
COBI	AUC_{tau} (ng·h/mL)	90	—	150	158 (126, 198)
	C_{max} (ng/mL)		—		127 (98, 165)
	C_{tau} (ng/mL)		—		171 (95, 310)
FTC	AUC_{tau} (ng·h/mL)	120	—	200	175 (160, 192)
	C_{max} (ng/mL)		—		164 (145, 184)
	C_{tau} (ng/mL)		—		125 (107, 146)
TAF	AUC_{tau} (ng·h/mL)	6	193 (166, 224)	10	171 (147, 199)
	C_{max} (ng/mL)		150 (116, 195)		182 (146, 225)
TFV	AUC_{tau} (ng·h/mL)		—		152 (142, 163)
	C_{max} (ng/mL)		—		173 (161, 186)
	C_{tau} (ng/mL)		—		143 (132, 155)

AUC_{tau} = area under the plasma concentration versus time curve over the dosing interval; C_{max} = maximum observed plasma concentration of drug; C_{tau} = observed drug concentration at the end of the dosing interval; CI = confidence interval; CV = coefficient of variation; GLSM = geometric least squares mean

[a] Adult pharmacokinetic parameters for elvitegravir, cobicistat, and emtricitabine were derived from intensive pharmacokinetic analysis from

Phase 2 study 102; data for tenofovir alafenamide and tenofovir were from population pharmacokinetic analyses in Phase 3 studies 104 and 111.

Formulations

EVG is an integrase strand transfer inhibitor that is metabolized by CYP3A4. EVG must be used in the FDC products Stribild[3] or Genvoya,[6] both of which contain COBI (see below). COBI itself does not have ARV activity, but it is a CYP3A4 inhibitor that acts as a PK enhancer, similar to RTV.[20]

Coadministration of Elvitegravir, Cobicistat, and Darunavir

The combination of Stribild or Genvoya plus darunavir (DRV) may provide a low pill-burden regimen for antiretroviral therapy-experienced individuals. However, an unfavorable drug interaction between EVG/c and DRV is possible, and the available data on the magnitude of the interaction are conflicting. Data on the efficacy of the combination in adults also are conflicting.[21–27]

The most rigorous drug interaction study, performed in HIV-seronegative adults, found 21% lower DRV trough concentrations and 52% lower EVG trough concentrations with DRV 800 mg plus EVG/c 150 mg/150 mg once daily compared to the administration of either darunavir/cobicistat 800 mg/150 mg once daily or

EVG/c 150 mg/150 mg once daily alone.[21] The actual trough values were 1,050 ng/mL for DRV and 243 ng/mL for EVG.

Despite the findings of the aforementioned drug interaction study in HIV-seronegative adults, the most rigorous efficacy evaluation found that among 89 treatment-experienced adults who were receiving five-tablet ARV regimens, 96.6% achieved virologic suppression (HIV RNA <50 copies/mL) 24 weeks after simplifying their regimens to a two-tablet regimen of Genvoya plus DRV 800 mg once daily.[25] Intensive PK sampling was performed in 15 of these patients (17%). Mean DRV and EVG troughs were 1,250 ng/mL and 464 ng/mL, respectively.

Given the uncertainty around the true magnitude of the drug interaction and the absence of data in children, this combination should be used with caution in children.

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