

Investigating the Effect of Steady State Cannabidiol on the Single Dose Pharmacokinetics of CYP2B6, CYP2C9, UGT2B7, and UGT1A9 Substrates

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Summary

- In vitro* metabolism data has previously indicated that highly purified cannabidiol (CBD; Epidyolex® [EU]/Epidiolex® [US], 100 mg/mL oral solution) has the potential to alter the metabolism of concomitantly administered drugs that are substrates for the enzymes CYP2B6, CYP2C9, UGT1A9, and UGT2B7¹⁻³
- Here we report data from two phase I drug–drug interaction studies that assessed the effect of steady-state CBD on the pharmacokinetics of substrates for these enzymes in healthy participants
- CBD at 7.5 mg/kg BID did not have a clinically meaningful interaction with CYP2B6 or UGT2B7 substrates; no changes in exposure were observed with CYP2C9 substrates
 - Dose modifications are not warranted for drugs metabolised by these enzymes when used concomitantly with CBD at this dose
- CBD at 7.5 mg/kg BID inhibited UGT1A9; increases in UGT1A9 substrate exposure may occur when coadministered with CBD
 - A reduction in the dosage of UGT1A9 substrates may be considered when administered concomitantly with CBD, as clinically appropriate, in cases where small changes in plasma concentrations could lead to serious adverse reactions

Methods

- The effect of CBD on metabolism mediated by CYP and UGT enzymes was investigated in two phase 1 drug–drug interaction studies in healthy adults aged 18 to 60 years
- Study 1 (EudraCT ID: 2019-000164-22), CYP substrates:
 - Part A (CYP2B6): bupropion 150 mg on Day (D) 1 and D8, and CBD 7.5 mg/kg twice daily (BID) from D4–10; concurrent dosing on D8
 - Part B (CYP2C9): tolbutamide 500 mg on D1 and D8, and CBD 7.5 mg/kg BID from D4–10, with concurrent dosing on D8
- Study 2 (EudraCT ID: 2019-000272-42), UGT substrates:
 - Part A (UGT2B7): zidovudine 300 mg on D1 and D6, CBD 7.5 mg/kg BID from D2–6, with concurrent dosing on D6
 - Part B (UGT1A9): mycophenolate mofetil (MMF) 1500 mg on D1 and D8, and CBD 7.5 mg/kg BID from D4–10, with concurrent dosing on D8
- Total drug exposure over time (area under the curve [AUC]) and maximum plasma concentration (C_{max}) were assessed with geometric least squares mean (GLSM) ratios and associated 90% confidence intervals (CIs) for substrates plus CBD versus substrates alone
- These phase 1 trials were conducted with Epidyolex®/Epidiolex®, and the results do not apply to other CBD-containing products

Results

Pharmacokinetic effects of CBD coadministration (Figures 1 and 2, Table 2)

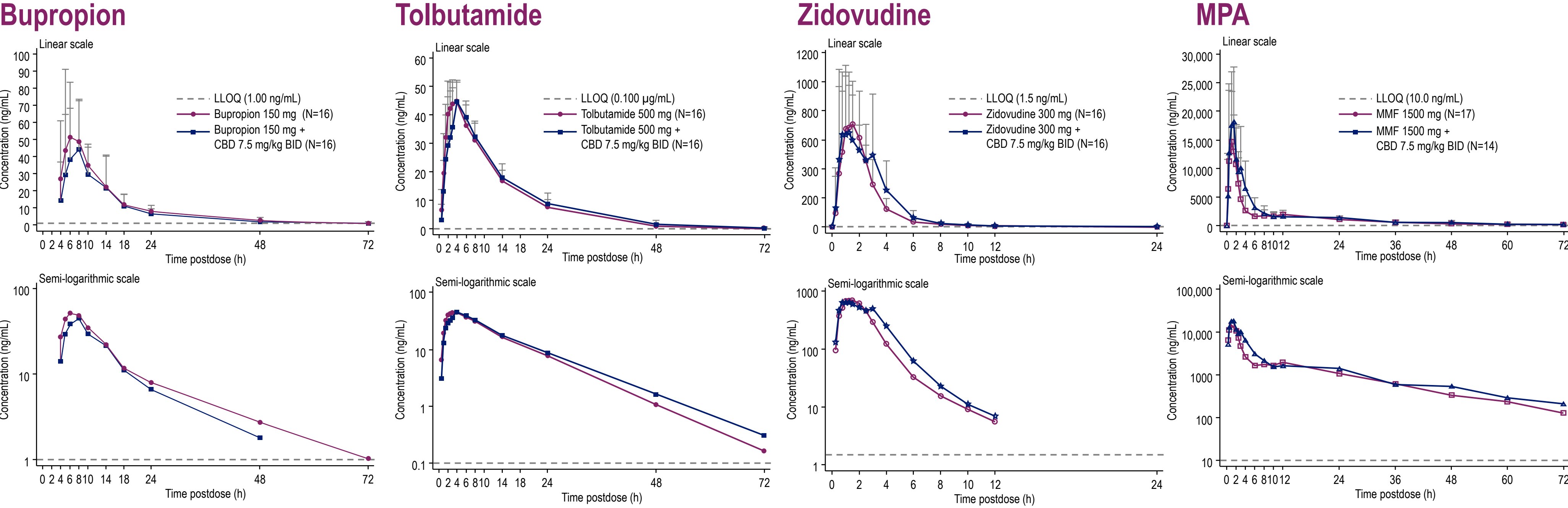
- CYP2B6 substrates:** Coadministration of CBD with bupropion decreased bupropion exposure by 19% for C_{max} and 20% for AUC, and increased hydroxybupropion exposure by 8% for C_{max} and 7% for AUC, compared with bupropion administered alone, which is not expected to be clinically meaningful
- CYP2C9 substrates:** Coadministration of CBD with tolbutamide did not result in changes in plasma exposure of tolbutamide or its metabolites compared with tolbutamide administered alone
- UGT1A9 substrates:** Coadministration of CBD with MMF increased mycophenolic acid (MPA) exposure by 16% for C_{max} and 35% for AUC, and decreased metabolite exposure by 26% for C_{max} and 14% for AUC, compared with MMF administered alone
 - The upper limit of the 90% CI of MPA for AUC was 54%, which exceeds the observed coefficient of variation of ~30%, and thus may be considered clinically meaningful
- UGT2B7 substrates:** Coadministration of CBD with zidovudine increased zidovudine exposure by 7% for C_{max} and 19% for AUC, and also increased exposure to zidovudine-5-glucuronide (the metabolite formed via UGT2B7) by 5% for C_{max} and 36% for AUC, compared with zidovudine administered alone, which is not expected to be clinically meaningful

Table 1. Demographics and baseline characteristics

	Bupropion (N=16)	Tolbutamide (N=16)	Zidovudine (N=16)	MMF (N=17)
Age, years, mean (SD)	43.6 (11.9)	42.9 (10.3)	37.1 (10.4)	48.1 (9.3)
Sex, n (%)				
Male	11 (68.8)	10 (62.5)	10 (62.5)	15 (88.2)
Female	5 (31.3)	6 (37.5)	6 (37.5)	2 (11.8)
Weight, kg, mean (SD)	78.3 (14.1)	76.1 (10.9)	72.1 (11.4)	80.7 (7.4)
BMI, kg/m ² , mean (SD)	24.9 (2.4)	25.5 (2.4)	25.3 (2.9)	26.7 (2.0)

BMI, body mass index; MMF, mycophenolate mofetil; SD, standard deviation.

Figure 1. Mean plasma concentration–time profiles



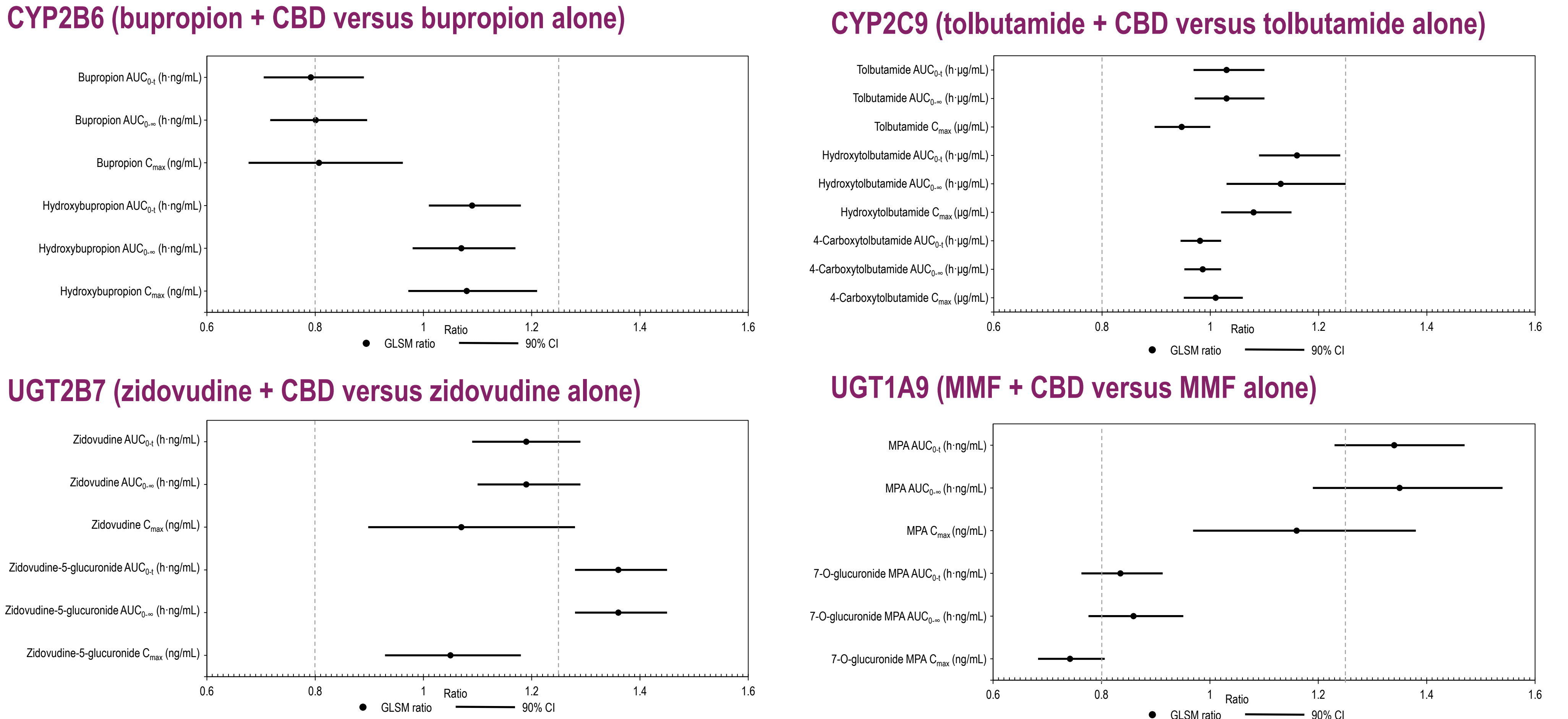
BID, twice daily; CBD, cannabidiol; LLOQ, lower limit of quantification; MMF, mycophenolate mofetil; MPA, mycophenolic acid.

Table 2. PK parameters following doses of substrate plus CBD versus substrate alone

Substrate (enzyme)	PK parameters	GLSM (GeoCV% ^a)		Test versus reference Ratio of GLSMs (90% CI)
		Test (n)	Reference (n)	
Bupropion (CYP2B6)		Bupropion 150 mg + CBD 7.5 mg/kg BID (n=16)		Bupropion 150 mg (n=16)
	AUC _{0-t} (h·ng/mL)	511 (39.2)	645 (32.5)	0.792 (0.705, 0.890)
	AUC _{0-∞} (h·ng/mL)	552 (35.9)	689 (32.0)	0.801 (0.717, 0.896)
Tolbutamide (CYP2C9)		Tolbutamide 500 mg + CBD 7.5 mg/kg BID (n=16)		Tolbutamide 500 mg (n=16)
	AUC _{0-t} (h·ng/mL)	626 (26.4)	608 (19.0)	1.03 (0.969, 1.10)
	AUC _{0-∞} (h·ng/mL)	633 (26.8)	613 (19.1)	1.03 (0.971, 1.10)
Zidovudine (UGT2B7)		Zidovudine 300 mg + CBD 7.5 mg/kg BID (n=16)		Zidovudine 300 mg (n=16)
	AUC _{0-t} (h·ng/mL)	2170 (24.7)	1830 (26.3)	1.19 (1.09, 1.29)
	AUC _{0-∞} (h·ng/mL)	2190 (24.5)	1840 (26.0)	1.19 (1.10, 1.29)
MMF ^b (UGT1A9)		MMF 1500 mg + CBD 7.5 mg/kg BID (n=14)		MMF 1500 mg (n=17)
	AUC _{0-t} (h·ng/mL)	110,000 (24.4)	81,900 (28.4)	1.34 (1.23, 1.47)
	AUC _{0-∞} (h·ng/mL)	115,000 ^c (26.3)	84,900 ^d (31.4)	1.35 (1.19, 1.54)
	C_{max} (ng/mL)	23,600 (35.1)	20,400 (43.1)	1.16 (0.969, 1.38)

^aGeoCV% is observed value and reported from summary statistics; ^bPK findings presented for MPA, the active metabolite of MMF; ^cn=11 participants; ^dn=15 participants. AUC_{0-∞}, area under the plasma concentration–time curve from time zero to infinity; AUC_{0-t}, area under the plasma concentration–time curve from time zero to the last observable concentration at time t; BID, twice a day; CI, confidence interval; C_{max} , maximum observed plasma concentration; CBD, cannabidiol; GeoCV%, geometric percent coefficient of variation; GLSM, geometric least squares mean; MMF, mycophenolate mofetil; MPA, mycophenolic acid; PK, pharmacokinetic.

Figure 2. GLSM ratios of PK parameters following doses of substrate plus CBD versus substrate alone



AUC_{0-∞}, area under the plasma concentration–time curve from time zero to infinity; AUC_{0-t}, area under the plasma concentration–time curve from time zero to the last observable concentration at time t; BID, twice a day; CI, confidence interval; C_{max} , maximum observed plasma concentration; CBD, cannabidiol; GLSM, geometric least squares mean; MMF, mycophenolate mofetil; MPA, mycophenolic acid; PK, pharmacokinetic.

References: 1. Electronic Medicines Compendium (eMC). Epidyolex® 100 mg/ml oral solution: summary of product characteristics. 2025. Available from: <https://www.medicines.org.uk/emc/product/10781/smpc/print> (Accessed 21 May 2025). 2. European Medicines Agency. Epidyolex® 100 mg/ml oral solution: summary of product characteristics. 2025. Available from: https://www.ema.europa.eu/en/documents/product-information/epidyolex-epar-product-information_en.pdf (Accessed 21 May 2025). 3. US Food and Drug Administration. Epidiolex® Prescribing Information. 2024. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/210365s021bl.pdf (Accessed 04 June 2025). **Acknowledgements:** The authors would like to thank all of the study investigators, study staff, study participants, and nursing team for their participation in this research. Writing and editorial assistance were provided to the authors by Lahoor Basha, PharmD, on behalf of Synecos Health, UK, and funded by Jazz Pharmaceuticals, Inc., in accordance with Good Publication Practice (GPP) 2022 guidelines. **Support:** This study was sponsored by Jazz Pharmaceuticals, Inc. **Disclosures:** All authors met the ICMJE authorship criteria and had full access to relevant data and information. Neither honoraria nor payments were made for authorship. **AV, HX, PC, SM, and CC** are employees of Jazz Pharmaceuticals, Inc. and hold stock and/or stock options in Jazz Pharmaceuticals, Inc. **Epidyolex®** is approved in the EU and UK for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome, in conjunction with clobazam, in patients ≥2 years of age; it is additionally approved in the EU and UK for the adjunctive treatment of seizures associated with tuberous sclerosis complex in patients ≥2 years of age. **Clinical trial (EudraCT) ID:** 2019-000164-22 (study 1) and 2019-000272-42 (study 2).



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