

# Trends in fluorouracil and Calcipotriene Utilization for Actinic Keratosis

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## To the Editor,

Actinic keratoses (AKs) are skin lesions that can progress to squamous cell carcinomas. When multiple AKs occur in one area, field treatment, often topical or photodynamic therapy, may be used.<sup>1</sup> While highly effective, topical 5-fluorouracil (5-FU) may be underutilized due to its intense treatment effects and 2–4 week duration.<sup>1,2</sup> To improve symptoms and shorten treatment duration, a regimen of 5-FU with topical calcipotriol or calcipotriene has been proposed, and a 2017 randomized trial showed promising efficacy.<sup>3</sup> We quantified the use of 5-FU and 5-FU with calcipotriene over time.

We conducted a retrospective cohort study using three de-identified datasets: MarketScan (insurance claims; 2015–2022; 72,200,665 patients), Medicare claims (2015–2021; 4,300,961 beneficiaries), and Epic Cosmos (Epic electronic health record (EHR) data; 2015–2024; 12,970,421,167 encounters; United States only). In MarketScan and Medicare, we included topical 5-FU prescriptions and calculated the percentage with same-day topical calcipotriene prescriptions. In Epic Cosmos, we included

encounters with a topical 5-FU prescription or administration and calculated the percentage with a topical calcipotriene prescription or administration. We used Joinpoint regression analysis to evaluate average annual percent changes.

We identified 499,649 5-FU prescriptions in MarketScan, of which 11,201 (2.24%) involved calcipotriene, 276,872 5-FU prescriptions in Medicare, of which 4,032 (1.46%) involved calcipotriene, and 497,692 encounters with 5-FU in Epic Cosmos, of which 15,020 (3.02%) involved calcipotriene. The proportion of prescriptions with 5-FU and calcipotriene increased from 0.09% in 2015 to 3.22% in 2022 in MarketScan; from 0.08% in 2015 to 2.23% in 2020 before decreasing to 2.04% in 2021 in Medicare; and from 0.08% in 2015 to 4.18% in 2021 before decreasing to 3.10% in 2024 in Epic Cosmos (Table 1). Average annual percent changes in proportions of 5-FU prescribed with calcipotriene were 53.62% (95% CI 37.99–87.61) in MarketScan, 64.87% (95% CI 50.39–98.68) in Medicare, and 53.96% (95% CI 39.40–76.84) in Epic Cosmos.

**TABLE 1.**

Percentage of Topical Fluorouracil With Calcipotriene By Year									
Year	MarketScan			Medicare			Epic Cosmos		
	5-FU (n)	With calcipotriene (n)	%	5-FU (n)	With calcipotriene (n)	%	5-FU (n)	With calcipotriene (n)	%
2015	66,421	61	0.09	30,049	24	0.08	21,704	17	0.08
2016	67,402	241	0.36	34,266	84	0.25	27,104	79	0.29
2017	60,223	923	1.53	36,562	315	0.86	33,016	304	0.92
2018	61,108	1,712	2.8	38,594	699	1.81	38,491	1,196	3.11
2019	59,363	1,971	3.32	39,333	825	2.09	43,106	1,541	3.57
2020	57,243	2,124	3.71	44,773	997	2.23	44,122	1,512	3.43
2021	66,367	2,191	3.3	53,295	1,088	2.04	53,492	2,238	4.18
2022	61,522	1,978	3.22	--	--	--	63,488	2,517	3.96
2023	--	--	--	--	--	--	77,198	2,639	3.42
2024	--	--	--	--	--	--	95,971	2,977	3.1

Our study demonstrates that the utilization of 5-FU with calcipotriene is increasing, though the percentage remains small. One limitation of our study is that 5-FU with calcipotriene may be ordered as a compounded medication rather than prescribed separately. Compounded formulas may not be covered by insurance or captured appropriately in EHR data, which could lead to underestimates.<sup>4</sup> Public information on compounded drug use remains sparse. Epic Cosmos was a valuable addition to claims data, as EHR data may include written prescription counts not reflected in billing. While overlapping counts could exist between datasets, these are random and would not affect our results.

We provide clinically relevant insight on the real-world uptake of 5-FU with calcipotriene for AK field treatment.

### DISCLOSURES

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### REFERENCES

1. Navsaria LJ, Li Y, Nowakowska MK, et al. Incidence and treatment of actinic keratosis in older adults with medicare coverage. *JAMA Dermatol.* 2022;158(9):1076-1078.
2. Eisen DB, Asgari MM, Bennett DD, et al. Guidelines of care for the management of actinic keratosis. *Journal of the American Academy of Dermatology.* 2021;85(4):e209-e233.
3. Cunningham TJ, Tabacchi M, Eliane JP, et al. Randomized trial of calcipotriol combined with 5-fluorouracil for skin cancer precursor immunotherapy. *J Clin Invest.* 2017;127(1):106-116.
4. U.S. Government Accountability Office. Drug Compounding: FDA has taken steps to implement compounding law, but some states and stakeholders reported challenges. Available at: <https://www.gao.gov/products/gao-17-64>. Accessed October 15, 2025.

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