

Cost-effectiveness of ingenol mebutate versus imiquimod 5% for Actinic Keratosis treatment in Spain

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INTRODUCTION

- Actinic keratosis (AK) is a precancerous skin lesion caused by proliferation of atypical epidermal keratinocytes due to prolonged exposure to exogenous factors such as ultra-violet radiation¹, on sun-exposed².
- Ingenol mebutate³ and imiquimod 5%⁴ are both authorized treatments for face and scalp AK.

OBJECTIVE

To assess the efficiency of ingenol mebutate vs imiquimod 5% for face and scalp AK treatment from the Spanish National Health System (NHS) perspective.

METHODS

- A Markov model with three distinct health states: AK, clearance and death (Figure 1), was used to simulate the 5-year evolution of a AK patient. Annual AK recurrence rate (20%)⁵ was applied.
- In the absence of head to head studies, effectiveness in terms of clearance rates were obtained by indirect comparison between clinical trials (42.24% for ingenol mebutate and 44.54% for imiquimod).
- Utilities values for AK (0.98) and clearance (1.00)⁶ were used to estimate quality-adjusted life years (QALY).
- Total cost estimation included: drug cost, and dermatology visits cost (for adverse events and disease management).
- A 3% annual discount rate was applied⁷.
- Recommended doses were considered for drug cost estimation, applying retail price plus VAT⁸ with 7.5% of mandatory deduction⁹. (Table 1)
- Unitary costs (€, 2015) were obtained from a national database¹⁰ (Table 1).
- Deterministic and probabilistic sensitivity analyses (SA) were performed.

Figure 1. Markov model structure

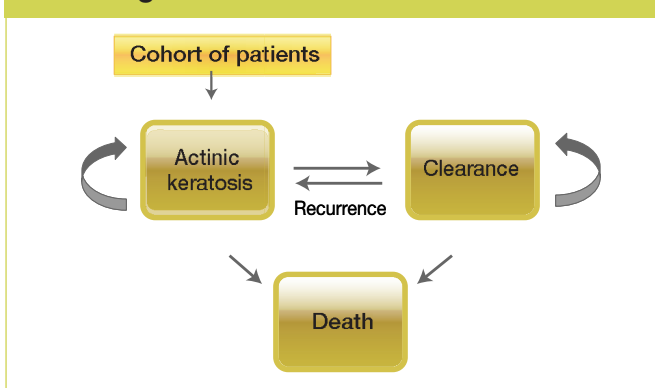


Table 1. Health resource consumption and unitary costs (€, 2015)

PHARMACEUTICAL COST			
Active ingredient	Presentations	Retail Price VAT ⁸	Treatment duration
Ingenol mebutate	Picato® 150 µg/g gel, 3 tubes of 0.47 g	€105.22	1 tube/day during 3 consecutive days
	Picato® 500 µg/g gel, 2 tubes of 0.47 g	€109.45	
Imiquimod 5%	Aldara® (50 mg/g cream contains 24 sachets 250 mg)	€125.93	1 sachet/day during 12 consecutive days
HEALTH RESOURCES			
Visits		Number	Unit cost ¹⁰
Dermatology	(First consultation)	1	€57.37
	(Successive consultation)	2	€31.43
Annual total visits		3 (regardless of treatment)	

RESULTS

- Ingenol mebutate showed higher effectiveness than imiquimod 5%: 0.535 vs 0.503 total gained clearances and 4.451 vs 4.449 total QALYs, and also higher costs, €551.50 vs €527.89 for imiquimod 5%. (Table 2)

Table 2. Base case results

INGENOL MEBUTATE VS IMIQUIMOD	Total Costs	Total Clearances	Total QALYs	ICER (€/additional clearance)	ICUR (€/QALY gained)
Ingenol mebutate	€551.50	0.536	4.451	€728.64/Clearance	€10,906/QALY
Imiquimod 5%	€527.89	0.503	4.449		

ICER: incremental cost-effectiveness ratio. ICUR: incremental cost-utility ratio. QALYs: Quality adjusted life years.

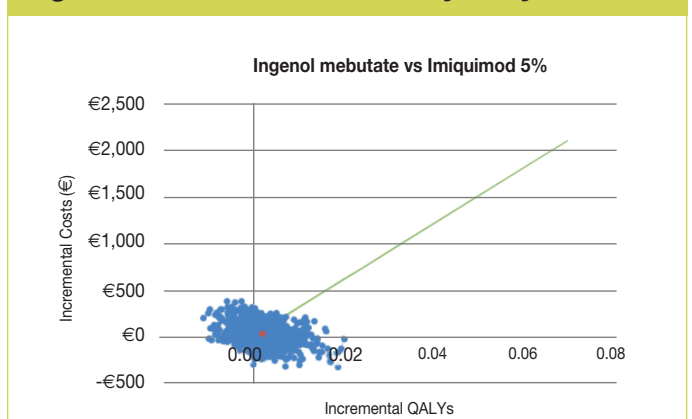
Table 3. One way deterministic sensitivity analyses results

INGENOL MEBUTATE VS IMIQUIMOD 5%	Incremental costs (€)	Incremental clearances	Incremental QALYs	ICER	ICUR
Emergency visits due to management of AEs in 5% of patients	4.82	0.032	0.002	€148.57/Clearance	€2,224.65/QALY
Intake of additional antibiotic (30% of patients in treatment with ingenol mebutate and 5% with imiquimod 5%)	21.63	0.032	0.002	€667.44/Clearance	€9,990.13/QALY
Decrement of efficacy (33%) in non-adherent	38.89	0.015	0.001	€2,567.74/Clearance	€37,428.80/QALY
Equivalent efficacy (42.24%) for both drugs	10.48	0.047	0.003	€222.58/Clearance	€3,377.00/QALY
Generic price for imiquimod (Imunocare®)	90.31	0.032	0.002	€2,786.33/Clearance	€41,706.62/QALY
Imiquimod 3,75% price (Zyclara®) for imiquimod drug cost estimation	-121.08	0.032	0.002	Dominant	
Discount rate (0%)	24.17	0.032	0.002	€745.61/Clearance	€10,475.15/QALY
Discount rate (5%)	23.28	0.032	0.002	€718.28/Clearance	€11,195.90/QALY
Time horizon (30 years)	40.28	0.032	0.002	€1,242.92/Clearance	€7,997.43/QALY

AEs: adverse events, ICER: incremental cost-effectiveness ratio; ICUR: incremental cost-utility ratio QALY: Quality adjusted life years.

- Estimated incremental cost-effectiveness ratio (ICER) was €728.65/clearance and incremental cost-utility ratio (ICUR) was €10,906/QALY gained with ingenol mebutate vs imiquimod 5%.
- Considering an acceptable willingness to pay threshold of €30,000/QALY¹¹ (commonly used as reference in Spain) ingenol mebutate could be considered a cost-effective alternative vs imiquimod 5%, in terms of ICUR.
- In deterministic SA ingenol mebutate resulted a cost-effective option in 7 from the 9 analyses performed (Table 3).
- ICUR was below €30,000/QALY in 78% of 1,000 simulations of probabilistic SA. (Figure 2)

Figure 2. Probabilistic sensitivity analysis results



CONCLUSIONS

Ingenol mebutate compared to imiquimod 5% resulted a cost-effective therapy for face and scalp AK treatment from the Spanish NHS perspective.

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