Common Drug Review
Pharmacoeconomic Review Report

April 2017

Drug	5-fluorouracil 0.5% and salicylic acid 10.0% (Actikerall)
Indication	Indicated for the topical treatment of slightly palpable and/or moderately thick hyperkeratotic actinic keratosis (grade I/II) of the face, forehead, and balding scalp in immunocompetent adult patients
Reimbursement request	As per indication
Dosage form (s)	Topical solution
NOC date	August 28, 2015
Manufacturer	Cipher Pharmaceuticals Inc.

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ABBREVIATIONS

5-FU/SA	5-fluorouracil (0.5%) combined with salicylic acid (10%)
AE	adverse event
AK	actinic keratosis
ICUR	incremental cost-utility ratio
OHIP	Ontario Health Insurance Plan
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	Fluorouracil/salicyclic acid (0.5%/10%, Actikerall)
Study Question	"The objective of this study was to assess, from a Canadian perspective, the economic impact of 5-fluorouracil 0.5%/salicylic acid 10% (Actikerall) for treatment of individual AK lesions."
Type of Economic Evaluation	Cost-utility analysis
Target Population	Immunocompetent adult patients with actinic keratosis lesions of moderate/severe intensity (grade II/III according to the Olsen scale) on the face, forehead or bald scalp.
Treatment	5-fluorouracil 0.5%/salicyclic acid 10% topical cream (5-FU/SA)
Outcome	Quality-adjust life-years (QALYs)
Comparator	Cryotherapy
Perspective	Canadian public payer
Time Horizon	1 year
Results for Base Case	Use of 5-FU/SA was a dominant strategy (i.e., patients receiving 5-FU/SA incurred lower costs and more QALYs than patients receiving cryotherapy)
Key Limitations	• Poor internal and external validity of the small, phase II trial from which effectiveness estimates for cryotherapy and 5-FU/SA were derived. In particular, the trial was conducted in a more severe population (grade II/III lesions) than reflected in the approved population (grade I/II lesions). As well, cryotherapy was administered according to investigator discretion without standardization or reporting of freeze times. This likely served to underestimate rates of lesion clearance and overestimate rates of recurrence and retreatment with cryotherapy, thereby biasing cost-effectiveness results in favour of 5-FU/SA. • Several assumptions regarding resource use likely do not reflect current Canadian clinical practice (e.g., biopsy for all lesions, treatment administered by dermatologist instead of general practitioner for all patients). • Failure to consider other topical drugs indicated for the treatment of actinic keratosis (e.g., imiquimod, ingenol mebutate, 5-FU). • Uncertainty in estimated QALYs given the availability of multiple utility values for actinic keratosis in the literature. • Unrealistic assumptions regarding full adherence and persistence to 5-FU/SA, which likely overestimates 5-FU/SA efficacy.
CDR Estimate(s)	• Based on CDR reanalyses accounting for some of the above limitations in consultation with the clinical expert (i.e., use of more plausible clearance and recurrence rates for cryotherapy, alternative assumptions regarding resource use), cryotherapy was found to dominate 5-FU/SA (i.e., use of cryotherapy is associated with lower costs and more QALYs). • This result should be interpreted with caution due to the lack of reliable comparative evidence, and the very small difference in QALYs (0.0036) between 5-FU/SA and cryotherapy. CDR noted that a price reduction of 20% is sufficient for total costs with 5-FU/SA to be similar to total costs for cryotherapy. • CDR noted that the estimated per-course cost of 5-FU/SA ($36.55) is substantially lower than for ingenol mebutate ($383.00) and imiquimod (generic, $264.72 to 397.08), but marginally higher than for 5-FU ($34.57). No comparative data for 5-FU/SA versus these drugs were submitted by the manufacturer; therefore, the cost-effectiveness of 5-FU/SA in relation to other topical drugs is unknown.

EXECUTIVE SUMMARY

Background

Actikerall is a topical solution of 0.5% fluorouracil and 10% salicylic acid (5-FU/SA) indicated for the treatment of slightly palpable and/or moderately thick hyperkeratotic actinic keratosis (grade I/II) of the face, forehead, and balding scalp in immunocompetent adult patients.[1] The manufacturer submitted a market price for 5-FU/SA of $36.55 per 25 mL bottle. As one bottle is considered adequate for a full treatment course of up to 12 weeks, the cost per course of treatment is thus $36.55.

The manufacturer submitted a cost-utility analysis based on a decision tree model comparing 5-FU/SA with cryotherapy for the treatment of hyperkeratotic actinic keratosis (AK) lesions of moderate to severe intensity (grade II/III) on the face, forehead and/or bald scalp among immunocompetent adult patients. The analysis used a one-year horizon and was undertaken from the Canadian public payer perspective.[2] Patients received either 5-FU/SA or cryotherapy. Patients were assessed for histological clearance of their AK lesions at week 14 based on the rates observed in a phase II clinical trial by Simon et al.[3] Patients who failed to achieve clearance were retreated with their initial treatment and reassessed. All patients who achieved clearance were assessed for lesion recurrence at six months with rates of recurrence also informed by Simon et al.[3] If there was recurrence, it was assumed that there was no further treatment due to a lack of data. Costs included treatment costs, treatment of adverse events and costs of disease management including medical visits and biopsies.

Summary of Identified Limitations and Key Results

According to the manufacturer's base-case analysis, 5-FU/SA is a dominant strategy (i.e., more effective and costs less) compared with cryotherapy.

CADTH's Common Drug Review CDR identified several limitations of the manufacturer's economic submission. Most notably, estimates of clinical effectiveness for cryotherapy and 5-FU/SA were derived from a small, unblinded phase II trial that was of low internal and external validity. In particular, the patient population assessed had grade II/III lesions and was more severe than that of the Health Canada indication (grade I/II lesions). There was no cost-effectiveness data on use of 5-FU/SA in grade I lesions and no stratified analysis assessing clinical and cost-effectiveness by lesion grade. Further, cryotherapy freeze times were left to the discretion of the investigator and were not reported in the trial; this likely served to reduce the apparent efficacy of this procedure in terms of clearance, recurrence, and retreatment rates, potentially biasing cost-effectiveness estimates in favour of 5-FU/SA. A further limitation was the inclusion of several assumptions regarding resource use that do not reflect current Canadian clinical practice.

Conclusions

In consultation with the clinical expert, more plausible values were considered for a number of key parameters in the CDR base case. As a result, cryotherapy was the dominant strategy (i.e., less costly and produced more QALYs) when compared with 5-FU/SA. In CDR's probabilistic base case, there is a 79.1% probability that 5-FU/SA is dominated by cryotherapy. However, these results should be interpreted with caution due to the lack of reliable comparative evidence for 5-FU/SA versus cryotherapy, and the very small difference in QALYs (0.0036) between these strategies. CDR noted that a price reduction of 20% is sufficient for total costs associated with 5-FU/SA to be similar to total costs for cryotherapy, based on CDR's base case. The manufacturer did not submit comparative clinical information for 5-FU/SA versus other topically administered comparators for AK such as 5-FU; therefore, the cost-effectiveness of 5-FU/SA in relation to these alternatives is unknown. CDR noted that the estimated per-course cost of 5-FU/SA appears substantially lower than for ingenol mebutate and imiquimod, but marginally higher than for 5-FU alone.

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION

The manufacturer submitted a cost-utility analysis based on a decision tree model (Figure 1) comparing 5-fluorouracil (0.5%) combined with salicylic acid (10%) (5-FU/SA) with cryotherapy among immunocompetent adult patients who have hyperkeratotic actinic keratosis (AK) lesions of moderate to severe intensity (grade II/III) on the face, forehead, or balding scalp. The modelled population was assumed to have similar baseline characteristics as patients enrolled in a clinical trial by Simon et al.,[3] an unblinded, phase II study that randomized a total of 66 patients with grade II/III AK lesions to 5-FU/SA or cryotherapy. Patients had a mean age of 70.6 and 71.3 in the 5-FU/SA and cryotherapy groups, respectively, a mean number of eight lesions, and a 75%/25% distribution of grade II and III lesions. The analysis was undertaken from the perspective of the Canadian public payer and used a time horizon of one year. Due to the short time horizon, neither costs nor outcomes were discounted.[2]

Patients on 5-FU/SA applied treatment daily for six weeks and it was assumed that all patients were fully compliant with treatment. Patients receiving cryotherapy underwent treatment on day one, and a proportion of patients (87.9%, based on retreatment rates observed in the Simon et al. study[3]) received a second treatment at week three. Freeze time was not specified and left to the investigator's discretion. Patients were assessed for histological clearance of AK lesions at week 14; rates of histological clearance (62.1% and 41.9% for 5-FU/SA and cryotherapy, respectively) were also obtained from the Simon et al. study. Patients who failed to achieve histological clearance were retreated with the initial treatment, at which point they either achieved histological clearance or again failed to achieve clearance. Rates of clearance for retreatment were assumed to be the same as rates for initial treatment. All patients who achieved clearance were assessed for lesion recurrence at six months with rates of recurrence also obtained from the Simon et al. trial (39.4% and 84.8% for 5-FU/SA and cryotherapy, respectively).[3] If recurrence occurred, no other treatment was considered due to lack of data. Patients experienced adverse events (AEs) at the rates observed in Simon et al., and all patients who experienced an AE were assumed to require a dermatologist visit. Mortality was not considered given the anticipated lack of differences between treatment groups for this outcome during the short time horizon of the model.

Health state utilities in the model were based on the amount of time spent with AK during the one-year model horizon as well as the presence or absence of AEs. The manufacturer undertook a literature search to identify studies reporting quality of life in patients with AK. Patients without AK were assumed to be in perfect health (i.e., they had a utility of 1); whereas patients with AK were assigned a utility of 0.981 based on values used in a previous economic evaluation of treatments for AK by Wilson et al.[4] Further, patients who experienced any AE were assumed to incur a disutility based on the values for "pruritus and related conditions" in Chen et al.[5]

Costs for treatment with 5-FU/SA or cryotherapy, dermatologist visits, and treatment of AEs were considered in the model. Resource use estimates were based on clinical expert opinion and observed resource use in the Simon et al. trial.[3] It was assumed that all doctor visits (whether for initial treatment, retreatment, assessment of clearance/recurrence, or treatment of AEs) were with a dermatologist. The cost of 5-FU/SA was based on the manufacturer's submitted price, while the costs of both cryotherapy and dermatologist visits were obtained from the OHIP schedule of benefits.[6]

2. MANUFACTURER'S BASE CASE

The manufacturer reported in their base case that treatment with 5-FU-SA is associated with a total cost of $254.88 and 0.9893 QALYs during the one-year time horizon. When compared with cryotherapy, the manufacturer reported that 5-FU/SA was $104 less costly and was associated with a gain of 0.0005 QALYs — 5-FU/SA is therefore a dominant strategy. Further details are reported in Table 11.

3. SUMMARY OF MANUFACTURER'S SENSITIVITY ANALYSES

The manufacturer undertook univariate deterministic sensitivity analyses as well as a probabilistic sensitivity analysis (PSA). The results of the univariate analyses indicated that results were most sensitive to the probability of histological clearance with 5-FU/SA (with low 5-FU/SA clearance rates leading to an incremental cost-utility ratio (ICUR) of $46,275/QALY for cryotherapy versus 5-FU/SA) and recurrence for both treatments (with low probability of recurrence leading to an ICUR of $904/QALY for cryotherapy versus 5-FU/SA).

The manufacturer's PSA was run for 1,000 simulations, in which it was found that 5-FU/SA remains a dominant strategy in 94.5% of simulations performed. The design of the model did not allow a PSA with a larger number of iterations, which is a major limitation of the PSA.

4. LIMITATIONS OF MANUFACTURER'S SUBMISSION

Uncertain internal validity of the Simon et al. trial:

Estimates of clearance, recurrence, and need for treatment after 5-FU/SA and cryotherapy were derived from a phase II clinical trial conducted by Simon et al.[3] As noted in the CDR clinical review, there were multiple concerns regarding the design and conduct of the trial that reduced the credibility of reported effective estimates.[3] In particular, the lack of blinding, the small sample size (a total of 66 patients, 33 randomized to each group), and lack of reporting on cryotherapy technique leads to a study which, as noted in CDR's clinical review, "adds little to the understanding of the relative efficacy/safety of 5-FU/SA to cryotherapy."

Uncertain external validity of the Simon et al. trial:

As noted in the CDR clinical review, there are several limitations of the Simon et al. trial that reduce the credibility of the reported effectiveness estimates:

- **Disease severity of study population:** The modelled population consists of patients with moderate to severe, markedly hyperkeratotic lesions (grade II/III), as per the population enrolled in the Simon et al. study. This is a more severe population than the population specified in the Health Canada indication and listing request (i.e., patients with grade I and II lesions, the former of which are non-hyperkeratotic by definition, which in turn has implications for the effectiveness of cryotherapy in particular). Cryotherapy is known to be less effective on hyperkeratotic lesions than it is on thinner lesions.[7] While there is little evidence of differential efficacy of 5-FU/SA by lesion grade, rates of histological clearance are higher in Stockfleth's phase III study with grade I/II lesions (72%) than in Simon et al. (62.1%).[3] Furthermore, hyperkeratotic lesions are known to recur more frequently than less hyperkeratotic ones, which is expected to affect both comparators.[8] As such, the studied patient population likely experienced lower clearance rates, higher recurrence rates, and higher retreatment rates than would be seen in practice, although the effect of using data from a more severe population on the estimated cost-effectiveness of 5-FU/SA is uncertain. Further, there is no cost-effectiveness information on the use of 5-FU/SA or cryotherapy in patients with grade I lesions.

- **Discretionary nature of the cryotherapy procedure in Simon et al.:** The effectiveness of cryotherapy is known to be related to freeze time, with longer freeze times producing higher clearance rates than shorter freeze times.[9,10] This is especially true of hyperkeratotic lesions as they require longer freeze times than thinner lesions.[11] Freeze time was left to the investigator's discretion in the Simon et al. study, and was not reported in either the paper or clinical study report.[3,12] The clearance rate observed in the cryotherapy group of this trial (41.9%) is markedly lower than what has been observed in other trials assessing cryotherapy in grade I/II AK (observed rates of clearance with cryotherapy ranging between 67% to 98.9%[13,14]). This may be due in part to suboptimal freeze time in Simon et al. The proportion of patients requiring repeat cryotherapy at 3 weeks (87.9%, based on retreatment rates in Simon et al.[3]) is also likely to be an artifact of the clinical trial; the clinical expert consulted by CDR suggested retreatment in clinical practice is required in approximately 10% of cases. Overestimation of retreatment rates is likely to bias cost-effectiveness results in favour of 5-FU/SA.

  There is also concern regarding the recurrence rate (84.8%) observed in the cryotherapy group, as compared with a recurrence rate of 39.4% among 5-FU/SA patients. The CDR clinical expert noted lack face validity, potentially reflected a suboptimal cryotherapy technique (i.e., inadequate freeze time) or the more severe patient population. Of note, even the vehicle group of the pivotal phase III trial of 5-FU/SA only demonstrated a recurrence rate of 20%.[15] European guidelines have noted an annual recurrence rate of 1.2% to 12% for cryotherapy-treated lesions,[10] while a study comparing photodynamic therapy with cryotherapy among patients with grade I/II AKs found an 18% recurrence at one year.[16] As such, the recurrence rate of 84.8% is likely an overestimate compared with recurrence rates observed in Canadian clinical practice. This is likely to underestimate the QALYs associated with use of cryotherapy and bias cost-effectiveness estimates in favour of 5-FU/SA.

- **Duration of 5-FU/SA therapy:** 5-FU/SA was applied for six weeks in Simon et al.; whereas it may be used for up to 12 weeks according to the product monograph.[1] This may have reduced the apparent efficacy of 5-FU/SA in the model.

Assumptions related to resource use:
The manufacturer made several assumptions relating to resource use that likely do not reflect typical Canadian practice. In particular:

- All patients were assumed to be treated by a dermatologist. In practice the majority of patients are likely to be seen by their general practitioner (GP). CDR's consulting clinical expert estimated that 90% of patients would be seen by a GP rather than a dermatologist.
- All patients were assumed to see their physician upon experiencing AEs; whereas this is unlikely to happen in practice. AEs for both 5-FU/SA and cryotherapy were thought to be sufficiently mild that they would be addressed at the next scheduled physician visit rather than requiring a stand-alone visit.
- While all patients were assumed to receive a biopsy in the manufacturer's submission, CDR's consulting clinical expert noted that only patients with high-risk or non-responsive AK lesions would receive biopsies in practice.

Exclusion of relevant comparators:
As per CDR submission guidelines, all relevant comparators for the Health Canada indication are to be assessed in economic submissions.[17] Other topical drugs available in Canada for the treatment of AK include imiquimod, ingenol mebutate, and 5-FU. While imiquimod and ingenol mebutate have

indications that only partially overlap with that of 5-FU/SA (indicated for non-hyperkeratotic lesions,[18,19] corresponding to grade I lesions[1]), 5-FU remains a valid comparator given its indication for "topical treatment of premalignant keratoses."[20] However, CDR acknowledges a paucity of data available to inform an indirect comparison. Further, 5-FU is marginally less expensive than the 5-FU/SA combination ($34.57 per 40 g tube versus $36.55 per 25 mL bottle, assuming one pack is enough for a full treatment course for both products, Table 3). The lack of clinical and cost-effectiveness comparisons of 5-FU/SA versus other pharmacological drugs for AK represents an important limitation of the manufacturer's submission.

Uncertain assumptions regarding patient adherence and persistence:
All patients taking 5-FU/SA were assumed to have 100% adherence and persistence with medication, even though this was not reported in the Simon et al. trial. Far lower rates of adherence and persistence to topical AK treatment are observed in clinical practice, with one recent review reporting a range for nonadherence rates of 10% to 63%.[21] In particular, 71% of patients were non-adherent for treatment cycles of six to 12 weeks, as would be indicated for 5-FU/SA. Further, the odds ratio for treatment non-persistence was 2.1 for treatment durations of greater than four weeks.[22] As such, the assumptions of 100% adherence and persistence are not supported. It is unclear how this would affect the cost-effectiveness of 5-FU/SA as both treatment costs and effectiveness are expected to be lower than what was reported.

Uncertainty in calculated QALYs:
The manufacturer conducted a literature search to identify utility values for use in the model, and the utility values used in Wilson's economic evaluation[4] were found to be the most fit for this purpose. These values are informed by time trade-off and standard gamble techniques among an American population. However, multiple utility values are available for AK.[4,5,23,24] Use of these utilities in the model did not have an appreciable impact on cost-effectiveness results for the most part. The exception was the use of utility values reported by Littenberg et al.,[23] which resulted in cryotherapy producing more QALYs than 5-FU/SA.

5. CADTH COMMON DRUG REVIEW REANALYSES

To account for the limitations identified above, the following analyses were undertaken. Further details for these analyses are available in Table 12.

1. **Alternative assumptions regarding rates of clearance, recurrence, and retreatment with cryotherapy to address limitations of the Simon et al. trial**
   Rates of clearance and recurrence were updated for both cryotherapy and 5-FU/SA, and alternative assumptions regarding rates of retreatment with cryotherapy were used. These were validated by the clinical expert consulted by CDR.
   - The clearance rate for cryotherapy was set to 67.2% based on the results of a large prospective study[25] assessing clearance rates for patients with grade I/II AK lesions of the face and scalp, matching the Health Canada population.[1] The British Academy of Dermatology's 2016 guidelines note that clearance rates ranging from 69% to 99% have been observed in studies of cryotherapy in AK,[13] thus CDR's assumption may be considered a conservative one.
   - Rate of retreatment with cryotherapy at three weeks was set to 10% based on clinical expert opinion.

- The clearance rate for 5-FU/SA was set to 55.4%, corresponding to the rates of clinical clearance observed among patients in the pivotal phase III trial of patients with grade I/II lesions.[15] The figure for histological clearance (72%) was noted to be difficult to interpret given the high rates of histological clearance among patients randomized to vehicle (44.8%).
- The rate of recurrence for cryotherapy was set to 18% (versus 84.8% in the manufacturer's base case) to reflect rates of recurrence in the cryotherapy group of a large study comparing cryotherapy with photodynamic therapy (more than 90% of patients with grade I/II lesions).[16] Given that previous guidelines have posited a range of 1% to 12% for lesion recurrence with cryotherapy,[10] this may be a conservative estimate.
- The recurrence rate for 5-FU/SA was set to 32.7% (versus 39.4% in Simon et al.[3]) reflecting values from a recent systematic review comparing 5-FU/SA with ingenol mebutate and imiquimod.[26]

2. Alternative assumptions regarding resource use

The following changes were made to resource use within the model based on consultation with the clinical expert:

- 90% of patients were assumed to see a GP rather than a dermatologist based on clinical expert input. Costs were adjusted to reflect a weighted average of general reassessment with a GP ($38.35, OHIP code A004) (90%) and repeat consultation with a dermatologist ($72.15, OHIP code A026) (10%).
- The extra physician visit upon appearance of AEs was removed.
- It was assumed that only 10% of patients underwent biopsy.

TABLE 2: CDR'S BASE CASE

Scenario		Incremental Costs (5-FU/SA vs. Cryotherapy)	Incremental QALYs (5-FU/SA vs. Cryotherapy)	ICUR ($ per QALY) for 5-FU/SA vs. Cryotherapy
	Manufacturer's base case	*–104.18*	*0.0005*	*5-FU/SA dominates cryotherapy*
1	Alternative clearance and recurrence rates for cryotherapy and 5-FU/SA, alternative retreatment rates for cryotherapy	$26.59	–0.0041	Cryotherapy dominates 5-FU/SA
2	Alternative resource use assumptions	–$98.58	0.0005	5-FU/SA dominates cryotherapy
1-2	**CDR base case**	**$10.39**	**–0.0041**	**Cryotherapy dominates 5-FU/SA**

5-FU = 5-fluorouracil (0.5%); CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SA = salicylic acid.

CDR also undertook price reduction analyses on its base case (Table 13).

- A price reduction of 15% for 5-FU/SA is sufficient for it to no longer be dominated. Beyond a 15% price reduction, ICURs for cryotherapy vs. 5-FU/SA are reported (i.e., since cryotherapy produces more QALYs and is more expensive, a $/QALY value is reported).
- Cryotherapy remains cost-effective compared with 5-FU/SA at conventional willingness-to-pay thresholds even if the price of 5-FU/SA is reduced by 90%. Despite a 90% price reduction for 5-FU/SA, cryotherapy was associated with an ICUR of $9,169 per QALY compared with 5-FU/SA.

Finally, a PSA was undertaken on CDR's base case. The standard error for all updated parameters was estimated to be 25% of the mean value, based on the manufacturer's submitted approach. In CDR's base case, there is a 79.1% probability that 5-FU/SA is dominated by cryotherapy (i.e., that cryotherapy is both less costly and more effective than 5-FU/SA). There is a 20.9% probability that cryotherapy is more effective and more costly than 5-FU/SA. There is a 0% probability that 5-FU/SA is economically dominant or produces more QALYs than cryotherapy. Cryotherapy is expected to cost $15 less than 5-FU/SA and to incur 0.0037 additional QALYs on average.

6. ISSUES FOR CONSIDERATION

Expected use below the neck:
While 5-FU/SA is currently indicated only for the treatment of lesions on the face, forehead, and balding scalp, it is expected based on clinical expert opinion that it would be used for all AK lesions. If so, the amount of 5-FU/SA per treatment course may be larger in clinical practice than what was modelled (i.e., a single bottle per round of treatment), potentially increasing the cost for 5-FU/SA. Further, there are indications that lesions on the trunk and dorsal hands are more difficult to treat than lesions above the neck,[7] to the extent that a higher concentration of ingenol mebutate is used for lesions on the trunk and hands than for lesions above the neck.[18] This may further contribute to use of larger quantities of 5-FU/SA and/or additional costs for retreatment.

Unclear place in therapy:
As noted in CDR's clinical review, the expected place in therapy of 5-FU/SA is unclear according to the clinical expert consulted by CDR. While the presence of SA is posited to allow better penetration of 5-FU into hyperkeratotic lesions, 5-FU/SA is indicated for grade I (non-hyperkeratotic) and grade II (moderate severity, some hyperkeratosis) lesions. Whether 5-FU/SA offers advantages compared with 5-FU alone is unclear given the lack of comparative data.

7. PATIENT INPUT

No patient input was provided specifically for this review — instead, patient input from a previous CDR review (ingenol mebutate for the treatment of AK[18]) was considered. Input was provided by the Canadian Skin Patient Alliance and the Save Your Skin Foundation. Patients noted that AK symptoms have an impact on their quality of life, primarily due to aesthetic concerns and worries regarding progression to non-melanoma skin cancers. This was accounted for in the model by including utility values obtained from patients with AK; disutilities for AEs were not specifically from an AK population, however this was considered to have minimal impact on the results.

Current therapies include cryotherapy, topical drugs, curettage, electrodessication, and surgery. Notable concerns included side effects and long treatment times. Side effects were accounted for by inclusion of AE-related disutilities in the model. Of note, AK was not perceived by patients as being as serious as other non-melanoma skin cancers and patients are reluctant to complete long courses of treatment, especially with drugs that have notable side effects, such as 5-FU and imiquimod. As noted earlier, it was considered a limitation that the effects of nonadherence and non-persistence were not modelled in the manufacturer's submission. Given that treatment lengths of up to 12 weeks are indicated for 5-FU/SA and given the presence of side effects that are likely to be similar to those of other topical drugs, it is unclear that 5-FU/SA addresses these patient concerns.

8. CONCLUSIONS

The manufacturer's submission had several limitations, most notably the poor internal and external validity of the Simon et al. trial. As a result, CDR considered that there was significant uncertainty regarding the comparative efficacy and safety of 5-FU/SA versus cryotherapy, hence the cost-effectiveness of 5-FU/SA is also uncertain. According to the CDR base case in which a number of key parameters were revised to more plausible values in consultation with the clinical expert, cryotherapy is a dominant strategy (i.e., incurs less costs and produces more QALYs) when compared with 5-FU/SA, however these results should be interpreted with caution due to the lack of reliable comparative evidence, and the very small difference in QALYs (0.0036) between treatments. CDR noted that a price reduction of 20% is sufficient for total costs with 5-FU/SA to be similar to total costs for cryotherapy, based on CDR's base case.

The manufacturer did not submit comparative clinical data for 5-FU/SA versus other topically administered comparators for AK such as 5-FU alone, therefore the cost-effectiveness of the combination 5-FU/SA in relation to these alternatives is unknown. CDR noted that the estimated per-course cost of 5-FU/SA is substantially lower than for ingenol mebutate and imiquimod, but marginally higher than for 5-FU (Table 3); however, there is uncertainty associated with this comparison due to differences in dosage form and uncertainty regarding the quantity required per treatment course for each product.

APPENDIX 1: Cost Comparison

The comparators presented in Table 3 below have been deemed to be appropriate by the clinical expert consulted by CDR. Costs are manufacturer list prices, unless otherwise specified. Existing Product Listing Agreements are not reflected in the table and as such may not represent the actual costs to public drug plans.

TABLE 3: COST COMPARISON TABLE FOR 5-FLUOROURACIL/SALICYLIC ACID

Drug/ Comparator	Strength	Dosage Form	Price, Range ($)	Recommended Treatment Course	Cost Per Treatment Course, Range ($)
5-fluorouracil/salicylic acid (Actikerall)	**0.5%/10% cream**	**1 x 25 mL bottle**	**36.5500**[a]	**Apply once daily until lesions clear for up to 12 weeks**	**36.55**
Ingenol mebutate (Picato)	0.015% gel	3 x 0.47 g single use tubes	383.0000[b]	Apply once daily for three days to the face and/or scalp	383.00[b]
	0.05% gel	2 x 0.47 g single use tubes	383.0000[b]	Apply once daily for two days to the trunk and/or extremities	383.00[b]
Imiquimod (Aldara)[c]	5% cream	250 mg Packs of 12 or 24	12.5300[d]	Apply twice weekly for 16 weeks	24 doses: 300.78[e] 36 doses: 451.18[e]
Imiquimod (generic)[c]	5% cream	250 mg Packs of 12 or 24	11.0300[d]	Apply twice weekly for 16 weeks	24 doses: 264.72[e] 36 doses: 397.08[e]
Imiquimod (Zyclara)	3.75% cream	250 mg Packs of 28	10.6679[b]	Apply daily (up to 2 packets) for 2 weeks followed by 2 weeks of no treatment and reapplication for another 2 weeks	298.70 to 597.40
Fluorouracil (Efudex)	5% cream	40 g tube	34.5700[d]	Apply twice daily for two to four weeks	34.57[f]

[a] Manufacturer's submitted price.
[b] DeltaPA, manufacturer's list price, accessed November 2016.[27]
[c] Imiquimod is not approved by Health Canada for use on the trunk or extremities.
[d] Source: Alberta formulary.[28]
[e] Assumes two packs are required for one course of treatment.
[f] Assumes one 40g tube is sufficient to cover 25 cm^2 for an entire treatment course.

TABLE 4: NON-DRUG COMPARATORS FOR 5-FLUOROURACIL/SALICYLIC ACID

Comparator	OHIP Code	Price, Range ($)	Cost per Treatment Course, Range ($)
Cryotherapy	Z119	29.00	29.00 to 58.00[a]
Curettage, electrodessication or cryosurgery	R018-R020 (face, head, neck)	68.55 to $225.75	68.55 to 225.75
	R031-R033 (other areas)	55.05 to $181.55	55.05 to 181.55

Source: OHIP schedule of benefits.[6]

[a] Assumes patients receive one or two cryotherapy sessions per course of treatment.

[b] Assumes patients receive one session of curettage or electrodessication, lower end of range is for single lesions while upper end is for three or more lesions.

APPENDIX 2: Summary of Key Outcomes

TABLE 5: WHEN CONSIDERING ONLY COSTS, OUTCOMES AND QUALITY OF LIFE —THE POSSIBLE ATTRACTIVENESS OF 5-FU/SA RELATIVE TO CRYOTHERAPY?

5-FU/SA Vs. Cryotherapy	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Costs (total)				X		
Drug/procedure costs alone			X			
Clinical outcomes			X			
Quality of life				X		
Incremental CE ratio or net benefit calculation	Cryotherapy dominates 5-FU/SA					

5-FU = 5-fluorouracil (0.5%); CE = cost-effectiveness; NA = not applicable; SA = salicylic acid.

The above is based on CDR's base case.

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 6: SUBMISSION QUALITY

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?		X	
	There was a dysfunction such that utility values from Soini et al. could not be used. Further, the upper bound of 1,000 on the PSA is a limitation.		
Was the material included (content) sufficient?		X	
Was the submission well organized and was information easy to locate?	X		
Comments			

PSA = probabilistic sensitivity analysis.

TABLE 7: AUTHORS INFORMATION

Authors of the Pharmacoeconomic Evaluation Submitted to CDR
☐ Adaptation of global model/Canadian model as done by the manufacturer
☒ Adaptation of global model/Canadian model done by a private consultant contracted by the manufacturer
☐ Adaptation of global model/Canadian model done by an academic consultant contracted by the manufacturer
☐ Other (please specify)

	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document		X	
Authors had independent control compared with the methods and right to publish analysis			X

APPENDIX 4: SUMMARY OF OTHER HEALTH TECHNOLOGY ASSESSMENT REVIEWS OF DRUG

CDR identified one HTA document, produced by the Scottish Medicines Consortium (SMC) in 2011, addressing the use of 5-FU/SA.

TABLE 8: OTHER HTA FINDINGS

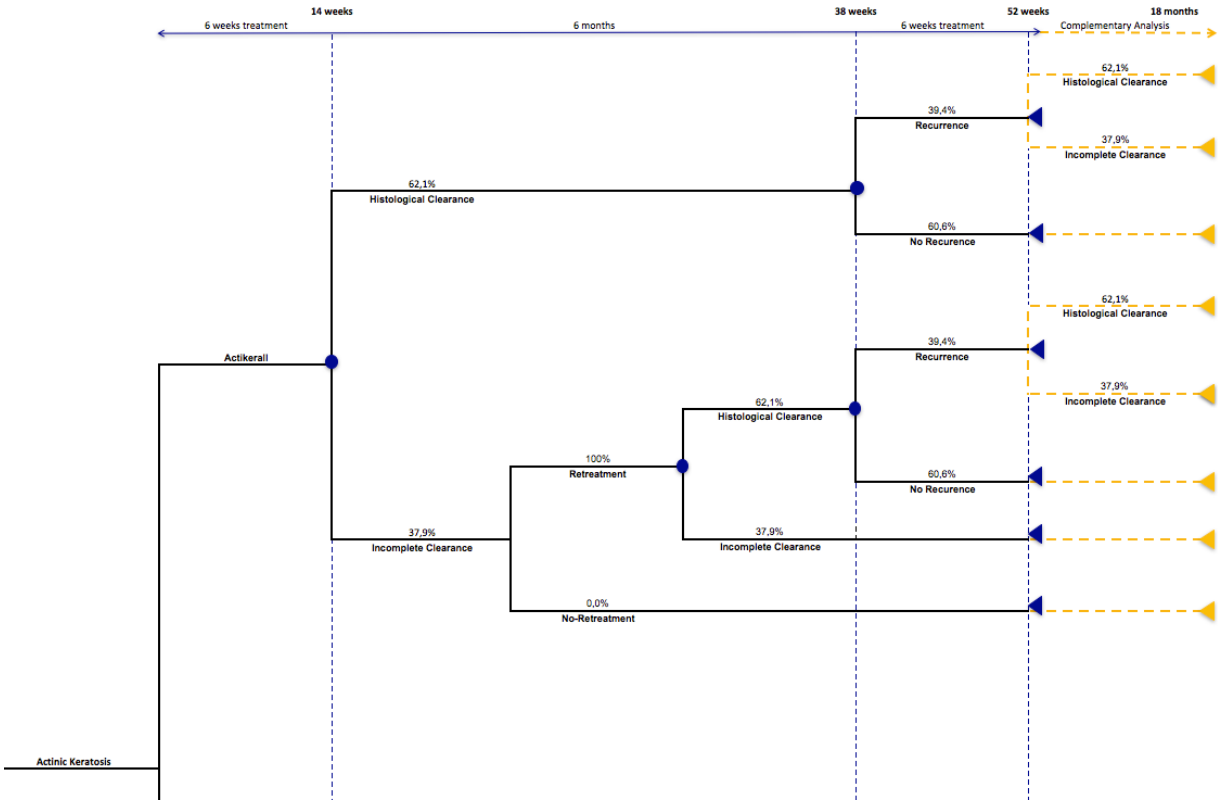
	SMC (2011)[29]
Treatment	Fluorouracil 0.5%/salicylic acid 10% (Actikerall)
Price	£77 per 12-week course of treatment (exchange rate: £1 = C$1.954)[30]
Similarities with CDR submission	– Use of a 1-year time horizon – Very little information provided on sources of effectiveness and utility inputs or model structure, making it difficult to judge comparability to CDR's evaluation.
Differences with CDR submission	– Use of diclofenac 3% gel as a primary comparator. – No explicit consideration of adverse events. – Different source of effectiveness data (presumably the Stockfleth phase III trial).[15] – No information on source of utilities.
Manufacturer's results	Use of 5-FU/SA was dominant (i.e., cheaper and more effective) when compared with diclofenac 3% gel.
Issues noted by the review group	– Unclear whether diclofenac is the most appropriate comparator given its unclear place in therapy, hence secondary analyses vs. 5-FU and cryotherapy were undertaken. – The economic model used data from the secondary lesion clearance end point. The data for progressive disease, stable disease, and partial response were pooled to give an estimate of incomplete clearance. While these patient groups may be quite different, this is unlikely to have caused any major bias as the majority of patients were partial responders. – The cost of recurrence may be slightly overestimated, but this would not affect the overall conclusion that 5-FU-SA is cost-saving versus diclofenac 3% gel.
Results of reanalyses by the review group (if any)	5-FU/SA was found to have an ICUR of £5,675 per QALY versus cryotherapy; however, this was based on a naive indirect comparison with a number of attendant limitations.
Recommendation	"Fluorouracil 0.5%/salicyclic acid 10% is accepted for use within NHS Scotland."

5-FU = fluorouracil (0.5%); CDR = CADTH Common Drug Review; HTA = health technology assessment; ICUR = incremental cost-utility ratio; SA = salicylic acid; SMC = Scottish Medicines Consortium.

APPENDIX 5: REVIEWER WORKSHEETS

Manufacturer's Model Structure

FIGURE 1: MODEL STRUCTURE FOR 5-FU/SA GROUP



Source: Manufacturer's economic submission.[2]

TABLE 9: DATA SOURCES

Data Input	Description of Data Source	Comment
Efficacy	Rates of histological clearance at 14 weeks, lesion recurrence at 6 months, and retreatment with cryotherapy at 3 weeks were based on a phase II clinical trial by Simon et al. comparing 5-FU/SA with cryotherapy among patients with grade II/III lesions.[3]	There are numerous concerns with the use of data in Simon et al. : • Inclusion of a more severe disease state for patient population (grade II/III) lesions than in the Health Canada indication (grade I/II lesions). • Small sample size and lack of blinding. • Lack of information about freeze time, which was left to the investigator's discretion. • All of the above reduce the credibility of estimates of clearance, recurrence, and retreatment for patients treated with cryotherapy.

Data Input	Description of Data Source	Comment
Utilities	Utilities associated with AK were based on an average of values from Chen et al. and Littenberg et al.[5,23] as used in Wilson.[4] These values were based on time trade-off and standard gamble techniques among American patients with dermatological disease. Patients were assumed to be in perfect health aside from the presence of AK. The disutility for adverse effects was based on Chen et al.'s reported disutility for "pruritus and related conditions," which was felt to be the most appropriate for the adverse events seen with 5-FU/SA and cryotherapy.	Appropriate in the absence of Canadian utility data. Alternative utilities identified in the literature included a Danish dermatological cohort,[24] which reported that AK was associated with a far lower utility than the American studies (0.884 vs. 0.981). Use of different utility values for AK did not materially affect results or conclusions for either the manufacturer's or CDR's base case. The only exception was use of Littenberg's utilities in the manufacturer's base case, which resulted in cryotherapy incurring more QALYs than 5-FU/SA.
Resource use	Treatment costs, management of adverse events, biopsies, medical visits. Largely based on expert opinion.	Appropriate in terms of categories of resource use considered. Specific items, however, were problematic; notably, assumptions that all medical visits were to dermatologists, the requirement that AEs receive a stand-alone visit, and that all patients receive a biopsy.
Adverse events (indicate which specific adverse events were considered in the model)	Incidence of adverse events (erythema, scabbing/crusting, burning, pain, pruritus, and hypopigmentation) for both 5-FU/SA and cryotherapy were based on the Simon et al. trial.[3]	Appropriate
Mortality	Not considered	Appropriate given the short horizon and the expected lack of differential mortality between the two treatments
Costs		
Treatment	Costs of 5-FU/SA were based on the manufacturer's submitted price, while costs of cryotherapy were based on the OHIP schedule of benefits.[6]	Appropriate
Administration	Costs of biopsies and dermatologist visits were both based on the OHIP schedule of benefits.[6]	Appropriate
AEs	AEs were assumed to require a stand-alone dermatologist visit.	Inappropriate based on clinical expert input, removed in CDR's base case.

AK = actinic keratosis; 5-FU = 5-fluorouracil (0.5%); AE = adverse event; CDR = CADTH Common Drug Review; SA = salicylic acid.

TABLE 10: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
One bottle is sufficient for one course of treatment	Appropriate
87.9% of patients undergo a second cryotherapy	Inappropriate. While CDR's clinical expert confirmed that patients with hyperkeratotic lesions often require a second cryotherapy treatment (generally 4-6 weeks after assessment), it was estimated that this would affect 10% of patients rather than nearly 90%. Further, high clearance rates have been observed in clinical studies with the use of a single round of cryotherapy.[9,13,14] Consequently, this parameter was changed in CDR's base case.
All treatments were administered by outpatient dermatologists and all visits were to dermatologists	Inappropriate. The majority of patients would be expected to see a GP according to clinical expert input. Changed in CDR's base case.
Treatment of AEs requires an additional dermatologist visit	Noted as inappropriate by clinical expert consulted by CDR. AEs would be addressed at the patient's next visit rather than requiring an additional, stand-alone visit.
Failure to achieve clearance is addressed by retreatment with the same therapy	Likely inappropriate as patients would be expected to receive different treatment upon failure of initial treatment.
There was full adherence and persistence to treatment	Inappropriate given that poor patient adherence and persistence to self-administered topical treatments has been noted in the literature.[11,21,22] However, CDR acknowledges a paucity of data regarding how this would affect the treatment efficacy of 5-FU/SA.
Patients without AK were otherwise in perfect health (i.e., had a utility of 1)	Given the advanced age of patients presenting with AK, it is expected that baseline utility is less than 1. However, this does not affect incremental QALYs or cost-effectiveness results.
The population assessed in Simon et al. (consisting of patients with grade II/III lesions) is appropriate to model cost-effectiveness in the Health Canada indication (grade I/II lesions)	Unclear whether the efficacy of 5-FU/SA in grade II/III AK is applicable to grade I/II. Likely inappropriate to apply efficacy of cryotherapy from more severe population to the indicated population based on clinical expert input, as the procedure may be less effective in markedly hyperkeratotic lesions.[7] Further, hyperkeratotic lesions may have higher rates of recurrence than non-hyperkeratotic lesions.[8] CDR revised clearance and recurrence rates with cryotherapy in its reanalyses.
Efficacy of repeat treatment is the same as that of initial treatment	Unclear whether appropriate — it is expected, based on clinical expert input, however, that patients who fail on one treatment would move onto another treatment.
Use of a 1-year time horizon is sufficient to capture relevant costs and outcomes	Use of a 1-year horizon fails to account for any possible downstream effects on occurrence of squamous cell carcinoma and fails to account for known features of AK's natural history (e.g., spontaneous lesion remission, further recurrence, malignant transformation).[31] However CDR acknowledges a paucity of data to inform long-term evaluations.

5-FU = fluorouracil (0.5%); AE = adverse event; AK = actinic keratosis; CDR = CADTH Common Drug Review; GP = general practitioner; QALY = quality-adjusted life-year; SA = salicylic acid.

Manufacturer's Results

TABLE 11: OVERVIEW OF MANUFACTURER'S BASE CASE

	Cost	Δ Costs	QALY	ΔQALY	ICUR
Cryotherapy	$359.06		0.9888		
5-FU/SA	$254.88	–$104.18	0.9893	0.0005	**Dominant**

5-FU = fluorouracil (0.5%); ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

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TABLE 12: CDR'S BASE CASE

	Total Costs	Total QALYs	Compared with SoC		
			Incremental Cost (C$)	Incremental QALYs	ICUR ($/QALY)
5-FU/SA	$176.84	0.9929	Reference		
Cryotherapy	$181.90	0.9893	5.06	–0.0036	**Dominated by cryotherapy**

5-FU = fluorouracil (0.5%); CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; SA = salicylic acid; SoC = standard of care; QALY = quality-adjusted life-year.

TABLE 13: PRICE REDUCTION ANALYSES FOR CDR'S BASE CASE

ICURs for Cryotherapy vs. 5-FU/SA	
Price	**ICUR ($/QALY)**
Submitted ($36.55/bottle)	Cryotherapy dominates 5-FU/SA
10% reduction ($32.90/bottle)	Cryotherapy dominates 5-FU/SA
15% reduction ($31.07/bottle)	Cryotherapy dominates 5-FU/SA
20% reduction ($29.24/bottle)	$44/QALY
25% reduction ($27.41/bottle)	$696/QALY
30% reduction ($25.59/bottle)	$1,347/QALY
40% reduction ($21.93/bottle)	$2,651/QALY
50% reduction ($18.28/bottle)	$3,955/QALY
60% reduction ($14.62/bottle)	$5,258/QALY
70% reduction ($10.97/bottle)	$6,562/QALY
80% reduction ($7.31/bottle)	$7,865/QALY
90% reduction ($3.66/bottle)	$9,169/QALY

CDR = CADTH Common Drug Review; 5-FU = fluorouracil (0.5%); ICUR = incremental cost-utility ratio; SA = salicylic acid; QALY = quality-adjusted life-year.

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