CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

5-FLUOROURACIL/SALICYLIC ACID (Actikerall — Cipher Pharmaceuticals Inc.) Indication: Actinic Keratosis

Recommendation:
The CADTH Canadian Drug Expert Committee (CDEC) recommends that 5-fluorouracil/salicylic acid (Actikerall) be reimbursed for the topical treatment of slightly palpable and/or moderately thick hyperkeratotic actinic keratosis (grade 1/2) of the face, forehead, and balding scalp in immunocompetent adult patients, if the following condition is met:

Condition:
The drug plan cost of treatment with 5-fluorouracil/salicylic acid should not exceed the drug plan cost of treatment with less costly alternative topical medications.

Reasons for the Recommendation:

1. One double-blind, randomized controlled trial (RCT) (Study 0702 [N = 470]) demonstrated that complete clearance of the primary target actinic keratosis lesion was achieved in 70% of 5-fluorouracil/salicylic acid versus 43% of placebo patients (between group difference of 27% [97.5% confidence interval (CI), 13% to 40%]; $P < 0.001$) eight weeks post-treatment. Furthermore, a statistically significantly larger proportion of lesions were cleared and the proportion of patients achieving clinical response at end of treatment was greater with the 5-fluorouracil/salicylic acid group than with the placebo. There were no consistent reports of specific serious adverse events noted with use of 5-fluorouracil/salicylic acid after 12 weeks of treatment.
2. No comparative clinical information for 5-fluorouracil/salicylic acid versus other topically administered comparators for grade 1/2 actinic keratosis was identified and therefore the comparative cost-effectiveness of 5-fluorouracil/salicylic acid is unknown. The estimated per-course cost of 5-fluorouracil/salicylic acid ($36.55 per 25 mL bottle for 12 weeks of treatment) is higher than for 5-fluorouracil ($34.57), but lower than for ingenol mebutate ($383.00) and imiquimod (generic, $264.72 to $397.08). There is uncertainty associated with these comparisons due to differences in dosage forms and uncertainty regarding the quantity required per treatment course for each product.

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Background:
5-Fluorouracil/salicylic acid has a Health Canada indication for the topical treatment of slightly palpable and/or moderately thick hyperkeratotic actinic keratosis (grade 1/2) of the face, forehead, and balding scalp in immunocompetent adult patients. 5-Fluorouracil/salicylic acid is a combination of the antimetabolite 5-fluorouracil (0.5%) and the keratolytic salicylic acid (10.0%). It is available as topical solution and the Health Canada–approved dosage is to apply to affected lesions once daily until they clear or for a maximum of 12 weeks.

Summary of CDEC Considerations:
CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of RCTs of 5-fluorouracil/salicylic acid, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group–submitted information about outcomes and issues important to patients.

Patient Input Information
No input was provided by patient groups. CADTH staff requested and received permission from the Canadian Skin Patient Alliance and the Save Your Skin Foundation to use patient group input they submitted jointly for a previous CDR review for almost the same indication (for patients with actinic keratosis but not hyperkeratotic actinic keratosis). The following is a summary of key information provided by both patient groups:

- Patients with actinic keratosis identified clearance of their lesions to be of primary importance to them.
- Patients also stated that actinic keratosis has an important impact on their day-to-day living. In particular, they expressed concern about the risk of their actinic keratosis progressing to more serious disease, including non-melanoma skin cancer.
- Current treatment options have negative side effects that cause discomfort and diminish the quality of life of some individuals undergoing treatment for actinic keratosis. These side effects can make it difficult to complete the treatment protocols. Patients also expressed a strong preference for treatments of relatively short duration.

Clinical Trials
The systematic review included one double-blind RCT of patients with grade 1/2 actinic keratosis, Study 0702.

Study 0702 was designed to test the non-inferiority of 5-fluoruracil/salicylic acid to diclofenac gel and its superiority to placebo. A total of 470 patients were randomized 2:2:1 to 5-fluoruracil/salicylic acid, diclofenac gel, or placebo, for a maximum treatment period of 12 weeks. Patients were followed post-treatment for up to 12 months. Only data comparing 5-fluoruracil/salicylic acid and placebo were included for this review because diclofenac gel is not an approved therapy for actinic keratosis in Canada. In the 5-fluoruracil/salicylic acid group 8% of patients withdrew from the study, while in the placebo group, 5% of patients withdrew. There were no active comparator studies that met the inclusion criteria for the review, and no indirect comparisons between 5-fluoruracil/salicylic acid and other topical treatments for actinic keratosis were identified; this limits conclusions that can be drawn about the relative efficacy and safety of 5-fluoruracil/salicylic acid versus other topical interventions.

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Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following:

- Proportion of patients achieving complete histological clearance of their pre-defined target lesion at eight weeks post-treatment (primary outcome in Study 0702).
- Outcomes related to change in lesion count, lesion area, lesion response (complete or partial, stable or progressive), and lesion recurrence.
- Health-related quality of life (this outcome was not investigated in Study 0702).
- Prevention of progression to squamous cell carcinoma (this outcome was not investigated in Study 0702).
- Patient satisfaction.
- Harms: adverse events, serious adverse events, and withdrawal due to adverse events.

Efficacy

- Complete histological clearance of the pre-defined target lesion 8 weeks post-treatment was achieved by 70% of patients in the 5-fluorouacil/salicylic acid group and 43% of patients treated with placebo; therefore, superiority of 5-fluorouracil/salicylic acid compared with placebo was demonstrated for the primary outcome (difference between groups: 27% [97.5% CI, 13% to 40%]; $P < 0.001$).
- Clinical response was assessed as a secondary outcome. There was a higher proportion of 5-fluorouracil/salicylic acid patients with a complete response at eight weeks post-treatment compared with placebo (55% versus 15%), and this difference was statistically significant.
- There was a larger proportion of lesions cleared at end of treatment in the 5-fluorouracil/salicylic acid versus placebo groups (50% versus 33%), and this difference was statistically significant.
- Of the 742 cleared lesions in the 5-fluorouracil/salicylic acid group, 8% had recurrence while 14% of the 189 lesions cleared in the placebo group recurred ($P = 0.023$). At 12 months, 14% of lesions in the 5-fluorouracil/salicylic acid group versus 20% of lesions in the placebo group had recurred ($P = 0.044$).
- A larger proportion of patients treated with 5-fluorouracil/salicylic acid rated their outcome as “very good” or “good” versus placebo (83% versus 72%; $P < 0.00001$).

Harms (Safety and Tolerability)

- In Study 702, there were fewer serious adverse events with 5-fluoruracil/salicylic acid (1% of patients) compared with placebo (4% of patients).
- Overall adverse events were more common with 5-fluoruracil/salicylic acid compared with placebo (95% versus 85% of patients, respectively).
- The most common adverse events were local skin reactions such as inflammation (73% in the 5-fluorouracil/salicylic acid versus 36% in the placebo group), irritation (86% versus 61%), and pruritus (45% versus 41%).
- For adverse events classified as severe, the numerical differences between groups were larger with 5-fluoruracil/salicylic acid treatment for inflammation (16% versus 1%), irritation (21% versus 3%), and pruritus (7% versus 0%).

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Cost and Cost-Effectiveness

5-fluorouracil/salicylic acid is available at the manufacturer submitted price of $36.55 per 25 mL bottle. One bottle is sufficient for a full treatment course of up to 12 weeks.

The manufacturer submitted a cost-utility analysis comparing 5-fluorouracil/salicylic acid to cryotherapy for the treatment of hyperkeratotic actinic keratosis lesions of moderate to severe intensity (grade 2/3) on the face, forehead and/or bald scalp among immunocompetent adult patients. The analysis was based on a decision tree with a one-year time horizon and was undertaken from the Canadian public payer perspective. Comparative efficacy data (defined in terms of rates of histological clearance of actinic keratosis lesions, rates of retreatment and rates of lesion recurrence) were derived from a single phase II clinical trial comparing 5-fluorouracil/salicylic acid and cryotherapy. The manufacturer reported that compared with cryotherapy, 5-fluorouracil/salicylic acid was dominant (i.e., more effective and less costly).

CDR identified the following key limitations with the manufacturer's economic submission:

- Estimates of clinical efficacy for cryotherapy and 5-fluorouracil/salicylic acid 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 2/3 lesions, which is more severe than the Health Canada indication (grade 1/2 lesions).
- Cryotherapy freeze times were left to the discretion of the investigator and were not reported in the trial. This potentially reduced the efficacy in terms of clearance, recurrence, and retreatment rates, potentially biasing cost-effectiveness estimates in favour of 5-fluorouracil/salicylic acid.

Based on re-analyses to account for alternative efficacy estimates for 5-fluorouracil/salicylic acid and cryotherapy including alternative lesion recurrence rates and retreatment rates for cryotherapy, CDR found that cryotherapy was dominant (i.e., more effective and less costly) than 5-fluorouracil/salicylic acid. At a price reduction of 20%, the total costs associated with 5-fluorouracil/salicylic acid are similar to total costs for cryotherapy; however, these results should be interpreted with caution due to the lack of reliable comparative evidence for 5-fluorouracil/salicylic acid versus cryotherapy.

The manufacturer did not submit comparative clinical information for 5-fluorouracil/salicylic acid versus other topically administered comparators such as 5-fluorouracil alone; therefore, the cost-effectiveness of 5-fluorouracil/salicylic acid in relation to these alternatives is unknown. CDR noted that the estimated per-course cost of 5-fluorouracil/salicylic acid appears marginally higher than for 5-fluorouracil alone ($34.57 per 40 g tube), but substantially lower than for ingenol mebutate ($383.00) and imiquimod (generic, $264.72 [24 doses] to brand name $397.08 [36 doses]).

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CDEC Members:

Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. Adil Virani, and Dr. Harindra Wijeysundera.

February 15, 2017 Meeting

Regrets:

One CDEC member did not attend.

Conflicts of Interest:

None

About This Document:

CDEC provides formulary listing recommendations or advice to CDR participating drug plans. CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has not requested the removal of confidential information.

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