

Section 1 – General Information

Name of the drug CADTH is reviewing and indication(s) of interest	Ingenol mebutate Topical treatment for actinic keratosis in adults
Name of patient group	Canadian Skin Patient Alliance (CSPA) and the Save Your Skin Foundation (SYSF)
Name of primary contact:	██████████
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1.1 Submitting Organization

This submission is being made jointly by the Canadian Skin Patient Alliance and the Save Your Skin Foundation.

The Canadian Skin Patient Alliance is a non-profit patient-centred organization serving patient needs to enhance care, promote skin health and find cures for Canadian skin patients. We provide education, information, and a supportive online community, and local support groups for Canadian skin patients and act as an umbrella organization for affiliated skin-disease-specific organizations.

Save Your Skin Foundation is a patient led registered non-profit organization dedicated to raising overall awareness of melanoma and non-melanoma skin cancers. We provide patients with access to information about treatment options, and offer emotional and financial support to patients and/or caregivers. We also lead a coalition of skin cancer organizations across Canada dealing in Melanoma and Non Melanoma Skin Cancer.

Section 2 – Condition and Current Therapy Information

2.1 Information Gathering

The Canadian Skin Patient Alliance and the Save Your Skin Foundation did research in order to gather relevant information on the patient experience with actinic keratosis (AK) and the drug under review. Six patients who are using or have used ingenol mebutate were interviewed on the phone. We contacted these patients through several dermatologists who were involved in clinical trials for the new medication. In addition to the telephone interviews, an online survey was created to collect information about patient experience with AK and AK treatments in general and loaded onto an online tool called Survey Monkey (while only 6 patients filled in the survey, their responses echoed those of the patients who were interviewed).

The questions for the telephone interviews with patients who have tried ingenol mebutate were designed to find out how satisfied patients were with the treatment, how well they feel it worked, how easy it was to use, the side effects they experienced, and how it impacted their day-to-day lives. We

also asked how the therapy under review compared to any other treatments they may have tried for AK. For the online survey, in addition to asking about living with AK in general, we also asked patients questions about their experience in general with any treatment for AK.

Note: Most of the patients who participated in telephone interviews had used other treatments for their AK lesions prior to trying ingenol mebutate (five out of six), although most could not recall the name of their previous treatment. Based on their descriptions, we assumed most were treated with either fluorouracil or imiquimod 5%, 3.75%.

2.2 Impact of Condition on Patients

Actinic keratosis is a pre-cancerous skin condition mostly caused by cumulative sun exposure. It's most common among those older than 65 and its prevalence is increasing as our population in Canada ages.

Actinic keratosis shows up as lesions or rough scaly patches that can feel like sandpaper on the skin. If not treated, AK can progress to non-melanoma skin cancer which clearly could have a significant impact on the individual. This includes dealing with treatments, the stress and anxiety related to having cancer, general co-morbidities, and the potential for it to spread and become more serious, as some non-melanoma skin cancers can lead to death. Unfortunately, there's no way of predicting which AK lesions will progress further into non-melanoma skin cancer.

In the online survey, respondents were asked if they feel AK has had an impact on their lives. Sixty percent responded to this question and all of them indicated they agree or strongly agree that AK has an impact on their life. When probed further to identify areas of their life it impacts, they said they have concern or stress about what more serious skin conditions could unfold, and that it impacts their work / employment because of missed days or not being able to work.

Here are some of the comments the respondents made:

- “When I need to have it burned off, the site blisters and looks horrible, weeping, etc. Yuk. I have been told that if it recurs again, I will need surgery, and they will take skin from my cheek up to my nose to accomplish this....very ugly!”
- “I missed some social activities. When in active treatment, I have had to stay home a few days each time over the past few years.”
- “I’m worried about it spreading.”

All respondents who answered this question agree or strongly agree with the statement: I am concerned about an AK spot progressing into a more serious form of skin cancer if it goes untreated. There was also concern about what it means to have skin cancer and what it could lead to: aggressive treatments (60%), impact on my quality of life (60%), missed time with family (20%), decreased ability to support my family (20%), early death (60%).

Given the increasing and high prevalence of AK and our inability to tell when it will progress to skin cancer, it's important that Canadians with AK can effectively treat the condition and prevent the possible progression to non-melanoma skin cancer. It's the uncertainty and risk of progression can cause anxiety and fear in Canadians with an AK diagnosis.

2.3 Patients' Experiences With Current Therapy

Based on patient feedback, some of the major concerns with current treatments include patients' inability to finish the treatment cycle due to extreme side effects, the negative impact of these side effects on their overall quality of life during the treatment, the length of treatment (up to 12 weeks);

severe discomfort associated with the existing treatment; and, the actual effectiveness of the treatment. The reaction to treatment caused anxiety and stress for some patients.

In total, five patients who had used a treatment other than ingenol mebutate were interviewed. These patients all said they experienced discomfort of varying degrees or suffering caused by the treatment. Side effects that patients are reported to experience with treatments like fluorouracil and imiquimod include skin irritation, burning, redness, dryness, pain, swelling, tenderness, blistering and changes in skin color. Our patient interviewees echoed these officially reported side effects.

Below are some quotes from patients describing these side effects and the impact they had on their well-being and on their day-to-day lives:

- One patient described the discomfort he experienced with the treatment: “The treatment is extremely painful, the sores bleed, and it’s upsetting. I am 80 years old, and I know people who have had this treatment and it’s extremely upsetting for them, and they say ‘ I don’t want to go through that again’ and I agree.”
- Patients also experience anxiety during the course of treatment, for example, one patient said “I would start feeling stressed out about it before I put it on, I knew it was going to hurt.”
- Another patient felt traumatized by a topical cream treatment which affected his ability to eat. The side effects were so bad he had to stop using the treatment. It caused “terrible, red, swollen sores”. In particular on his lip it was “so bad” he couldn’t eat.
- The same patient in the quote above said he had sores on his upper chest and face and he took time off work because he “didn’t want to show his face in public.” He compared his side effects to “what it must be like to have leprosy.” He said he “thought something was really wrong” with him.

The course of treatment for imiquimod, for example, is approximately 12 weeks. Given the side effects of the treatment, many of the patients said that it is a very long time to have to cope with the side effects:

- Patients often experience an increase in the amount of discomfort as the treatment progresses, one patient said “Using a cream treatment on my scalp would make my head red, scabby and sores would appear. It lasted 10 or 11 weeks, and it got more sore as time went on.”
- “For the cream treatment I used at home, I would have to apply it for 11 weeks as tolerated’ – but I couldn’t tolerate the treatment for the full 11 weeks.”
- Painful reactions to the treatments can send a patient back to their physician’s office for further treatment due to the side effects. One patient said “with the imiquimod, the side effects were extreme blistering for 4 to 6 weeks all over my head, very uncomfortable, sore and itchy. I had to go back to the doctor to get some medication to put on it to ease the soreness and itching.”

In terms of effectiveness, many patients find that even **if** they were able to complete the course of treatment with imiquimod or fluorouracil, they did not experience a complete resolution of their AK lesions.

- One patient remarked that “there was a lot of suffering with the treatment. And the treatment did not totally clear all of the lesions up.”

- Other patients found that after an initial clearing up, the lesions returned. One patient noted that it “worked, but the lesions returned after a while, but with the ingenol mebutate the lesions have not yet returned.”

In our online survey we asked patients what they would hope to see in a new treatment that previous treatments they’ve tried didn’t offer. Here are some comments:

- “One of the benefits would be a type of cream that does not seem to attack the skin quite so aggressively that looks like it burns the skin but is equally effective.”
- “Less localized visible reactions.”

2.4 Impact on Caregivers

As AK treatments are self-administered, caregivers aren’t impacted unless the patient is elderly (as many can be) and the caregiver must apply the current treatment on already inflamed and painful skin. This can be as grueling for someone trying to help as it is for the patient who must suffer through the application. With existing treatments, patients may stay home from work, stop participating in recreational activities and this can impact the entire family.

Section 3 – Information about the Drug Being Reviewed

3.1 Information Gathering

For section three (patients with ingenol mebutate experience), telephone interviews were conducted with six patients who are using or have used ingenol mebutate. We contacted these patients through several dermatologists who were involved in clinical trials for the new medication. The questions for the telephone interviews with patients who have tried ingenol mebutate were designed to find out how satisfied patients were with the treatment, how well they feel it worked, how easy it was to use, the side effects they experienced, and how it impacted their day-to-day lives. We also asked how the new treatment, ingenol mebutate, compared to any other treatments they may have tried for AK.

3.2 What Are the Expectations for the New Drug or What Experiences Have Patients Had to Date With the New Drug?

We expect the availability of ingenol mebutate will improve patients’ lives, even if many don’t realize it yet. AK is still not perceived to be as serious as other non-melanoma skin cancers and many patients can be reluctant to complete any of the currently available long (4+ weeks) and debilitating courses of treatments available simply to reduce their increased risk of cancer. A shorter treatment with considerably less trauma to the skin will be more acceptable to the growing population of patients diagnosed with AK. This treatment option meets the current need for a treatment that is easily tolerated and is in line with the perceived overall risk of the disease it treats.

The short length of treatment (two to three days), and the more tolerable side effects, will also have a real impact on patients who in the past have felt stress, anxiety and pain related to other treatments they’ve tried for their AK. Current treatment options involve lengthy applications, coupled with considerable discomfort and are harder for patients to stick with. Given the shorter treatment time, patients can avoid time off work, stay productive, use fewer pain medications and experience considerably less distress.

On the positive side, patients need only apply the new treatment for 2- 3 days (much easier to use), before their skin has had a chance to react. Side effects include pain and itch and redness that develops after the last application of the ointment. This skin reaction lasts up to two weeks, by which time the skin has recovered. This short period of adverse effects is considered positive and quite acceptable considering the alternatives. Given that compliance with the treatment regime is very high, the patient’s long term health and well-being are improved as the risk of skin cancer at the lesion site is addressed.

The patients interviewed had experienced painful side effects from other treatments they'd tried, and were often not able to complete their course of treatment due to the length and skin trauma, potentially leaving the lesion or surrounding area to grow or develop new lesions.

With ingenol mebutate's two to three day course of treatment, and much more tolerable side effects, patients said it was easier for them to take and to complete their course of treatment.

Patients said the treatment was effective and that when side effects occurred they were tolerable:

- Patients who have tried other treatments found that the ingenol mebutate was effective and less painful in comparison; one patient commented that it is very difficult for elderly people who are often treated for AK to tolerate the side effects of the other treatments "I see it as a very effective drug. I also see it as an extremely useful treatment for seniors."
- Patients generally find the side effects tolerable: "With the ingenol mebutate I had some light blistering two to three days after treatment, which went away very quickly. Very little soreness or itching, I didn't have to put anything on it."
- One patient saw gradual but effective results of the treatment, he said: "At first the results were not obvious because I didn't have strong side effects. At the end the results were quite evident, the lesion was completely gone. No side effects at all, no skin reaction, no pain and I didn't get red or blistered."

Patients found the treatment easy to use:

- Patients also found the method of application easy to follow: "It was easier to apply. It was not painful. It was not stressful. Putting on the other cream, I would start feeling stressed out about it before."
- One patient said that the treatment worked well once he was able to master the application process: "You have to be careful you don't get it in your eyes but then it worked well. Anything can be a bit difficult when you are doing something different. It was three treatments in three days, it cleared up my face, and I got used to it."
- Another patient found it much easier compared to other treatments: "Extremely easy, I went through other drugs before and compared to that it was a walk in the park."

Because of the effectiveness of the treatment and patients' ability to complete the treatment cycle, all of the patients agreed that they felt peace of mind knowing that they were preventing their AK lesions from potentially developing into non-melanoma skin cancer.

All of the patients interviewed said that they would use ingenol mebutate again, and that they would speak to their doctor about receiving that treatment over and above another one.

- One patient felt "comforted" by the fact that he was potentially preventing NMSC and said it was the main reason he was taking ingenol mebutate and treating his AK.

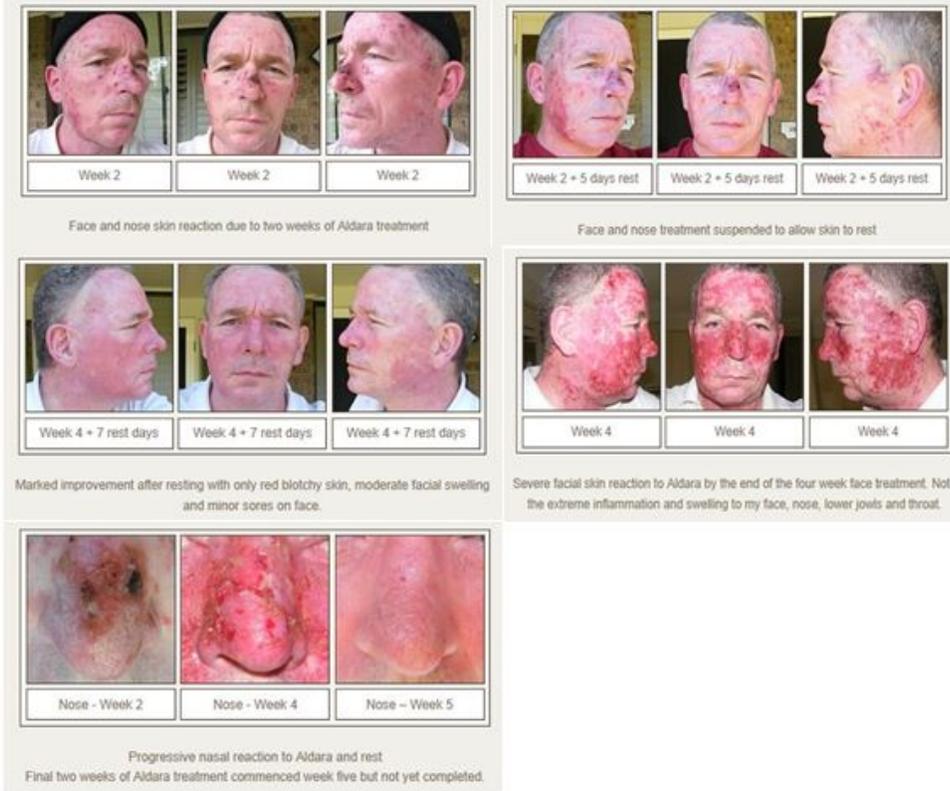
Section 4 – Additional Information

Given that AK is not taken as seriously as it perhaps should be, some patients with an AK diagnosis would be much more likely to embrace a treatment that is less invasive, is easier and less painful to apply and potentially only minimally impacts their lives.

To provide a sense of what the two current topical treatments for AK can look like, we have provided photos from patients we have found online (please see below).

Imiquimod (Aldara) Treatment Photos

Source: <http://stvincentsdarlinghurstmalenurses.blogspot.ca/2011/02/aldara-skin-cancer-treatment-patients.html>



Fluorouracil (Efudex) Treatment Photos*

Source: <http://texaspamrides-efudex.blogspot.ca/p/testing.html> (some of patient comments abbreviated to fit page)

