Submission for Reclassification of Topical Adapalene

Executive Summary

This application requests the reclassification of adapalene from prescription-only availability to availability through a pharmacist without a prescription. Adapalene is a topical retinoid-like medicine used to treat acne.

Acne vulgaris is a common condition primarily affecting adolescents and young adults. Acne occurs at a key developmental time when self-esteem is important and easily impaired.[1] In addition to the obvious immediate effects on the skin, acne can cause psychological effects, scarring, and dyspigmentation.[1,2]

Acne is often self-diagnosed and self-treated, with various medicines available without prescription typically containing benzoyl peroxide, azelaic acid or salicylic acid. In New Zealand (NZ), pharmacists were able to recommend a topical antibiotic to treat acne from the early 1990s until 2002. When this medicine was returned to prescription-only status owing to resistance concerns, the Medicines Classification Committee noted that it left a gap in patient management.[3] Research shows barriers to access for acne treatment exist in NZ.[4]

For mild to moderate acne, topical adapalene is a first-line agent that can be used as monotherapy, or in combination with benzoyl peroxide.[2,5,6]

Benefits of this reclassification include access by New Zealanders to a first-line agent for acne, with efficacy advantages over other non-prescription medicines, convenient access, and possibly cost-saving. Further, acne sufferers who would otherwise self-treat or remain untreated without health professional consultation will be better informed through a discussion with the pharmacist about adapalene. The Pharmacy Council Protocol for the Sale and Supply of Pharmacist Only Medicines for Chronic Conditions has requirements for pharmacists that are beyond those for other pharmacist-only medicines or pharmacy-only medicines. People will be well-informed about the time lag for medicine effect, and how to minimise and manage side effects of the products. People will benefit from early referral to a doctor by the pharmacist where scarring is likely or where response to treatment is inadequate, maximising the benefits of treatment.

As a topical retinoid-like agent, adapalene is to be avoided in pregnancy on theoretical grounds. Women of child-bearing age often suffer from acne, and some such women already use this product. For the Differin® brand, both the product tube and the product leaflet within the box carry a warning to avoid use when pregnant. Unlike oral isotretinoin, the datasheet has no requirement for a negative pregnancy test prior to prescribing, nor special requirements around contraceptives. Pharmacist-only medicines, or those that are prescription only except when supplied by a pharmacist under certain conditions, cannot be placed in areas allowing self-selection in the pharmacy, and a pharmacist must be involved in all supplies of these medicines. Pharmacists will be well-informed through multiple sources

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about avoiding use in pregnancy. The screening tool will include a question for women about pregnancy, and a prompt to advise to avoid pregnancy. We propose encouraging pharmacists to use a dispensing label with the patient's name on it and a warning against use in pregnancy and sharing the medicine. This provides safety around pregnancy that is at least as thorough as that currently occurring. Despite being marketed internationally for over 15 years, evidence in people does not support any increased risk of retinoid embryopathy with adapalene.[7,8] Systemic absorption is extremely low, with topical retinoid application unlikely to significantly increase endogenous levels of retinol. Furthermore, researchers have noted a lack of biological plausibility for teratogenicity of topical retinoids.[7]

Side effects of adapalene are primarily local skin effects. These side effects are not particularly different in nature to those occurring with benzoyl peroxide, a medicine commonly used in NZ with a general sales classification in some strengths.

Informing the person about how to use the product, potential side effects and their management and advising a return to the pharmacy for follow-up will aid education and appropriate management. These points will be included in the screening tool.

Pharmacists receive training about acne and its treatment as undergraduates, and can easily access resources for further information. Pharmacists can be relied upon to refer to general practitioners the people with acne who need medical management, and advise how to use treatments. However, a screening tool will maximise best practice.

The pharmacy process will be comprehensive including thorough screening, record-keeping, referral if necessary, and reporting of adverse events to the GP and the Centre for Adverse Reactions Monitoring (CARM).

Reclassifying adapalene will give people with acne, many of whom will not have consulted a health professional before about their condition, access to such care from pharmacists. This availability is likely to improve management of acne for many people, and see people being who may not otherwise have sought treatment triaged to general practice and dermatologists.

Part A

1. International Non-proprietary Name (or British Approved Name or US Adopted Name) of the medicine

Adapalene

2. Proprietary name(s)

Differin
Epiduo (adapalene plus benzoyl peroxide)

3. Name of company/organisation/individual requesting reclassification

The applicants for this reclassification are Green Cross Health Ltd, the parent company for Life and Unichem Pharmacies in New Zealand (NZ), and Natalie Gauld Ltd. Neither are sponsors for the medicine.

4. Dose form(s) and strength(s) for which a change is sought

Cream and gel containing adapalene 1 mg/g (Differin)
Gel containing adapalene 1 mg/g plus benzoyl peroxide 2.5% (Epiduo)

5. Pack size and other qualifications

30 g

6. Indications for which change is sought

For the topical treatment of comedo, papular and pustular acne (acne vulgaris) of the face, chest or back.

7. Present classification of medicine

Adapalene is a Prescription Medicine.

The benzoyl peroxide classification depends on the strength as follows:

- General sale: For external use in medicines containing 5% or less
- Pharmacy Only: For external use in medicines containing more than 5% and not more than 10%
- Prescription: **Except** for external use in medicines containing 10% or less

8. Classification sought

Adapalene

Prescription: **except** in medicines containing not more than 1 mg/g and when supplied in a pack of not more than 30 grams by a pharmacist.

The manufacturer will not be able to provide NZ-specific non-prescription packaging. Following the example of calcipotriol topical and vaccinations for which the same rationale occurred, we request prescription-only except when supplied by a pharmacist.

For reference, the classification wording for calcipotriol is as follows:

> [Prescription] **except** in medicines containing not more than 50 micrograms per gram or per millilitre and when sold in a pack of not more than 30 grams or 30 millilitres by a pharmacist to an adult with mild to moderate psoriasis previously diagnosed by a doctor

Adapalene plus benzoyl peroxide

It is intended that the proposed wording for adapalene permit the pharmacist to supply the combination product (adapalene plus benzoyl peroxide) since benzoyl peroxide is a general sales medicine in the strength used in the marketed combination product.

9. Classification status in other countries (especially Australia, UK, USA, Canada)

To the best of our knowledge, adapalene is a prescription medicine in other developed countries. Adapalene is being considered for reclassification in Germany.[9]

10. Extent of usage in New Zealand and elsewhere (e.g. sales volumes) and dates of original consent to distribute

See Appendices for sales data.

Differin topical gel was given consent in 1997, followed by the cream in 1998. Epiduo (adapalene plus benzoyl peroxide) was granted consent in 2011.

11. Labelling or draft labelling for the proposed new presentation(s)

There would be no change to labelling for the proposed change in classification owing to the difficulty of production for NZ alone. The current labelling and the Consumer Medicine Information are attached in the appendices.

12. Proposed warning statements if applicable

Current packaging would remain. The Differin® packaging includes clear warnings about pregnancy on the tube and the consumer medicine information leaflet in the pack. The Epiduo® packaging contains similar warnings. We will recommend that pharmacists apply a

patient specific dispensing label to the product which includes a further warning to avoid pregnancy and not share the medicine with others.

13. Other products containing the same active ingredient(s) and which would be affected by the proposed change.

No other products currently marketed will be affected.

Part B

Reasons for requesting reclassification change including benefit-risk analysis.

The primary aim of the reclassification is to increase the accessibility of a first-line acne treatment. This availability will be convenient for acne sufferers and their caregivers. Secondarily, the reclassification will utilise the pharmacist whose expertise and judgement can be used to improve management of a common, and often under-treated condition that has an important impact on quality of life in many adolescents and young adults.

1. Benefits to acne sufferers from the proposed change

Benefits from the proposed change are likely to include:

- Improved access to first-line treatment for acne, and therefore better self-management and reduced opportunity for sequelae including psychological effects, scarring and dyspigmentation
- Encouraging early appropriate treatment
- Helping to address barriers to access
- Convenience including time saving for acne sufferers and caregivers
- Medical referral of people with acne when necessary, who may not otherwise have consulted a doctor about their condition, or may have waited too long to consult a doctor
- Patient education through health professional involvement and prompted advice on the screening tool
- Reduced use of topical and oral antibiotics – prompt and adherent treatment with adapalene or adapalene-benzoyl peroxide may reduce the need for antibiotics

Acne is the eighth most common disease in the world.[10] Acne vulgaris is a condition of the pilosebaceous follicules in which the follicles fill with oil and dead skin cells resulting in formation of comedones (blackheads and whiteheads), papules and pustules. Four factors aid the development of acne lesions: excessive sebum production from sebaceous glands; hyperkeratinisation, obstructing the pilosebaceous canal; inflammation from leakage of the follicle contents into the surrounding tissue; and colonisation with *Propionibacterium acnes*, a commensal bacterium, causing infection in the follicle.[11]

The face is the most commonly affected area, with the back and chest sometimes also involved. It is considered to be a chronic disease, typically occurring over a prolonged period.[5,10] Males tend to be worse affected than females,[10] although prevalence in females tends to be greater than males, both in the younger ages and following the teen years.[10] Two-thirds of NZ high school students reported having acne, and 14% reported having 'problem acne'.[4] Up to 12% of women and 3% of men over 25 years have acne.[6]

Around two-thirds of acne sufferers have mild acne, a further third have moderate acne and severe acne occurs in under 10%.[10] Scarring can even occur from superficial inflamed lesions in some patients. Dyspigmentation is common in people with dark skin colouring.

Acne can impair quality of life, lower self-esteem, affect personal relationships and impact psychological well-being.[1,12] People with acne can feel embarrassed, low in confidence, depressed, sad, anxious, angry, frustrated and despairing.[1] At a time of heightened concern about what is thought of them, acne is usually obvious to others, and can impact their social behaviour. NZ secondary school students with self-reported 'problem acne' have double the likelihood of depressive symptoms or anxiety and around 75% greater likelihood of experiencing suicidal thoughts or attempting suicide (all significant differences).[13] Another study on NZ adolescents found that embarrassment, and lack of enjoyment of and participation in social activities are affected by the severity of the acne.[14] Scarring is common, particularly in those with longer lasting and more severe acne.[10] Given these risks, early identification of adolescents negatively affected by acne is important.[12] Teenagers are not the only ones to suffer psychologically, with post-adolescents suffering more from appearance-related distress than teenagers.[10]

Evidence exists in NZ of barriers to access for acne treatment.[4] Parents lacking knowledge may delay or prevent the teenager from seeking medical advice, and health professionals sometimes underestimate acne.[1] The embarrassment of acne may make adolescents reluctant to discuss it with their parent or doctor.

A pharmacist is readily available during opening hours in community pharmacies throughout New Zealand. Many pharmacies are open extended hours including weekends. People can go to a pharmacy that is most convenient at the time of need. There is no need for an appointment, and pharmacists tend to be youth-friendly (as discussed for oral contraceptives). Youth will be comfortable about walking into a pharmacy alone. Being seen by many as a life stage and superficial, acne may not be thought of as something to see the doctor about, whereas seeing a pharmacist without the need for an appointment may be less formal. Additionally, advice on acne from the pharmacist is readily available, although if a product is purchased it will incur a cost.

A multi-disciplinary stakeholder working party in the UK in 2002 convened to identify potential reclassification candidates. They included adapalene in their list of reclassification candidates.[15]

A gap exists in the non-prescription market in NZ. Topical clindamycin became available as a pharmacist-only medicine in NZ in the early 1990s, and was returned to prescription only status in 2002 following concerns about potential emergence of resistance to this antibacterial that had important systemic usage.[3] However, at the time, the Medicines Classification Committee agreed that this action would create a gap for acne sufferers. Our proposal will help to fill this gap.

New UK guidelines produced by the Primary Care Dermatology Society[6] state that topical retinoids are first-line treatment for comedonal acne. These can be combined with benzoyl peroxide 2.5%.[6] Azelaic acid is recommended second-line. For treatment of mild popular/pustular acne the first-line treatment in these guidelines is adapalene with benzoyl peroxide or a clindamycin-benzoyl peroxide combination. For moderate inflammatory acne, a systemic antibiotic is recommended, usually combined with a topical retinoid. After

sustained improvement to treatment, systemic treatment can be discontinued, and topical treatments can be continued.

People with severe acne and moderate acne need to be referred to doctors early, as well as those with poor response to treatments and those with psychological symptoms.[6]

Adapalene is a topical retinoid that works by modulating cellular differentiation, keratinisatin and inflammatory processes[16]. By normalising the differentiation of follicular epithelial cells, fewer microcomedones are formed. Inflammatory dermatitis starts with microcomedones, so adapalene reduces the number of both non-inflammatory and inflammatory lesions. Adapalene is the preferred topical retinoid according to the UK's Primary Care Dermatology Society,[6] and the European Dermatology Forum,[5] and is considered better tolerated than other retinoids.[11]

Given the prolonged course of acne, maintenance therapy is needed in many people to maintain a remission, whether the remission occurs with systemic therapy or topical.[5] Topical retinoids, particularly adapalene, have been shown to reduce relapses, and are recommended by the European Dermatology Forum guidelines. These are preferred to topical or oral antibiotics in the long-term to minimise antibiotic resistance. Resistant strains of staphylococci in the skin flora are common in acne patients, increasing with a longer duration of antibiotic treatment.[17] In some areas, skin carriage of resistant strains has been seen in 60% of acne patients, and half of their close contacts. Acne maintenance therapy needs to be tolerable and convenient and to accommodate the person's lifestyle. Choices are needed to maximise the likelihood of achieving all three criteria.

Early diagnosis and treatment of acne is important,[1,5,6,18] given possible scarring, dyspigmentation and psychological concerns. Acne scars are mostly preventable by using the correct treatment given in a timely fashion.[6]

Prognostic factors of more severe disease include: family history, course of inflammation, persistent or late-onset disease, hyperseborrhoea, androgenic triggers, truncal acne, psychological concerns, early onset with mid-facial comedones, and/or early and more severe seborrhoea.[5] If scarring is present, aggressive management is advisable – this would require referral to a doctor, as pharmacists would already facilitate.

Effectiveness of adapalene and adapalene-benzoyl peroxide in combination

Topical retinoids, including adapalene, are first-line treatments for comedonal and mild pustulopapular acne according to multiple guidelines.[5,6,18] As the most effective medicine for comedones which are common alone, or precursors for inflammatory acne, they aid both non-inflammatory and inflammatory lesions.[19] Adapalene reduces the number of inflammatory and noninflammatory lesions, and, at the strength marketed in NZ, has similar efficacy to the marketed strength of topical tretinoin in mild-to moderate acne.[20] The fixed combination of adapalene and benzoyl peroxide is more effective than adapalene alone[21] for mild to moderate acne.

Benzoyl peroxide has antimicrobial activity (without resistance issues) and is sebostatic, reducing the sebum produced. Fixed combination therapy containing adapalene 0.1% and benzoyl peroxide 2.5% is significantly more effective in reducing acne lesion counts than adapalene 0.1% or benzoyl peroxide 2.5% monotherapy.[21,22] Both inflammatory and non-inflammatory acne lesion counts are lower with the combination, and onset of action is earlier. Fixed combination therapy (with only one application needed) aids adherence.[6]

2. **Potential risk of harm to the consumer as a result of the proposed change, and factors to mitigate this risk.**

Consumer harm is low. Side effects (see attached datasheet) primarily involve the skin and are reversible.[16] Very few (2.2%) patients withdrew from trials owing to side effects. Systemic allergy to adapalene occurs rarely.

The greatest risk is use in pregnancy, an issue that exists with prescription use also. Adapalene is category D in the TGA's Prescribing medicines in pregnancy database, defined as follows:

> Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

Briggs' Drugs in Pregnancy and Lactation notes that the pregnancy recommendation is "limited human data – animal data suggest low risk."[8] Furthermore, it states that adapalene is not teratogenic in animal studies and has very low bioavailability, so risk is "very low" from inadvertent exposure. The single report mentioned was anophthalmia and small size in a 22 weeks' gestation foetus which was terminated, but the defects were not thought to be typical of retinoid-induced malformations. The European Network of Teratology Information Services studied congenital malformations following first-trimester topical retinoid exposure with 235 exposed pregnant women[7] and found no child had features of retinoid embryopathy.

Vitamin A teratogenicity has been observed with long-term high doses (25,000 IU/day) or a single high dose (500,000 IU). There has been a suggestion that doses under 10,000 IU are not teratogenic, with Briggs advising to avoid exceeding the recommended daily allowance of 8000 IU/day.

Other category D medicines include oral fluconazole which is available as a pharmacist-only medicine, and vitamin A supplementation, which carries a general sales classification in NZ in 3 mg or less of retinol equivalents per recommended daily dose, in parenteral nutrition and for external use in medicines containing 1% or less. Pharmacists are aware of the importance of avoiding other non-prescription medicines in pregnancy, e.g. anti-inflammatories particularly in the third trimester.

Community pharmacies are easily accessible to and used by most of the population, healthy and unwell, across all age groups. Healthy teenagers on minimal or no medication are not

enrolled in a single pharmacy, so they can use the one most conveniently located for them at the time.

3. Ease of self-diagnosis or diagnosis by a pharmacist for the condition indicated

A high awareness of acne exists amongst health care consumers, with self-diagnosis and self-management typical. However, health care consumers are unlikely to be aware of the best treatment for the different levels and types of acne, and therefore hold important misconceptions.[14]

A US survey[23] of females aged 25-45 years with acne found that only half of the participants had ever visited a health care professional for acne. The visit most commonly occurred owing to frustration with inadequate efficacy of self-management. Acne management respondents commonly stated using included behavioural changes (e.g. diet, sleep), and complementary remedies. In the previous four weeks, half of the participants had used OTC treatments for their acne, and 15% prescription medicines. Thus, self-treatment of various forms is the mainstay of acne management in women.

Pharmacists learn about acne as under-graduates, and are well-versed in the non-prescription and prescription products. The Medicines Classification Committee has considered acne a self-diagnosed condition, given their previous reclassifications of medicines for acne to pharmacist-only, pharmacy-only and general sales.

For more than mild or occasional acne, a health professional such as a pharmacist or doctor should be involved to ascertain potential for scarring and dyspigmentation in particular. If necessary the pharmacist will refer to medical care to ensure best practice management to avoid scarring and dyspigmentation.

A NZ study of adolescents found a highly significant relationship between adolescent views of the severity of their acne with objective clinical assessment.[14] The patient is also best placed to evaluate response. NICE from the UK states that for acne treatment "failure is probably best based upon a subjective assessment by the patient."[24]

Consumers self-diagnose acne. The pharmacist already diagnoses acne, provides management advice and refers patients for further care where necessary. The screening tool will aid this diagnosis and referral pathway to maximise benefits for people and use of best practice.

4. Relevant comparative data for like compounds

Oral Vitamin A

While not used for acne, it is relevant to consider the status of Vitamin A in NZ. Vitamin A is available as general sales in NZ under the following conditions:

"for internal use in medicines containing 3 milligrams or less of retinol equivalents per recommended daily dose; in parenteral nutrition replacement preparations; for external use in medicines containing 1% or less"

Otherwise Vitamin A is a prescription medicine. Like adapalene, vitamin A has category D status in pregnancy, under Australian categorisation.

OTC acne preparations

Self-treatment of acne has long existed in NZ. For many years this has included the non-prescription availability of various products including benzoyl peroxide, azelaic acid, salicylic acid and sulphur. Benzoyl peroxide is currently the only non-prescription medicine with strong evidence of good efficacy in acne.[2]

Benzoyl peroxide is available as a general sales medicine in 5% strength or less, and a pharmacy-only medicine above 5% but no more than 10%. The effect on *P acne* is considered to be the main mechanism of action for benzoyl peroxide with a mild comedolytic effect.[2] It is less effective on comedones than topical retinoids.[25] Over a two-month treatment period in a double-blind, randomised trial, adapalene 0.1% gel performed better in patients with mild acne vulgaris than benzoyl peroxide 2.5% gel.[25] While the mean number of inflammatory lesions was significantly lower with the benzoyl peroxide patients at the first month time point, adapalene was superior at the second and third (post-treatment) month time points on total lesions and comedones, and similar on inflammatory lesions. At two-months, comedones were 33% fewer in adapalene patients than benzoyl peroxide patients, and total lesions were lower by 21%. At the post-treatment point (month 3), adapalene showed significantly greater continued effect on total lesions and comedones than benzoyl peroxide. Patient satisfaction was higher with adapalene than benzoyl peroxide (93% versus 73%, p=0.08, non-significant). Benzoyl peroxide causes local skin irritation including redness, burning, dryness, itching, peeling or slight swelling, and it has a 1 in 500 rate of allergic contact dermatitis.[2] To minimise side effects, benzoyl peroxide should be started in a low dose, and initially may need to be washed off at night rather than left on overnight to help to manage local adverse reactions. It can cause bleaching of hair, clothing and bedding, and increased risk of sunburn.

In 2014 the Food and Drug Administration (FDA) in the US published a safety alert warning that "certain over-the-counter (OTC) topical acne products can cause rare but serious and potentially life-threatening allergic reactions or severe irritation."[26] The FDA was unable to determine if the serious reactions were from benzoyl peroxide or salicylic acid, the inactive ingredients, or a combination of both. These reactions occurred within minutes to a day or longer after product use. Most of the 131 hypersensitivity cases with benzoyl peroxide or salicylic acid containing acne products with serious outcomes that were the basis for this report were reported to the FDA since 2012. No fatalities occurred, but 44% required hospitalisation.

Azelaic acid is a pharmacy only medicine for dermal use in NZ. It receives little mention in guidelines for the treatment of acne.

Salicylic acid is a general sales medicine for dermal use containing 40% or less, in NZ. It receives little if any mention in guidelines for the treatment of acne. See above information about hypersensitivity.

Topical clindamycin became a pharmacist-only medicine in NZ in the early 1990s,[27] but was up-scheduled to prescription-only around 2002 because of concerns about bacterial resistance. It is not government-funded for acne, presumably to discourage its use. Topical antibiotics should not be used as monotherapy for acne owing to concerns about resistance according to guidelines. Topical adapalene is a more appropriate agent for pharmacist-only provision.

Topical tretinoin was reclassified from prescription only to pharmacist-only for acne in NZ in the early 1990s.[27] It was noted that the Department of Health "will need to vet the new packaging and labelling for Retin-A with particular reference to warning statements in pregnancy." However, the Medicine Classification Committee later seemed to suggest that the warning may not have been applied.[28] Australia appeared to have had topical tretinoin available without prescription around this time also.[28] Following two reports of birth defects in Australia, up-scheduling occurred in both countries, despite the Medicines Classification Committee minutes reporting that information was conflicting. The Medicines Classification Committee minutes indicate that the NZ decision was influenced in part by the fact that international packaging used in NZ, without a pregnancy warning, could not expect to be changed in the short-term to include a pregnancy warning.

Prescription treatments of acne

Various prescription treatments for acne exist.

Two topical retinoids, adapalene and tretinoin, are funded. These may be needed for long-term maintenance, possibly years.

Combined oral contraceptives[6] or systemic hormonal antiandrogens can be indicated for use in acne for women. European Guidelines include hormonal antiandrogens in severe acne.[5] The UK Primary Care Dermatology Society Guidelines recommend the cyproterone ethinylestradiol combination is used in moderate to severe acne where other treatments have failed, and is discontinued three months after the acne has been controlled.[6]

Oral antibiotics can be indicated, except for acne with only comedones, but should not be used as sole treatment,[6] or used for a long time. [19]Topical antibiotics are unfunded in NZ (see above for further information).

Oral isotretinoin is indicated in NZ for severe forms of nodulo-cystic acne which are resistant to therapy.[29] Until recently it was only funded through dermatologist prescription because of the dangers of the medicine, particularly its highly teratogenic nature. The funding of isotretinoin was opened to general practitioners to help overcome barriers to access for acne treatment in NZ, and particularly inequities of access for Maori, Pacific people and those in deprived areas. However, research following this policy change found supply remained similar, suggesting that barriers to treatment for acne remain.[30] While we are not proposing

that adapalene is used as monotherapy in people who have severe acne or acne that is insufficiently responsive to first-line treatments, availability of more effective options in pharmacy should lead to more conversations between pharmacists and patients which would encourage a visit to a doctor if necessary.

Availability of topical adapalene through the pharmacist would circumvent the need for a medical appointment, but allow a first-line agent to be available from a health professional who would evaluate the acne sufferer, and refer him or her to the doctor for treatment if necessary. These referrals would include cases in which scarring is likely or already evident, or where first-line topical agents have insufficient efficacy or are poorly tolerated. This availability is likely to increase the numbers of people with mild to moderate acne being treated with first-line agents, and, through referral, encourage those with severe acne to be treated by the doctor.

5. Local data or special considerations relating to New Zealand

Acne is a common part of life as an adolescent, and occurs in some adults too. In NZ, 91% of male adolescents and 79% of females in the final two years of high school had acne.[14] Evidence exists in NZ of barriers to access for acne treatment. Twenty per cent of secondary school students with acne wanted treatment but were unable to access or afford treatment from a doctor or specialist.[4] Access difficulties were more often reported by females than males, by Māori or Pacific adolescents than NZ European, and by those who self-reported 'problem acne' versus those with acne that was 'not too bad'. The authors suggested that lack of awareness of the availability of treatments could be a concern, and that there is a need to "urgently respond to this important youth health issue". Where affordability aspects arise in supply of non-prescription products, the pharmacist would be able to refer patients to a local GP to ensure funded treatment is available. After researching the effects of acne on adolescents in Auckland, New Zealand, Pearl et al[14] noted *"a need for all students to have access to appropriate information and health services so that the social and psychological consequences of acne are minimised."*

Māori and Pacific adolescents have greater difficulties than NZ Europeans accessing treatment for acne, and health care generally.[4,30] Disparities were evident in treatment with isotretinoin (at the time only funded through dermatologist prescription) and cyproterone acetate with ethinylestradiol (available through primary care),[30] despite similar incidence of 'problem acne' in Maori to NZ European adolescents, and a higher rate of 'problem acne' reported by Pacific adolescents than NZ European adolescents.[4]

Prolonged dyspigmentation in darker skins needs consideration by health professionals in managing acne. Having multiple effective (first-line) options available without prescription will limit dyspigmentation in the increasing numbers of New Zealanders who may be affected by this concern. Pharmacists will consider this issue when recommending treatment or needing to refer patients.

People-centered education about how to use the treatment, when improvement occurs with therapy, adherence to therapy and adverse events is important to maximise treatment benefits. The pharmacist-only chronic medicine use protocol from the Pharmacy Council of

New Zealand (see appendices) provides an excellent mechanism to maximise the benefits of acne treatment, or refer if necessary. Consultation records would be kept and referred to in future supplies at the same pharmacy, and information provision and monitoring are outlined. Verbal and written information for the patient is expected, a factor that can help compliance with acne treatment in the short-term.[31]

Health literacy issues exist in New Zealand.[32] Pharmacists receive under-graduate training in communication and are aware of health literacy issues. Additionally, the pharmacist-only chronic medicine use protocol will ensure ongoing evaluation and education is a clear part of the provision of these medicines.

Fragmentation of care has been raised as an issue with previous reclassifications. Many people already self-treat acne without seeing the doctor, so generally doctors may be unaware that acne is a problem for the patient, or that the patient is already managing their acne. Thus, fragmentation is unlikely to increase. Rather there is likely to be greater integration with medical practices given the Pharmacy Council's Protocol stating that other health practitioners caring for the patient are to be referred to or consulted with if necessary and with the patient's permission. The screening tool includes provision to check what the patient has used and is currently using for their acne. To support collaboration, pharmacists have shown their willingness to discuss with the person the importance of communicating information to their doctor.

NZ government strategy

The proposed reclassification is in line with the NZ government strategy of people-centred care, and healthcare workers working to the tops of their scopes of practice. Implementing the Medicines New Zealand action plan (2015-2020) highlights the need to remove barriers to access, and emphasises that access should take into account an individual's personal preferences.[33] Furthermore, this extension empowers individuals and families/whanau to manage their own medicines and health.

Population growth, an aging population and developments in health are increasing demand for health services in a constrained fiscal environment. These pressures require better use of the existing health workforce, including extending existing roles.[34] Reclassification means many people with mild to moderate acne could be treated appropriately by the pharmacist, and that pharmacists will be well-placed to refer people with greater health needs to the doctor for care, some of whom may be currently untreated or self-managing inadequately with the limited range of topical treatment currently available without prescription.

6. Interactions with other medicines

There are no known interactions with other medication. However, adapalene should not be used concurrently with other retinoids. Pharmacists would be aware of this contraindication and the screening tool will include a check for it.

7. Contraindications and precautions

The only contraindication is hypersensitivity to ingredients.

Precautions for adapalene are as follows[16]:

- Avoid contact with eyes, lips, mouth and mucosal membranes, angles of the nose or broken skin.
- Avoid use in patients with eczema or seborrheic dermatitis
- Discontinue in severe irritation
- Additive irritant effects can occur with concomitant use of abrasive cleaners, astringents or strong drying agents
- Cosmetics should be non-comedogenic, and moisturisers used should be oil free
- Avoid excessive sunlight or UV irradiation

The combination adapalene-benzoyl peroxide product has an additional warning to avoid contact with coloured material including hair and dyed fabrics owing to potential for bleaching and discolouration.[35] It also notes the inclusion of propylene glycol which can cause skin irritation.

Pregnancy

Adapalene should be avoided in pregnancy. The Differin cream datasheet[16] notes:

> "Because of the risk of teratogenicity shown in animals, and since there are no adequately controlled studies in pregnant women, adapalene should not be used by women who are pregnant or who plan to become pregnant during treatment."

The Epiduo gel datasheet[35] notes:

> "Animal studies by the oral route have shown reproductive toxicity at high systemic exposure.
>
> Clinical experience with locally applied adapalene and benzoyl peroxide in pregnancy is limited but the few available data do not indicate harmful effects in patients exposed in early pregnancy. Due to the limited available data and because a very weak cutaneous passage of adapalene is possible, Epiduo should not be used during pregnancy. In case of unexpected pregnancy, treatment should be discontinued."

Further details are available above in section B 2.

All precautions are manageable by pharmacists.

8. Possible resistance

Not applicable.

9. Adverse events - nature, frequency etc.

The adverse events are compatible with availability without prescription, being quite similar to benzoyl peroxide, and reasonably tolerated.[36] The Differin cream datasheet reports that "no systemic reactions have been attributed to the application of the cream to date."[16] Very common side effects (>10%) are: redness, dry skin, burning sensation at application site, scaling. Common side effects (> 1% and < 10%) are: skin irritation, pruritis, and sunburn. Uncommon side effects are: contact dermatitis/eczema, skin discomfort, skin exfoliation, acne flare, facial and eyelid oedema, vesiculobullous eruptions, herpes labialis, conjunctivitis. Reactions typically occur within a month of initiating therapy and resolve with continued use or temporary modification.

A review reported that topical adapalene 0.1%/benzoyl peroxide 2.5% gel had generally good tolerability with the most common adverse events being erythema, scaling, dryness and stinging/burning, typically of mild to moderate severity, soon after starting therapy and resolving.[22] Dryness was the most common effect on prolonged use.

See the SMARs report from the Medsafe website in the appendices. Only one report, in a male patient, was listed in this report.

Pharmacists will provide advice on possible side effects and their management if they occur. Pharmacists are readily available in the pharmacy in person or by telephone should people experience side effects.

10. Potential for abuse or misuse.

Abuse seems highly unlikely.

Misuse is unlikely. Possibly someone could use two retinoids concomitantly, this is unlikely but will be checked for.

11. Other information

Time to effect

People expect quick results with their acne treatments.[37] They need to be educated about how long response can take, as it is not immediate but can take weeks.[38] This will be included in the screening tool.

Adherence

Adherence is an issue with acne treatment. In a US study in women, prescription product users self-reported use of prescription treatments on average on 18 days of the last 4 weeks.[23] OTC products were similar with benzoyl peroxide products users averaging 17 days of use in the last 4 weeks. Adherence difficulties can limit efficacy, result in increased visits to doctors and cause unnecessary treatments,[39] which could include antimicrobials when first-line agents could have been sufficient. Side effects cause non-adherence, but pharmacists can address that by providing a non-comedogenic moisturiser and advice about thin application, appropriate initiation of therapy and how to manage side effects. Pharmacists will be readily

available for queries about side effects. Pharmacist advice to aid compliance of first-line agents may limit the use of antimicrobial therapies.

Underlying conditions

Underlying conditions or medication can sometimes cause acne. Pharmacists are aware of polycystic ovarian syndrome and that some medication can cause acne, and should refer people to their general practitioner if either are suspected. Polycystic ovarian syndrome could be suspected in women where acne is accompanied by hirsutism and/or irregular menstruation, and the woman may be overweight or obese.

Collaboration with GPs

Supply of adapalene through the pharmacist using the Pharmacy Council Protocol for the Sale and Supply of Pharmacist Only Medicines for Chronic Conditions includes a provision for referral to and consultation with other health practitioners caring for the person if necessary, and with the person's permission. Self-management of acne already occurs, and thus doctors should be asking patients what non-prescription medicines they have already used or are using as a matter of course when treating them for acne. Pharmacists will be asking about prescription medicines being used for their acne or other conditions. However, the person's general practitioner will be notified of the treatment provided to the person with their consent.

This supply does not replace general practice but offers another option for people. It is possible that more people with concerning acne may present and be referred for medical management than currently are treated, given the under-treatment occurring in NZ.[4,30] Care will be no more fragmented than for benzoyl peroxide, but there is no suggestion that this agent needs up-scheduling to prescription medicine to prevent fragmentation of care.

Around three-quarters of graduating family physicians surveyed in Canada agreed that pharmacists should initiate topical treatment, according to a collective prescription for patients with juvenile acne.[40]

Opportunistic screening

While there could be potential for opportunistic screening by a doctor, or discussion about contraception with visits for acne, this has not been a reason to make benzoyl peroxide a prescription medicine, and nor should it prevent a medicine with a positive benefit-risk profile from being reclassified.

Cost

Cost is not a consideration of the Medicines Classification Committee. This reclassification application considers the benefit-risk of whether adapalene should be available without prescription. Funding for adapalene is not affected by this reclassification decision.

Summary

Adapalene is an effective first-line agent for mild to moderate acne. Widening access through the pharmacist will ensure health professional contact remains, but help address barriers that currently exist to access. It will save time for sufferers and their caregivers compared with prescription supply. We have addressed potential risks and maximised benefit through use of a screening tool that also includes prompts of advice to give. Pharmacist delivery of adapalene and the combination adapalene-benzoyl peroxide treatment has an appropriate benefit-risk equation, and would be welcomed by the public.

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