

## **Dermatology Subcommittee of PTAC**

### **Meeting held 30 November 2015**

**(minutes for web publishing)**

The Dermatology Subcommittee minutes are published in accordance with the *Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2008*.

Note that this document is not necessarily a complete record of the Dermatology Subcommittee meeting; only the relevant portions of the minutes relating to Dermatology Subcommittee discussions about an Application or PHARMAC staff proposal that contain a recommendation are generally published.

The Dermatology Subcommittee may:

- a) recommend that a pharmaceutical be listed by PHARMAC on the Pharmaceutical Schedule and the priority it gives to such a listing;
- b) defer a final recommendation, and give reasons for the deferral (such as the supply of further information) and what is required before further review; or
- c) recommend that PHARMAC decline to list a pharmaceutical on the Pharmaceutical Schedule.

These Subcommittee minutes were reviewed by PTAC at its meeting on 5 & 6 May 2016, a record of which will be available in due course.

**Record of the Dermatology Subcommittee of the Pharmacology and Therapeutics  
Committee (PTAC) meeting held at PHARMAC on 30 November 2015**

## **1 Matters arising / correspondence**

### *Occlusive ointment*

- 1.1 The Subcommittee noted correspondence from an editor of New Zealand Formulary requesting an occlusive emollient (very greasy) ointment to be funded.
- 1.2 Members noted that this product type had been discussed at the Dermatology Subcommittee December 2013 meeting and there had been enthusiasm for the product which was recommended with a high priority.
- 1.3 The Subcommittee noted that liquid paraffin with soft white paraffin (50:50 ointment) is currently listed on the HML with no restrictions. Members noted that 50:50 ointment is listed on the Community Schedule with partial subsidy and restrictions to be funded only in combination with a dermatological galenical or as a diluent for a proprietary plain topical corticosteroid.
- 1.4 The Subcommittee noted that an emollient like 50:50 ointment would also be useful for people with very dry skin, such as the elderly, where regular moisturisers were ineffective. Members also noted that 50:50 ointment could be used for many different indications such as eczema and ichthyosis.
- 1.5 The Subcommittee considered anecdotal reports of prescribers prescribing occlusive ointment with a small amount of menthol to obtain the subsidy. Members considered that these products, compounded in community pharmacies, are often given a 3-month expiry date which is inappropriate as the product does last longer. Members considered that there was an inequity of access as not all prescribers were aware that the compounded mixture would be partially funded when mixed with another product such as menthol.
- 1.6 The Subcommittee **recommended** widening access of liquid in paraffin in white soft paraffin (50:50 ointment) by removing current restrictions and fully funding the product. Members noted that this product was included in the 2015/2016 tender. Members also considered that this product should not be expensive and should not have a significant impact on the pharmaceutical budget.

### *Wound irrigation and cleansing agents Definition*

- 1.7 The Subcommittee noted that PHARMAC had received a number of communications from suppliers regarding listing wound irrigation and cleansing products. The Subcommittee considered that the discussed inclusion of wound irrigation and cleansing agents could be of significant financial impact to DHB hospitals.
- 1.8 Members noted that these products are generally registered as Medical Devices, requiring only the submission of the name of the product to the Web Assisted Notification of Devices (WAND) with no clinical evaluation being required. Members considered that if products had a therapeutic claim, then they should be assessed as medicines.

- 1.9 Members considered that there was no consistency to how DHBs currently accessed these products as there was significant variation around how they are sourced, for example some are bought through DHB stores departments and others through a hospital pharmacy. It may not be possible to obtain accurate figures on quantities purchased.
- 1.10 The Subcommittee considered that it may be appropriate for PHARMAC's Wound Care Advisory Group to classify this range of products into categories and set up a framework for evaluating the products. The Subcommittee **recommended** that PHARMAC seek the Wound Care Advisory Group's advice to do this and produce an algorithm/framework to help evaluation, and bring the information back to this Subcommittee for review.
- 1.11 The Subcommittee considered that sole supply contracts would be inappropriate for these products. Members considered that winning bids from any competitive process should instead be awarded 90% of market contracts to ensure there were alternatives available as necessary for patients intolerant to a primary supply product.

### *Omalizumab*

- 1.12 The Subcommittee noted that PTAC had reviewed an application for omalizumab for the treatment of severe spontaneous chronic urticaria at their recent meeting in November 2015. PTAC, at its November 2015 meeting, recommended that access to omalizumab should be widened with a low priority and that they sought advice from the Dermatology Subcommittee to determine appropriate Special Authority (SA) criteria.
- 1.13 The Subcommittee noted that severe spontaneous chronic urticaria is defined as itchy weals (hives) that last for at least 6 weeks, with or without angioedema and that have no apparent external trigger(s). The condition generally has a prolonged duration of 1 to 5 years and has a detrimental effect on patients' quality of life.
- 1.14 The Subcommittee reviewed the evidence provided to PTAC and considered that the trials listed showed a significant improvement in clinical features; however, the beneficial effects of omalizumab wore off after discontinuation of use.
- 1.15 Members noted that the European Medicines Agency (EMA), NICE, and the *Canadian Expert Drug Advisory Committee* (CEDAC) had all approved omalizumab for the treatment of severe spontaneous chronic urticaria, though CEDAC's approval was subject to an appropriate price reduction. Members noted that the *Pharmaceutical Benefits Advisory Committee* (PBAC) was to review the product in November 2015.
- 1.16 The Subcommittee that the SA should be restricted to patients 12 years and older as there was no evidence for use in this indication for children below 12 years of age.
- 1.17 The subcommittee considered that continuation criteria be restricted to: The continuation criteria is relapse with Urticaria Activity Score 7 days (UAS7)>6, Dermatology Life Quality Index (DLQI) >5 on stopping omalizumab after every 6 doses.
- 1.18 The Subcommittee noted that listing omalizumab for severe spontaneous chronic urticaria posed some fiscal risk to the CPB and DHB hospitals, and proposed the following SA criteria for initiation:

- For severe chronic spontaneous urticaria only.
  - Restricted to recommendation by an immunologist or dermatologist only.
  - Only consider if the patient continues to be symptomatic (Urticaria Activity Score 7 (UAS7) 20 or above) and a DLQI of 10 or greater on high dose antihistamines (e.g. 4x standard dose) and either systemic corticosteroids (>20mg/day) or ciclosporin (>3mg/kg day) given for 3/12, or if the patient has significant adverse effects on corticosteroids and/or ciclosporin. Relapse of chronic urticaria on stopping prednisone/ciclosporin would not justify funded omalizumab.
  - Ciclosporin has been trialled in combination with prednisone and discontinued because of unacceptable side effects or inadequate clinical response. Treatment is stopped after 4 doses if not significantly improved (reduction of 50% of UAS7 score and DLQI).
  - Treatment is stopped at the end of the sixth dose to determine if patient has gone into remission. Only restart if UAS score is 6 or above and DLQI is above 5.
- 1.19 The Subcommittee considered that a patient in remission would have a UAS score of less than 6 and a DLQI of less than or equal to 5.
- 1.20 The Subcommittee noted that a group of immunologists had provided a different set of SA criteria and **recommended** that PHARMAC write to that group to inform them of the Subcommittee's recommendation and proposed criteria.
- 1.21 The Subcommittee **recommended** that omalizumab for severe chronic spontaneous urticaria be reviewed after 24 months to look at patient numbers and expenditure.

*Additional correspondence*

- 1.22 The Subcommittee noted correspondence from one of its Members, requesting that the Subcommittee discuss adding the indication of tinea capitis in small children to the SA criteria for liquid itraconazole.
- 1.23 The Subcommittee considered that widening access for liquid itraconazole would be a new investment and required a funding application. Members noted that the liquid form was considerably more expensive than the capsules and **recommended** that PHARMAC investigate the possibility of breaking open the capsules to be administered as liquid.
- 1.24 The Subcommittee noted that it was possible for pharmacies to compound terbinafine suspension which could be used for the same indication. Members noted that there was a standard formula in the schedule for terbinafine suspension and that there were no funding restrictions in place. The Subcommittee considered that compounded terbinafine suspension from the standard formula was clinically appropriate and sufficient for treating tinea capitis in small children.
- 1.25 The Subcommittee noted correspondence from one Member, requesting that the Subcommittee discuss extending the renewal period for biologics for psoriasis from 6 to 12 months.

- 1.26 The Subcommittee noted that the Rheumatology Subcommittee had discussed changing the renewal period for biologics from 6 months to 12 months. Members considered that the renewal period for biologics for psoriasis should be changed accordingly if the renewal period was altered for rheumatological indications to ensure consistency.

## **2 Sirolimus**

### **Application**

- 2.1 The Subcommittee noted an application generated by PHARMAC staff to list sirolimus ointment for tuberous sclerosis associated facial angiofibromas due to a high number of NPPA applications for this indication in the past 12 months.

### **Recommendation**

- 2.2 The Subcommittee deferred making a recommendation on sirolimus 0.1% ointment for the treatment of tuberous sclerosis complex (TSC) associated facial angiofibromas subject to the outcome of a phase two study by Koenig et al on 177 patients with TSC associated facial angiofibromas treated with topical sirolimus (NCT01526356).

### **Discussion**

- 2.1 The Subcommittee noted the prevalence of TSC to be estimated at between 0.7 – 8.8 per 100,000, and facial angiofibromas to be the most common presentation in tuberous sclerosis complex (TSC) which are prevalent in 70-80% of patients with TSC. Members considered there could be 399 patients in New Zealand with TSC, and of that there may be 40-80 patients in New Zealand with moderate/significant facial angiofibromas with an additional 7 new cases per year.
- 2.2 The Subcommittee noted the small trials by Koenig et al. *Drugs R D*:2012;12:121-126, Tu et al *Australas J Dermatol.* 2014; 55: 63-69 and Salido et al. *JEADV*:2012;26:1315-1318. Members noted that tuberous sclerosis associated facial angiofibromas was a lifelong disease and noted that while trial patients continued to suffer facial lesions during disease relapses, patients using the treatment found the facial lesions were not as severe during these times.
- 2.3 The Subcommittee noted that the topical formulations of 0.015% to 1 % sirolimus ointment were efficacious in facial angiofibromas and that responses were usually rapid and could be seen within the first 2 weeks of treatment. Members noted that studies reported the treatment had a greater effect in younger patients with milder symptoms where some achieved complete clearance. Members noted studies reported that 0.1% sirolimus ointment daily until clearance and then reducing to thrice weekly was effective and considered this a clinically appropriate treatment regime. Members noted in clinical practice, treatment usually lasted 4-8 weeks at a time, which would then restart when relapse occurred, and therapy could be life-long. Members also noted that most patients would likely need 3-6 months of treatment per year.
- 2.4 The Subcommittee considered there was an unmet health need in younger patients with mild disease as they were most responsive while older patients with severe disease would not obtain sufficient response to this treatment. Members also

considered that there was a lack of funded alternatives, and that there were barriers to accessing laser treatment as it was not available in all regions.

- 2.5 The Subcommittee considered that if sirolimus ointment was to be listed, it would require a Special Authority (SA) and, as such, it should be determined by a dermatologist. Members noted that any SA or restriction criteria should indicate treatment for mild to moderate patients only, as evidence for more severe patients indicated little to no efficacy for this group.
- 2.6 The Subcommittee considered that patients would need 1-2 g per week and no more than 30–50 g per prescription. Members considered that patients using the ointment found it to be tolerable and that formulations appeared more stable when compounded from sirolimus powder than the tablet. The Subcommittee recommended that initial approvals be valid for 3 months to determine if the product provided benefit, and all subsequent renewals to be valid for 2 years.

### **3 Pimecrolimus**

#### **Application**

- 3.1 The Subcommittee noted a supplier's application for pimecrolimus 1% cream (Elidel) to be listed for atopic dermatitis including proposed Special Authority criteria.

#### **Recommendation**

- 3.2 The Subcommittee deferred making a recommendation for pimecrolimus 1% cream for atopic dermatitis (eczema) until such time that PHARMAC can determine if tacrolimus ointment would be made available.
- 3.3 The Subcommittee considered that if pimecrolimus 1% cream was listed, then the Special Authority criteria should include a maximum of 2 tubes per 6 months.

#### **Discussion**

- 3.4 The Subcommittee noted that atopic dermatitis (eczema) was a health issue that affects a substantial proportion of New Zealanders. Members considered the condition to affect 15-20% of children and 35% of adults, but is more prevalent in Maori and Pacific patients.
- 3.5 The Subcommittee considered the supporting evidence provided by the supplier; five key clinical trials in support of the efficacy of pimecrolimus in paediatric atopic dermatitis: Eichenfield et al, *J Am Acad Dermatol* 2002;46:495-505, Ho et al, *J Paediatrics* 2003;142:155-62, Kapp et al, *J Allergy Clin Immunol* 2002;110:277-84, Wahn et al *Pediatrics* 2002;110:1-8, and Sigurgeirsson et al *Pediatrics* 2015;135:597-606. Members also noted 3 key clinical trials in support of the efficacy of pimecrolimus in adults with atopic dermatitis: Luger et al, *British Journal of Dermatology* 2001;144:788-94, Luger et al, *J Dermatol Treat* 2004;15:169-78, and Meurer et al *Dermatology* 2002;205:271-77.
- 3.6 The Subcommittee considered that the quality and strength of evidence was good; the evidence indicated that pimecrolimus was more effective than vehicle cream with around 30-35% clearance compared with around 15% clearance, respectively, in infants and children with mild atopic dermatitis and children and adults with facial

atopic dermatitis. Members noted that when compared with topical corticosteroids in Kapp et al 2002, efficacy was similar to weak topical corticosteroid creams (TCS), and less effective than moderate-strong TCS.

- 3.7 The Subcommittee considered that hydrocortisone 1% cream would have a similar therapeutic effect to pimecrolimus 1% cream and that pimecrolimus 1% would only have benefit for those with mild to moderate atopic dermatitis. Members noted that in terms of efficacy in treating atopic dermatitis, most topical corticosteroids (with the exception of hydrocortisone 1%) were more effective than pimecrolimus 1%. Members also noted that evidence suggested that pimecrolimus was more effective as a pre-emptive treatment in-between acute flares of atopic dermatitis.
- 3.8 The Subcommittee noted that while the application for pimecrolimus 1% cream was for atopic eczema, the treatment was applicable for many inflammatory dermatoses. Members noted that pimecrolimus 1% cream would be a topical steroid alternative and would be most suitable for facial and eyelid dermatoses which were more prevalent in younger aged patients, particularly <1 year olds.
- 3.9 The Subcommittee noted that pimecrolimus cream had been reviewed by the PBAC, NICE and SMC (Scottish Medicines Consortium). Members noted that SMC had recommended not to list pimecrolimus due to the lack of evidence that it had a clinical advantage in terms of efficacy or safety when compared with mild to moderate TCS and that the economic case for using it was unproven. Members also noted that both the PBAC and NICE recommended to list pimecrolimus 1% cream with Special Authority (SA) restrictions. Members considered that the SA criteria set by the PBAC was reasonable, and considered that the SA criteria proposed by the supplier was too loosely defined and if listed, it would need significant revision to minimise slippage.
- 3.10 The Subcommittee reviewed the side effect profile of pimecrolimus cream, and considered that it was generally well tolerated in patients and that the most common adverse effect was a temporary burning sensation around the area of application. Members also considered that there was no apparent risk of developing glaucoma when used around the eye region. Members noted an FDA black box warning from 2006 related to a possible link between topical calcineurin inhibitors and cancer. In summary, the warning recommended that prescribers should avoid the use of pimecrolimus in children younger than 2 years of age; use pimecrolimus only for short periods of time; avoid use in immunocompromised patients; and only use a minimal amount when required as increased doses in animals has resulted in higher rates of cancer. The Subcommittee also noted that the most recent Uptodate.com statement on safety concerns of pimecrolimus cream had stated that no definite causal relationship had been established. The Subcommittee considered that the risk of lymphoma from the use of pimecrolimus cream, as noted by black box warning issued by the FDA, was very low; however, it should not be used long-term.
- 3.11 The Subcommittee noted the supplier's assumption of 70% response rate and 85% adherence rate to pimecrolimus was much higher than real life indicated; Members considered that in a real life clinical setting, they would expect a maximum response rate of approximately 50%.
- 3.12 The Subcommittee noted the supplier's estimate of budget impact and considered that there was a significant risk of slippage due to the following:

- Supplier's estimate on prevalence of severe atopic dermatitis (eczema) was lower than actual rates in NZ and considered that location of disease was of a greater concern than severity. Members considered the supplier's estimation on pimecrolimus eligible population that would meet the proposed SA criteria to be an underestimate, and were unsure how the supplier came to this figure.
  - Studies did not fully capture the unmet health need in treatment of facial atopic dermatitis. Members considered that approximately 40% of patients treated with pimecrolimus cream for facial atopic dermatitis would respond at 3 weeks
  - A sizable private market which could shift if funded as well as significant amount of unfounded TCS phobia in patients and parents who would request pimecrolimus if funded
  - Indications that would be hard to restrict with an SA, such as patients that presented with moderate to severe symptoms, eye-lid inflammation and vitiligo on the face in patients with darker pigmented skin.
- 3.13 The Subcommittee considered that pimecrolimus could be used for any mild-moderate dermatoses rather than just atopic dermatitis, which could be a significant risk to the pharmaceutical budget if listed. Members considered that eczema was very prevalent in New Zealand, and that approximately 85% of all eczema patients would be categorised as mild.
- 3.14 The Subcommittee considered that pimecrolimus had little advantage over 1% hydrocortisone cream, whilst being significantly more expensive. However, members considered there may be a need in East and South Asian populations where there was a higher prevalence of atopic dermatitis around the eyes. The Subcommittee considered that pimecrolimus may be better tolerated than topical corticosteroids around steroid-sensitive areas such as the eyelids. Members considered that there was a lack of alternatives for patients with eyelid dermatitis who were unable to apply topical steroids, and indicated that this would be the primary patient group for the funding of pimecrolimus. Members considered that patients with darker skin would likely prefer a non-steroidal treatment and that the patient group had the potential to be very large.
- 3.15 The Subcommittee considered that there is a small unmet health need for patients who TCS are not appropriate and access was currently limited due to its high price. Members considered that currently funded TCS and barrier creams were appropriate for the vast majority of patients with mild to moderate atopic dermatitis, and that the unmet need was more in patients with severe disease who need a stronger steroid sparing agent such as tacrolimus ointment.

## 4 Topical antibiotics

### Recommendations

- 4.1 The Subcommittee **recommended** that PHARMAC change the tube size of fusidic acid 2 % cream and ointment; and mupirocin 2% ointment to a single use tube of 5g for dermatological indications.

- 4.2 The Subcommittee **recommended** that PHARMAC seek a 2% hydrogen peroxide cream and, if possible, in 50 g tubes rather than the current 15 g tubes to promote its use over topical antibiotics.
- 4.3 The Subcommittee **recommended** that PHARMAC provide follow-up education for primary care clinicians on the management of cutaneous skin infections to back up these actions.

## Discussion

- 4.4 The Subcommittee noted the Anti-infective Subcommittee of PTAC recommendation that PHARMAC work towards delisting fusidic acid amid concerns of increasing antibiotic resistance and reviewed this Subcommittee's previous recommendations for topical antibiotics.
- 4.5 The Subcommittee noted an increase of Staphylococcal skin and soft tissue infections from 80 per 100,000 people/year in the year 2000 to approximately 150 per 100,000 people/year in 2011. Members noted that *S. aureus* infections were significantly more prevalent in patients under the age of 5 and in Māori and Pacific Island populations.
- 4.6 The Subcommittee noted that the unrestricted over the counter (OTC) sale of topical mupirocin resulted in a high rate of mupirocin resistance in community isolates of *S. aureus* in the 1990's, as reported by Upton et al JAC 2003;51:613-617, who noted that by 1999, mupirocin resistance of *S. aureus* averaged around 28% and was associated with higher prevalence rates of a community-acquired strain of Western Samoan phage pattern methicillin-resistant Staphylococcus aureus (WSPP MRSA). The study also noted that antibiotic resistance rates at the time were markedly higher than rates reported in other countries.
- 4.7 The Subcommittee noted that there was an increase of fusidic acid prescriptions associated with when restrictions were placed on mupirocin in 1991. Members noted that this change was also associated with a parallel increase in resistance rates of MRSA to fusidic acid from <20 % in 2008 to around 40% in 2012.
- 4.8 The Subcommittee noted that Western Australia had appeared to have reversed the trend of increasing mupirocin resistant MRSA, with rates peaking at 18% in 1993 when topical mupirocin was an OTC medicine. In 1993, the Department of Health, Western Australia changed its classification of topical mupirocin to a prescription only medicine, with restricted use to 10 days with no repeat prescriptions for 1 month. This resulted in a dramatic decrease in resistance rates, and by 1997 mupirocin resistance in Western Australia fell to 0.3%. However, this saw an increase of fusidic resistance from 4.6% in 1994 to 12.4% in 1997. Members considered that any change to restrictions of topical antibiotics should be consistent and applied to all topical antibiotics to prevent the shifting of resistance rates from one topical antibiotic to another.
- 4.9 The Subcommittee considered that if topical antibiotics were delisted, patients would most likely use systemic antibiotics instead. Members considered that hydrogen peroxide could be used as an alternative in many cases; however, only 1% hydrogen peroxide was available in New Zealand despite the 2% presentation being used overseas and in clinical trials.
- 4.10 The Subcommittee noted a double-blind, randomised study by Christensen and Anehus *Acta Derm Venereol.* 1994;74:460-462 of 256 patients with impetigo

compared the efficacy of topical hydrogen peroxide 2% against topical fusidic acid. Results reported no statistical difference between both treatments after a three-week course, with 72% in the hydrogen peroxide group 'healed' (resolution of impetigo lesions) compared with 82% in the fusidic acid group.

- 4.11 The Subcommittee considered that current evidence suggested topical antiseptics, such as povidone iodine, and chlorhexidine use in established infections remained limited. However, Members considered that these products did not impair wound healing, nor were they associated with bacterial resistance.
- 4.12 Members noted that they had recently seen decreases in the use of mupirocin and fusidic acid in the community setting and an increase in hydrogen peroxide cream use. Members considered this was due to increased education on topical antibiotics and bacterial resistance, and that this was evidenced by the publishing of the BPJ no. 64 December 2014 which had an article named 'Topical antibiotics, very few indications for its use'. Members noted PHARMAC dispensing data that showed a 16% and 13% decrease in average prescriptions per month for fusidic acid and mupirocin, respectively, post the publishing of BPJ no. 64.
- 4.13 The Subcommittee agreed with the main points of the BPJ 64 article, that antibiotics were not required for all skin infections and that there were very few evidence-based indications for using topical antibiotics. Members also considered that Vaseline or 50:50 ointment would have similar efficacy to nasal mupirocin to decolonise nasal carriage of *S. aureus*. However, Members considered that there may be a role for topical mupirocin for decolonisation of nasal carriage of *S. aureus* in an intensive care setting.
- 4.14 The Subcommittee noted correspondence from two leading clinicians in the field of Microbiology and Infectious Diseases. The correspondence considered that restriction through Special Authority (SA) or through indication would have impacts on prescribing through primary care and suggested restricting access may be appropriate if there was a good non-antibiotic alternative.
- 4.15 The correspondence noted that current evidence on efficacy for hydrogen peroxide was based on the 2% formulation whereas; the listed product was the 1% formulation.
- 4.16 Members considered the potential option to delist a topical antibiotic formulation, and, based on the information provided, de-listing would be an extreme option. Members recommended replacing the current presentations of fusidic acid and mupirocin with 5 g single-use tubes would be more appropriate.

## 5 Rosacea and acne treatments

### Recommendation

- 5.1 The Subcommittee **recommended** that low dose doxycycline in the range of 20 mg to 40 mg should be funded for dermatological indications with a medium priority.
- 5.2 Subcommittee **recommended** PHARMAC to seek suppliers for brimonidine tartrate gel 0.5% and ivermectin cream 1%, should these products be available.

The Decision Criteria particularly relevant to this recommendation are: (i) *The health needs of all eligible people within New Zealand;* (iii) *The availability and suitability of existing medicines, therapeutic medical devices and related products and related things;* (iv) *The clinical benefits and risks of pharmaceuticals;* (v) *The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services;* (vi) *The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Schedule;* (vii) *The direct cost to health service users.*

## Discussion

### *Rosacea epidemiology & pathophysiology*

- 5.3 The Subcommittee noted the following literature in relation to the epidemiology of rosacea: *Abram K et al. Acta Derm Venereol. 2010;90:269–273. Tan J, et al. Am Acad Dermatol. 2013;69:S27–S35. Lomholt G. 1964;11:1–7.*
- 5.4 The Subcommittee noted that the prevalence of rosacea in recent years had ranged from 1% to 22% depending on the methodology and population sample analysed. Members considered that rosacea was more prevalent in people aged 30-60, of Celtic origin and affected women more than men. Members considered that rosacea subtype I (erythematotelangiectatic rosacea) was found to be most prevalent, followed by subtype II (papulopustular rosacea). Members noted that rhinophyma was seen mostly in men over 40 years of age.
- 5.5 The Subcommittee noted the following papers in relation to the pathophysiology and pathogenesis of rosacea: *Steinhoff M, et al. J Am Acad Dermatol. 2013;69:S15–S26. Meyer-Hoffert U, et al. J Investig Dermatol Symp Proc. 2011;15:16–23. Georgala S, et al. J Eur Acad Dermatol Venereol. 2001;15:441–444. Holmes AD. J Am Acad Dermatol. 2013;69:1025–1032.*
- 5.6 The Subcommittee considered triggers for activation and upregulation of these molecules which stimulate an inflammatory response included the mite *Demodex folliculorum*. Members noted that other microbes reportedly associated with rosacea are *Bacillus oleronius*, *Staphylococcus epidermidis*, *Helicobacter pylori*, and *Chlamydophila pneumoniae*.

### *Non-antibiotic treatments for rosacea*

- 5.7 The Subcommittee considered other treatments for rosacea. The Subcommittee noted the following Deeks paper in relation to ivermectin (Deeks. Am J Clin Dermatol. 2015;16:447–452).
- 5.8 The Subcommittee noted that Ivermectin 1 % cream was available and registered in several countries, including the USA, Canada and the EU but not in New Zealand. Members noted that ivermectin's main effects were through anti-parasitic activity and its anti-inflammatory effects. Members noted that 1% ivermectin cream reduced the symptoms of moderate to severe papulopustular rosacea over 12 weeks in adults, with this benefit continuing for up to 52 weeks. Members noted that 1% ivermectin cream was considered to be more effective than twice-daily metronidazole 0.75 % cream in reducing the symptoms of rosacea in patients from as early as week 3 of treatment. Members noted that, the most common adverse reactions reported in the study (incidence  $\leq$  1%) included a skin burning sensation and skin irritation.

- 5.9 The Subcommittee noted the following two papers in relation to brimonidine gel for rosacea: Moore A, et al. *J Drugs Dermatol*. 2014;13:56–61; Joseph Fowler et al. *J Drugs Dermatol*. 2013;12:650.
- 5.10 The Subcommittee noted that brimonidine tartrate gel, an  $\alpha$ -2 adrenergic receptor agonist, was the only FDA approved topical treatment for the persistent facial redness of rosacea. Members noted that brimonidine tartrate gel 0.5% applied once daily had a good safety profile and provided significantly greater efficacy relative to vehicle gel for the treatment of moderate to severe erythema of rosacea.

#### *Non-antibiotic treatment for acne*

- 5.11 The Subcommittee noted the following papers in relation to acne treatments: *Katsambas, G K, et al. Acta Derm Venereol Suppl (Stockh)*. 1989;143: 35-9. *Gollnick et al. J Eur Acad Dermatol Venereol* 2014 Nov 14. *Ellis et al. Br J Derm* 1998;139:42-47.
- 5.12 The Subcommittee noted that evidence indicated azelaic acid cream was effective as an anti-acne treatment. Members noted that in the study of comedonal acne, 20% azelaic acid cream was equally effective as 0.05% tretinoin cream in reducing the number of comedones. Additionally, azelaic acid cream was better tolerated and caused fewer side effects than tretinoin cream. The Subcommittee noted the study Gollnick et al. indicated azelaic acid was non inferior to adapalene in improvement in acne severity and lesion counts, but dryness and scaling were significantly lower in the azelaic acid group.
- 5.13 The Subcommittee considered that adapalene and tretinoin were equally effective in acne. The Subcommittee **recommended** that an application on azelaic acid for acne be submitted for consideration at the next Subcommittee meeting.

#### *Antibiotic treatment for acne and rosacea*

- 5.14 The Subcommittee noted the following literature in relation to the use of tetracyclines: *Griffin MO, et al. Am J Physiol Cell Physiol*. 2010;299:539-48. *Bahrami F, et al. Mini Rev Med Chem*. 2012;12:44-52. *Chopra I, et al. Microbiol Mol Biol Rev*. 2001;65:232-60.
- 5.15 The Subcommittee noted that tetracyclines, broad-spectrum antibiotics were active against a wide range of microorganisms including gram-positive and gram-negative bacteria. Members also noted a wide spectrum of anti-inflammatory effects ascribed to tetracyclines was probably due to their ability to interfere with the synthesis or activity of several mediators of inflammation.
- 5.16 The Subcommittee noted the role that antimicrobial stewardship was playing a part in practice and that increased bacterial resistance was a growing concern.
- 5.17 The Subcommittee noted the following literature in relation to antibiotic use for acne: *Knagga, H E, et al. J. Dermatol. Treat*. 1993;4: 53–56. *Brigitte Dreno et al. Eur J Dermatol* 2004; 14: 391-9.
- 5.18 The Subcommittee considered that the duration of use of antibiotics for the treatment of acne had not been adequately researched and that current published recommendations were not supported by robust scientific evidence.

- 5.19 The Subcommittee considered that a minimum of 3 months of consecutive treatment was required before any obvious improvement was likely to be seen. Members considered that doctors were often prescribing antibiotics for acne for shorter durations, but almost one-fifth of antibiotic therapies for acne still exceeded 6 months.
- 5.20 The Subcommittee noted that the Commercial Claims and Encounters database examined the duration of antibiotic therapy among 31,634 courses prescribed and that most courses (93 percent) lasted for less than 9 months. Members noted that the mean course duration was 129 days, according to the study, and that nearly 58 percent of treatment courses did not include concomitant topical retinoid therapy.

#### *Low dose doxycycline for acne*

- 5.21 The Subcommittee noted a multicentre, double-blind, randomised, parallel-group study by Skidmore R, et al. Arch Dermatol. 2003;139:459-464 on the effects of doxycycline 20 mg twice daily compared with placebo in 40 patients with moderate acne over a 6-month treatment course. By 6 months, patients receiving doxycycline reported a statistically significant improvement compared with placebo in inflammatory lesions, non-inflammatory lesions, and global assessment and there was no evidence of bacterial resistance.
- 5.22 The Subcommittee noted a randomised, double-blind study (n=100) by Toossi P, et al. J Drugs Dermatol. 2008;7:1149-1152 which examined on the effects of subantimicrobial-dose doxycycline in the treatment of moderate acne. Patients in the study were randomised to receive doxycycline 20 mg twice daily, doxycycline 100 mg once daily or placebo pill once daily for 3 months. Members noted results indicated both doxycycline treatment groups had similar outcomes, with an 84% reduction in papules and a 90% reduction in pustules in the subjects who received doxycycline 20 mg twice daily.
- 5.23 The Subcommittee noted a study by Parish LC et al. Acta Dermatovenerol Croat. 2005;13:156-159 on the treatment of acne vulgaris with low dosage doxycycline. Members noted that this was a small 'step-down dosing' study in which all subjects were treated with doxycycline 100 mg daily for 8 weeks. Once improved, subjects were randomised to either doxycycline 20 mg twice daily or placebo twice daily for 8 weeks. Results indicated patients in doxycycline 20 mg twice daily group maintained their improvement, whereas the placebo group did not maintain its improvement.

#### *Ocular complications in rosacea*

- 5.24 The Subcommittee considered that more than 10% of the general population exhibited dermatologic characteristics of rosacea; of these, up to 60% experienced ocular complications: dry eyes, irritation, redness, itching, burning, foreign body sensation, and photophobia; recurrent styes, cysts and eye infections. The Subcommittee considered that topical azithromycin may represent an additional treatment for ocular rosacea, with a shorter duration of treatment and absence of gastrointestinal side effects as compared with systemic doxycycline.

#### *Low dose doxycycline for rosacea*

- 5.25 The Subcommittee noted the following literature in relation to doxycycline dosage: Skidmore T, et al, Archives of Dermatology. 2003;139: 459–464, Golub LM, et al, Advances in Dental Research. 1998;12: 12–26. Del Rosso JQ, et al., J Am Acad Dermatol. 2007;56:791–802. Di Caprio, R, et al. Mediators of Inflammation, 2015; 2015.

- 5.26 The Subcommittee noted the observation that the traditional antimicrobial doses of doxycycline can exert selection pressure, altering normal commensal microflora and increasing the risk of bacterial resistance. The Subcommittee considered that this effect has not been detected, even during long-term treatment, using low doses of doxycycline (20–40 mg/day). Low dose doxycycline (20–40 mg/day) was able to exert an anti-inflammatory activity without altering bacteria susceptibility to antibiotics. The Subcommittee noted that in vitro studies showed both low and high doxycycline doses were able to modulate the expression of inflammatory mediators, in accordance with previous studies illustrating the capability of both anti-inflammatory and antimicrobial low doses to be equally effective. The Subcommittee noted a paper by Di Caprio, R, et al. 2015 which reported that high dose administration of doxycycline (100 or 200 mg/day) is often responsible for development of bacterial resistances and endogenous flora alterations, whereas low doses (20–40 mg/day) do not alter bacteria susceptibility to antibiotics and exert anti-inflammatory activities. The Subcommittee considered that currently the dermatology community may be using fully subsidised 100 mg doxycycline for dermatological indications due to a lack of fully subsidised alternatives. The Subcommittee considered that there is not a dermatological requirement to have the 50 mg doxycycline tablets available.
- 5.27 The Subcommittee noted that low dose doxycycline provided anti-inflammatory effects with sub antimicrobial dosing. The Subcommittee noted the results of a large-scale, phase 4 trial of low dose doxycycline in papulopustular rosacea. (Del Rosso JQ. The ORCA (Oracea for rosacea: a community-based assessment) trial: *Cutis*. 2010;86:4–6). The Subcommittee considered the results support the use of daily doxycycline 40 mg monotherapy (30 mg immediate-release and 10 mg delayed-release beads) in patients with moderate to severe rosacea.

#### *Doxycycline vs minocycline*

- 5.28 The Subcommittee noted a paper by Schwartz et al. *Clinical Infectious Diseases*. 2009;48:1483-1484 which reported that differences in susceptibility indicated that doxycycline, but not minocycline, is a substrate for the drug-inducible efflux pump encoded by tet(K). The Subcommittee considered that minocycline may be an efficacious option as it did not identifiably cause this inducible resistance. The Subcommittee considered that the current Special Authority for minocycline was appropriate.

#### *Other issues*

- 5.29 The Subcommittee noted a comment from the February 2015 meeting of the Tender Medical Evaluation Subcommittee of PTAC (TMESC) in which it was suggested that PHARMAC staff may wish to consider investigating lymecycline as an alternative to minocycline. The Subcommittee noted a randomised, evaluator-blinded, parallel, prospective study by Ocampo-Candiani et al. *J Drugs Dermatol* 2014 13;671-6 which compared the safety and efficacy of minocycline microgranules vs lymecycline in the patients with mild to moderate acne for 8 weeks. The Subcommittee noted that 36 (42.9%) of patients receiving minocycline suffered 55 adverse events (22 of them gastrointestinal), while 28 (33.3%) lymecycline patients had 37 adverse events (15 of them gastrointestinal). The Subcommittee noted that there were no differences reported between the groups in non-inflammatory and inflammatory lesion counts, and in the safety profile. The Subcommittee noted that treatment with minocycline induced a statistically significant decrease in facial porphyrin counts compared with the group treated with lymecycline.

- 5.30 The Subcommittee noted a further comment from the February 2015 meeting of TMESC in relation to the risk of systemic lupus erythematosus associated with minocycline use. One member noted the Cochrane review in relation to the use of minocycline for acne vulgaris (Garner, S.E. et al. Minocycline for acne vulgaris: efficacy and safety (Review) Cochrane Database Syst Rev. 2012 Aug 15;8:CD002086). It was suggested that systemic lupus erythematosus associated with minocycline use occurred in 8.8/100,000 patients, most of whom were women, who were receiving minocycline at higher dose, after a mean of 19 months, and resolved following treatment cessation. Members noted that the risk was classified as low (<http://www.dermnetnz.org/reactions/drug-induced-lupus.html>).

## 6 Super Oxidising Solution

### Application

- 6.1 The Subcommittee noted an application from TeArai BioFarma for Super Oxidising Solution (SOS) in a number of different brands for various indications including ulcers, burns, atopic dermatitis, acne vulgaris, and sinusitis.

### Recommendation

- 6.2 The Subcommittee **recommended** that the application for Super Oxidising Solution (SOS) be declined due to a lack of quality evidence proving its efficacy over currently available treatments.
- 6.3 The Subcommittee **recommended** that Super Oxidising Solution (SOS) be reviewed and categorised by the Wound Care Advisory Group as part of their larger classification project in order to compare SOS to similar products.

The Decision Criteria particularly relevant to this recommendation are: (i) *The health needs of all eligible people within New Zealand;* (iii) *The availability and suitability of existing medicines, therapeutic medical devices and related products and related things;* (iv) *The clinical benefits and risks of pharmaceuticals;* (v) *The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services;* (vi) *The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Schedule.*

### Discussion

- 6.4 The Subcommittee considered the evidence provided by the supplier in its application for Microdaycn, and in particular the studies by Landsman et al. J Am Podiatr Med Assoc 2011;101: 484-496 , Paola et al. Wounds 2006;18:262-270, Piagessi et al. Int J Low Extrem Wounds. 2010;9:10-15., Goretti et al. Int J Low Extrem Wounds. 2007;6:22-27, and Martinez-De et al. Int Wound J. 2007;4:353-362. Members noted that the evidence provided in the application was largely composed of small studies or case studies of poor quality and weak strength. Members considered that there was no evidence to show the products would reduce venous leg ulcers and considered that an antiseptic would perform equally as well, and that it was not relevant for diabetic foot ulcers (DFU) as it had a neuropathic pathology. Members also considered that in wound care, the key for treatment was irrigation rather than the specific solution used for irrigation.

- 6.5 The Subcommittee considered that the comparators used in the studies such as povidone iodine, were inappropriate for the New Zealand market as they were not widely used in this country in that clinical setting. Members also considered that the suppliers' assumption of prevention of amputation was optimistic. Members considered that the cost minimisation did not clearly define a specific patient population and did not examine the Microdacyn hydrogel or 120ml form, which have different prices. Members considered the study used by the supplier, Goretti et al 2007 was small, non-blinded, non-randomised and non-concurrent.
- 6.6 The Subcommittee considered that there was insufficient evidence to indicate that SOS provided any additional health benefit to currently listed products.
- 6.7 The Subcommittee considered that the use of SOS would incur additional nursing costs as the products were applied 3-4 times daily, and was not practical in realistic clinical settings. Members noted that the application stated that SOS could be used as an antiseptic which causes no harm to surrounding tissues; however, the products used in the clinical trials supplied were different from the products stated in the application. Members also noted that some instillation therapies were patented and therefore extra costs may be incurred as it may require an additional device and solutions for use.
- 6.8 The Subcommittee considered that it was difficult to justify the price of Microdaycn as it was possible to make SOS at home using inexpensive equipment and saline. Members considered that the cost presented by the supplier would result in considerable budget impact and was susceptible to slippage as it would be difficult to restrict.
- 6.9 The Subcommittee considered the evidence presented for Pediaycn, Gramaderm and Synodox. Members noted that the evidence for Pediaycn were from studies containing small sample sizes, inappropriate comparators and were not clear if the intervention was the same as Pediacyn. Members noted the evidence for Gramaderm consisted of small studies and of weak quality; the study by Desai et al 2004 was not the same product as Gramaderm and Tirado-Sanchez et al 2009 and did not indicate what strength of benzyl peroxide used in the study. Members considered there was no evidence for the use of Synodox for rhinosinusitis.
- 6.10 The Subcommittee considered that from a dermatological view, there was no evidence to recommend SOS for the indications listed in the supplier's application for either community or HML use. Members considered that current listed alternatives were sufficient and SOS did not show superiority over these products.
- 6.11 The Subcommittee considered that SOS could be reviewed by the Wound Care Advisory Group for further investigation.