Record of the Dermatology Subcommittee of PTAC Meeting held via videoconference on 25 November 2020

Dermatology Subcommittee records are published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2016.

Note that this document is not necessarily a complete record of the Dermatology Subcommittee meeting; only the relevant portions of the meeting record 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.

PTAC Subcommittees make recommendations, including priority, within their therapeutic groups of interest.

The record of this Subcommittee meeting will be reviewed by PTAC at its February 2021 meeting.

PTAC Subcommittees and PTAC may differ in the advice they provide to PHARMAC, including recommendations' priority, due to the committees' different, if complementary, roles, expertise, experience, and perspectives.

PHARMAC is not bound to follow the recommendations made below. Applications are prioritised by PHARMAC against other funding options and progressed accordingly. The relative priority of any one funding choice is dependent on a number of factors, including (but not limited to) the recommendation of PTAC and/or PTAC Subcommittees, the mix of other applications being assessed, the amount of funding available, the success of commercial negotiations and/or the availability of clinical data.

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Present from the Dermatology Subcommittee:
Lisa Stamp (Chair)
Diana Purvis
Julie Betts
Marius Rademaker (PTAC member)
Melissa Copland
Paul Jarrett
Sharad Paul

Apologies:
Martin Denby

1. Summary of recommendations

1.1. The Subcommittee noted its 2017 recommendation to list ichthammol powder with medium priority. Members noted that ichthammol powder remained on PHARMAC's work programme, however, to date no supplier had been identified. The Subcommittee **recommended** removing ichthammol from the list of Action Points.

1.2. The Subcommittee noted their 2015 recommendation that PHARMAC seek a supplier for brimonidine tartrate 0.5% gel and that a product has since been registered by Medsafe for the treatment of facial erythema of rosacea in adult patients. Members noted that no funding application has been submitted and **recommended** that PHARMAC staff approach the supplier.

1.3. The Subcommittee noted their 2017 recommendation that PHARMAC seek a funding application for a topical azelaic acid 20% preparation for acne. Members noted the update from PHARMAC that there are two Medsafe approved products and **recommended** that suppliers should be encouraged to submit a funding application for 20% topical azelaic acid lotion. The Subcommittee considered azelaic acid was a useful treatment option alongside benzoyl peroxide. The Subcommittee noted the requirement to move away from using topical antibiotics as part of antibiotic stewardship and the availability of azelaic acid would help satisfy an unmet health need for treating acne topically.

1.4. The Subcommittee **recommended** funding hydrocortisone ointment to address an unmet health need.

1.5. The Subcommittee **recommended** imiquimod should be moved to other skin preparations rather than wart preparations.

1.6. The Subcommittee **recommended** that the current Special Authority restrictions for ivermectin remain in place. The Subcommittee noted the Anti-Infectives Subcommittee of PTAC had considered correspondence proposing widening of access in order to reduce incidence of rheumatic fever and had recommended to maintain the current restrictions.

1.7. The Subcommittee noted that oral alitretinoin is the standard of care in the treatment of moderate/severe chronic hand dermatitis in the EU and USA. PHARMAC has funded alitretinoin via the NPPA pathway. The Subcommittee **recommended** alitretinoin should be funded via the Pharmaceutical Schedule.

1.8. The Subcommittee **recommended** that risankizumab for the first-line treatment of moderate to severe chronic plaque psoriasis be listed with a high priority within the context of dermatology treatments subject to the following Special Authority criteria:

Initial application – (severe chronic plaque psoriasis, first line biologic) only from a dermatologist. Approvals valid for 4 months for applications meeting the following criteria:
Either:
1 Both:
1.1 The patient has had an initial Special Authority approval for adalimumab, etanercept or secukinumab, or has trialled infliximab in accordance with the General Rules of the Pharmaceutical Schedule, for severe chronic plaque psoriasis; and
1.2 Either:
1.2.1 Patient has experienced intolerable side effects from adalimumab, etanercept, infliximab or secukinumab; or
1.2.2 Patient has received insufficient benefit from adalimumab, etanercept, infliximab or secukinumab; or
2 All of the following:
2.1: Either:
2.1.1 Patient has "whole body" severe chronic plaque psoriasis with a Psoriasis Area and Severity Index (PASI) score of greater than 10, where lesions have been present for at least 6 months from the time of initial diagnosis; or
2.1.2 Patient has severe chronic plaque psoriasis of the face, or palm of a hand or sole of a foot, where the plaque or plaques have been present for at least 6 months from the time of initial diagnosis; and
2.2 Patient has tried, but had an inadequate response* to, or has experienced intolerable side effects from, at least three of the following (at maximum tolerated doses unless contraindicated): phototherapy, methotrexate, ciclosporin, or acitretin; and
2.3 A PASI assessment or Dermatology Life Quality Index (DLQI) assessment has been completed for at least the most recent prior treatment course, preferably while still on treatment but no longer than 1 month following cessation of each prior treatment course; and
2.4 The most recent PASI or DLQI assessment is no more than 1 month old at the time of application.

*A treatment course is defined as a minimum of 12 weeks of treatment. "Inadequate response" in defined as: for whole body severe chronic plaque psoriasis, a PASI score of greater than 10, as assessed preferably while still on treatment but no longer than 1 month following cessation of the most recent prior treatment; for severe chronic plaque psoriasis of the face, hand or foot, at least 2 of the 3 PASI symptom sub scores for erythema, thickness and scaling are rated as severe or very severe, and the skin area affected is 30% or more of the face, palm of a hand or sole of a foot, as assessed preferably while still on treatment but no longer than 1 month following cessation of the most recent prior treatment.

Renewal – (severe chronic plaque psoriasis) only from a dermatologist or practitioner on the recommendation of a dermatologist. Approvals valid for 6 months for applications meeting the following criteria:
Both:

1. Either:
    1.1 Patient's PASI score has reduced by 75% of more (PASI 75) as compared to baseline PASI prior to commencing risankizumab; or
    1.2 Patient has a Dermatology Life Quality Index (DLQI) improvement of 5 or more, as compared to baseline DLQI prior to commencing risankizumab; and
2. Risankizumab is to be administered at a maximum dose of 150 mg every 12 weeks, following induction doses at 0 and 4 weeks

1.9. The Subcommittee **recommended** that risankizumab for the second-line treatment of moderate to severe chronic plaque psoriasis be listed with a high priority within the context of dermatology treatments subject to the following Special Authority criteria:

Initial application – (severe chronic plaque psoriasis, second line biologic) only from a dermatologist. Approvals valid for 4 months for applications meeting the following criteria:
All of the following:
1 The patient has had an initial Special Authority approval for adalimumab, etanercept or secukinumab, or has trialled infliximab in accordance with the General Rules of the Pharmaceutical Schedule, for severe chronic plaque psoriasis; and
2 Either:
    1.1 Patient has experienced intolerable side effects from adalimumab, etanercept, infliximab or secukinumab; or
    1.2 Patient has received insufficient benefit from adalimumab, etanercept, infliximab or secukinumab; and
3 A PASI assessment or Dermatology Life Quality Index (DLQI) assessment has been completed for at least the most recent prior treatment course, preferably while still on treatment but no longer than 1 month following cessation of each prior treatment course; and
4 The most recent PASI or DLQI assessment is no more than 1 month old at the time of application.

*A treatment course is defined as a minimum of 12 weeks of treatment. "Inadequate response" in defined as: for whole body severe chronic plaque psoriasis, a PASI score of greater than 10, as assessed preferably while still on treatment but no longer than 1 month following cessation of the most recent prior treatment; for severe chronic plaque psoriasis of the face, hand or foot, at least 2 of the 3 PASI symptom sub scores for erythema, thickness and scaling are rated as severe or very severe, and the skin area affected is 30% or more of the face, palm of a hand or sole of a foot, as assessed preferably while still on treatment but no longer than 1 month following cessation of the most recent prior treatment.

Renewal – (severe chronic plaque psoriasis) only from a dermatologist or practitioner on the recommendation of a dermatologist. Approvals valid for 6 months for applications meeting the following criteria:
Both:
1. Either:
1.1 Patient's PASI score has reduced by 75% of more (PASI 75) as compared to baseline PASI prior to commencing risankizumab; or
1.2 Patient has a Dermatology Life Quality Index (DLQI) improvement of 5 or more, as compared to baseline DLQI prior to commencing risankizumab; and
2. Risankizumab is to be administered at a maximum dose of 150 mg every 12 weeks, following induction doses at 0 and 4 weeks

1.10. The Subcommittee **recommended** that rituximab for pemphigus be funded with a high priority within the context of dermatology treatments subject to the following Special Authority criteria:

Initial Application - (pemphigus) only from a dermatologist or relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:

Either:

1 All of the following:

1.1 Patient has severe rapidly progressive pemphigus; and

1.2 Is used in combination with systemic corticosteroids (20 mg/day); and

1.3 Either:

1.3.1 Skin involvement ≥5% body surface area; or

1.3.2 Significant mucosal involvement (≥10 mucosal erosions), diffuse gingivitis, confluent large erosions; or

1.3.3 Involvement of two or more mucosal sites; or

2 All of the following:

2.1 Patient has pemphigus; and

2.2 Patient has not responded to systemic corticosteroids (20 mg/day) in combination with a steroid sparing agent, unless contraindicated

Renewal – (pemphigus) only from a dermatologist or relevant specialist. Approvals valid for 26 weeks for applications meeting the following criteria:

1 Patient has demonstrated benefit from rituximab treatment in terms of symptom reduction, improved healing of skin ulceration and reduction in steroid requirement; and

2 Rituximab re-treatment not to be given within 6 months of the previous course of treatment.

2. The role of PTAC Subcommittees and records of meetings

2.1. This meeting record of the Dermatology Subcommittee of PTAC is published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2016, available on the PHARMAC website at https://www.pharmac.govt.nz/assets/ptac-terms-of-reference.pdf.

2.2. The Terms of Reference describe, *inter alia*, the establishment, activities, considerations, advice, and the publication of such advice of PTAC Subcommittees and PTAC.

2.3. Conflicts of Interest are described and managed in accordance with section 7.2 of the PTAC Terms of Reference.

2.4. The Dermatology Subcommittee is a Subcommittee of PTAC. The Dermatology Subcommittee and PTAC and other PTAC Subcommittees have complementary roles, expertise, experience, and perspectives. The Dermatology Subcommittee and other PTAC Subcommittees may therefore, at times, make recommendations for treatments for dermatological conditions that differ from PTAC's, including the priority assigned to recommendations, when considering the same evidence. Likewise, PTAC may, at times, make recommendations for treatments for dermatological conditions that differ from the Dermatology Subcommittee's, or PTAC Subcommittees may make recommendations that differ from other PTAC Subcommittees.

PHARMAC considers the recommendations provided by both the Dermatology Subcommittee and PTAC and any other relevant PTAC Subcommittees when assessing applications for treatments for dermatological conditions.

3. Record of Subcommittee meeting held Friday, October 20, 2017

3.1. The Subcommittee reviewed the minutes of the Dermatology Subcommittee of PTAC meeting held on 20 October 2017 and agreed that the minutes be accepted.

4. Previous recommendations and Action Points

4.1. The Subcommittee noted the Summary of Previous Recommendations and Action Points; only those items where a change or new information arose are minuted below.

4.2. The Subcommittee noted its 2017 recommendation to list ichthammol powder with medium priority. Members noted that ichthammol powder remained on PHARMAC's work programme, however, to date no supplier had been identified. The Subcommittee **recommended** removing ichthammol from the list of Action Points.

4.3. The Subcommittee noted their previous recommendation to tender for metronidazole gel 0.5% to 0.75% for the treatment of fungating wounds, but advised that the indication should be amended to odiferous wounds only. Members considered that this pharmaceutical should be listed with restrictions for use on odiferous wounds only, but that any medical or nurse practitioner could prescribe it.

4.4. The Subcommittee noted its 2017 recommendation that PHARMAC seek a 2% hydrogen peroxide cream. Members noted the update from PHARMAC that no 2% product was registered with Medsafe, but this remained on PHARMAC's workplan as an option to consider should a 2% strength product gain registration.

4.5. The Subcommittee noted their 2015 recommendation that PHARMAC seek a supplier for brimonidine tartrate 0.5% gel and that a product has since been registered by Medsafe for the treatment of facial erythema of rosacea in adult patients. Members noted that no funding application has been submitted and **recommended** that PHARMAC staff approach the supplier.

4.6. The Subcommittee noted their 2017 recommendation that PHARMAC seek a funding application for a topical azelaic acid 20% preparation for acne. Members noted the update from PHARMAC that there are two Medsafe approved products and **recommended** that suppliers should be encouraged to submit a funding application for 20% topical azelaic acid lotion. The Subcommittee considered azelaic acid was a useful treatment option alongside benzoyl peroxide. The Subcommittee noted the requirement to move away from using topical antibiotics as part of antibiotic stewardship and the availability of azelaic acid would help satisfy an unmet health need for treating acne topically.

4.7. The Subcommittee noted their 2017 recommendation that PHARMAC seek a funding application for zinc paste. The Subcommittee noted zinc paste has a niche role but is a useful barrier preparation as it 'sticks' better than cream and / or ointment preparations. The Subcommittee considered potential uses would include small ulcers or areas of varicose eczema and considered the advantage zinc paste provides as it allows for dithranol or ichthammol to be incorporated. Numbers of patients using zinc paste therapeutically are likely to be a maximum of 1,000 patients per annum.

5. Therapeutic Group Review

Anti-Acne Preparations

5.1. The Subcommittee noted the long-term decline in use of isotretinoin 20 mg and an increase in use of the 10 mg presentation. Members considered this reflected current best clinical practice to use lower average doses.

5.2. The Subcommittee discussed the Special Authority criteria for isotretinoin and considered that prescribers are well experienced in the safety and appropriate use of this pharmaceutical, therefore, revisions could be made to the Special Authority renewal criteria. The Subcommittee considered the current Special Authority criteria was unlikely to limit access to isotretinoin. Members advised that the criteria could be amended as follows (deletions in strikethrough and additions in bold):

Initial from any relevant practitioner. Approvals ~~valid for 1 year~~ **without further renewal unless notified** for applications meeting the following criteria:
All of the following:

1 Applicant is a vocationally registered dermatologist, vocationally registered general practitioner, or nurse practitioner working in a relevant scope of practice; and
2 Applicant has an up to date knowledge of the safety issues around isotretinoin and is competent to prescribe isotretinoin; and
3 Either
  3.1 Patient is female and has been counselled and understands the risk of teratogenicity if isotretinoin is used during pregnancy and the applicant has ensured that the possibility of pregnancy has been excluded prior to the commencement of the treatment and that the patient is informed that she must not become pregnant during treatment and for a period of one month after the completion of the treatment; or
  3.2 Patient is male.

Note: Applicants are recommended to either have used or be familiar with using a decision support tool accredited by their professional body.

~~Renewal from any relevant practitioner. Approvals valid for 1 year for applications meeting the following criteria:~~
~~Either:~~

~~1 Patient is female and has been counselled and understands the risk of teratogenicity if isotretinoin is used during pregnancy and the applicant has ensured that the possibility of pregnancy has been excluded prior to the commencement of the treatment and that the patient is informed that she must not become pregnant during treatment and for a period of one month after the completion of the treatment; or~~
~~2 Patient is male.~~

~~Note: Applicants are recommended to either have used or be familiar with using a decision support tool accredited by their professional body.~~

5.3. The Subcommittee noted its 2017 recommendation to list a fully funded topical benzoyl peroxide in the range of 2.5 % to 5 % for the treatment of acne. Members reiterated that this remains relevant as providing funded topical non-antibiotic anti-acne alternatives assists with reducing oral and topical antibiotics use. The Subcommittee also considered that there needs to be funded alternatives for patients unable to use systemic therapy, such as oral isotretinoin which is contraindicated in pregnancy. Members suggested that PHARMAC approach the New Zealand Dermatological Society to request a funding application for topical benzoyl peroxide.

5.4. PHARMAC staff suggested an update via email could be provided to the Subcommittee with regards to progress in sourcing and funding topical benzoyl peroxide 2.5 % - 5 % for the treatment of acne.

5.5. The Subcommittee suggested that topical benzoyl peroxide in the range of 2.5 % - 5 % for the treatment of acne be funded as a non-prescription medication / pharmacy only medicine to ensure equity of access within the patient demographic.

Antibacterials Topical

5.6. The Subcommittee noted that whilst prescriptions had declined for fusidic acid cream and mupirocin ointment, there was a significant increase in use of fusidic acid ointment in the last year. Members considered that in the interests of antimicrobial stewardship, use of these topical antibiotics should be reduced.

5.7. The Subcommittee noted the tube size of mupirocin ointment had been decreased to minimise over-use. The Subcommittee considered this to be appropriate in promoting antimicrobial stewardship.

5.8. The Subcommittee considered the equity issues surrounding further restricting topical antibiotics, given the increased risk of topical infections in Māori and Pasifika populations. The Subcommittee was not supportive of introducing additional funding restrictions on topical antibiotics, given the potential access equity issues.

5.9. The Subcommittee considered the existing part charge on mupirocin ointment to be appropriate given the funded alternatives available.

5.10. The Subcommittee considered whether a specific group of prescribers (e.g. prescriber group or geographic region) prescribed topical antibiotics more frequently. The Subcommittee considered further information could be beneficial in order to better support antimicrobial stewardship among prescribers.

5.11. The Subcommittee noted the long-term increase in use of hydrogen peroxide cream and considered this reflected current best clinical practice and widespread compliance with antibiotic stewardship.

Antifungals Topical

5.12. The Subcommittee considered that topical antifungals exhibit poor effectiveness compared to systemic agents for the treatment of fungal nail infections and that they are often overused, as up to 50% of all fungal nail infections are misdiagnosed. However, the Subcommittee considered diagnosis by culture methods costly and, on balance, they supported the maintenance of the status quo.

Antipruritic Preparations

5.13. The Subcommittee noted the information provided on antipruritic preparations.

Barrier Creams and Emollients

5.14. The Subcommittee noted cetomacrogol with glycerol appeared to be classified as both a barrier cream and an emollient in the Therapeutic Review Paper, which complicated interpretation of usage. The Subcommittee commented positively on the utility and user-friendly benefit of the pump dispensing mechanism and considered pump packs may increase usage due to increased suitability. The Subcommittee considered the benefit in tendering for smaller sizes to provide a more suitable pack type for use through the day (e.g. taking the product to school). The Subcommittee considered patients are likely being prescribed urea cream for use throughout the day, as it is supplied in a smaller pack size than cetomacrogol with glycerol. The Subcommittee considered a tub pack had lower suitability as it would be easier to contaminate the contents, can be difficult for patients with limited mobility and may be more obtrusive in school and work settings.

5.15. The Subcommittee noted zinc and ichthammol was no longer available and considered the niche clinical use for this product. The Subcommittee did not consider it likely it would be become available again in future.

Corticosteroids Topical – Combination and Plain

5.16. The Subcommittee noted clobetasone butyrate and diflucortolone valerate are part funded and considered there was benefit in fully funding these items.

5.17. The Subcommittee advised that there are benefits in having a variety of moderate potency topical steroids available and fully funded, such as when patients experience tolerability issues. The Subcommittee considered if one formulation of clobetasone butyrate was to be funded, the preference would be for an ointment presentation.

5.18. The Subcommittee **recommended** funding hydrocortisone ointment to address an unmet health need.

5.19. The Subcommittee considered there is a risk betamethasone dipropionate has been mis-prescribed due to different bases being used as a vehicle. The Subcommittee also considered there is a risk of confusion when prescribing due to the varying strengths of corticosteroids. It was highlighted that Australia has placed prescribing restrictions on potent topical corticosteroids. However, the Subcommittee noted that several classification systems exist and considered it difficult to decide which system is the most consistent. The Subcommittee noted Medsafe does not collect potency data as part of its registration process. The Subcommittee considered there is the potential to use a corticosteroid strength classification system next to drug names in the Schedule and align with the NZF (New Zealand Formulary).

5.20. The Subcommittee commented that the prescribing data provided by PHARMAC suggested combination corticosteroids were over-prescribed. The Subcommittee considered it would be beneficial if PHARMAC's responsible use provider released prescriber information on steroid potency and good prescribing practice. The Subcommittee considered it important to highlight the need to treat the underlying skin condition (i.e. dermatitis) rather than the acute issue (i.e. bacterial/fungal infection).

5.21. The Subcommittee considered the expenditure on hydrocortisone butyrate to be high and noted the funded hydrocortisone butyrate product is more expensive than other topical plain corticosteroid products. The Subcommittee noted hydrocortisone butyrate was a commonly prescribed topical corticosteroid.

Disinfecting and Cleansing Agents

5.22. The Subcommittee noted the information provided on disinfecting and cleansing agents.

Minor Skin Infections

5.23. The Subcommittee noted the information provided on minor skin infection treatments and suggested these be considered with antiseptics/antibiotics treatments at future meetings.

Other Skin Preparations

5.24. The Subcommittee considered the benefit of a fluorouracil sodium and calcipotriol combination product due to the improved patient response.

5.25. The Subcommittee **recommended** imiquimod should be moved to other skin preparations rather than wart preparations.

Parasiticidal Preparations

5.26. The Subcommittee considered ivermectin to be an effective treatment for scabies outbreaks in communal housing and institutions. The Subcommittee considered ivermectin usage is low in New Zealand (approximately 900 prescriptions per annum) and it was noted the Special Authority restrictions may be restricting community access. The Subcommittee considered an education campaign designed to improve diagnostic technique (e.g. identification of at-risk areas and at-risk patients) would likely improve ivermectin prescribing usage.

5.27. The Subcommittee **recommended** that the current Special Authority restrictions for ivermectin remain in place. The Subcommittee noted the Anti-Infectives Subcommittee of PTAC had considered correspondence proposing widening of access in order to reduce incidence of rheumatic fever and had recommended to maintain the current restrictions.

Psoriasis and Eczema Preparations

5.28. The Subcommittee noted the information provided on psoriasis and eczema preparations. The Subcommittee noted several items in this sub-group are currently subject to part-charges.

Scalp Preparations

5.29. The Subcommittee noted the information provided on scalp preparations.

Sunscreens

5.30. The Subcommittee considered the high cost of sunscreens available commercially to patients, and considered that there was a lack of awareness regarding the PHARMAC funding criteria. The Subcommittee considered the low prescribing numbers to be surprising considering the incidence of cutaneous lupus erythematosus, photosensitive dermatoses and the number of organ transplant patients. The Subcommittee was keen to increase access to sunscreens and suggested prescribing by endorsement. The Subcommittee considered this would likely increase the annual spend in sunscreens.

5.31. The Subcommittee suggested the restriction could be amended to clarify access for patients taking immunosuppressive and photosensitising drugs, noting photosensitivity could also be caused by clinical conditions.

5.32. The Subcommittee discussed the preferred criteria to be included in the next tender for sunscreen. The Subcommittee considered a preference for a UVB SPF > 50, UVA rating of 4 or 5 stars, or compliant with current AS/NZS 2604 standard, and that a lotion would be the preferred topical preparation due to low viscosity and its use on the face. The Subcommittee considered it would be reasonable to limit sunscreens to lotions only given the funding status.

Warts Preparations

5.33. The Subcommittee considered the relatively low usage of podophyllotoxin solution for warts and suggested that a salicylic acid product be added to the next tender.

5.34. The Subcommittee noted a previously funded product used to formulate wart paint is no longer available and therefore patients are now obliged to visit GP for cryotherapy or purchase an alternative funded treatment (e.g. duofilm). The Subcommittee considered some patients may be referred to hospital as a result of a lack of treatment options in the community. The Subcommittee considered this likely creates additional costs and may result in an unmet health need in this population. The Subcommittee suggested PHARMAC investigate the lack of availability of wart paint and alternative suppliers.

5.35. The Subcommittee suggested PHARMAC consider extension of HPV vaccination to all organ transplant patients, patients who are immunosuppressed, and patients on, or about to start, long-term immunosuppressive treatments. Subcommittee members considered that HPV vaccination had been effective in treating confluent peri-anal warts in post-transplant patients. US evidence suggests vaccination is effective in patients up to age of 45 years and immunosuppressive patients. The Subcommittee suggested this would be well placed to be considered by the Immunisation Subcommittee of PTAC.

Horizon Scanning

5.36. The Subcommittee considered topical cidofovir could be funded for treating genital warts and topical fluorouracil for plantar warts (although the Subcommittee considered the evidence base for using fluorouracil in the treatment of plantar warts was limited and anecdotal). The Subcommittee considered adapalene and fluorouracil could be used in the treatment of facial warts.

5.37. The Subcommittee noted a high unmet need for the treatment of hyperhidrosis and noted that glycopyrronium bromide was an older medication which would be useful in this indication.

5.38. The Subcommittee noted the need for tacrolimus ointment for treatment of atopic dermatitis of the face and that this product was subject to an unresolved tender.

5.39. The Subcommittee noted that there was emerging use of biologics and IL-4 antagonists in the treatment of atopic dermatitis. The Subcommittee noted that dupilumab is used in the USA to treat moderate to severe atopic dermatitis, however, that this was not registered in New Zealand. The Subcommittee considered there would likely be growing interest in the availability of these treatment options in the future.

5.40. The Subcommittee noted the use of crisaborole, a non-steroidal topical agent, was useful in the treatment of atopic dermatitis, particularly in children.

5.41. The Subcommittee noted a lack of funded treatments for mild to moderate rosacea and considered that ivermectin (1% cream) or brimonidine would be effective treatment options.

5.42. The Subcommittee noted that a combination of fluorouracil sodium and calcipotriol was more effective in the treatment of keratoses than the fluorouracil alone.

5.43. The Subcommittee noted that oral alitretinoin is the standard of care in the treatment of moderate/severe chronic hand dermatitis in the EU and USA. PHARMAC has

funded alitretinoin via the NPPA pathway. The Subcommittee **recommended** alitretinoin should be funded via the Pharmaceutical Schedule.

6. Risankizumab for moderate to severe plaque psoriasis

Application

6.1. The Subcommittee reviewed the application from AbbVie for risankizumab in the treatment of moderate to severe chronic plaque psoriasis.

Recommendation

6.2. The Subcommittee **recommended** that risankizumab for the first-line treatment of moderate to severe chronic plaque psoriasis be listed with a high priority within the context of dermatology treatments subject to the following Special Authority criteria:

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1.2 Either:
1.2.1 Patient has experienced intolerable side effects from adalimumab, etanercept, infliximab or secukinumab; or
1.2.2 Patient has received insufficient benefit from adalimumab, etanercept, infliximab or secukinumab; or
2 All of the following:
2.1: Either:
2.1.1 Patient has "whole body" severe chronic plaque psoriasis with a Psoriasis Area and Severity Index (PASI) score of greater than 10, where lesions have been present for at least 6 months from the time of initial diagnosis; or
2.1.2 Patient has severe chronic plaque psoriasis of the face, or palm of a hand or sole of a foot, where the plaque or plaques have been present for at least 6 months from the time of initial diagnosis; and
2.2 Patient has tried, but had an inadequate response* to, or has experienced intolerable side effects from, at least three of the following (at maximum tolerated doses unless contraindicated): phototherapy, methotrexate, ciclosporin, or acitretin; and
2.3 A PASI assessment or Dermatology Life Quality Index (DLQI) assessment has been completed for at least the most recent prior treatment course, preferably while still on treatment but no longer than 1 month following cessation of each prior treatment course; and
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Renewal – (severe chronic plaque psoriasis) only from a dermatologist or practitioner on the recommendation of a dermatologist. Approvals valid for 6 months for applications meeting the following criteria:
Both:
1. Either:

1.1 Patient's PASI score has reduced by 75% of more (PASI 75) as compared to baseline PASI prior to commencing risankizumab; or
1.2 Patient has a Dermatology Life Quality Index (DLQI) improvement of 5 or more, as compared to baseline DLQI prior to commencing risankizumab; and
2. Risankizumab is to be administered at a maximum dose of 150 mg every 12 weeks, following induction doses at 0 and 4 weeks

6.3. The Subcommittee **recommended** that risankizumab for the second-line treatment of moderate to severe chronic plaque psoriasis be listed with a high priority within the context of dermatology treatments subject to the following Special Authority criteria:

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3 A PASI assessment or Dermatology Life Quality Index (DLQI) assessment has been completed for at least the most recent prior treatment course, preferably while still on treatment but no longer than 1 month following cessation of each prior treatment course; and
4 The most recent PASI or DLQI assessment is no more than 1 month old at the time of application.

*A treatment course is defined as a minimum of 12 weeks of treatment. "Inadequate response" in defined as: for whole body severe chronic plaque psoriasis, a PASI score of greater than 10, as assessed preferably while still on treatment but no longer than 1 month following cessation of the most recent prior treatment; for severe chronic plaque psoriasis of the face, hand or foot, at least 2 of the 3 PASI symptom sub scores for erythema, thickness and scaling are rated as severe or very severe, and the skin area affected is 30% or more of the face, palm of a hand or sole of a foot, as assessed preferably while still on treatment but no longer than 1 month following cessation of the most recent prior treatment.

Renewal – (severe chronic plaque psoriasis) only from a dermatologist or practitioner on the recommendation of a dermatologist. Approvals valid for 6 months for applications meeting the following criteria:
Both:
1. Either:
1.1 Patient's PASI score has reduced by 75% of more (PASI 75) as compared to baseline PASI prior to commencing risankizumab; or
1.2 Patient has a Dermatology Life Quality Index (DLQI) improvement of 5 or more, as compared to baseline DLQI prior to commencing risankizumab; and
2. Risankizumab is to be administered at a maximum dose of 150 mg every 12 weeks, following induction doses at 0 and 4 weeks

6.4. The Subcommittee made these recommendations based on the high health need of these patients (particularly after failure of a previous biologic), the increased benefit and efficacy of risankizumab compared to currently funded treatments, and an appropriate suitability profile with the option for community use.

Discussion

6.5. The Subcommittee noted that chronic plaque psoriasis is an immune-mediated disease, which presents with well-demarcated erythematous plaques and patches with adherent silvery-white scale. Typical histological features include acanthosis, parakeratosis, dilated blood vessels and a perivascular inflammatory infiltrate. Chronic plaque psoriasis is the most common type of psoriasis (approximately 80-

90%). The Subcommittee noted that approximately 2% of the New Zealand population are affected, but that the majority of patients have clinically mild psoriasis which is not extensive enough to warrant treatment with biologics.

6.6. The Subcommittee noted there is no evidence that suggests the prevalence of psoriasis in Māori and Pacific peoples is significantly different from the rest of the population. The Subcommittee noted that the prevalence of comorbidities associated with psoriasis, such as cardiovascular disease, is greater in Māori and Pacific peoples, which suggests the health needs are greater for Māori and Pacific people with psoriasis. The Subcommittee noted the higher rates of obesity in Māori and Pacific populations also lead to higher co-morbidities associated with psoriasis.

6.7. The Subcommittee noted that psoriasis is a systemic disease; disease associations including disorders of the gastrointestinal tract, eye, and joints. The Subcommittee noted that moderate to severe plaque psoriasis is a risk factor for cardiovascular disease and metabolic syndrome. The Subcommittee noted that psoriasis has a profound psychosocial effect, with patients suffering from depression and anxiety. The Subcommittee noted that plaque psoriasis is associated with levels of impairment leading to an inability to work, and that regaining the ability to work is an important outcome for patients.

6.8. The Subcommittee noted that interleukin (IL)-23 is a key cytokine because of its role in the development, maintenance, and activation of T helper (Th17) cells which produce pro-inflammatory cytokines including IL17, that play a key role in the pathogenesis of psoriasis. The Subcommittee noted that there are currently 4 biologic treatments funded for the treatment of moderate to severe plaque psoriasis in New Zealand: the 3 TNF-α inhibitors adalimumab, etanercept, and infliximab, and IL-17A inhibitor secukinumab. The Subcommittee noted that there are no funded IL-22 or IL-23 inhibitors available for the treatment of psoriasis. The Subcommittee considered that, although funded for this indication, infliximab is not the drug of choice for most clinicians as it requires a day stay infusion centre and incurs a significant cost in time and money to both patients and the health sector. The Subcommittee also considered that etanercept is less commonly used than adalimumab, as it is less efficacious than the other funded biologic agents and it requires weekly administration.

6.9. The Subcommittee noted that there is evidence for a decrease in the efficacy of biologics over time; a 2018 study by Egeberg et al reported that 30-60% of moderate to severe plaque psoriasis patients using biologics had discontinued treatment at 75 months due to loss of efficacy, with secukinumab having the lowest drug-survival (Egeberg et al. Br J Dermatol. 2018;178:509-519).

6.10. The Subcommittee noted that risankizumab is a humanised immunoglobulin G1 (IgG1) monoclonal antibody that selectively binds with high affinity to the p19 subunit of IL-23 cytokine and inhibits its interaction with the IL-23 receptor complex, thus inhibiting IL-23-dependent cell signalling and the release of pro-inflammatory cytokines. The Subcommittee noted that there are currently no funded treatment options which follow this mechanism of action.

6.11. The Subcommittee noted that the renewal criteria for biologics in the treatment of severe plaque psoriasis defines a response to treatment as a reduction in the Psoriasis Area Severity Index (PASI) score of 75% from baseline (PASI 75). The Subcommittee considered that a PASI 75 is an older measure of success to treatment, and PASI 90-100 is more significant goal for patients and clinicians, and becoming the new standard.

6.12. The Subcommittee noted two parallel double-blind, randomised, placebo-controlled and ustekinumab-controlled phase III trials (UltIMMa-1 and UltIMMa-2) in which adults with moderate to severe chronic plaque psoriasis with body surface area involvement 10% or greater, PASI score of ≥12, and static Physician's Global Assessment (sPGA) score of ≥3 were given either risankizumab (n=598, 150 mg subcutaneously at week 0, week 4, and 12-weekly thereafter), ustekinumab (n=199, 45 mg or 90 mg subcutaneously based on screening weight at weeks 0 and 4, then 12-weekly thereafter), or placebo (n=200, subcutaneously at Weeks 0 and 4, then given risankizumab 150 mg subcutaneously at weeks 16, 28, and 40) (Gordon et al. Lancet. 2018;392:650-61). The Subcommittee noted that 44-51% of patients in the ustekinumab group achieved a PASI score of 90 which was sustained out to 52 weeks, compared to 81-82% of patients in the risankizumab group, and 78-85% of patients who switched to risankizumab from placebo. The Subcommittee noted that less than half of the participants in these trials had received previous biologic therapy.

6.13. The Subcommittee noted a randomised, double-blind, active-comparator-controlled phase III trial (IMMvent) in which adults with moderate to severe chronic plaque psoriasis with body surface area involvement 10% or greater, PASI score of ≥12, and sPGA score of ≥3 were given either 150 mg risankizumab subcutaneously at weeks 0 and 4 or 80 mg adalimumab subcutaneously at week 0 and then 40 mg every second week from week 1 up to the end of week 15, at which point patients continuing adalimumab were given study drug every second week from week 17 up to the end of week 41; patients switching to risankizumab were given study drug at weeks 16, 20, and 32 and patients remaining on risankizumab were given study drug at weeks 16 and 28 (Reich et al. Lancet. 2019;394:576-86).The Subcommittee noted that 72% of patients taking risankizumab achieved a PASI 90 at 16 weeks, compared to 47% on adalimumab. The Subcommittee also noted that 21% adalimumab patients who were re-randomised to adalimumab achieved PASI 90 at week 44, compared to 66% of patients on adalimumab who were re-randomised to receive risankizumab. The Subcommittee noted that 37-39% of participants in the IMMvent trial had received previous biologic treatment.

6.14. The Subcommittee noted a phase II trial in which 166 patients received subcutaneous injections of risankizumab (a single 18-mg dose at week 0 or 90-mg or 180-mg doses at weeks 0, 4, and 16) or ustekinumab (45 or 90 mg, according to body weight, at weeks 0, 4, and 16) (Papp et al. N Engl J Med. 2017;376:1551-1560). The Subcommittee noted that at week 12, the percentage of patients with a PASI 90 score was 77% (64 of 83 patients) for risankizumab (90-mg and 180-mg groups, pooled), as compared with 40% (16 of 40 patients) for ustekinumab (P<0.001). The Subcommittee also noted that the percentage of patients with a PASI 100 score was 45% in the pooled 90-mg and 180-mg risankizumab groups, as compared with 18% in the ustekinumab group, and that efficacy was generally maintained up to 20 weeks after the final dose of 90 or 190 mg risankizumab.

6.15. The Subcommittee noted a phase III, international, multicentre, randomized, open-label, efficacy-assessor-blinded, active-comparator study (IMMerge) in which adults with stable moderate to severe plaque psoriasis (body surface area involvement ≥10%; PASI ≥12; sPGA ≥3) were given either risankizumab administered as two subcutaneous injections of 75 mg (150 mg total) at weeks 0 and 4, and every 12 weeks thereafter until the last dose at week 40 (n=164), or secukinumab administered as two subcutaneous injections of 150 mg (300 mg total) at weeks 0, 1, 2, 3 and 4, and every 4 weeks thereafter until the last dose at week 48 (n=163) (Warren et al. Br J Dermatol. 2020 online ahead of print). The Subcommittee noted that at week 16 risankizumab was non-inferior to secukinumab at achieving a PASI 90 score and was superior at week 52 (adjusted difference 29.8%, 95% CI 20.8 to 38.8, P<0.001).

6.16. The Subcommittee noted a systematic review evaluating different biologic treatments for moderate to severe plaque psoriasis (Sawyer et al. PLoS One. 2019;14:e0220868). The Subcommittee noted that IL-17A and IL-23 inhibitors were found to be more effective in the treatment of psoriasis than all TNF-α inhibitors investigated.

6.17. The Subcommittee considered that improved disease control from risankizumab would likely result in less requirement for specialist visits. The Subcommittee noted that hospitalisation is generally uncommon for patients with psoriasis and considered that in some of the larger DHBs, a patient is hospitalised every 4-6 weeks. The Subcommittee considered hospitalisation may not be due to treatment failure, but instead due to lack of adherence to therapy.

6.18. The Subcommittee noted that most patients will start on adalimumab as their first biologic, and then switch to either another anti-TNF (such as etanercept) or to secukinumab (an IL-17 inhibitor). The Subcommittee noted that adalimumab would therefore be the appropriate comparator when risankizumab is used first-line, while secukinumab would be the most appropriate comparator if risankizumab was restricted to second-line use. The Subcommittee noted that risankizumab, if used first-line, would commonly be followed with an anti-TNF such as adalimumab. The Subcommittee considered that use of secukinumab immediately following risankizumab discontinuation would be unlikely, due to both agents being interleukin inhibitors.

6.19. The Subcommittee noted that risankizumab is more effective than currently funded treatment options with a side-effect profile consistent with other biologics. The Subcommittee noted there is no evidence to inform the optimal sequencing of treatment, and whether it is better to start with risankizumab and switch to an anti-TNF, or vice versa. The Subcommittee noted that, while there is no evidence about the efficacy of treatments after risankizumab, it is clinically appropriate to use the most effective drug as the first biologic treatment. The Subcommittee noted that the superior efficacy and suitability of risankizumab would mean it would be the treatment of choice for biologic-naïve patients.

6.20. The Subcommittee noted that methotrexate and anti-TNFs are associated with lower cardiovascular mortality in patients with plaque psoriasis, with this primarily due to these agents' ability to reduce inflammation. The Subcommittee noted that greater disease severity is generally associated with more comorbidities (including cardiovascular morbidity) and considered that it was reasonable to assume that risankizumab, by reducing the severity of psoriasis, would be associated with a reduction in these comorbidities.

6.21. The Subcommittee again noted the high health need for patients with moderate to severe plaque psoriasis, and considered that the less frequent dosing schedule, sustained efficacy, and superiority of risankizumab compared to other funded options would potentially offer patients better treatment outcomes and a different mechanism to treat their psoriasis if it were to be funded.

7. Rituximab - Pemphigus (all types)

Application

7.1. The Subcommittee reviewed a clinician application for rituximab for the first- and second-line treatment of all subtypes of severe and recalcitrant pemphigus.

Recommendation

7.2. The Subcommittee **recommended** that rituximab for pemphigus be funded with a high priority within the context of dermatology treatments subject to the following Special Authority criteria:

> **Initial Application - (pemphigus)** only from a dermatologist or relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
>
> Either:
>
> 1 All of the following:
>
> 1.1 Patient has severe rapidly progressive pemphigus; and
>
> 1.2 Is used in combination with systemic corticosteroids (20 mg/day); and
>
> 1.3 Either:
>
> 1.3.1 Skin involvement ≥5% body surface area; or
>
> 1.3.2 Significant mucosal involvement (≥10 mucosal erosions), diffuse gingivitis, confluent large erosions; or
>
> 1.3.3 Involvement of two or more mucosal sites; or
>
> 2 All of the following:
>
> 2.1 Patient has pemphigus; and
>
> 2.2 Patient has not responded to systemic corticosteroids (20 mg/day) in combination with a steroid sparing agent, unless contraindicated
>
> **Renewal – (pemphigus)** only from a dermatologist or relevant specialist. Approvals valid for 26 weeks for applications meeting the following criteria:
>
> 1 Patient has demonstrated benefit from rituximab treatment in terms of symptom reduction, improved healing of skin ulceration and reduction in steroid requirement; and
>
> 2 Rituximab re-treatment not to be given within 6 months of the previous course of treatment.

7.3. The Subcommittee made this recommendation based on the high morbidity and potential mortality from severe pemphigus and the significant side effects from current treatments, and the increased efficacy and reduced adverse events with rituximab compared to current treatments, and the potential savings to the health system resulting from a decrease in hospitalisations related to pemphigus.

Discussion

7.4. The Subcommittee noted a clinician application for rituximab for the first- and second-line treatment of all subtypes of severe and recalcitrant pemphigus. The Subcommittee noted that a number of Named Patient Pharmaceutical Assessment (NPPA) applications have been received by PHARMAC, and that the patient group approved was previously defined as those with an urgent requirement for an immunosuppressive agent, or where all funded alternative treatments had been trialled and had not provided adequate disease control.

7.5. The Subcommittee noted that rituximab is a monoclonal antibody against CD20 expressing B-lymphocytes currently funded for the treatment of a number of haematology and rheumatology disorders such as Non-Hodgkin lymphoma, chronic lymphocytic leukaemia, rheumatoid arthritis, and Wegner's granulomatosis. The Subcommittee noted that rituximab is administered by infusion with different treatment schedules depending on if an oncological or rheumatological protocol is needed.

7.6. The Subcommittee noted that pemphigus is a group of chronic, autoimmune skin diseases which are characterised by acantholysis, resulting in the formation of intraepithelial blisters in mucous membranes and skin caused by autoantibodies

against desmosomes in the epidermis leading to erosions. The Subcommittee noted that the process of acantholysis is induced by the binding of circulating autoantibodies to intercellular adhesion molecules. The Subcommittee noted that there are several subtypes of pemphigus including vulgaris, foliaceus, vegetans, paraneoplastic, and IgA; the most common of which are vulgaris and foliaceus which form approximately 95% of diagnoses globally. The Subcommittee noted there is limited data on incidence and prevalence of pemphigus in New Zealand but noted pemphigus vulgaris is the more common subtype overseas.

7.7. The Subcommittee noted that the health need for patients with pemphigus is high, with common symptoms being widespread skin blisters, erosions and mucosal loss (commonly intractable oral ulceration), and direct disease complications due to skin failure from extensive skin loss and mucosal involvement including pain, secondary systemic infection, secondary cutaneous infection (both bacterial and viral), fluid loss and inability to eat due to oral involvement. The Subcommittee noted that the average age of onset is usually between 45 and 65 years and more common in females. The Subcommittee noted that incidence globally is estimated to be 0.6 to 10 per million, with some populations experiencing higher rates; Jewish populations experience prevalence as high as 32 per million, and 3-5% of the South American population suffers from an endemic form of pemphigus foliaceus. The Subcommittee noted that pemphigus may disproportionately affect the New Zealand Indian community, which may explain the higher prevalence of pemphigus in the Auckland region.

7.8. The Subcommittee noted the various scoring systems for pemphigus, and dermatology disease in general; the autoimmune bullous skin disorder intensity score (ABSIS), the pemphigus disease area index (PDAI), the physician's global assessment (PGA), the dermatology life quality index (DLQI). The Subcommittee noted that these systems are used to measure the extent of disease, the degree of healing, lesion counts, and circulating antibody levels. The Subcommittee noted that values for defining moderate, significant, and extensive types of pemphigus are derived from the ABSIS and PDAI systems primarily (Boulard et al. Br J Dermatol. 2016;175:18-19).

7.9. The Subcommittee noted that, prior to the use of glucocorticoids, 75-90% of patients with pemphigus would die as a result of their pemphigus. The Subcommittee noted that the estimated mortality rate with current treatments is less than 5-10%, which is still 2-4 times higher than that of the general population. The Subcommittee noted that primary causes of mortality and morbidity in patients with pemphigus are infection, cancer, cardiovascular disease, and gastrointestinal bleeding, which are all more common in pemphigus patients. The Subcommittee noted that treatment related adverse events also contribute to the increased mortality and morbidity of pemphigus patients, and that patients also experience psychological effects; depression and anxiety are common, experienced by approximately 77% of patients (Ghodsi et al. J Dermatol. 2012;39:141-144). The Subcommittee noted that patients with severe disease are often unable to work, and that hospitalisation for severe disease is common and can last many weeks while waiting for the skin to heal.

7.10. The Subcommittee noted that the current treatment paradigm for pemphigus is glucocorticoids in the first line, usually oral prednisone at 0.5-2 mg per kg per day, which continues until the patients experiences for at least two weeks with no new blisters, and with clinical resolution of most of the erosions, at which point treatment is slowly tapered to prevent relapse. The Subcommittee noted that 52-76% of patients achieve disease control on less than 10 mg per day of prednisone at 12 months, and that relapse occurs in about 50% of patients. The Subcommittee noted that the negative side-effect profile of long-term prednisone treatment is well documented.

7.11. The Subcommittee noted that adjuvant treatments are also used in the management of pemphigus; azathioprine, mycophenolate, intravenous immunoglobulins, cyclophosphamide, and immunoadsorption are all treatment options to reduce steroid requirement and prevent relapse. The Subcommittee were made aware of a systematic review and meta-analysis of randomized controlled trials investigating the role of adjuvant therapy in pemphigus (Atzmony et al. J Am Acad Dermatol. 2015;73:264-271). The Subcommittee noted that although adjuvants were not beneficial for achieving remission, they were found to collectively decrease the risk of relapse by 29% (relative risk 0.71, 95% CI 0.53 to 0.95).

7.12. The Subcommittee noted a prospective, multicentre, parallel-group, open-label, randomised trial (Ritux 3 trial, ClinicalTrials.gov identifier: NCT03790293) in which 90 patients aged 18-80 years with newly diagnosed pemphigus (i.e. Being treated for the first time) were randomly assigned participants (1:1) to receive either oral prednisone alone, 1.0 or 1.5 mg/kg/day tapered over 12 or 18 months (n=44), or 1000 mg of intravenous rituximab on days 0 and 14, and 500 mg at months 12 and 18, combined with a short-term prednisone regimen, 0.5 or 1.0 mg/kg/day tapered over 3 or 6 months (n=46) (Joly et al. Lancet. 2017;389:2031-2040). The Subcommittee noted that 82% of patients had pemphigus vulgaris and 18% had pemphigus foliaceus. The Subcommittee noted that in the prednisone alone group, 12 participants withdrew (8 due to side-effects and 4 due to treatment failure), and that 2 participants withdrew from the rituximab group (1 due to pregnancy, and the other due to treatment failure). The Subcommittee noted that complete remission off therapy (no lesions, and off steroids for 2 months) at 24 months occurred in 34% of the prednisone group and 89% of the rituximab group (RR 2.61; 95% CI 1.71 to 3.99; p<0.0001).

7.13. The Subcommittee noted that relapse at 24 months occurred in 45% of the prednisone group and 24% of the rituximab group. The Subcommittee also noted that after adjusting for sex or baseline PDAI score, a strong beneficial effect of rituximab was still evident with an RR of complete remission off-therapy of 2.66 (95% CI 1.73 to 4.07; P<0.0001) and 2.55 (1.41 to 3.69; p<0.0001), respectively. The Subcommittee noted that five patients (11%) in the rituximab group and 28 patients (64%) in the prednisone group still had active lesions at month 24 or had no lesions but still took a prednisone dose higher than 10 mg/day (RR 2.45; 95% CI 1.64 to 3.67; p<0.0001). The Subcommittee noted that the median time to complete remission off therapy was 277 days in the rituximab group vs 677 days in the prednisone group, and the total cumulative steroid dose was lower in the rituximab group compared to the prednisone group (6143 mg vs 17,973 mg, respectively). The Subcommittee also noted that 16 participants in the rituximab treatment group experienced a total of 27 severe adverse events (mean 0.59), whereas 29 patients experienced a total of 53 severe events (mean 1.20) in the prednisone treatment group (p=0.0021).

7.14. The Subcommittee were made aware of a review on the results from the Ritux 3 trial regarding use of rituximab in the treatment of pemphigus vulgaris specifically (Frampton JE. Am J Clin Dermatol. 2020;21:149-156). The Subcommittee noted that the results were similar to that of the total pemphigus population in the Ritux 3 trial, and that response rates were similar between pemphigus vulgaris and pemphigus foliaceus groups.

7.15. The Subcommittee noted a prospective open-label study in which 21 patients with pemphigus whose disease had not responded to an 8-week course of 1.5 mg of prednisone per kilogram of body weight per day (n=5), who had had at least 2 relapses despite doses of prednisone higher than 20 mg per day (n=11), or who had severe contraindications to corticosteroids (n=5) were treated with rituximab 375 mg/m^2 every week for 4 weeks, with a 2 year follow-up (Joly et al. J Engl Med.

2007;357:545-52). The Subcommittee noted that corticosteroids were maintained at the initial dose until the disease was controlled, and the corticosteroid dose was then reduced by 10% twice a month, and patients with contraindications to corticosteroids were treated with rituximab alone.

7.16. The Subcommittee noted that 86% (n=18) of patients had a complete remission at 3 months and of these patients, 9 had a relapse after a mean period of 18.9±7.9 months. The Subcommittee also noted that after a median follow-up time of 34 months, 18 patients (86%) were free of disease, including 8 patients (38%) who received no further corticosteroids. The Subcommittee noted that the mean dose of prednisone for patients with corticosteroid-refractory disease decreased from 94.0±10.2 mg per day at baseline to 12.0±7.5 mg per day at the end of the study (P=0.04) and that the mean dose of prednisone for patients with corticosteroid-dependent disease decreased from 29.1±12.4 mg per day at baseline to 10.9±16.5 mg per day at the end of the study (P=0.007).

7.17. The Subcommittee noted a retrospective study of 45 pemphigus patients (39 with pemphigus vulgaris and 6 with pemphigus foliaceus who had received at least one cycle of two infusions of rituximab (375 mg/m^2), weekly (Kim et al. J Dermatol. 2017;44:615-20). The Subcommittee noted that all patients received concomitant corticosteroids or immunosuppressive therapy during rituximab treatment and that corticosteroids were gradually tapered over the following months, according to clinical conditions. The Subcommittee noted that after the first cycle of rituximab, 100% of patients achieved complete or partial remission, with a median time to remission of 4.2 months. The Subcommittee noted that 76% of participants relapsed (median time to relapse 17.1 months). The Subcommittee noted that two participants died during the trial (acute respiratory distress syndrome and gastric perforation).

7.18. The Subcommittee noted a retrospective analysis comparing the use of rituximab to conventional adjuvant therapy (CAT) for 40 pemphigus vulgaris patients between 1999 and 2015 (Agarwal et al. PLoS One. 2018;13:e0198074). The Subcommittee noted that 32.5% of patients with moderate to severe pemphigus vulgaris failed prednisone and traditional CAT treatment and required rituximab therapy, which reduced the monthly prednisone intake in these patients by 73%.

7.19. The Subcommittee noted a systematic review and meta-analysis of the efficacy of different dosing regimens containing rituximab in treating pemphigus (N=578; Wang et al. Acta Derm Venereol. 2015;95:928-932). The Subcommittee noted that 76% of patients of patients achieved complete remission after one cycle of rituximab, and that mean time to remission was 5.8 months with a remission duration of 14.5 months and a 40% relapse rate. The Subcommittee noted that a higher dose of rituximab was associated with a shorter time to disease control (5.35 months with high dose vs 6.39 months with low dose; p=0.04), and a longer duration of complete remission (16.7 months high dose vs 9.1 months low dose; p=0.001). The Subcommittee also noted that patients in the oncology protocol group reached disease control more rapidly than patients in the rheumatological (RA) protocol group (5.16 vs. 6.68 weeks; p=0.04), that the remission duration (18.85 vs. 7.96 months; p=0.001) and that follow-up times (37.66 vs. 17.3 months; p=0.002) were significantly longer in the lymphoma protocol group than in the RA protocol group.

7.20. The Subcommittee also noted 2 other studies regarding dosing of rituximab for the treatment of pemphigus (Loi et al. Dermatol Ther. 2019;32:e12763, Kanwar et al. Br J Dermatol. 2014;170:1341-1349). The Subcommittee noted that the results from these studies indicate a potential benefit of the oncology protocol over the RA protocol, and higher dosing. The Subcommittee also noted a retrospective case

review of 146 pemphigus vulgaris (n=130) and foliaceus (n=16) patients who had received two doses of 1000 mg biosimilar rituximab which reported a 73.3% remission rate, indicating an equivalent response rate to originator rituximab (De et al. Ind J Dermatol Venereol Leprol. 2020;86:39-44).

7.21. The Subcommittee also noted the following reviews and studies on the efficacy of rituximab in the treatment of pemphigus:

- Tavakalpour et al. Int Immunopharmacol. 2018;54:131-138
- Ahmed AR, Shetty S. Autoimmun Rev. 2015;14:323-31
- De Sena Nogueira Maehara et al. BJD. 2015;172:1420-1423

7.22. The Subcommittee also noted some reported cases of paradoxical worsening of pemphigus after treatment with rituximab but considered that these were isolated events (Mahmoudi et al. Int Immunopharmacol. 2019;71:40-42, Feldman RJ. Br J Dermatol. 2015;173:858-859, Sharma et al. Indian J Dermatol Venereol Leprol. 2016;82:389-394).

7.23. The Subcommittee considered that evidence for health benefits gained from rituximab was of good strength and moderate quality, and that the participants in the studies were reflective of the New Zealand patient population. The Subcommittee considered that, while there is no evidence of rituximab treatment reducing mortality/improving survival (due to immaturity of data and lack of long-term follow-up), it is reasonable to assume successful treatment with rituximab may improve overall survival by decreasing the burden on patients from comorbidities.

7.24. The Subcommittee noted that intravenous immunoglobulins (IVIg) are sometimes used to treat treatment-refractory patients, however it was unclear how frequent IVIg infusions are used for treating this patient population in New Zealand. The Subcommittee noted that it was becoming increasingly difficult to access IVIg, and the number of patients accessing IVIg is likely to be small.

7.25. The Subcommittee considered the comparator for patients refractory to a prior course of systemic steroids would be steroids in combination with conventional adjunctive treatment, such as azathioprine or mycophenolate. The Subcommittee considered that cyclophosphamide would not be an appropriate comparator as it is not as widely used or effective as other steroid-sparing agents.

7.26. The Subcommittee considered that funding rituximab for this indication would not place significant additional burden on hospital infusion facilities, and rituximab is already widely used and there is a familiarity with administration and protocols among healthcare workers. The Subcommittee considered that funding rituximab for this indication may lead to savings for the health sector relating to reduced use of corticosteroid and adjuvant therapies which require regular monitoring, as well as a reduction in hospitalisation which involves inpatient care, medications, wound dressing, nursing, dental care, treatment for infections and adverse events, and occasionally nutrition supplements. The Subcommittee considered that an estimate of 13-15 new patients per year with pemphigus needing treatment with rituximab was a reasonable estimate, and that 25% of these patients may need additional maintenance dosing.

7.27. The Subcommittee noted again the high health need, morbidity, and mortality experienced by pemphigus patients, and the significant side effects from current

treatments. The Subcommittee also noted the increased efficacy of, and reduced adverse events with, rituximab compared to current treatments as well as the potential savings to the health system resulting from a decrease in hospitalisations related to pemphigus.