Reproductive and Sexual Health Subcommittee of PTAC

Meeting held 10 April 2017

(minutes for web publishing)

Reproductive and Sexual Health Subcommittee minutes 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 Reproductive and Sexual Health Subcommittee meeting; only the relevant portions of the minutes relating to Reproductive and Sexual Health Subcommittee discussions about an Application or PHARMAC staff proposal that contain a recommendation are generally published.

The Reproductive and Sexual Health 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 10 & 11 August 2017, the record of which will be available in due course.

Record of the Reproductive and Sexual Health Subcommittee of PTAC meeting held at PHARMAC on 10 April 2017

1. Record of the Previous Subcommittee Meeting

1.1. The Subcommittee noted and accepted the record of its previous meeting held on 28 July 2014.

2. Levonorgestrel Intrauterine Systems for Contraception

Application

2.1. The Subcommittee reviewed funding applications from four organisations: New Zealand Nurses Organisation (NZNO); Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG); Royal New Zealand College of General Practitioners (RNZCGP); and Family Planning New Zealand, for widened access to levonorgestrel intrauterine systems as a funded contraception option for all women of reproductive age.

Recommendation

2.2. The Subcommittee **recommended** that levonorgestrel intrauterine systems (LIUS) be listed on the Pharmaceutical Schedule with a high priority as a contraception option for women of reproductive age who are unable to use (due to contraindications) or tolerate (due to side effects) other LARCs.

Discussion

2.3. The Subcommittee noted the currently funded forms of contraceptives used in the New Zealand market by women are condoms, oral contraceptives (both combined and progestogen only), medroxyprogesterone injection, levonorgestrel subcutaneous implant, and copper intrauterine devices (IUD).

2.4. The Subcommittee noted that currently LIUS (Mirena) is only funded for women with heavy menstrual bleeding or surgically confirmed endometriosis, and not solely as a contraceptive. Members noted that a number of New Zealand women are choosing to self-fund LIUS for contraception.

2.5. The Subcommittee noted that the Mirena brand (52 mg levonorgestrel) of LIUS is approved by Medsafe for the indications of contraception; treatment of idiopathic menorrhagia provided there is no underlying pathology; and prevention of endometrial hyperplasia during oestrogen replacement therapy.

2.6. The Subcommittee noted that there are also two other Medsafe approved brands of LIUS. Members noted that Levosert (52 mg levonorgestrel) is approved for the indications of contraception and treatment of idiopathic menorrhagia for up to three years; and that Jaydess (13.5 mg levonorgestrel) has Medsafe approval for the indication of contraception up to three years.

2.7. The Subcommittee noted that the National Institute for Health and Care Excellence (NICE) 2014 Guidelines on Long-acting Reversible Contraception state that all LARC methods, including intrauterine systems, are suitable for nulliparous women.

2.8. The Subcommittee noted evidence for the use of LIUS as a preferred contraceptive from The Contraceptive CHOICE Project (Secura et al. Am J Obstet Gynecol 2010;203:115.e1-7), where of the 2500 women willing to start a new method or not using contraception, 47% chose a LIUS, 9% chose a copper IUD, 11% the subdermal implant, 6% the medroxyprogesterone depot, and 27% chose combined hormonal forms of contraception (including 12% choosing an oral contraceptive). Members noted that all forms of contraception offered in this study were at no cost to the participants and tiered counselling was used with the most effective contraceptives presented first.

2.9. The Subcommittee noted the Diedrich et al (Am J Obstet Gynecol 2015; 213:662.e1-8) analysis of The Contraceptive CHOICE Project, which showed similar continuation rates between LIUS (69.8%) and copper IUD (69.7%) at three years. Members also noted the overall continuation rate for the subdermal implant was 56.2%, medroxyprogesterone depot was 33.2% and 31.5% for oral contraceptives. Members noted that in adolescent participants (14 to 19 years of age), LARC continuation rates at three years were 52.6% for 14-19 year olds and 69.2% for 20-45 year olds.

2.10. The Subcommittee noted that the reasons reported for LARC discontinuation in CHOICE participants included bleeding changes, pain and intolerance of side effects (Diedrich et al, 2015). The Subcommittee noted that in this analysis, of the LIUS users, 56% discontinued for these reasons; and 62% of copper IUD users and 75.9% of subdermal implant users cited these reasons for discontinuing while expulsion occurred in 13.5% of LIUS users and in 12.2% of copper IUD users.

2.11. The Subcommittee noted the Cochrane Systematic Review by Krashin et al (Cochrane Database of Systematic Reviews 2015;8:CD009805) comparing contraceptive failure (pregnancy) rates and contraception continuation rates for hormonal and intrauterine contraception among young women aged 25 years and younger. The Subcommittee noted that five randomised control trials met the review inclusion criteria, of which only these three used LIUS as a comparator:

- Godfrey et al. Contraception 2010;81:123-7
- Nelson et al. Obstet Gynecol 2013;122:1205-13
- Suhonen et al. Contraception 2004;69:407-12.

2.12. The Subcommittee noted that the Godfrey et al (2010) trial of 23 women compared the copper IUD with the LNG-IUS 20 µg/day and only one pregnancy occurred (which was in the copper group). Six-month continuation rates were 75% for the LNG-IUS 20 and 45% for the copper IUD (OR 3.60, 95% CI 0.62 to 21.03). Members noted that bleeding problems were the reason for discontinuation by one woman in each group; and in the copper IUD group, other reasons for discontinuation were excessive cramping and expulsion.

2.13. The Subcommittee noted that the Kaunitz et al (2013) trial of 2884 women compared LIUS 12 µg/day (LNG-IUS 12) with 16 µg/day (LNG-IUS 16). Unadjusted Pearl Indices were similar: 0.22 (95% CI 0.01 to 1.22) for LNG-IUS 12 and 0.21 (95% CI 0.01 to 1.18) for LNG-IUS 16 at one year. At three years, the unadjusted Pearl Indices were 0.36 (0.10 to 0.92) for the LNG-IUS 12 and 0.17 (0.02 to 0.60) for the LNG-IUS 16. Members noted that the risk of expulsion was 4.78% overall, and two cases (0.2%) of pelvic inflammatory disease were reported overall. Twenty-two percent of women

discontinued the LIUS due to adverse events; however, overall continuation was not stated.

2.14. The Subcommittee noted that the Suhonen et al (2004) trial of 200 women compared the LNG-IUS 20 versus the combined oral contraceptive (COC). This trial also showed no important differences in pregnancy rates or continuation rates. No pregnancies occurred in either group over 12 months. Twelve-month continuation rates were 80% in the LNG-IUS group and 73% in the COC group (OR 1.48, 95% CI 0.76 to 2.89). Members noted that women in the LNG-IUS 20 group were more likely than women in the COC group to discontinue their method of contraception because of pain (OR 14.62, 95%CI 0.81 to 263.16) and less likely to discontinue because of personal reasons (OR 0.27, 95% CI 0.09 to 0.85). In the LNG-IUS 20 group, four out of six discontinuations were due to pain and occurred within the first three months after insertion.

2.15. The Subcommittee noted that Krashin et al (2015) concluded that the current evidence was insufficient to compare efficacy and continuation rates for hormonal and intrauterine contraceptive methods in women aged 25 years and younger.

2.16. Members noted that the Winner et al (N Engl J Med 2012;366:1998-2007) prospective cohort study showed a contraceptive failure rate among participants using pills, patch, or ring of 4.55 per 100 participant-years, compared with 0.27 among participants using long-acting reversible contraception (hazard ratio after adjustment for age, educational level, and history with respect to unintended pregnancy, 21.8; 95% confidence interval, 13.7 to 34.9).

2.17. Members considered that real-life experience does not always reflect what happens in randomised control trials, such as those in the Cochrane Systematic Review (Krashin et al, 2015), with regard to contraceptive efficacy. Members considered that the reasons for differences include participant selection, closer supervision and closer monitoring in trials; also, real-life use of implants and IUDs may be less successful due to problems with insertion by a variety of inserters, compared to the 'expert inserters' usually involved in clinical trials.

2.18. The Subcommittee noted the provisional, unpublished, results of the Ministry of Health's 2014-2015 Reproductive Health Survey, which found 38.1% of New Zealand women of reproductive age used no contraception. Members also noted that this is supported by the data in the 2015 Report of the Abortion Supervisory Committee, where the Subcommittee noted that in 54.7% of the 2014 abortions, no contraception was used. Members considered that there was a need to raise awareness of contraception and the range of options available with women of childbearing age.

2.19. The Subcommittee noted that the 2015 Report of the Abortion Supervisory Committee on abortion rates in New Zealand. Members considered that abortion rates were a surrogate measure of unintended pregnancy rates in New Zealand. Members noted that in this report the increased use of LARCs, which includes subdermal implants, was identified as a factor leading to the decline in abortion numbers. Members noted that 44% of abortions in 2014 occurred in women 24 years of age and younger, suggesting a high need for effective contraception in this age group.

2.20. Members considered that it would be useful to raise awareness of the long-acting contraceptive options available for women, particularly as members' clinical experience is that sterilisation is sometimes seen by women as the only effective long-term contraceptive option available. The proposed BPAC article about contraception could be one channel for communicating this information. Members considered that

there is also a contraception education and awareness role for the broader health sector.

2.21. The Subcommittee noted the New Zealand study by Rose et al (Contraception 2010;82:345-53) showed a significant increase in the uptake of LARC by women post-abortion, with close to a six-fold increase in use of LIUS accounting for this significant difference. This study found that when information about long-acting contraception was provided, and the cost barrier removed, LIUS was the LARC method favored by 36% of post-abortion women. Members noted that the subdermal implant was not available at this study clinic. Members noted that contraceptive method retention at six months was 81% for LIUS, 74% for copper IUD and 71% for medroxyprogesterone depot.

2.22. The Subcommittee noted the NICE 2014 Guidelines on Long-acting Reversible Contraception, which state that all LARCs including the LIUS, are more cost-effective than oral contraceptives, even if the LIUS is removed after one year.

2.23. The Subcommittee noted the Mavranezouli and Wilkinson (J Fam Plann Reprod Health Care 2006;32:3-5) UK economic analysis, which showed medroxyprogesterone depot was the least cost effective for time frames longer than 1 year, as it prevented a lower number of unintended pregnancies and incurred higher costs compared to LARCs. The Subcommittee noted that the subdermal implant was the most effective but most costly of the remaining LARCs, but the additional costs associated with the implant relative to the copper IUD and LIUS greatly reduce as duration of contraceptive use increases. The Subcommittee noted that the copper IUD was the least costly but also the least effective option for most time frames examined. The LIUS was ranked between the copper IUD and the subdermal implant regarding associated costs and outcomes. Discontinuation was identified by members as a major driver of the relative cost effectiveness of the IUD, IUS and implant.

2.24. The Subcommittee noted PHARMAC's estimated number of women (24,000) who might switch from their existing form of contraception to LIUS. However, members considered that this was an over-representation as the figure did not take into account personal choice and preferences, such as women opposed to foreign devices or hormones in their bodies. Members considered that 10 to 20% of users might switch from an oral contraceptive, depot or implant to LIUS.

2.25. Members considered that if the LIUS were to be funded for contraception there would be a number of women who would switch from a copper IUD or oral contraceptive to using LIUS as their contraceptive of choice. The Subcommittee considered that clinically defining and quantifying this population is very difficult. Members advised that about half of women using a copper IUD might choose the LIUS, but noted that some women may still prefer a copper IUD as a non-hormonal form of long-acting contraception.

2.26. The Subcommittee discussed whether LIUS offered greater contraceptive efficacy over other available LARCs. Members considered that LIUS has greater contraceptive efficacy than medroxyprogesterone depot, and similar efficacy to copper IUD and levonorgestrel subdermal implants. Members considered that there needs to be a range of funded contraceptive options available for women.

2.27. The Subcommittee noted that in March 2016, the Medicines Adverse Reactions Committee (MARC) advised that subdermal levonorgestrel implants were less effective after four years in women over 60 kilograms and that current evidence was insufficient to determine at what time point efficacy may be reduced. The Subcommittee noted that MARC's advice is that patients over 60 kg should be informed of their option to replace

the implants after four years rather than five, due to reducing levonorgestrel concentrations with increasing weight and time. Members felt that the evidence to support this recommendation was weak and that economic evaluation did not need to take this into account.

2.28. The Subcommittee considered that if LIUS were to be funded in the community for contraception, it was their opinion this would decrease demand on secondary care services as there would be fewer terminations, fewer unintended pregnancies, fewer referrals to gynaecology services for heavy menstrual bleeding (that do not meet the current criteria for funded LIUS), and decreased incidence of bleeding-related iron deficiency and anaemia.

2.29. The Subcommittee noted that time resource is required by health providers undergoing insertion training and considered that removal of LIUS is less resource-intense as women can have it taken out at the time of cervical screening.

2.30. The Subcommittee noted that LIUS insertion costs could be a barrier to uptake of LIUS; and that access to trained inserters is likely to be a significant barrier for many rural women, especially if more than one visit is required.

2.31. The Subcommittee considered that the benefits of LIUS are effective long-acting reversible contraception in conjunction with less propensity to exacerbate heavy menstrual bleeding that can occur with copper IUDs. Additionally, the Subcommittee considered that, like the levonorgestrel implant, LIUS have very low contraceptive failure rates and due to their long-acting nature can mitigate adherence issues. Members considered that for these reasons, LIUS provide a useful contraceptive option for women of child-bearing age, in addition to the currently funded contraceptives.

2.32. The Subcommittee considered that widening access of LIUS as a funded contraceptive could be particularly beneficial to women unable to use (due to contraindications) or tolerate (due to side effects) other LARCs. Members noted that it may be difficult to predict the side effect profile that an individual woman may experience with each LARC.

2.33. Members also considered that there are other patient groups, such as women who have had terminations and young women at high risk of unintended pregnancy, who may benefit from access to LIUS as a contraceptive, but members recognised that it may be difficult to clinically define why the already funded LARCs are unsuitable for these groups.

2.34. The Subcommittee considered that funding of both a three-year and a five-year LIUS device could be appropriate to accommodate women's plans to bear children and improve cost-effectiveness. However, members noted that as the three-year LIUS would need more frequent replacement, this may be associated with higher risks of expulsion and infection (risks that are highest following insertion).

3. Levonorgestrel Intrauterine Systems for Heavy Menstrual Bleeding, Endometrial Hyperplasia and Endometriosis

Application

3.1. The Subcommittee reviewed a funding application from four health professional organisations, being the NZNO, RANZCOG, RNZCGP and Family Planning New

Zealand, to widen access to levonorgestrel intrauterine systems by relaxing the restrictions for heavy menstrual bleeding, community funding for endometriosis and inclusion of a new indication of endometrial hyperplasia without atypia.

Recommendation

3.2. The Subcommittee **recommended** that access be widened to levonorgestrel intrauterine systems, with a high priority, for women with heavy menstrual bleeding, endometrial hyperplasia without atypia, and endometriosis in the community.

Discussion

3.3. The Subcommittee noted that levonorgestrel intrauterine systems (LIUS) is currently funded in community and hospital for women with HMB who meet certain clinical criteria (including a serum ferritin level of <16 mg/l or a haemoglobin level of <120 g/l) and in DHB hospitals only for patients with a clinical diagnosis of endometriosis confirmed by laparoscopy.

3.4. The Subcommittee noted that the Mirena brand of LIUS is approved by Medsafe for the treatment of idiopathic menorrhagia provided there is no underlying pathology; and prevention of endometrial hyperplasia during oestrogen replacement therapy; and as a contraceptive. The Subcommittee noted that there are also two other Medsafe approved brands of LIUS but that only Levosert (52 mg levonorgestrel) is also approved for the treatment of heavy menstrual bleeding for up to three years.

3.5. The Subcommittee noted that applicants considered the only risks associated with LIUS are related to insertions where there is a 1-6/1000 perforation rate, 5% expulsion rate, <1% infection rate, and a higher ectopic pregnancy rate in the event of failure; however, the Subcommittee considered these would be similar with all intra-uterine devices.

Heavy Menstrual Bleeding (HMB)

3.6. The Subcommittee noted that HMB is a common and disruptive condition for many New Zealand women, which is currently thought to affect around 10% (110,000) of women. Members considered that between 2 and 4% of women aged < 50 years of age will consult their general practitioner each year with menstrual problems and around 25% of all referrals to gynaecology outpatient clinics are for menstrual problems. The Subcommittee advised that HMB resolves after menopause.

Endometriosis

3.7. The Subcommittee noted that endometriosis is a common non-malignant disorder which can cause dysmenorrhea, dyspareunia, chronic pain, and infertility. The Subcommittee considered it was difficult to determine the prevalence of endometriosis in the general population because many women are asymptomatic. Members noted that for women with symptoms, presentations can be varied and nonspecific with symptoms ranging from minimal to debilitating, and women are often managed symptomatically rather than having surgery to confirm the diagnosis.

3.8. The Subcommittee considered that pelvic pain was often a symptom of endometriosis, which if left untreated could lead to chronic pelvic pain. Members considered that the majority of women with endometriosis presented with pelvic pain.

Endometrial hyperplasia

3.9. The Subcommittee noted that endometrial hyperplasia typically presents with abnormal menstrual bleeding and is most common in women who are peri-menopausal and rarely found in women younger than age 30. The Subcommittee considered that HMB was often a symptom of endometrial hyperplasia, although many women would not seek treatment for their HMB. Members considered that a proportion of this population would be eligible for funded LIUS under the currently HMB access criteria.

3.10. Members noted that women with high body mass index (BMI) have an increased risk of endometrial hyperplasia and endometrial cancer and, therefore, Māori and Pacific women are at higher risk of endometrial disorders.

3.11. The Subcommittee noted that funding for LIUS for atypical endometrial hyperplasia was not requested and is not a registered indication. The Subcommittee considered that the presence of atypia was the most important indication of the risk of endometrial carcinoma. Members considered that the prevalence of endometrial hyperplasia was uncertain and it was also uncertain how many women with endometrial hyperplasia without atypia would progress to cancer.

3.12. The Subcommittee considered that there was an unmet health need for effective treatment for women with endometrial hyperplasia without atypia. Members noted that many women with symptoms of endometrial hyperplasia would generally not be managed in secondary care services and that this was currently a barrier for access to treatment.

Evidence for widening access to LIUS

3.13. The Subcommittee noted that the applicants provided a large number of published articles in support of widened access to LIUS. The Subcommittee noted that following as key points put forward by applicants in terms of non-contraceptive benefit from LIUS:

- LIUS and other LARCs enable women to manage their menstruation and contraceptive protection, enabling them to participate more fully in society (and undertake usual activities), whether that be in the workforce, education, community or family settings.
- Suitability for women with HMB who wish to use an IUD but for whom copper-containing IUDs are inappropriate due to increased bleeding. Copper IUD result in 50% greater blood loss due to increased duration and amount of menstrual bleeding.
- The LUIS is suitable for women with coagulation disorders who cannot use OCs.
- More predictable bleeding effects over copper IUDs or sub-dermal implants, as both these methods can result in prolonged menstrual bleeding, heavy bleeding, prolonged spotting or spotting between periods.
- LIUS (Mirena) provides up to a 94% reduction in menstrual blood loss at 12 months (Petta et al. Human Reprod 2005;20:1993-8, and Varma et al. Eur J Obstet Gynecol Reprod Biol 2008;139:169-75) and results in lower rates of anaemia and improved quality of life.
- Greater tolerance compared with levonorgestrel sub-dermal implants, which can cause unacceptable bleeding irregularities (erratic or worsening bleeding) in some women, resulting in removal of the implants from up to 18% of women in the first year (Roke et al. J Prim Health Care 2016;8:13-19).

- More effective for endometrial hyperplasia without atypia than cyclical progestogens compared to continuous oral therapy and LIUS (Orbo et al. BJOG 2014;121:477-86). Lowered hysterectomy rate and achieved a higher regression than oral progesterone (El Behery et al. Reprod Sci 2015;22:329-34).
- Suitability for women with high BMI (greater than 35), unlike COCs which are contraindicated. The LIUS is also more suitable for obese women than the copper IUD, due to protective effect on endometrium from long term exposure to higher oestrogen levels associated with obesity (Grimes et al. Contraception 2005;72:1-4).
- Reduced risk of progression to hyperplasia with atypia and endometrial cancer, especially for women with high BMI (for reasons noted above). The LIUS (Mirena) is associated with a 50% risk reduction in endometrial cancer (Soini et al. Obstet Gynecol 2014;124:292-9).

3.14. The Subcommittee noted the Effectiveness and Cost-Effectiveness of Levonorgestrel-Containing Intrauterine System in Primary Care against Standard Treatment for Menorrhagia (ECLIPSE) randomised trial compared clinical effectiveness of LIUS with usual medical treatment (tranexamic acid, mefenamic acid, combined oestrogen-progestogen, or progesterone alone) in the primary care setting in 571 women with menorrhagia (Gupta et al. NEJM 2013;368:128-37).

3.15. The Subcommittee noted that patients were eligible if between 25-50 years and had presented to primary care with menorrhagia involving at least 3 consecutive menstrual cycles and had normal endometrial biopsy (if had heavy, irregular bleeding). Members noted exclusion criteria included if they intended to become pregnant over the next 5 years, or had contraindications to or a preference for either LIUS or usual medical treatments.

3.16. The Subcommittee noted that the primary outcome was the patient reported score on the Menorrhagia Multi-Attribute Scale (MMAS) ranging from 0-100 with lower scores indicating greater severity assessed over a 2-year period. The Subcommittee noted that MMAS scores were reported to have improved from baseline in both arms but were greater in the LIUS group both overall (mean group difference 13.4 points), in all MMAS domains (practical difficulties, social life, family life, work and daily routine, psychological well-being, and physical health), and 7/8 quality of life domains. Members noted that at 2 years, continuation with LIUS was higher (64%) than usual medical treatment (38%) and there was no difference in adverse events.

3.17. The Subcommittee considered that the LIUS was more effective than other funded medical treatments for HMB, particularly in terms of improving quality of life.

3.18. The Subcommittee considered that defining HMB on the basis of measured blood loss was not clinically appropriate, as demonstrated by the eligibility criteria in published clinical trials such as Gupta et al (2013) which do not include this as a requirement. The Subcommittee noted that in the UK NICE defines HMB for clinical purposes as “excessive menstrual blood loss which interferes with the woman's physical, emotional, social and material quality of life, and which can occur alone or in combination with other symptoms”. Members noted that NICE also notes any intervention should aim to improve quality of life, rather than focus in terms of absolute menstrual blood loss.

3.19. The Subcommittee considered that if the objective blood test measures were removed from the current access criteria for LIUS for HMB there would likely be around a 50% increase in use. Members noted that uptake was unlikely to be higher as currently

many women, even if they meet current criteria, put up with their HMB symptoms rather than seeking treatment or prefer alternate treatments.

3.20. The Subcommittee noted that use of LIUS in some DHB hospitals is currently broader than the current funding criteria allow. The Subcommittee considered that this had introduced inequities of access to LIUS. The Subcommittee considered that widened access to funded LIUS in the community would be preferred to reduce time delays and costs associated with secondary care services, however, widened access in the hospital only would help to reduce the current regional differences in access to LIUS.

3.21. The Subcommittee noted that there were costs for patients associated with insertion and removal of LIUS in primary care, which represented a barrier to access for some patients. The Subcommittee noted that the Ministry of Health currently has a programme to assist with these costs, however, uptake had been limited. Members considered that the low uptake may be due to the multi-step process for accessing this funding.

3.22. The Subcommittee considered that funding LIUS in the community for the proposed population of women may be a significant new investment for PHARMAC and it would be appropriate to run a competitive process that would result in reduced pricing for either a 3-year or 5-year LIUS.

3.23. The Subcommittee considered it would be valuable to prompt consideration of women's fertility plans in the next 2 years by including a criterion regarding this in the access criteria for LIUS, noting that the longer LIUS remained in place to provide benefit the more cost-effectiveness would improve.

3.24. The Subcommittee considered that the populations that would benefit most from widened access to LIUS for HMB, endometrial hyperplasia without atypia and endometriosis would be those with a history of abnormal menstrual bleeding (with or without chronic pelvic pain) that impacts on their quality of life, and has not responded to other medical management options or other medical options are not appropriate.

4. Lactic acid and Thymol Gel for Bacterial Vaginosis

Application

4.1. The Subcommittee reviewed a funding application from TeArai BioFarma Limited for Lactigel (5% lactic acid and 1% thymol plus glycogen hydrogel) for the treatment of bacterial vaginosis.

Recommendation

4.2. The Subcommittee **recommended** that the application for Lactigel for the treatment of bacterial vaginosis be declined.

Discussion

4.3. The Subcommittee considered that bacterial vaginosis (BV) results from an overgrowth of certain bacteria (*Gardnerella*, *Bacterioides* etc) and is a common vaginal flora imbalance that is often asymptomatic and often spontaneously resolves. Members considered that best practice is to leave asymptomatic or mild BV untreated as it usually self-resolves.

4.4. The Subcommittee advised that the healthy vaginal microbiome, and its disruptive factors, have been under-studied for many years but this is now an area of rapidly evolving medical knowledge, including determining the importance of vaginal biofilms and this would likely influence clinical management of BV in the near future.

4.5. The Subcommittee noted that many of the clinical studies supplied as supporting information with the application were neither large nor recent and had relatively short-term follow up. Members considered that longer term studies, with better diagnostic criteria, would be more appropriate given that BV can spontaneously resolve and also frequently recurs. Members discussed the studies and noted that several of the studies did not include the same active ingredient/s as those in Lactigel.

4.6. The Subcommittee noted that the Andersch et al (Gynaecol Obstet Invest 1986:21; 19-25) study on treatment of BV with lactate-gel compared to oral metronidazole did not use the standard accepted current diagnostic criteria or treatment. Members considered that the end points of being symptom-free and diagnosis of *Gardnerella* to be inappropriate for demonstrating effectiveness of BV treatment.

4.7. The Subcommittee considered that the Decena et al (J Obstet Gynaecol Res 2006:32;243-51) study comparing BV treatment with lactic acid gel, oral metronidazole or both was open-label, short term and the findings suggested adjunctive treatment was superior.

4.8. The Subcommittee noted Milani et al (Eur J Obstet Gynaecol Repro Bio 2003:109;67-71) study compared vaginal clindamycin to oral tinidazole plus an acidic buffering vaginal gel. While there was a four-week follow-up, Members considered the treatment combination not to be relevant to the proposal for funding of Lactigel.

4.9. The Subcommittee considered that there were small participant numbers in the Holst and Brandberg (Scand J Inf Dis 1990:22;625-26) and Andersch et al (Gynecol Obstet Invest 1990:30;114-19) studies, n = 10 and n = 43, respectively.

4.10. The Subcommittee noted that the Andreeva et al (Akush Ginekol 2002:41;36-9) study of 45 patients used adjunctive treatment comprising vaginal metronidazole with a vaginal lactic acid tablet, and a comparison included lactic acid shampoo. Members considered that these treatments were not relevant to the proposal for funding of Lactigel.

4.11. The Subcommittee noted the Fredstorp et al (J Infect Non Infect Dis 2015:1;005) study used sustained-release oligomeric lactic acid pessary. Members considered this study not to be relevant to the proposal for funding of Lactigel.

4.12. The Subcommittee considered that the Swidsinski et al (Arch Gynaecol Obstet 2012:285;1619-25) study of recurrent *E.coli* cystitis in 20 women was not relevant to the funding application for Lactigel, nor was the Jones & Bayard (Gynaecologia 1960:149;128-38) study treating vaginal trichomoniasis.

4.13. The Subcommittee considered that the Ferris et al (J Fam Pract 1995:41;443-49) study was irrelevant in terms of the funding application for Lactigel as it did not use any lactic acid treatments.

4.14. The Subcommittee noted that while the Eusaph et al (J Pak Med Assoc 2016: 66; 521-527) was a recent publication and included over 900 women, the study treatment product was an external wash containing lactic acid and lactoserum, therefore members considered this study not to be relevant to the funding application for Lactigel.

The Subcommittee considered the Bahamondes et al (Rev Assoc Med Bras 2011:57;415-20) study was also not relevant for this same reason.

4.15. The Subcommittee considered the Holley et al (Sex Trans Dis 2004:31;236-38) study not to be relevant to the funding application for Lactigel as it used an acetic acid vaginal gel as the comparator to placebo treatment.

4.16. The Subcommittee noted the NICE 2008 Guideline on Antenatal Care for Uncomplicated Pregnancies, which states that "Pregnant women should not be offered routine screening for bacterial vaginosis because the evidence suggests that the identification and treatment of asymptomatic bacterial vaginosis does not lower the risk of preterm birth and other adverse reproductive outcomes". Members considered that the literature on the role of BV in pre-term birth is ambivalent.

4.17. The Subcommittee considered that the supplier's estimate of the New Zealand population of women with persistent BV to be an over-estimate as this would equate to 5,000 patients presenting for treatment each week. Members considered they do not see these numbers in their practices or clinics.

4.18. The Subcommittee acknowledged the importance of antimicrobial stewardship and the therapeutic value of an effective non-systemic topical treatment option for BV; however, members considered that they would need to see robust evidence for such a product. Members noted high-quality evidence is likely to be available in the future, given the renewed research interest in this field.

4.19. The Subcommittee noted that nonoxynol-9, a spermicidal lubricant, had been found to cause harm rather than benefit; specifically, it increased human immunodeficiency virus (HIV) transmission to women who were at high risk of HIV when they used the product frequently, and appeared to have no protective effect either against HIV or other STIs when used less frequently. The Subcommittee considered this highlights the critical need to ensure any new vaginal products do not cause harm. The Subcommittee noted the Verstraelen et al (PLoS ONE 2016;11:e0153441.) study provided by PHARMAC that included a robust safety assessment. While this study looked at a sustained release lactic acid-containing vaginal device, the Subcommittee considered that the safety of any product intended for vaginal use needs to be demonstrated by colposcopic monitoring according to the WHO/CONRAD guidelines for the evaluation of vaginal products. The Subcommittee considered that it would expect to see such (or similar) safety data for any new vaginal product to reassure that the product does not cause harm.

4.20. The Subcommittee considered that on balance, there is an absence of quality evidence for the health benefits and therapeutic efficacy of Lactigel. For these reasons, the Subcommittee recommended that the Lactigel application for bacterial vaginosis be declined for listing on the Pharmaceutical Schedule.

5. Clindamycin 2% Vaginal Cream for the Treatment of Desquamative Inflammatory Vaginosis

Application

5.1. The Subcommittee reviewed a funding application from a clinician for clindamycin 2% vaginal cream for the treatment of desquamative inflammatory vaginosis (DIV).

Recommendation

5.2. The Subcommittee **recommended** that clindamycin 2% vaginal cream be listed on the Pharmaceutical Schedule, with a high priority, for the treatment of desquamative inflammatory vaginosis.

Discussion

5.3. The Subcommittee noted that DIV is a rare chronic condition of unclear aetiology characterised by vaginal rash, inflammation, dyspareunia, and profuse discoloured (often green) discharge. Members noted that examination of vaginal walls reveals inflammation, erythema and petechiae. Members considered that DIV has a significant impact on quality of life due to its unpleasant symptoms.

5.4. One member advised that dermatologist peers tend to consider DIV to be immune-mediated, while gynaecologist peers suspect it is due to aerobic pathogen overgrowth; but consensus is that DIV is due to altered vaginal flora with aerobic overgrowth arising from epithelial damage.

5.5. Members noted that DIV occurs mainly in Caucasians, with peak occurrence in peri-menopause.

5.6. Members noted that DIV is mostly seen at tertiary clinics and by the time of diagnosis, patients may have had symptoms for 12 months or more, during which time there have been multiple GP visits and multiple therapies tried.

5.7. The Subcommittee considered that diagnosis of DIV is by exclusion of known infections and confirmed by the presence of cell breakdown observed on wet-mount microscopy; other diagnostic markers are vaginal pH above 4.5 and that vaginal flora are abnormal.

5.8. The Subcommittee considered that clindamycin 2% vaginal cream or (off-label) use of vaginal corticosteroids are effective for treating DIV.

5.9. The Subcommittee noted the Bradford and Fischer (J Low Genit Tract Dis 2010;14:306-10) study, where 95 out of 101 women with DIV were treated low doses of clindamycin 2% vaginal cream; and the remaining women used mupirocin 2% cream applied vaginally. The Subcommittee noted that the mean duration of symptoms before diagnosis was 3.4 years and that after four weeks of treatment, 95% of all the women experienced improvement in DIV symptoms, and 55% had not relapsed at three months.

5.10. The Subcommittee noted the Sobel et al (Obstet Gynecol 2011;117:850-5) chart review of 98 DIV cases, where 53 women were treated with clindamycin 2% vaginal cream and 45 women were treated with 10% hydrocortisone administered vaginally. The Subcommittee noted that at the 3-week follow-up, 85.7% of all women were asymptomatic or had dramatic improvement. More women in the clindamycin group had success with their treatment, although the Subcommittee noted the authors advised caution in interpreting these findings due to inconsistent recruitment criteria for allocating treatment.

5.11. One member advised that about four patients with DIV present to their clinic annually, and in their experience clindamycin 2% vaginal cream is effective in managing vaginal discharge, while vaginal hydrocortisone (off-label use of rectal formulation) is useful for anti-inflammatory maintenance to prevent relapse. The member noted that in their region, one pharmacy dispenses an average of one prescription for compounded clindamycin 2% vaginal cream each week for treatment of DIV or bacterial vaginosis.

5.12. The Subcommittee noted that all women in New Zealand being treated with clindamycin 2% vaginal cream for DIV were self-funding.

5.13. The Subcommittee considered that there was a high health need for patients with DIV due to the extent to which symptoms can affect quality of life and the lack of availability of effective alternative funded treatments. Members acknowledged the likelihood that there will never be an extensive evidence base for DIV treatments due to the low prevalence of DIV.