Record of the Reproductive and Sexual Health Subcommittee of PTAC
Meeting held on 1 November 2021

Reproductive and Sexual Health 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 Reproductive and Sexual Health Subcommittee meeting; only the relevant portions of the meeting record 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.

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

The record of this Subcommittee meeting will be reviewed by PTAC at an upcoming 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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1. Attendance

Present

Simon Wynn Thomas
Rhiannon Braund
Debbie Hughes
Jane Morgan
Ian Page
Helen Paterson
Christine Roke

2. The role of PTAC Subcommittees and records of meetings

2.1. This meeting record of the Reproductive and Sexual Health 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 Reproductive and Sexual Health Subcommittee is a Subcommittee of PTAC. The Reproductive and Sexual Health Subcommittee and PTAC and other PTAC Subcommittees have complementary roles, expertise, experience, and perspectives. The Reproductive and Sexual Health Subcommittee and other PTAC Subcommittees may therefore, at times, make recommendations for treatments for Reproductive and Sexual Health 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 Reproductive and Sexual Health that differ from the Reproductive and Sexual Health Subcommittee's, or PTAC Subcommittees may make recommendations that differ from other PTAC Subcommittees'.

Pharmac considers the recommendations provided by both the Reproductive and Sexual Health Subcommittee and PTAC and any other relevant PTAC Subcommittees when assessing applications for treatments for Reproductive and Sexual Health.

3. Matters Arising

Lidocaine with prilocaine for IUD insertion

3.1. The Subcommittee noted that lidocaine with prilocaine cream is currently only funded in the community for children with a chronic medical condition requiring frequent injections or venepuncture. The Subcommittee noted that in June 2021, Pharmac consulted on declining funding applications to widen access to lidocaine with prilocaine cream in the community (to open list and for pain) following decline recommendations from PTAC.

3.2. The Subcommittee considered that there is currently an unmet health need for pain management during intrauterine device (IUD) insertion and that this unmet need could be somewhat met by the availability of lidocaine with prilocaine cream.

3.3. The Subcommittee noted the following evidence for lidocaine with prilocaine use during IUD insertion:

3.3.1. A systematic review and network meta-analysis evaluating different pain lowering medications during intrauterine device insertion (Samy et al. Fertil Steril. 2019;111).

3.3.2. An expert opinion publication regarding the impact on pain of lidocaine in IUD insertion (Lerman and Nunes. EBP. 2021;24:38-9).

3.3.3. A randomised double-blind controlled trial of cervical lidocaine-prilocaine cream on pain perception during copper IUD insertion (Abbas et al. Contracept Elsevier Inc. 2017;95:251–6).

3.4. The Subcommittee noted the New Zealand Aotearoa's guidance on contraception (Ministry of Health 2020). This notes that the United Kingdom's Faculty of Sexual and Reproductive Healthcare does not recommend routinely using topical lidocaine, misoprostol, or nonsteroidal anti-inflammatory drugs to improve ease of insertion or reduce pain during the insertion of IUC. The Subcommittee also noted that New Zealand Family Planning similarly does not recommend the routine use of topical pain relief agents, with oral analgesia (paracetamol and/or ibuprofen) instead recommended to be taken prior to insertion.

3.5. The Subcommittee noted that currently lidocaine urethral syringes are available on Practitioners Supply Order (PSO) and can be used for cervical administration. A cervical or paracervical block is not commonly used in the community. Members noted that misoprostol may also be used, however considered that none of these treatments adequately meet the health need for pain management associated with IUD insertion in the community.

3.6. The Subcommittee noted that lidocaine with prilocaine should not be used routinely for IUD insertion and that likely uptake would be a significant minority of all IUD insertions. Members considered that it would most likely be used, and the most benefit gained, in situations where an individual is hesitant to receive an IUD due to fear and/or anxiety of associated pain, and those anticipated to experience

difficulties during insertion. Members considered that 2 ml (one 5 g tube) of lidocaine with prilocaine cream would likely be required per procedure.

3.7. Members considered that there may be an element of placebo effect with lidocaine with prilocaine use during IUD insertion and that some benefit may also result from additional lubrication from the cream. However, noting that a barrier to IUD access is fear related to insertion, the Subcommittee considered that, on balance, the availability of an evidence-based treatment to reduce pain would improve equitable access to IUDs and further support uptake. The Subcommittee **recommended** that lidocaine with prilocaine cream be funded for intra-uterine device insertion, noting that availability of appropriate pain relief, with evidence of benefit, is likely to improve the acceptability of IUDs and positively impact equitable uptake in the community setting.

Tranexamic acid

3.8. The Subcommittee noted that in 2019, the Haematology Subcommittee of PTAC considered that an increase in tranexamic acid utilisation was most likely due to treatment for menorrhagia, and recommended that advice be sought from the Reproductive and Sexual Health Subcommittee.

3.9. The Subcommittee noted that in the community, tranexamic acid prescribing has been gradually increasing, with recent data suggesting that over 90% of those prescribed it are female. The Subcommittee noted that a large proportion of use was in those aged 30-49 years.

3.10. The Subcommittee considered that the increase in use was for use in menorrhagia. Members considered that this was likely due to a range of reasons including a service shift to primary care and increasing clinician familiarity with tranexamic acid, influencing comfort in prescribing. Members also noted that menorrhagia is associated with higher body mass index (BMI); Members considered that as the average BMI increases in the population, in combination with increased recognition of menorrhagia, has likely influenced increased prescribing of tranexamic acid.

3.11. The Subcommittee noted that tranexamic is an appropriate treatment for menorrhagia, with suitability benefits of it being a non-hormonal treatment, and the requirement for use only when bleeding (rather than consistently, as with hormonal treatments). Members considered that, while the use of tranexamic acid is generally a positive intervention as it reflects appropriate treatment, there is the risk that its use without investigation (especially in older women with irregular bleeding) might miss potentially harmful conditions such as endometrial hyperplasia.

4. Therapeutic Group Review

Update on funding decisions

4.1. The Subcommittee noted the update on funding decisions since the last Reproductive and Sexual Health Subcommittee meeting, which included the removal of funding restrictions for Mirena (levonorgestrel intrauterine system, LIUS) and the funding of a lower-strength IUS (Jaydess) in late 2019, and the funding of mifepristone in the community in response to the Abortion Legislation Act 2020.

4.2. The Subcommittee noted that pharmaceutical expenditure in this therapeutic group is increasing over time, especially following the funding of LIUS.

4.3. The Subcommittee considered that, while the funding of products such as LIUS and mifepristone was positive, inequities continue to be present in the access to and use of these agents. The Subcommittee noted that this was predominantly due to other expenses borne by the patient and the healthcare system such as cost of insertion of the IUS, and all abortion services (beyond the medicine) which are not consistently funded by all DHBs.

Outstanding funding applications

4.4. The Subcommittee noted the outstanding funding applications in reproductive and sexual health.

Long-acting reversible contraceptives (LARCs)

4.5. The Subcommittee noted that there is variation in the funding by DHBs for insertion costs in a range of circumstances. The Subcommittee noted that uptake of LARCs would increase further if there was comprehensive funding for insertion services across New Zealand.

4.6. The Subcommittee noted that it was difficult to audit the rates of early removal of LARCs, as many patients move between DHBs for these services, and that there are many possible reasons for early removal.

4.7. The Subcommittee noted that Mirena and Jaydess are not currently available on Practioners Supply Order (PSO), however considered this would be appropriate.

Oral contraceptives

4.8. The Subcommittee noted that there have been a number of supply issues for oral contraceptives, primarily due to COVID-19-related supply disruptions.

4.9. The Subcommittee noted that there is a private market in New Zealand, as well as substantial use overseas, of a progestogen-only contraceptive pill, desogestrel. The Subcommittee considered that desogestrel has preferable suitability over other progestogen-only preparations as it suppresses ovulation more effectively and has a 12-hour leeway for a missed dose. The Subcommittee **recommended** that desogestrel be funded and considered that most people taking the currently funded progestogen-only preparation (norethisterone, branded as Noriday) would change to desogestrel if it were funded.

4.10. The Subcommittee noted that ethinyloestradiol with drosperinone has also been approved in New Zealand for some time, although Pharmac has never received a funding application. The Subcommittee considered that there were safety concerns with this medicine regarding the risk of venous thromboembolism.

4.11. The Subcommittee noted that combined oral contraceptives are less commonly prescribed as per the ‘standard’ calendar packs (ie. 21 days active, 7 days inert) than in previous years. Members considered that there are three other dosing regimens commonly used in New Zealand: continuous dosing (only taking active tablets), tri-cycling (9 weeks active, 7 days inert) and four-day ‘breaks’ (24 days active, 4 days inert). Members noted that tri-cycling is currently the most common regimen used. As such, the Subcommittee considered that there was still a need for products which contained inert tablets, however that access to products without inert tablets was also beneficial.

Medroxyprogesterone acetate

4.12. The Subcommittee noted that the use of medroxyprogesterone acetate injection has remained relatively steady for many years, with minimal change in use following the open listing of levonorgestrel implants and LIUS. The Subcommittee noted that, even though longer-acting alternatives are funded, medroxyprogesterone injections are preferred for some indications, especially due to superior efficacy in relation to the induction and maintenance of amenorrhea. The Subcommittee noted that medroxyprogesterone injections are especially beneficial for those for whom more invasive procedures may not be appropriate. Members also noted that medroxyprogesterone injections are particularly suitable for the induction and maintenance of amenorrhea for transgender individuals, particularly when there is preference to not use oestrogen-based treatments.

4.13. Members noted that overseas, subcutaneous medroxyprogesterone injections which can be self-administered are available. Members considered that such a presentation may assist in equitable access to appropriate treatments, particularly for rural populations.

Emergency contraception

4.14. The Subcommittee noted that the use of levonorgestrel 1.5 mg tablets has steadily increased and is trending for a continued rise. The Subcommittee noted a substantial increase in funded use was observed from late 2017 following the availability of funded access to levonorgestrel tab 1.5 mg on the prescription of a pharmacist.

4.15. Members considered that, while levonorgestrel use is trending up, the somewhat recent advances in availability of LARCs, and pharmacist prescribing of oral contraceptives (although currently only a private market), may result in a reduced need for emergency contraception. Members considered that the ability of pharmacists to adequately counsel individuals at the time of emergency contraceptive prescription, and prescribe oral contraceptives, was positive.

4.16. The Subcommittee considered that the requirement for a double dose of levonorgestrel for patients weighing over 70 kg may be playing some role in the increased use observed over time. The Subcommittee noted that there is little to no evidence that double dosing of levonorgestrel for emergency contraceptive is efficacious in individuals weighing over 70 kg, and as a result that there may be unmet health need for this population. Members considered that this health need may be better met with other agents such as mifepristone or ulipristal, which are better supported by evidence for this indication compared to current available treatment. The Subcommittee noted that mifepristone is currently only available on PSO and that Pharmac has not received a funding application for ulipristal for this indication.

Condoms

4.17. The Subcommittee noted that from late 2019, the number of funded condoms available on PSO has reduced and that this, in combination with COVID-19 lockdowns, has resulted in a substantial decrease in the number of condoms dispensed. Members considered that the general reduction in GP visits from COVID-19 lockdowns has reduced the opportunities to give prescriptions for condoms.

4.18. The Subcommittee noted, excluding the above reasons, that funded condom use has seen a substantial reduction over time, and considered that the funding of long-acting contraceptives and PrEP, have had a significant impact on this. The Subcommittee also noted that the current cohort of teenagers are less sexually active than previous generations.

4.19. The Subcommittee noted that, while recent New Zealand data were not available, anecdotally condom use by men who have sex with men (MSM) has significantly reduced in recent years, and condom use in the MSM population group is now estimated to be comparable to that of heterosexual male condom use.

Medical Abortion

4.20. The Subcommittee noted that Pharmac funded mifepristone in the community in response to the Abortion Legislation Act 2020. Misoprostol, which was already funded in the community, was made available directly to clinicians under a PSO.

4.21. The Subcommittee considered that it would be advantageous to have a funded combination pack of misoprostol and mifepristone, particularly if approved for medical abortion. Members considered that a combination pack would improve safety and would assist in the prevention of dispensing errors compared to the individual products.

Other items

4.22. Members considered that there is currently an unmet health need for those experiencing miscarriage and that the use of mifepristone and misoprostol following miscarriage would improve current care.

4.23. The Subcommittee considered that reproductive and sexual health care is further shifting from secondary to primary health providers and that this comes with both benefits and challenges, notably that often costs can be shifted to the patient in primary care which presents equity issues.

4.24. The Subcommittee noted that pharmacological therapies for transgender individuals have been traditionally prescribed by specialist endocrinologists, however noted that GPs are gaining confidence in prescribing for this population, and that this may result in increased uptake in relevant treatments over time as access becomes available through GP visits.

5. Progesterone for recurring early pregnancy loss

Application

5.1. The Subcommittee noted a funding application from a clinician for the use of progesterone for recurring early pregnancy loss with vaginal bleeding.

5.2. The Subcommittee also noted that Pharmac was seeking advice regarding the current access criteria for progesterone for pre-term labour, and the potential removal of restrictions for progesterone.

Recommendation

5.3. The Subcommittee **recommended** that progesterone for recurrent early pregnancy loss be listed with a high priority within the context of treatment in reproductive and sexual health subject to the following Special Authority criteria:

Initial Application. Approvals valid for one year for applications that meet the following criteria:
All of the following:
1 Patient is pregnant; and
2 Patient has previously experienced three or more miscarriages; and
3 Patient has experienced bleeding in the first 12 weeks of pregnancy; and
4 Pregnancy is confirmed to be intrauterine and viable

Renewal Application. Approvals valid for one year for applications that meet the following criteria:
1 Treatment is required for a subsequent pregnancy

5.4. The Subcommittee made this recommendation based on the high health need of this patient population, evidence of benefit and the favourable safety profile of progesterone for this indication.

Discussion

5.5. The Subcommittee noted that recurrent early pregnancy loss/ miscarriage is historically defined as the loss of three of more clinically recognised pregnancies by the same partner, in the first 12 weeks of gestation. The Subcommittee noted that approximately 15% of clinically recognised pregnancies will miscarry, and that about 25% of women will have at least one miscarriage in their lifetime, with 0.4 -1.0% of women experiencing recurrent miscarriage.

5.6. The Subcommittee noted that miscarriage causes significant emotional distress for the parents, families and whānau, and also noted that there is no clear data about ethnic differences in miscarriage rates in New Zealand. The Subcommittee noted that the care and management of women with recurrent miscarriage is within the scope of all gynaecology departments, however that access to secondary care can have barriers and often treatment occurs in primary care. The Subcommittee noted that while weekly ultrasound scanning from 6 – 12 weeks gestation has been shown to improve live birth rates, it is not commonly employed in New Zealand due to resource constraints.

5.7. The Subcommittee noted that the application specified that progesterone treatment would be initiated from the first time of episode of bleeding (following confirmation that pregnancy location was intrauterine, viable and ongoing) and stopped at 16 weeks gestation.

5.8. The Subcommittee noted that progesterone capsules have all the properties of endogenous progesterone with induction of a full secretory endometrium and in particular gestagenic, antiestrogenic, slightly antiandrogenic and anti-aldosterone effects. The Subcommittee also noted that progesterone is not currently Medsafe approved for recurring pregnancy loss and is currently only approved for adjunctive use with an oestrogen in postmenopausal women with an intact uterus (for hormone replacement therapy). The Subcommittee noted that the proposed dosing regimen for progesterone for recurrent early pregnancy loss is 400 mg progesterone being inserted into the vagina (or rectum if preferred) twice daily. The Subcommittee considered that it would be preferable if a higher dose capsule were available, noting the requirement for multiple capsules to be administered every day, however acknowledged that no higher dose capsules were currently approved in New Zealand.

5.9. The Subcommittee noted the following evidence in relation to the use of progesterone in recurrent early miscarriage:

5.9.1. Coomarasamy et al. Health Technol Assess. 2020;24: the multicentre, double-blind, placebo-controlled, randomised PRISM trial of over 4,000 women aged 16–39 years with early pregnancy bleeding treated twice-daily vaginal suppositories containing either 400 mg of progesterone or a matched placebo. The live birth rate was 75% in the progesterone group and 72% in the placebo group (relative rate (RR) 1.03, 95% confidence interval 1.00 to 1.07; p = 0.08). Subgroup analysis by previous number of miscarriages showed that for women with three or more prior miscarriages, 72% in the progesterone group had live births, compared to 57% in the placebo group (RR 1.28, 95% CI 1.08 to 1.51; p = 0.004).

5.9.2. Coomarasamy et al. Health Technol Assess. 2016;20:1-92: the randomised, double-blind, placebo-controlled, international multicentre PROMISE trial of women with unexplained recurrent miscarriage, aged 18 to 39 years, conceiving naturally who were treated twice daily 400 mg progesterone vaginally or placebo. The live birth rate in the progesterone group was 65.8% (262/398) and in the placebo group it was 63.3% (271/428), giving a relative risk of 1.04 (95% CI 0.94 to 1.15; p=0.45). No significant differences in clinical pregnancy at 6–8 weeks, ongoing pregnancy at 12 weeks, miscarriage, gestation at delivery, neonatal survival at 28 days of life, congenital abnormalities and resource use were observed.

5.9.3. Wahabi et al. Cochrane Database of Systematic Reviews. 2018, 8. DOI: 10.1002/14651858.CD005943.pub5: a review of randomised, quasi-randomised or cluster-randomised controlled trials that compared progestogen with placebo, no treatment or any other treatment for the treatment of threatened miscarriage in women carrying singleton pregnancy. Treatment of miscarriage with progestogens compared to placebo or no treatment probably reduces the risk of miscarriage; (risk ratio (RR) 0.64, 95% confidence interval (CI) 0.47 to 0.87; 7 trials; 696 women; moderate-quality evidence). Treatment with oral progestogen compared to no treatment also probably reduces the miscarriage rate (RR 0.57, 95% CI 0.38 to 0.85; 3 trials; 408 women; moderate-quality evidence). However, treatment with vaginal progesterone compared to placebo, probably has little or no effect in reducing the miscarriage rate (RR 0.75, 95% CI 0.47 to 1.21; 4 trials; 288 women; moderate-quality evidence).

5.10. The Subcommittee were also made aware of the following additional information relating to progesterone and progestogens for early recurrent pregnancy loss:

5.11. Haas et al. Cochrane Database of Systematic Reviews. 2019, 11. DOI: 10.1002/14651858.CD003511.pub5: a review of randomized or quasi-randomized controlled trials comparing progestogens with placebo or no treatment given in an effort to prevent miscarriage. The evidence suggests that there may be a reduction in the number of miscarriages for women given progestogen supplementation compared to placebo/controls (average risk ratio (RR) 0.73, 95% confidence interval (CI) 0.54 to 1.00, 10 trials, 1684 women, moderate-quality evidence). There was potentially a slight benefit for women receiving progestogen seen in the outcome of live birth rate (RR 1.07, 95% CI 1.00 to 1.13, 6 trials, 1411 women, moderate-quality evidence), but there was uncertainty about the effect on the rate of preterm birth because the evidence was very low-quality (RR 1.13, 95% CI 0.53 to 2.41, 4 trials, 256 women, very low-quality evidence).

5.12. The Subcommittee noted that there is no evidence to suggest that progesterone for the treatment of recurrent pregnancy loss causes any short term or long term adverse effects for the mother or baby.

5.13. The Subcommittee considered that the strength and quality of evidence was moderate; but considered that the nature of the indication means that better quality data will likely never be available. Members considered that the majority of data for most pregnancy related care is of a lower quality because higher quality evidence, such as randomised controlled trials, is not and will never be undertaken in this population group. The Subcommittee considered that it is therefore unrealistic to expect further randomised controlled data for indications such as recurrent pregnancy loss, and that not widening access to progesterone based on the quality of the data available would be inappropriate.

5.14. The Subcommittee noted that miscarriage care is mainly given in the primary healthcare setting, and that if access is widened to progesterone it should be available for primary healthcare providers, including midwives, to prescribe.

5.15. The Subcommittee noted that any benefits from progesterone would be highly impactful for parents and whānau experiencing recurrent early pregnancy loss, particularly for improved mental and social health. The Subcommittee considered that the access criteria should be the same as the entry criteria for the PRISM trial (i.e. previously experienced three or more miscarriages, has experienced bleeding in the first 12 weeks of pregnancy). The Subcommittee also considered that if a patient was prescribed progesterone while pregnant and did not experience a miscarriage, that clinicians would likely to prefer to prescribe progesterone again before any incidence of bleeding in any subsequent pregnancies.

5.16. The Subcommittee considered it would be reasonable to assume that progesterone would be initiated around week six of gestation. The Subcommittee considered that treating patients up to 16 weeks of gestation may be longer than necessary but were unsure of the optimal treatment duration.

5.17. The Subcommittee considered that currently there are limited options for people experiencing recurrent pregnancy loss in New Zealand and that widening access to progesterone for recurrent early pregnancy loss would improve the standard of care.

5.18. The Subcommittee considered that the below table summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for progesterone if it were to be funded in New Zealand for recurrent early pregnancy loss. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Subcommittee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	Pregnant individuals who have experienced three or more consecutive miscarriages, are experiencing bleeding in the first 12 weeks gestation, and have confirmed viable, intrauterine pregnancy.
Intervention	400 mg progesterone twice daily up to 16 weeks gestation
Comparator(s)	Best supportive care
Outcome(s)	1. Ongoing pregnancy 2. Live birth at term
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the patient population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.	

Pre-term labour

5.19. The Subcommittee noted that 300-400 individuals per year access progesterone for the prevention of pre-term labour for patients with a short cervix on ultrasound (defined as < 25 mm at 16 to 28 weeks) or a history of pre-term birth at less than 28 weeks. The Subcommittee noted a NICE review (NICE guideline. 2015), which recommended that progesterone should be offered for individuals who have had both a pre-term birth and have a short cervix in the current pregnancy and considered for those who have had pre-term birth or have a short cervix. The Subcommittee considered that this would also be an appropriate approach in New Zealand and that the current Special Authority restriction for this indication could be updated as appropriate.

Open listing

5.20. The Subcommittee considered that removing all funding restrictions for progesterone would allow use in the requested indication, as well menopausal hormone therapy, and hormone therapy for transgender individuals. Members noted that there is currently no evidence of benefit of progesterone in transgender individuals, however that there is demand for its use. The Subcommittee considered that the number of patients that would access progesterone if it was open listed over the range of indication is unknown but considered that the transgender population would make up about 3,000-5,000 people taking progesterone as a lifelong medication.

6. Ring pessaries – pelvic prolapse

Application

6.1. The Subcommittee considered an application from a clinician to widen the funding of ring pessaries for pelvic prolapse to include community funding.

Recommendation

6.2. The Subcommittee **recommended** that ring pessary for the treatment of symptomatic pelvic prolapse be listed with a high priority within the context of treatment in reproductive and sexual health with no restriction.

6.3. The Subcommittee made this recommendation based on the unmet health need for those who do not currently have access to treatment, the potential to improve health equity by increasing accessibility of ring pessaries, particularly for Māori and Pacific peoples, and the favourable cost-effectiveness compared to alternative treatments.

Discussion

6.4. The Subcommittee noted that ring pessaries for the treatment of pelvic prolapse are currently funded through DHB hospitals as devices, but not in the community, and that the current application is related to a service delivery and budget shift rather than availability of new treatment option.

6.5. The Subcommittee noted that international surveys suggest that 87% to 98% of clinicians report using pessaries in their clinical practice (Bugge et al. Int Urogynecol J. 2013;24:1017-24; Cundiff et al. Obstet Gynaecol. 200;95:931-5; Gorti et al. J Obstet Gynaecol. 2009;39:129-31; Pott-Grinstein E, Newcomer JR. J Reprod Med. 2001;46:205-8), while 77% of gynaecologists report using pessaries as a first-line treatment for prolapse (Cundiff et al. Obstet Gynaecol. 2000;95:931-5).

6.6. The Subcommittee noted that pelvic organ prolapse is common and can be detected in 40-50% of parous individuals although many may be asymptomatic, and is known to increase with age, meaning incidence may increase with New Zealand's ageing population. The Subcommittee noted that approximately 10% of women will have prolapse or incontinence surgery in their lifetime (Bugge et al. Cochrane Database of Systematic Reviews. 2020;11:DOI: 10.1002/14651858.CD004010.pub4). The Subcommittee noted that current treatment options include pelvic floor muscle training, lifestyle changes, pessary, or surgery, and that treatment choice depends on a number of factors including age, severity of symptoms, surgical history, treatment preference and cultural factors. The Subcommittee noted that clinicians are most likely to fit pessaries in women aged over 60 years or in those who are unfit for surgery.

6.7. The Subcommittee noted that current barriers to access in New Zealand include delays in availability of public gynaecology services in some areas, as well as limited specialist pelvic floor physiotherapists, and the cost of primary care and private services. The Subcommittee noted that there is significant variability nationwide in access to funding in community settings for ring pessaries, with some DHBs providing community-based funding.

6.8. The Subcommittee noted that symptomatic pelvic prolapse has a significant and negative impact on the individual including physical symptoms such as urinary, bowel, and sexual discomfort, as well as having a negative effect on body image, quality of life, mental wellbeing and the ability to perform daily activities, undertake work or recreational activities. The Subcommittee considered that there was a direct cost on family and whānau, such as the cost of continence products and primary healthcare services. The Subcommittee considered that Māori and Pacific women are likely disproportionately affected by pelvic floor prolapse (though there is no direct evidence for this) due to increased risk factors (eg. high parity, obesity rates, manual work), and have more limited access to treatment options. The Subcommittee also considered that there are other groups experiencing health disparities relating to pelvic prolapse, such as patients with disabilities, or those who are non-binary.

6.9. The Subcommittee considered that community funding of ring pessaries would have a positive impact on the government health priorities of improving mental wellbeing, and creating a strong and equitable public health system.

6.10. The Subcommittee considered that funding of ring pessaries in the community would benefit individuals by providing improved access to options for care, reduce time and make it easier for patients to access services (such as those in regional and rural

communities), and offer more people the solution of a low-risk intervention compared to surgery. The Subcommittee also considered that there would be a benefit to whānau and family in that patients would be able to take part in whānau and community activities if accessible treatment was more available.

6.11. The Subcommittee considered that there would also be a benefit to the wider health system in that there would be a reduced demand on gynaecology services, and a potential reduction in the demand for surgery. However, the Subcommittee considered that funded ring pessaries in the community may shift the demand onto an already overloaded primary healthcare system. Members also considered that cost could shift to patients if their DHB did not fund insertion services in primary care and that this could present a barrier to access and uptake in some areas. In addition there would be the need for further training for some primary healthcare providers, although Members noted that ring pessary insertion is relatively straightforward. The Subcommittee noted that ring pessaries are a relatively low-cost intervention compared to pelvic floor muscle training and surgery.

6.12. The Subcommittee noted that pessaries are not without risk, in that failure rates of up to 50% have been recorded (compared to a 30% risk of failure from surgery), and that there is a small risk of bleeding, ulceration, and loss of the device. The Subcommittee noted that the risks from surgery for pelvic prolapse are most commonly associated with anaesthetic use and thrombosis, and that the thrombosis risk is increased for Māori and Pacific patients. The Subcommittee noted that overall, the severity of risks associated with surgery were higher than those for ring pessary use.

6.13. The Subcommittee noted the Cochrane systematic review of the use of ring pessaries in the management of pelvic organ prolapse in women (Bugge et al. Cochrane Database of Systematic Reviews. 2020;11. DOI: 10.1002/14651858.CD004010.pub4). The Subcommittee noted that the review included four studies involving a total of 478 women with various stages of prolapse, which concluded that there is uncertainty regarding whether or not pessaries improve prolapse symptoms for women with no treatment of pelvic floor muscle training. The Subcommittee noted, however, that pessaries in combination with pelvic floor muscle training probably improved patient's symptoms but noted that there may be an increased risk of adverse events with pessaries when compared to pelvic floor muscle training alone.

6.14. The Subcommittee noted that the review (Bugge et al. Cochrane Database of Systematic Reviews. 2020;11. DOI: 10.1002/14651858.CD004010.pub4) also reported on two economic evaluation studies which compared pessary treatment to alternative interventions (pelvic floor muscle training, expectant management, and surgical procedures) and indicated better outcomes and lower costs for pessary treated groups when compared to pelvic floor muscle training rather than no intervention.

6.15. The Subcommittee noted that recently published NICE guidance recommends consideration of pessary use in women who have symptomatic prolapse, but that the quality of evidence was considered to be low to very low. The Subcommittee also noted that evidence from observational studies suggests that about 76% of women who try a pessary continue to use it for at least four weeks and, of those women who continue pessary use for more than four weeks, 86% continued to use the pessary for over five years (Lone et al. Int J Gynaecol Obstet. 2011;114:56-9). Furthermore, the Subcommittee noted that pessaries have been shown to improve symptoms in women with pelvic floor prolapse in observational studies (Manchana T,

Bunyavejchevin S. Int Urogynecol J. 2012;23:873-7; Lamers et al. Int J Gynaecol Obstet. 2011;22:637-44).

6.16. The Subcommittee noted the Ontario health technology assessment of vaginal pessaries for pelvic organ prolapse or stress urinary incontinence which included 15 studies (Ont Health Technol Assess Ser. 2021;21: 1–155). The Subcommittee noted that the findings were that pessary use may improve symptoms of pelvic floor prolapse but that the evidence was low-grade, and that pessary use may be cost-effective when used within a 'stepped-care' model (a sequence of interventions followed after the current treatment proves ineffective). The Subcommittee noted that direct patient interviews reported that ring pessary use was an effective treatment option for symptom management, and that conflicting evidence from health providers and long wait times were seen as common barriers to access.

6.17. The Subcommittee noted that the majority of evidence for the use of pessaries comes from non-randomised studies with small patient numbers, and as such, the effectiveness of pessaries for managing pelvic organ prolapse still needs to be clearly established. The Subcommittee noted that there is a lack of consensus as to the optimal treatment for women. The Subcommittee reiterated that this funding application related to a service shift and improved access, rather than the availability of a new treatment as ring pessaries are currently administered in secondary care. The Subcommittee considered that while the evidence for the use of ring pessaries for pelvic prolapse was of low quality, that ring pessaries are widely recommended as a cost-effective treatment option for women with symptomatic pelvic floor prolapse.

6.18. The Subcommittee considered that pessaries are an acceptable option for many women, and that the ability to provide pessaries through primary care facilities may decrease the wait times often experienced with secondary care services. The Subcommittee considered that the ability of nurse practitioners and pelvic floor physiotherapists to perform insertions of pessaries may alleviate some pressure on GPs in terms of appointment volume.

6.19. The Subcommittee considered that it was unclear how the funding of pessaries in primary care would impact patient numbers, however that it would be likely to increase their use, due to improved accessibility. The Subcommittee also noted that many women see pelvic prolapse as a consequence of childbirth and as a condition to be 'lived with', and often do not seek treatment. The Subcommittee considered that these women may contribute to an increased uptake of pessary use if information is provided to them through a primary care service.

6.20. The Subcommittee noted that there are suitability elements of ring pessary use, and that patients are more likely to accept ring pessaries as a treatment if they are appropriately counselled about the intervention and in some circumstances taught to remove them themselves, as this can enable individuals to feel more in control of their treatment.

6.21. The Subcommittee noted that there are multiple shapes and types of pessaries and considered that ring pessaries are the most appropriate and easiest to insert in most cases, as well as having the least risk associated. The Subcommittee considered that if non-ring pessaries were to be funded, additional training and education would be necessary to mitigate the risk of adverse events.

6.22. The Subcommittee considered there are no other indications in which a ring pessary would be used other than pelvic prolapse and as such it did not recommend that a

Special Authority be imposed noting that it would predominantly present as a barrier to access rather than appropriate targeting of treatment. However, Members considered if a restriction were required as financial tool that it would be important to restrict use to symptomatic prolapse only.

7. Riboflavin - perioperative use (cystoscopy)

Application

7.1. The Subcommittee considered a clinician application for riboflavin (vitamin B2) for perioperative use for the assessment of ureteric patency during cystoscopy.

Recommendation

7.2. The Subcommittee **recommended** that riboflavin for perioperative use for the assessment of ureteric patency during cystoscopy be listed with a high priority within the context of treatment in reproductive and sexual health, subject to the following Special Authority criteria:

Initial Application. Applications valid for 3 months for applications meeting the following criteria:
1 Patient is scheduled for assessment of ureteric patency during cystoscopy

7.3. The Subcommittee made this recommendation based on the favourable safety, reduced risk of adverse reactions, and mode of administration of riboflavin compared to current options.

Discussion

7.4. The Subcommittee noted that cystoscopy is undertaken for various reasons, but that this application relates specifically to patients undergoing assessment of ureteric patency during cystoscopy, and that the riboflavin is not intended to be therapeutic. The Subcommittee noted also that there are currently no funded oral agents to induce colouration to the urine to assist in visualising the ureteric jets at the time of intraoperative cystoscopy. The Subcommittee noted that intravenous indigo carmine, methylthioninium chloride (methylene blue), or fluorescein are used in this setting, and that indigo carmine is not an approved product and that fluorescein is used off-label for this indication.

7.5. The Subcommittee noted that currently available treatments are administered intravenously and pose a higher risk of adverse events such as anaphylaxis, which requires monitoring post-administration.

7.6. The Subcommittee noted that the applicant proposed that 400 mg riboflavin would be taken orally the night before surgery to colour the urine, for improved visualisation of vesicoureteric anatomy. The Subcommittee noted that, as an endogenous vitamin, oral riboflavin does not pose the same level of risk compared with other coloured intravenous agents. The Subcommittee also noted that there is evidence of riboflavin being used for this purpose in the following studies:

7.6.1. Stitely et al. Obstet Gynecol. 2019;133:301-7: a randomised controlled trial of patients scheduled for gynaecologic surgery where cystoscopy was a planned component of the procedure who were given 400 mg of riboflavin versus placebo the night before surgery. Patients had significantly increased coloured urine, ureteral jets were more easily visualised, and that bilateral ureteric

patency was confirmed in 30 of 33 women (91%) in the riboflavin group and in 28 of 33 women (85%) in the placebo group (P=0.71).

7.6.2. Fernando et al. Int Urogynexol J. 2011;22:947-51: an observational study of women booked to receive cystoscopy as main procedure or were likely to require one as an adjunct to vaginal surgery who were given three vitamin B complex tablets 1-4 hours prior to cystoscopy (total 45 mg riboflavin). 72.1% participants had yellow-coloured urine and indigo carmine was only used twice (2.9%); one of which was due to clinician preference.

7.7. The Subcommittee noted that the applicant also provided a case report study of an individual who had anaphylactic shock after administration of intravenous sodium fluorescein for the assessment of ureteral efflux (Lee et al. Obstet Gynecol. 2018;131:727-9).

7.8. The Subcommittee noted that the number of patients who might require riboflavin for assessment of ureteric patency during cystoscopy was unknown and considered that funding riboflavin would result in its use in a minority of procedures and would not lead to a significant uptake by clinicians. The Subcommittee considered that from a gynaecological perspective the majority of patients undergoing cystoscopy would require visualisation as a part of their procedure. Members were not aware if this proportion differed substantially in urology practice. The Subcommittee considered that including patients undergoing cystoscopy or hysterectomy would give the largest possible potential patient population.

7.9. The Subcommittee considered that using riboflavin for this purpose would reduce the requirement for intravenous administration of agents and thus reduce the risk of anaphylactic reactions. While this might reduce the requirement for monitoring for the latter, it was noted that, as patients are routinely monitored perioperatively regardless of agent used, this would not impact hugely on clinician time. The Subcommittee also considered that careful planning would be needed to provide patients with the riboflavin in advance of cystoscopy, as they would take it at home, the night before the procedure. However, because patients undergo some form of preadmission process prior to these procedures, this should not pose a barrier to its use.

7.10. The Subcommittee considered that the below table summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for riboflavin if it were to be funded in New Zealand for perioperative use for cystoscopy. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Subcommittee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	Individuals undergoing assessment of ureteric patency during cystoscopy
Intervention	Riboflavin 400 mg prior to cystoscopy
Comparator(s)	Indigo carmine Fluorescein Methylthioninium chloride (methylene blue)
Outcome(s)	Coloured urine Reduced anaphylaxis
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the patient population would receive currently (status	

quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.