Reproductive and Sexual Health Subcommittee of PTAC
Meeting held 25 June 2012

(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 2008*.

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 8 & 9 November 2012, the record of which will be available in January 2013.

Some material has been withheld, in accordance with the Official Information Act 1982 (OIA) in order to:

(i) enable PHARMAC to carry out, without prejudice or disadvantage, commercial activities (section 9(2)(i)); and/or
(ii) enable PHARMAC to carry on, without prejudice or disadvantage, negotiations, including commercial negotiations (section 9(2)(j));

1 Previous recommendations/action points

The Hormone and Contraceptive Subcommittee May 2009

1.1 The Subcommittee noted that prednisolone oral solution had been included in the 2010/2011 tender but the tender had not yet been awarded.

1.2 The Subcommittee noted that propylthiouracil was listed on the Pharmaceutical Schedule in May 2012.

1.3 The Subcommittee noted that copper IUDs had been included in the 2010/11 tender but the tender had not yet been awarded.

1.4 The Subcommittee noted that the long acting reversible contraceptive, levonorgestrel subdermal 2 x 75 mg implant (Jadelle), was listed on the Pharmaceutical Schedule in August 2010, clomiphene citrate has been retained on the Pharmaceutical Schedule and the Special Authority for goserelin was removed in August 2009.

2 Therapeutic group review

Contraceptives non-hormonal

2.1 The Subcommittee noted a review of funded non-hormonal contraceptives provided by PHARMAC staff. The Subcommittee noted that expenditure and prescriptions in this group were relatively stable.

2.2 The Subcommittee noted that PHARMAC had consulted upon listing latex free condoms. The Subcommittee noted that PHARMAC were unable to do so prior to registration of latex free condoms which was dependent on Environment Science and Research (ESR) approving a standard testing method. The Subcommittee recommended PHARMAC write to ESR and New Zealand Standards to request urgency on approving a standard method for the validation of products being latex free. [withheld under s 9(2)(i) and 9(2)(j) of the OIA]. The Subcommittee considered that prevention of infections, rather than the prevention of pregnancy, was the key in being able to offer latex free condoms and that for an estimated 1% of the population that have a latex allergy, listing a latex free condom should be considered urgent.

2.3 The Subcommittee noted there were no lubricants listed on the Pharmaceutical Schedule and recommended that PHARMAC seek a submission from Family Planning for listing lubricants. The Subcommittee noted that lubricants were essential when using condoms and that listing lubricants would result in a lower rate of condom breakage and fewer sexually transmitted infections (STIs). The Subcommittee considered that listing lubricants would be most beneficial for younger members of the population with high STI rates.

2.4 The Subcommittee noted the decline in use of diaphragms and considered that diaphragms are no longer a popular choice and any use is primarily renewals. The Subcommittee noted that supply of the spermicidal jelly that had previously been listed

on the Pharmaceutical schedule had been discontinued by the supplier and that purchase on the internet was the only way to obtain spermicidal jelly.

2.5 The Subcommittee noted that there was an outstanding funding application for female condoms. [withheld under s 9(2)(i) and 9(2)(j) of the OIA].

Hormonal Contraceptives

2.6 The Subcommittee discussed the risk of venous thrombosis rates (VTEs) associated with hormonal contraceptives and considered that, due to the concern of higher risk of VTEs with third generation hormonal contraceptives, it is appropriate that the ethinyloestradiol with desogestrel combination contraceptives, Marvelon and Mercilon, remain only partially subsidised. The Subcommittee considered that the newer generation products (including ethinyloestradiol with drospirenone products) offered no benefits over currently listed combination hormonal contraceptives and should not be fully subsidised either because of similar VTE concerns.

2.7 The Subcommittee noted that in the United Kingdom there was a recommendation that patients should not be prescribed cyproterone acetate for more than one to two years and considered that it would be appropriate for BPAC to run an article reinforcing the current safety messages associated with hormonal contraceptives. The Subcommittee requested that cyproterone acetate with ethinyloestradiol (Ginet) be made available on a PSO to allow demonstration to patients.

2.8 The Subcommittee noted that ethinyloestradiol 30 µcg with levonorgestrel 150 µcg and ethinyloestradiol 20 µcg with levonorgestrel 100 µcg would be sole supply from 1 September 2012 and 1 December 2012 respectively. The Subcommittee had no concerns on sole supply of these products.

2.9 The Subcommittee noted the prescribing of the levonorgestrel implant, Jadelle, had levelled out after a strong initial uptake following listing this product in August 2010. The Subcommittee noted that approximately 15 – 20% of the implants were removed shortly after insertion largely due to abnormal bleeding, hormonal side effects such as migraines and mood changes and patients not liking the feel of the rods. The Subcommittee noted that approximately 1% of removals required radiographical assistance to locate the implant and expressed concern about the added cost to the DHBs and patients of this procedure. The Subcommittee noted that there is a correlation between the number of IUDs a doctor inserted and how well they were inserted and considered the same would likely apply to the implant.

2.10 The Subcommittee recommended that PHARMAC seek an application for ulipristal acetate, a new form of emergency contraceptive pill. The Subcommittee considered that ulipristal is effective up to five days after unprotected sex and is more effective than levonorgestrel emergency contraception in women with a Body Mass Index greater than 30. The Subcommittee noted that Family Planning recommend a Copper IUD as being the most effective form of emergency contraception.

2.11 The Subcommittee recommended PHARMAC reassess the application to list desogestrel 75 µg (Cerazette) and request the supplier to supply post-marketing information. [withheld under s 9(2)(i) and 9(2)(j) of the OIA]

2.12 The Subcommittee noted that the vaginal ring contraceptive was available internationally and PHARMAC should be aware of this development.

Levonorgestrel intrauterine system

2.13 The Subcommittee noted PHARMAC had received two letters requesting access to the levonorgestrel intrauterine system (IUS) be widened. The Subcommittee reviewed three review papers supplied by PHARMAC staff:

- Non-contraceptive applications of the levonorgestrel intrauterine system, Rodriguez and Darney, Int J Women's Health 2010:2 63-68. The authors reviewed the evidence for use of intrauterine progestin delivery for menorrhagia, endometriosis management, uterine fibroids, endometrial hyperplasia and its concurrent use in women on hormone replacement therapy or tamoxifen. The authors concluded that progestin plays a critical role in gynaecologic treatments beyond their current use in contraception and that intrauterine delivery is an effective localized therapy. The Subcommittee noted that many of the trials that were reviewed were of poor quality and the review had poor quality critical appraisal.

- Non-contraceptive uses of levonorgestrel-releasing hormone system (LNG-IUS) – a systematic enquiry and overview. Varma et al, EJOG 125(2006) 9-28. The Subcommittee noted that this was a good quality systematic review. The authors qualitatively and quantitatively analysed the results form observational and experimental trials of the use of LNG-IUS in gynaecology. The recommendations for use were strong (Level 1 evidence) only for use in menorrhagia and in uterine protection when used in combination with oestrogen as HRT and tamoxifen. In relation to fibroids, the studies were largely cohort studies with no comparator arms. There are three randomised clinical trials where indirect data was available where women with fibroids had been included in trials for other indications. The results are inconsistent in determining whether LNG-IUS is associated with decreased fibroid size or no change in fibroid size. One randomised controlled trial suggested there may be decreased incidence with LNG-IUS compared with Cu-IUD and when used with tamoxifen when compared to tamoxifen alone. In relation to endometriosis, the heterogeneity of population in the studies combined with the small sample size limited the strength and validity of the findings. Uncontrolled studies suggested a reduction in bleeding and dysmenorrhoea and controlled studies suggested that LNG-IUS may be better than GnRH and endometriotic surgery. Endometrial suppression and symptomatic improvement of menopausal symptoms was achieved in all studies examining LNG-IUS use in women receiving hormone replacement therapy. There were no trials in obesity or cervical stenosis.

- Application for inclusion of levonorgestrel-releasing intrauterine system for contraception in the 14th WHO MODEL list of essential medicines. Wannmacher, January 2005. This was a review of current use of LNG-IUS with endometriosis

being the only non-menorrhagia, non-contraceptive use studied. One small study included in the review found that recurrence of moderate or severe dysmenorrhoea one year after laparoscopic surgery versus treatment with LNG-IUS was 10% in the LNG-IUS group versus 45% in the post-surgery group (p=0.03).

2.14 The Subcommittee considered that there is no evidence to say that, in relation to contraception, LNG-IUS is any better than other long acting reversible contraceptives. The evidence in relation to controlling pain is poor and, to date, there has been insufficient evidence of benefit in treating endometriosis to support this becoming a licensed indication. The Subcommittee also noted that Mirena is not registered for treatment of uterine fibroids and should not be used in this condition.

2.15 The Subcommittee noted that LNG-IUS is registered for the prevention of endometrial hyperplasia during estrogen replacement therapy and that endometrial protection is particularly an issue for morbidly obese women. The Subcommittee recommended against expanding access to hormone replacement therapy per se but considered it could be widened to those women being treated with hormone replacement therapy (HRT) who are at significant risk of endometrial hyperplasia. The Subcommittee noted that endometrial protection is particularly an issue with Maori and Pasifika women. The Subcommittee noted that women with high BIMs who are not taking oestrogens but who produce high levels of endogenous oestrogen are also at increased risk of endometrial hypoplasia however, as noted above, there are no trials of LNG-IUS in this setting.

2.16 The Subcommittee noted that in a hospital setting, the levonorgestrel intrauterine system may be used instead of hysterectomy. The Subcommittee recommended PHARMAC review the possibility of using the Clinical Priority Assessment Criteria (CPAC) grading system for hysterectomies as a suitable system for guiding the use of a levonorgestrel IUS instead of a hysterectomy and evaluate the cost effectiveness of using an LNG-IUS over performing a hysterectomy. The Subcommittee noted that there were a number of other areas where the LNG-IUS is currently used in a hospital setting including for women requesting sterilisation because of abnormal uterine bleeding and pelvic pain. The Subcommittee considered that a more thorough review of the evidence may needs to be undertaken prior to any consideration of defining access for use in the hospital setting.

2.17 The subcommittee recommended that access to the levonorgestrel intrauterine system be widened to include those women wanting an intrauterine device for contraception who already had heavy periods and those who had used a copper intrauterine device for contraception and had experienced unacceptable heavy periods with it. It was acknowledged that it was difficult to set up objective criteria to allow the use of Special Authority for these indications.

Progesterone 100 mg capsules

2.18 The Subcommittee noted that PHARMAC had recently received an application for listing progesterone 100 mg capsules on the Pharmaceutical Schedule for adjunctive hormone replacement therapy. In addition to the application the Subcommittee noted the vaginal use of progesterone capsules through the Named Patient Pharmaceutical assessment (NPPA) pathway for prevention of pre-term births. The Subcommittee noted that there had been a number of applications through NPPA and considered the viability of listing

progesterone 100 mg capsules on the Pharmaceutical Schedule for this unregistered indication.

2.19 The Subcommittee reviewed five papers – two key randomised controlled trials, one meta-analysis, one cost effectiveness study and the Canadian Guidelines. Two of the papers reviewed were:

- Progesterone and the risk of preterm birth among women with a short cervix, Fonseca et al, N Engl J Med 2007;357:462-9. There was a multicentre, RCT in which 24,630 women underwent transvaginal ultrasonographic measurement of cervical length at 20 to 25 weeks gestation. Of these, 413 (1.7%) had a cervical length of <15 mm and 250/413 were randomised to receive one 200 mg progesterone capsule intravaginally daily or placebo from 24/40 to 34/40 gestation. The rate of the primary outcome – spontaneous birth before 34 weeks of gestation was 19.2% in the progesterone group and 34.4% in the placebo group (Absolute risk difference 15.2%, RR 0.5 95%, CI 0.36-0.86). No significant adverse events were reported.

- Vaginal progesterone reduces the rate of preterm birth in women with a sonographic short cervix: a multicentre, randomized, double-blind, placebo controlled trial. Hassan et al ISUOG 2011; 38:18-31. Comparison of 8% vaginal progesterone gel (equivalent to 90 mg) versus placebo with a primary endpoint of delivery prior to 33 weeks. The cervical length of 32091 women were measured sonographically; 465 women with cervical length <20 mmm were randomised to receive daily gel or placebo. The Subcommittee noted a significant reduction of risk of a preterm birth in the progesterone group (8.9%) versus placebo (16.1%) (RR 0.52, 95% CI 0.31-0.91, p=0.02). While there was a significant reduction in preterm births before weeks 28, 33 and 35, the difference narrows by week 37. There was a non-significant trend to a reduction in mortality and morbidity and a significant reduction in respiratory distress syndrome in the progesterone group (RR 0.42, 95% CI 0.18-0.97). Adverse reactions were the same in both groups and were minor and local.

2.20 The Subcommittee considered that while there is moderate evidence that daily progesterone prevented pre-term births in women with a short cervix, there was a lack of evidence on the long term benefits for infant and long term safety of using progesterone for this indication. The subcommittee noted that there is uncertainty over the use of progesterone in women who have previously had a cone biopsy and recommended PHARMAC contact the supplier for more information on the use of vaginal progesterone in these women. The Subcommittee noted that the alternative treatment is a cervical cerclage and there is some debate about which women are eligible for this.

2.21 The Subcommittee noted that there was an ongoing study in New Zealand to determine the effectiveness of intra-vaginal progesterone to determine its efficacy in preventing pre-term birth and that funding should not be made available until this was completed.

2.22 The Subcommittee did not recommend that progesterone 100 mg capsules be listed on the Pharmaceutical Schedule for prevention of preterm birth at this stage as there was not sufficient evidence on the long term benefits or safety data for the infants.

Gynaecological Anti-infectives

2.23 [withheld under s 9(2)(i) and 9(2)(j) of the OIA]

2.24 The Subcommittee considered that the restrictions on fluconazole were too restrictive considering this product was available through community pharmacies without a prescription. The Subcommittee considered that fluconazole should not be available without a prescription.

2.25 The Subcommittee noted that the current restriction on fluconazole prevented Family Planning clinicians from prescribing greater than one fluconazole 150 mg capsule. Members noted that wider access to fluconazole would be beneficial.