

Application for addition: 25mg medroxyprogesterone acetate + 5mg estradiol cypionate combined injectable contraceptive

Review of submissions by Reviewers 1 and 2

Reviewer 1

This submission gives a full review of the relative advantages of this formulation.

On p8, it states that the product costs \$30/month – the actual range of costs is \$1-5.

Also on p8, under effectiveness, I should like to refer to the attached extract from WHO/RHR's 2004 publication "Selected Practice Recommendations for Contraceptive Use" (see Annex 1). This shows a far better effectiveness of the combined injectable contraceptive over combined oral contraceptives in typical use, since many women, particularly younger women, often forget to take the contraceptive on a regular basis, which results in a far higher pregnancy rate in typical use.

On p9, the fact that the monthly injectable has a more predictable bleeding and a more rapid return of fertility compared to the three-monthly progestogen-only injection; the use of 5mg estradiol cypionate monthly with the three-monthly progestogen-only injection gives rise to an increase in bone density (see Annex 2); and the fact that effectiveness, compared with oral contraceptives, is unrelated to remembering to take a pill on a daily basis (young women between 18 to 25 years have the highest rates of unintended, unwanted pregnancies due to failing to take pills on a regular 24 hour schedule), makes it a product of choice for younger women.

Reviewer 2

On p1, under efficacy, the reviewer refers to the withdrawal of Lunelle from the US market in 2002, referencing the release issued by the manufacturer, Pharmacia, and concludes that "...the product was withdrawn because of concerns about suboptimal efficacy.". This was might be true of the suboptimal product being manufactured by Pharmacia but is not true of a correctly manufactured product. The Pharmacia document states:

"Pharmacia Corporation is voluntarily recalling Lunelle prefilled syringe lots due to a lack of assurance of full potency and possible risk of contraceptive failure. A recent review of production records indicates the potential for sub-potency. Therefore, as a precaution, we are voluntarily recalling all Lunelle prefilled syringe lots currently on the market and the product will be unavailable for the immediate future. No other Pharmacia products are affected by this recall. This recall is being conducted with the knowledge of the Food and Drug Administration and has been designated a Class I recall."

The key statement in this release is "A recent review of production records indicates the potential for sub-potency.", ie, it was a production problem – not a product problem! In fact, Concept Foundation was informed by staff of Pharmacia that they had been inspected by the USFDA which had found deficiencies in the manufacturing process and had instructed the company that it had to make a significant upgrading of its manufacturing facility at Kalamazoo. This coincided with the takeover of the company by Pfizer, which declined to do this and decided to stop production instead.

On p1, the reviewer states that “A combined injectable contraceptive does not appear to be marketed in Europe”. This is true – but no injectable contraceptive is widely used in Europe, rather the monthly contraceptive has become a well-used product in a number of developing countries, mainly in South-east Asia and Latin America. An estimated 1.2 million women are now regular users of the method, and strong year-to-year increase rates are reported for several countries.

On p1, the last para discusses the lack of a distinctive indication for the product. The indication is to provide broader choice for contraceptive users, particularly in developing countries, as discussed in an additional document provided to the Expert Committee; as well as that it is a product of choice for younger women, as discussed above.

On p2, the reviewer states that “...a significant minority of women will not be able to fulfil the relevant medical eligibility criteria for combinations.”. Certainly, any hormonal method of contraception will have some women who will not fulfil medical eligibility criteria. However, it is worth referring to WHO/RHR’s Medical eligibility criteria for contraceptive use (3rd edition. 2004. World Health Organization, Geneva. pp1-186), which states:

“Because the estrogens in combined injectable contraceptives (CICs) may be more physiologic and may be less potent compared with the synthetic estrogens of combined oral contraceptives (COCs), the type and magnitude of estrogen-related side-effects associated with CICs may be different from those experienced by COC users. In fact, short-term studies of CICs have shown little effect on blood pressure, haemostasis and coagulation, lipid metabolism, and liver function in comparison with COCs.⁶⁻⁸ In addition, the parenteral administration of CICs eliminates the first-pass effect of the hormones on the liver.”

On p3, it states that “Good arrangements are required to ensure injection at the right time each month;...”. This is correct but must be balanced with the comments made on oral contraceptive compliance above.

In conclusion, inclusion of 25mg medroxyprogesterone acetate + 5mg estradiol cypionate combined injectable contraceptive in the Model List of Essential Medicines will provide a stimulus to use of this product, which will provide additional choice to women in many countries and which is a safe and effective a product of choice for younger women.

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Annex 1

Extract from WHO/RHR publication:

Selected Practice Recommendations for Contraceptive Use Second edition, 2004. World Health Organization, Geneva. pp1-170

Effectiveness of method

Contraceptive choice is in part dependent on the effectiveness of the contraceptive method in preventing unplanned pregnancy, which, in turn, is dependent for some methods not only on the protection afforded by the method itself, but also on how consistently and correctly it is used. Table 1 compares the percentage of women experiencing an unintended pregnancy during the first year of contraceptive method use when the method is used perfectly (consistently and correctly) and when it is used typically. Both consistent and correct use can vary greatly with such characteristics as age, income, users' desire to prevent or delay pregnancy, and culture. Methods that depend on consistent and correct use by clients have a wide range of effectiveness. Most men and women tend to be more effective users as they become more experienced with a method. However, programmatic aspects also have a profound effect on how effectively the method will be used.

Table 1. Percentage of women experiencing an unintended pregnancy during the first year of use and the percentage continuing use at the end of the first year. (United States of America).

Method (1)	% of women experiencing an unintended pregnancy within the first year of use		% of women continuing use at one year ³
	Typical use ¹ (2)	Perfect use ² (3)	(4)
Combined pill and minipill	8	0.3	68
DMPA (Depo-Provera)	3	0.3	56
Combined injectable (Lunelle)	3	0.05	56

Double-blinded randomized controlled trial of estrogen supplementation in adolescent girls who receive depot medroxyprogesterone acetate for contraception.

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OBJECTIVE: The purpose of this clinical trial was to evaluate the effect of estrogen supplementation on bone mineral density in adolescent girls who received depot medroxyprogesterone acetate for contraception. **STUDY DESIGN:** One hundred twenty-three adolescents who began receiving depot medroxyprogesterone acetate injections every 12 weeks were assigned randomly to receive monthly injections of estradiol cypionate or placebo. The main outcome was bone mineral density that was measured by dual energy x-ray absorptiometry for 12 (n = 69) to 24 (n = 36) months. Participants, technicians, and physicians were blinded to estrogen treatment. **RESULTS:** Over the 24-month period, the percentage of change from baseline bone mineral density at the lumbar spine was 2.8% in the estradiol cypionate group versus -1.8% in the placebo group (P <.001). At the femoral neck, the percentage of change from baseline bone mineral density was 4.7% in the estradiol cypionate group versus -5.1% in the placebo group (P <.001). **CONCLUSION:** Our results suggest that estrogen supplementation is protective of bone in adolescent girls who receive depot medroxyprogesterone acetate injections.

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