

NEW MEDICINES ON THE MARKET

Evaluated Information for NHS Managers, Budget Holders and Prescribers.

ETONOGESTREL IMPLANT

Summary

- Etonogestrel implant is a contraceptive device consisting of a single rod which is inserted subdermally into the inner side of the upper arm.
- Etonogestrel is released gradually from the rod, 60-70 μ /day in weeks 5-6 decreasing gradually to 25-30 μ /day at the end of the 3rd year.
- There have been no reported pregnancies during clinical trials.
- The product is generally well tolerated, with 82% women continuing use beyond 2 years. Primary responses for discontinuation were amenorrhoea (0.9%), bleeding irregularities (9.4%), adverse effects (4.6%), and other reasons (3.3%).
- Etonogestrel implant costs £30 pa, more than most contraceptives, but less than the most expensive oral contraceptive. The manufacturer claims a clear overall economic advantage compared to levonorgestrel intrauterine system (Mirena) and oral contraceptives. Further evidence is required to confirm this.
- Etonogestrel implant is a very effective and generally well tolerated contraceptive of particular use in women where compliance may be a problem. It has several advantages over the levonorgestrel implant Norplant (with 6 rods). However, the UK market may prove a difficult market for etonogestrel implant given the problems of adverse publicity following litigation and payment for GPs experienced with Norplant.

Date Published: December 1999

Monograph Number: 4/99/20

Marketed: October 1999

Region of Origin to whom queries should be directed: Southampton

ETONOGESTREL IMPLANT

APPROVED NAME:	Etonogestrel
BRAND NAME: (Manufacturer)	Implanon (Organon Laboratories Ltd)
SYNONYM (S):	
PRESENTATION:	Implant containing 68mg of etonogestrel. 60-70µ/day is released in weeks 5-6 decreasing to approximately 35-45µ/day at the end of the first year, to approximately 30-40µ/day at the end of the second year and to approximately 25-30µ/day at the end of the third year. The implant rod (40 x 2mm) is preloaded into a sterile, single use implantation device.
THERAPEUTIC CLASS:	Progestogen implant contraceptive (BNF 7.3.2.2)
LICENSED INDICATIONS:	Contraception
DOSE/ADMINISTRATION:	One implant is inserted subdermally by a physician who is familiar with the procedure at the inner side of the upper arm (non-dominant arm). The implant can be removed at any time, but should not be left in place more than 3 years. SEE SUMMARY OF PRODUCT CHARACTERISTICS AND PRODUCT PACK FOR FULL DETAILS.
COST/COURSE:	1 implant providing 3 years contraception - £90.00 (MIMS Nov 1999), ie £30.00 pa.
THERAPEUTIC COMMENT:	Etonogestrel implant is a very effective and well tolerated contraceptive of particular use where compliance may be a problem. Subdermal insertion and removal of the implant rod is likely to be a disadvantage for many women.
TREATMENT ALTERNATIVES:	Cost per Annum (MIMS and Drug Tariff - Nov 1999)

Combined oral contraceptives	£8.97 (Eugynon 30) - £37.14 (Mercilon)
Levonorgestrel intra-uterine system	£17.85 (Mirena)
Standard intra-uterine device	£7.01 - £24.75 (single cost)
Diaphragm	£5.49 - £6.53 (single cost)

ETONOGESTREL IMPLANT

INTRODUCTION

Despite the wide availability of effective contraception, unplanned pregnancies remain a common problem [1]. Annual percentage failure rates have been reported as:- diaphragm 18%, male condom 12%, progesterone only oral contraceptives 3%, levonorgestrel intra-uterine system (Mirena) 0.2%, tubal ligation 0.17%, combined oral contraceptive 0.08%, and vasectomy 0.04% [2]. Although some of these events may be put down to direct failure of the contraceptive method, most unplanned pregnancies, especially in younger age groups, appear to result from poor patient compliance [1]. There would therefore seem to be a place for a reliable method of contraception which does not require compliance on a daily basis or at the time of intercourse. Etonogestrel Implant, inserted into the upper arm, provides effective contraception for 3 years.

PHARMACOLOGY

Etonogestrel implant gradually releases etonogestrel at a rate of 60-70 μ /day in weeks 5-6 decreasing gradually to approximately 25-30 μ /day at the end of the third year [3]. Etonogestrel is the biologically active metabolite of desogestrel, a progestogen widely used in oral contraceptives [3]. The contraceptive effect is primarily achieved by inhibiting ovulation which is inhibited for at least 2½ years. Ovulation started to occur after 2½ years in 2 of 46 women (4%). Etonogestrel also increased the viscosity of cervical mucus, thus hindering the passage of spermatozoa [3,4,5].

PHARMACOKINETICS

After insertion of etonogestrel implant, serum etonogestrel concentrations increased rapidly and reached levels sufficient for ovulation inhibition within 8 hours [4]. Maximum serum concentrations between 472 and 1270 pg/ml are reached within 1 to 13 days. Serum concentrations decline with time, falling to 150-261 pg/ml by the end of the first year

and 111-202 pg/ml by the end of the third year [3,6]. Bioavailability over this time was constant and close to 100% [6,7]. After removal of etonogestrel implant, serum etonogestrel levels declined to less than 20 pg/ml within 1 week [7]. Etonogestrel is 95-99% bound to serum proteins. It is metabolised in the liver by hydroxylation and reduction. Mean elimination half-life is approximately 25 hours. Excretion of etonogestrel and its metabolites is via urine and faeces (1.5:1) [3,4,6,7].

Increases in total bilirubin of 11.85% and gamma glutamyl transferase of 9.81%, and decreases in alanine transferase of 4.42% and aspartate aminotransferase of 8.17% were recorded in women with etonogestrel implants [8].

EFFICACY

Results of clinical trials are mainly reported only as a meta-analysis. Six non-comparative trials of etonogestrel implant, and seven randomised comparisons of etonogestrel implant (Implanon) and levonorgestrel implant (Norplant 6), all trials conducted according to Good Clinical Practice [1,4]. Analysis of the meta-analysis is difficult given the lack of detail, eg how studies were included, and statistical significance.

Female volunteers were recruited to the trials according to a number of inclusion and exclusion criteria. The studies were either single or multi-centre trials with a designed duration of 24 months once a woman had the etonogestrel or levonorgestrel implant in place. All volunteers were aged 18-40 years, sexually active, of childbearing potential, in good physical and mental health, with regular menstrual menses. Details of the volunteers and the results of the meta-analysis were as follows:-

ETONOGESTREL IMPLANT

	Etonogestrel Implant	Levonorgestrel Implant (now discontinued)
No. of volunteers	1716	689
No. of menstrual cycles	53,530	23,815
No. of discontinuations within 2 yrs	313 (18.2%)	-
No. of pregnancies	none	none
Median insertion time	1.0 mins (0.5 - 2.0)	4.0 mins (2.0 - 5.0)
Median removal time	2.0 mins (1.0 - 6.5)	8.0 mins (5.0 - 15.0)
Insertion complications*	0.3%	none
Removal complications*	0.2%	3.7%
<u>Bleeding patterns*</u>		
Amenorrhoea		
1st 3 months	2.9%	2.7%
by 12 months	37.5%	25.6%
by 24 months	38.3%	24.4%
Infrequent bleeding		
1st 3 months	56.4%	50.6%
by 12 months	30.7%	28.2%
by 24 months	26.9%	30.4%
Frequent bleeding		
1st 3 months	6.5%	5.7%
by 12 months	3.1%	5.3%
by 24 months	2.3%	2.5%
Body mass increase >10%*	19.6%	17.2%
<u>Changes in acne, insertion to removal</u>		
None	+3.6%	-9.0%
Occasional	-6.6%	+2.6%
Continuous	+3.0%	+6.5%
<u>Primary reason for discontinuation</u>		
<u>up to 24 months</u>		Not available
Amenorrhoea	16 (0.9%)	
Bleeding irregularities	161 (9.4%)	
Adverse experiences	79 (4.6%)	
Other reasons	57 (3.3%)	
Return of menses within 3 months of removing implant	484 of 614 (79%)	38 of 56 (68%)

* from comparative studies
statistical significances are not included in the papers

N.B. 102 women with a body weight greater than 70kg used the etonogestrel implant between 2 and 3 years. There were no pregnancies. No data from the comparative studies are available for the levonorgestrel implant, but previous studies have shown a higher pregnancy rate after 18 months use in women over 70kg.

ETONOGESTREL IMPLANT

PROMOTIONAL DATA

None.

ADVERSE EFFECTS (see SPC)

Etonogestrel implant is generally well tolerated with 82% women started on therapy in clinical trials continuing its use beyond 2 years [1].

In clinical studies there was very considerable variability between the studies in terms of percentage of reported adverse effects.

In comparative studies 25.1% women using etonogestrel implant and 28% women using norgestrel implant reported adverse effects [1]. Adverse effects occurring with a frequency of more than 5% were:- acne, headache, increase in body weight, breast tenderness and pain.

Those occurring with a frequency of 2.5 % - 5% were:- alopecia, depressive moods, emotional lability, changes in libido, abdominal pain, dysmenorrhoea [3].

Hypertension occurred in 0.6% patients using etonogestrel implant and 0.7% patients using norgestrel implant [1].

A study in 60 women using etonogestrel or levonorgestrel implants showed no evidence of an increasing risk of endometrial hyperplasia, endometrial carcinoma, cervical intra-epithelial neoplasia or cervical carcinoma after 2 years[9]. A similar study over 2 years showed no evidence of an increased risk of coronary heart disease from apolipoproteins A-I, A-II and B [10].

Note that the levonorgestrel implant (Norplant) has been withdrawn by the manufacturers, although its confidence in the safety and efficacy of the product remains unchanged. This follows well publicised litigation undertaken by a number of women who claimed medical problems as a result of Norplant, including irregular bleeding, spotting, and in some cases difficulties in removing the implant. In addition, in October 1995 the BMA advised GPs not to insert Norplant until the NHS Executive provided a suitable fee for counselling and insertion [11].

CONTRA-INDICATIONS (see SPC)

Active venous thromboembolic disorders; progestogen-dependent tumours; presence or history of severe hepatic disease as long as liver function values have not returned to normal; known or suspected pregnancy; undiagnosed vaginal bleeding; hypersensitivity to any of the components of Implanon.

PRECAUTIONS (see SPC)

Benefits versus possible risks of:- breast cancer, venous thromboembolism, hypertension, liver function disturbance, peripheral insulin resistance and glucose tolerance, chloasma, reduced effect in heavier women, expulsion if inserted incorrectly, follicular development beyond normal size, ectopic pregnancy, changes in vaginal bleeding pattern, etc.

A complete medical history should be taken.

Interactions may occur with enzyme inducing drugs, and with some laboratory tests.

References

1. Edwards JE and Moore A
Implanon. A review of clinical studies.
Br J Fam Plan 1999;24:3-16.
2. Anon
Effectiveness of contraceptives.
Bandolier 1998;5(4):3 and 1998;5(6):8.
3. UK Summary of Product Characteristics - Implanon Implant.
Organon Laboratories. Date of Authorisation 9 June 1999.
4. Croxatto HB and Makarainen L
The pharmacodynamics and efficacy of Implanon.
Contraception 1998;58:91S-97S.

ETONOGESTREL IMPLANT

5. Makarainen L et al
Ovarian function during the use of a single
contraceptive implant. Implanon compared with
Norplant.
Fertil Steril 1998;69(4):714-721.
6. Wenzl R et al
Pharmacokinetics of etonogestrel released from the
contraceptive implant Implanon.
Contraception 1998;58:283-288.
7. Huber J
Pharmacokinetics of Implanon.
Contraception 1998;58:85S-90S.
8. Egberg N et al
Effects on the hemostatic system and liver function
in relation to Implanon and Norplant.
Contraception 1998;58:93-98.
9. Mascarenhas L et al
A 2 year comparative study of endometrial histology
and cervical cytology of contraceptive implant users
in Birmingham, UK.
Hum Reprod 1998;13(11):3057-3060.
10. Mascarenhas L et al
Twenty-four month comparison of apolipoproteins
A-I, A-II, and B in contraceptive implant users
(Norplant and Implanon) in Birmingham, United
Kingdom.
Contraception 1998;58:215-219.
11. Anon
Norplant to be discontinued.
Pharm J 1 May 1999;262:610.