

Medical Officer's Comments

- **Two of the 4 subjects completed their study, and of the 4 vascular related SAEs, only the TIA was judged to be possibly related to Implanon™ use. This reviewer agrees that the TIA may be related to the use of Implanon™, but the symptoms were transient and the women recovered. Given the large number of subjects (635+330) and the 2-year duration of the trials, these events are acceptable and do not raise a safety concern.**

Cardiac disorders. In the Clinical Development Program for Implanon™ 1 subject had an SAE that was categorized as a cardiovascular disorder. Subject 01014 from the U.S. study experienced repeated episodes of rapid heart rate. She was diagnosed with congenital heart disease, mitral valve prolapse, and proxymal atrial tachycardia. The event was judged by the investigator to be unrelated to Implanon™ use, and the subject continued in the study without further problems.

Medical Officer's Comments

- **In summary, the low report rate of vascular and cardiac thromboembolic events in the clinical studies suggests the risk is not significantly increased over that for nonpregnant individuals not exposed to contraceptives and is lower than the event rate found in similar individuals who use combination hormonal contraceptives or who become pregnant.**

Platelet, bleeding and clotting disorders. In the Clinical Development Program for Implanon™ 3 subjects had SAEs that were categorized as platelet, bleeding, and clotting disorders. A brief summary of these subjects follows.

1. Subject 00010 from Study 34507 was hospitalized with a diagnosis of fever and purpura of unknown origin. She was treated with antibiotics, recovered and completed the study. The event was judged by the investigator to be unrelated to Implanon™ use.
2. Subject 0212 from Study 34502 suffered from acute high fever with epistaxis, nausea, and vomiting. Subject was treated with medication and recovered. The subject completed the study.
3. Subject 0247 from Study 34507 had a secondary thrombosis. The thrombosis was considered a complication of an accident and immobilization, and was hence judged by the investigator to be unrelated to Implanon™. The subject continued Implanon™ use and recovered.

Medical Officer's Comments

- **Based on the information provided from the sponsor, none of these three events raises a safety concern. All three subjects recovered from the event and completed the study.**

7.6.3 Adverse Events Associated with Premature Discontinuations

7.6.3.1 Principal Safety Studies

A total of 323 out of 1117 (29%) of subjects in the principal safety studies discontinued due to an adverse event.

The most frequently reported reasons for discontinuation were bleeding irregularities (n=166, 14.9% subjects), weight increase (n=29, 2.6% subjects), emotional lability (n=23, 2.1% subjects), acne (n=13, 1.2% subjects), headache (n=12, 1.1% subjects), and amenorrhea (n=12, 1.1% subjects).

Regional differences were observed, such that the incidence of discontinuations due to AEs was generally higher in the U.S. compared to Europe/Canada/Thailand. A total of 119 out of 330 (36%) subjects in the U.S. study discontinued due to AEs. In the studies conducted in Europe/Thailand, 204 out of 787 subjects (26%) discontinued due to AEs.

Specific AEs (>1% incidence) that were reported as the reason for discontinuation more frequently in the U.S. compared to Europe/Canada/Thailand included: emotional lability (6.1% vs. 0.4%), weight increase (3.3% vs. 2.3%), depression (2.4% vs. 0.3%), acne (1.5% vs. 1%) headache (1.2% vs. 1%) and sexual function abnormal (1.2% vs. 0%).

Specific AEs (>1% incidence) that were reported as the reason for discontinuation more frequently in Europe/Canada/Thailand include bleeding irregularities (15.6% vs. 13.0%) and amenorrhea (1.5% vs. 0%).

Adverse events resulting in premature termination in more than one subject and the number [%] of subjects reporting the event are listed in Table 26).

Medical Officer's Comments

- **A total of 323 out of 1117 (29%) of subjects in the principal safety studies discontinued due to an adverse event. The most common single reason for discontinuation (based on the Applicant's classification) was bleeding irregularities, with 166 subjects (14.9%) discontinuing primarily for this reason.**

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Table 26 Adverse Events Resulting in Premature Termination in More than One Subject (Number [%] of Subjects Reporting the Event)

Preferred term	Principal Safety Studies						Principal Safety and Clinical Pharmacology Studies Combined	
	U.S. only (N=330)		Non-U.S. (N=787)		U.S. plus non-U.S. (N=1117)		(N=1414)	
	n	(%)	n	(%)	n	(%)	n	(%)
Bleeding Irregularities	43	13.0	123	15.6	166	14.9	211	14.9
Weight increase	11	3.3	18	2.3	29	2.6	32	2.3
Emotional lability	20	6.1	3	0.4	23	2.1	23	1.6
Acne	5	1.5	8	1	13	1.2	17	1.2
Headache	4	1.2	8	1	12	1.1	13	0.9
Amenorrhea	0 ^a	--	12	1.5	12	1.1	14	1.0
Depression	8	2.4	2	0.3	10	0.9	12	0.8
Alopecia	2	0.6	4	0.5	6	0.5	6	0.4
Nervousness	3	0.9	2	0.3	5	0.4	5	0.4
Libido decreased	0	--	4	0.5	4	0.4	7	0.5
Sexual function abnormal	4	1.2	0	--	4	0.4	4	0.3
Injection site pain	3	0.9	1	0.1	4	0.4	4	0.3
Breast pain	0	--	3	0.4	3	0.3	4	0.3
Anxiety	2	0.6	1	0.1	3	0.3	3	0.2
Weight decrease	0	--	3	0.4	3	0.3	3	0.2
Fatigue	2	0.6	0	--	2	0.2	3	0.2
Paraesthesia	1	0.3	1	0.1	2	0.2	2	0.1
Dizziness	0	--	2	0.3	2	0.2	2	0.1
Dysmenorrhea	2	0.6	0	--	2	0.2	2	0.1
Premenstrual tension	2	0.6	0	--	2	0.2	2	0.1
Hypertrichosis	0	--	1	0.1	1	0.1	2	0.1
Injection site reaction	0	--	1	0.1	1	0.1	2	0.1
Hypertension	0	--	1	0.1	1	0.1	2	0.1

^a Category may not have been accurately reported in U.S. Study.

Source: Tables 5, 6, 7, 32, and 35; Revised ISS.

7.6.3.2 Principal Safety Studies and Supportive Clinical Pharmacology Studies

Approximately 387 out of 1414 (27%) subjects from the principal and supportive safety studies discontinued due to AEs. Adverse events resulting in premature termination in more than one subject and the number [%] of subjects reporting the event are listed in Table 26

The most frequently reported reasons for discontinuation (>1%) were bleeding irregularities (n=211, 14.9% subjects), weight increase (n=32, 2.3% subjects), emotional lability (n=23, 1.6% subjects), and acne (n=17, 1.2% subjects).

Medical Officer's Comments

- Across the principal and supportive studies, approximately 387 out of 1414 subjects (27%) discontinued from the studies because of an adverse event. The most common single reason for discontinuation was bleeding irregularities, with 211 subjects (14.9%) discontinuing primarily for this reason.

- **It is widely accepted that menstrual irregularities are a common side effect of all the progestin-only forms of hormonal contraception. Although this fact does not raise a safety concern it does need to be addressed in labeling.**

7.6.4 Adverse Events (All Adverse Events and Treatment-Related Adverse Events)

7.6.4.1 Adverse Events in Principal Safety Studies Classified by Organ-Body System

The numbers (%) of subjects reporting an adverse event classified by WHO system-organ class and the relationship of the events to Implanon in the principal safety studies are listed in Table 27. Listed in the Table are (1) the number (%) of subjects reporting adverse events in the respective organ system that were considered by the Investigators to be related to treatment and (2) the number (%) of subjects reporting adverse events of any relationship to study drug (“All AEs”).

- *In this listing, bleeding irregularities (for the most part) are not included under the category reproductive disorders, as they were not classified as an adverse event in accordance with the convention of the Applicant.*

Adverse Events Related to Treatment Classified by Organ-Body System.

Within the population of subjects from the 4 principal safety studies (U.S./Europe/Thailand), the system-organ classes with the highest incidence of treatment related AEs were: Reproductive Disorders, Female, (212/1117 subjects or 19%); skin and appendages disorders (192/1117 subjects or 17.2%; CNS disorders (164/1117 subjects or 14.6%; and Psychiatric disorders (159/1117 subjects or 14.2%)

Medical Officer’s Comments

- **Despite the inconsistent inclusion of bleeding irregularities, the system class “reproductive disorders” still had the highest incidence of subjects reporting events. The high incidences of subjects reporting AEs in the other system classes probably reflect specific common AEs such as acne, headache and emotional lability/depression.**

Adverse Events (All Relationships to Treatment) Classified by Organ-Body System

Within the population of subjects from studies conducted in U.S./Europe/ Thailand, the system-organ class with the highest incidence of adverse events (all relationships to treatment) was Reproductive Disorders, Female (426/1117 subjects or 38.1%). The system-organ classes with the next three highest incidences of AEs were the Skin and Appendages Disorders (24.6%), Central and Peripheral Nervous System Disorders (23.8%) and Gastro-intestinal System Disorders (22.3%).

Medical Officer’s Comments

- **The top three system organ classes were the same as the system organ classes thought to be drug related. Psychiatric disorders were 7th in this category, vs. 4th in the “drug related” category.**

Table 27 Adverse Events by WHO System-Organ Classification and Relationship to Study Drug in Principal Safety Studies

Organ System	U.S. ^a (N=330)			Europe/Thailand ^b (N=787)			U.S./Europe/Thailand (N=1117)		
	Related n	(%)	All AEs n (%)	Related n	(%)	All AEs n (%)	Related n	(%)	All AEs n (%)
Reproductive disorders, female ^c	88	26.7	150 45.5	124	15.8	276 35.1	212	19.0	426 38.1
Skin and appendages disorders	58	17.6	94 28.5	134	17.0	181 23.0	192	17.2	275 24.6
CNS disorders	49	14.8	92 27.9	115	14.6	174 22.1	164	14.7	266 23.8
Gastro-intestinal system disorders	29	8.8	80 24.2	67	8.5	169 21.5	96	8.6	249 22.3
Body as a whole -general disorders	32	9.7	93 28.2	37	4.7	155 19.7	69	6.2	248 22.2
Respiratory system disorders	0	--	82 24.8	0	--	148 18.8	0	--	230 20.6
Psychiatric disorders	74	22.4	91 27.6	85	10.8	129 16.4	159	14.2	220 19.7
Metabolic and nutritional disorders	44	13.3	49 14.8	89	11.3	104 13.2	133	11.9	153 13.7
Urinary system disorders	0	--	44 13.3	3	0.4	56 7.1	3	0.3	100 9.0
Neoplasms	8	2.4	27 8.2	36	4.6	57 7.2	44	3.9	84 7.5
Application site disorders	22	6.7	26 7.9	48	6.1	53 6.7	70	6.3	79 7.1
Musculo-skeletal system disorders	2	0.6	28 8.5	1	0.1	50 6.4	3	0.3	78 7.0
Secondary terms	8	2.4	50 15.2	0	--	8 1.0	8	0.7	58 5.2
Resistance mechanism disorders	1	0.3	32 9.7	1	0.1	25 3.2	2	0.2	57 5.1
Liver and biliary system disorders	1	0.3	7 2.1	2	0.3	10 1.3	3	0.3	17 1.5
Vascular (extracardiac) disorders	0	--	1 0.3	2	0.3	12 1.5	2	0.2	13 1.2
Hearing and vestibular disorders	0	--	7 2.1	0	--	5 0.6	0	--	12 1.1
Cardiovascular disorders, general	1	0.3	4 1.2	4	0.5	8 1.0	5	0.4	12 1.1
Vision disorders	2	0.6	8 2.4	1	0.1	3 0.4	3	0.3	11 1.0
White cell and res disorders	0	--	7 2.1	0	--	3 0.4	0	--	10 0.9
Endocrine disorders	1	0.3	3 0.9	2	0.3	7 0.9	3	0.3	10 0.9
Platelet, bleeding and clotting disorders	0	--	1 0.3	0	--	9 1.1	0	--	10 0.9
Red blood cell disorder	1	0.3	2 0.6	3	0.4	7 0.9	4	0.4	9 0.8
Fetal disorders	0	--	1 0.3	0	--	2 0.3	0	--	3 0.3
Special senses other, disorders	0	--	1 0.3	0	--	0	0	--	1 0.1
Uncodeable	0	--	0	1	0.1	12 1.5	1	0.1	12 1.1
Heart rate and rhythm disorders	0	--	0	1	0.1	6 0.8	1	0.1	6 0.5
Collagen disorders	0	--	0	0	--	2 0.3	0	--	2 0.2

^a Study 069001

^b Studies 34505, 34507, and 34507 CDN.

^c does not include irregular bleeding

Columns showing All AEs include the total number of AEs that were related, not related, or where the relationship is unknown. Source: Table 36, P125, revised ISS, 04May04

7.6.4.2 Common Adverse Events in Principal Safety Studies (Both All Adverse Events and Treatment-Related Events) Classified by Preferred Term

The adverse events (other than menstrual bleeding disorders) reported by at least 5% of subjects in the Principal Safety Studies (either U.S. study 069001 or the non-U.S. studies combined) are listed in Table 28. The numbers (%) of subjects reporting these adverse events are represented in both terms of treatment related events and all events (any relationship to treatment).

Common Adverse Events Related to Treatment.

The Applicant identified drug-related AEs by applying the following criterion: AEs that were considered by the investigators to be possibly, probably, or definitely related to Implanon™. The more common AEs that met this criterion are presented in Table 28 for the 4 principal safety studies. Adverse events are presented in terms of the U.S. study alone, the non-U.S. studies, and the pooled population of subjects. Drug-related AEs associated with the use of Implanon™ in the pooled population and the percentage of subjects reporting them included acne (14.3%), headache (12.6%), weight increase (11.0%), breast pain (10.0%), emotional lability (5.4%), and dysmenorrhea (4.8%).

Medical Officer's Comments

- **Although acne meets the criteria for a common and drug-related AE, it should be noted that an equivalent number of subjects showed an improvement in acne during Implanon™ treatment. The effects of Implanon™ on acne are presented in detail in Section 10.3 of the revised ISS document. Breast pain is a common complaint in women who use hormonal contraception.**
- **Changes in weight are discussed in detail in Section 7.10.2. Uterine (menstrual) bleeding irregularities are discussed in detail in Section 7.8.**

Common Adverse Events (Any Relationship to Treatment).

Adverse events that occurred in $\geq 5\%$ of subjects in either the U.S. principal safety study or the non-U.S. safety studies combined are listed in Table 28. Adverse events that occurred in $\geq 5\%$ of the 1117 subjects in the 4 principal safety studies combined were as follows: headache (19.9%), acne (15.2%), vaginitis (14.5%), breast pain, female (12.25%), weight increase (11.6%), upper respiratory tract infection (9.6%), abdominal pain (9.4%), pharyngitis (7.8%), leukorrhea (7.3%), dysmenorrhea (6.9%), influenza-like symptoms (6.0%), emotional lability (5.7%), nausea (5.2%) and depression (5.0%).

Medical Officer's Comments

- **Most of the AEs that occur in $\geq 5\%$ of subjects consist of minor symptoms/illnesses. The psychiatric AEs (emotional lability and depression) will need to be addressed in the label.**

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Table 28 Adverse Events (Other Than Irregular Bleeding) Reported in at Least 5 Percent of Subjects in Principal Safety Studies

Preferred term	U.S. ^a (N=330)				Europe/Thailand ^b (N=787)				U.S./Europe/Thailand (N=1117)			
	Related		All AEs		Related		All AEs		Related		All AEs	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Headache	42	12.7	78	23.6	99	12.6	144	18.3	141	12.6	222	19.9
Acne	48	14.5	55	16.7	112	14.2	115	14.6	160	14.3	170	15.2
Vaginitis	8	2.4	56	17.0	6	0.8	106	13.5	14	1.3	162	14.5
Breast pain	23	7.0	28	8.5	89	11.3	108	13.7	112	10.0	136	12.2
Weight increase	40	12.1	42	12.7	83	10.5	88	11.2	123	11.0	130	11.6
Upper respiratory infection	0	--	44	13.3	0	--	63	8.0	0	--	107	9.6
Abdominal pain	1	0.3	9	2.7	46	5.8	96	12.2	47	4.2	105	9.4
Pharyngitis	0	--	14	4.2	0	--	73	9.3	0	--	87	7.8
Leukorrhea	2	0.6	5	1.5	3	0.04	76	9.7	5	0.4	81	7.3
Dysmenorrhea	32	9.7	50	15.2	22	2.8	27	3.4	54	4.8	77	6.9
Influenza-like symptoms	0	--	11	3.3	1	0.01	56	7.1	1	0.1	67	6.0
Emotional lability	47	14.2	48	14.5	13	1.7	16	2.0	60	5.4	64	5.7
Nausea	11	3.3	25	7.6	15	1.9	33	4.2	26	2.3	58	5.2
Depression	24	7.3	33	10.0	11	1.4	23	2.9	35	3.1	56	5.0
Back pain	3	0.9	24	7.3	1	0.1	31	3.9	4	0.4	55	4.9
Nervousness	11	3.3	11	3.3	22	2.8	44	5.6	33	3	55	4.9
Sinusitis	0	--	29	8.8	0	--	18	2.3	0	--	47	4.2
Flatulence	15	4.5	17	5.2	17	2.2	29	3.7	32	2.9	46	4.1
Urinary tract infection	0	--	33	10.0	1	0.1	12	1.5	1	0.1	45	4.0
Pain	7	2.1	17	5.2	1	0.1	25	3.2	8	0.7	42	3.8
Allergy	0	--	20	6.1	0	--	23	2.9	0	--	43	3.8
Fatigue	13	3.9	26	7.9	5	0.6	11	1.4	18	1.6	37	3.3
Accidental injury	0	--	21	6.4	0	--	0	--	0	--	21	1.9
Sexual function abnl	16	4.8	17	5.2	0	--	0	--	16	1.4	17	1.5

Source: Table 45, P 153-154, revised ISS, 04May04

7.6.5 Summary of Adverse Events

Medical Officer's Comments

- As already noted, there were no deaths and no SAEs that were a concern. No clinically significant cardiovascular, cerebral vascular or thromboembolic events were reported. In the medical officer's opinion, the only SAE of potential concern is the number of cases of gallbladder disease, inclusive of gallstones, acute and chronic cholecystitis.
- A review of adverse events does not reveal any issues that would not support approval of Implanon™ for prevention of pregnancy.

7.7 Clinical Laboratory Parameters

Laboratory parameters (hematology, chemistry and urinalysis) were assessed in U.S. Study 069001 and in non-U.S. study 34507 (Austrian site only, N=8). The U.S. laboratory parameters included the following:

1. Hematology: hemoglobin, hematocrit, RBC, WBC and differentials, and platelet count

2. Blood Chemistry: sodium, potassium, chloride, calcium, alkaline phosphatase, total bilirubin, SGOT, SGPT, SGGT, total protein, LDH, BUN, creatinine, uric acid, glucose, phosphorus, total cholesterol, and triglycerides
3. Urinalysis: pH, protein, ketones, glucose, and WBCs

In Study 34507, for the 69 subjects in the Budapest center of Hungary (H 003), limited biochemistry parameters (ALAT, ASAT, bilirubin and gamma-GT) were measured at the end of the 2-year treatment period and before continuation into the third year.

For the 52 subjects in Study 34507 CDN, limited safety laboratory parameters (creatinine, ALAT, ASAT and total bilirubin) were measured at baseline and after 6, 12 and 24 months during treatment.

Hemoglobin was the sole laboratory parameter assessed in Study 34505, in Clinical Pharmacology Studies 34502, 34511, 34514 (UK), and RM01, in Controlled Study RM04, and in Uncontrolled Study RM02.

Laboratory values were categorized as potentially clinically significantly low, low, normal, high, or potentially clinically significantly high based on the normal reference ranges established by the laboratories where the assays were performed. Potentially clinically significant levels were defined by FDA guidelines (“Supplementary Suggestions for Preparing an Integrated Summary of Information in an Original NDA Submission and for Organizing Information in Periodic Safety Updates,” Division of Neuropharmacology, U.S. Food and Drug Administration, 1987) or by Organon personnel.

For U.S. Study 069001 shift tables were presented for the laboratory parameters to show categorical shifts from baseline to the minimum and maximum post baseline value. Subjects' laboratory values that changed categories from the baseline to the post baseline evaluation were reported as either a notable shift or not a notable shift. For most laboratory parameters, a change was considered a notable shift under the following circumstances:

1. Notable Upward Shift: The subject's value increased (shifted) to high or clinically significantly high at the post-baseline maximum from a lower category at baseline.
2. Notable Downward Shift: The subject's value decreased to low or clinically significantly low at the post-baseline minimum from a higher category at baseline.

7.7.1 Hematology Assessments

Medical Officer's Comments

- **The only study of value for assessing hematology parameters is the U.S. study. The most frequently observed notable shifts (significant values) during treatment were low lymphocytes found in 3.0% of subjects and high eosinophils found in 2.7% of subjects. Although these values met the Applicant's definition of clinically significant, none of these abnormalities are clinically meaningful. None of the 327 U.S. subjects had clinically significant low hemoglobin and 1 of 108 subjects in the Europe/Thailand group had a clinically significantly low hemoglobin. Overall, this comprised 0.2%, 1 of the 435 subjects, and is not a safety concern.**
- **The mean hemoglobin in the U.S. study was 8.43 mmol/L (13.9g/dL) at baseline and 8.38 mmol/L (13.8g/dL) at the last measurement, which is essentially unchanged.**

7.7.2 Blood Chemistry Assessments

A shift analysis on blood chemistry parameters was done only for the U.S. Study 069001 and is summarized in Table 29.

Downward Shifts: The most frequent downward notable shifts to minimum or maximum post baseline values were for triglycerides (97 subjects to minimum and 11 subjects to maximum post baseline values, respectively) and total cholesterol (56 subjects to minimum and 14 subjects to maximum post baseline values, respectively). Of these, seven subjects had shifts to clinically significantly low total cholesterol values (one to maximum and six to minimum post baseline values). Other downward notable shifts to clinically significantly low values included phosphorus (six subjects), and glucose (three subjects).

Medical Officer's Comments

- **Although there was a downward shift in total cholesterol and triglycerides in the U.S. study and some of these values met the Applicant's definition of clinically significant, none of the values were considered by the Applicant to be clinically meaningful, and this reviewer concurs with this interpretation. Important to note is that there does not appear to be any worrisome downward shift changes in the chemistry profile with the extended use of Implanon™. No special labeling claims will be allowed relative to lipid changes while using Implanon™.**

Upward Shifts: The most frequent upward notable shifts to minimum or maximum post baseline values were for total protein (29 subjects to maximum and 2 subjects to minimum post baseline values), calcium (14 subjects to maximum and 1 subject to minimum post baseline values) and bilirubin (16 subjects to maximum and 1 subject to minimum post baseline values). Upward notable shifts to clinically significant high values were noted in 2 subjects each for total bilirubin and SGGT. Other upward notable shifts to clinically significantly high values included potassium (four subjects), glucose (three subjects), phosphorus, total bilirubin, and SGGT (two subjects each), and BUN (one subject).

7.7.3 Parameters of Liver Function

Liver function tests (LFTs), specifically total bilirubin, ALAT, ASAT, SGGT, and alkaline phosphatase, were measured as part of the routine laboratory assessment in the U.S. Study 069001. Upward notable shifts to clinically significant high values were noted in 2 subjects each for total bilirubin and SGGT (see Table 29). Mean blood LFT parameters were all within normal limits. Neither mean nor median percent changes from baseline to any subsequent visits were remarkable for any parameter.

Medical Officer's Comments

- **Table 29 shows that 42 LFT measurements in the U.S. study had "upward notable shifts": this included 7 ALAT, 12 ASAT, 7 SGGT, and 16 total bilirubin values. However, as noted above by the Applicant, only 4 of these 42 values (2 bilirubin [37.6umol/L-2.2mg/dL, 47.8umol/L-2.8mg/dL] and 2 SGGT [3.4ukat/L, 3.1ukat/L]) were clinically significant (SGGT > 2.805ukat/L or bilirubin > 34.2umol/L [2.0mg/dL]). None of the four subjects were hospitalized and follow-up values were lower and not clinically**

significant in all cases. The other LFT parameters in these 4 subjects were in the normal range at all visits.

Table 29 Number of Subjects with Notable Shifts in Chemistry Parameters in U.S. Study (N= 330)

Laboratory parameter	Minimum postbaseline value		Maximum postbaseline value	
	Downward notable shift ^a	Upward notable shift ^b	Downward notable shift	Upward notable shift
ALAT/SGPT	-	0	-	7
Alk. Phosphatase	-	0	-	0
ASAT/SGOT	-	0	-	12
BUN	-	0	-	1
Calcium	0	1	0	14
Chloride	10	0	1	10
Creatinine	-	0	-	0
Glucose	25	1	0	10
LDH	-	0	-	6
Phosphorus	31	0	0	6
Potassium	5	0	1	5
SGGT	-	0	-	7
Sodium	2	1	0	12
Total bilirubin	-	1	-	16
Total cholesterol	56	1	14	6
Total protein	5	2	0	29
Triglycerides	97	0	11	2
Uric acid	3	1	0	4

^a A downward notable shift is defined as a shift where the postbaseline value (minimum or maximum) decreased to a low or clinically significantly low category from a higher category at baseline.

^b An upward notable shift is defined as a shift where the postbaseline value (minimum or maximum) increased to a high or clinically significantly high category from a lower category at baseline.

NOTE: Laboratory data were recorded in conventional units and converted to S.I. units where applicable. Downward notable shifts in the following parameters are irrelevant and therefore excluded from this analysis: total bilirubin, alkaline phosphatase, LDH, SGOT, SGPT, SGGT, BUN and creatinine.

Source: Table 55, p 170, revised ISS, 04May04

Limited LFTs were measured over a minimum of 24 months in 28 subjects in Study 34524 and in 129 subjects in Study 34507 (69 in Budapest, Hungary, 52 in Canada, and 8 in Austria). Clinically significant changes in the LFTs were not observed.

The effect of Implanon™ on liver metabolism was evaluated in comparative Study 34509 (Sweden and Finland, N=43+43). Analysis of liver function parameters showed a few treatment differences that reached statistical significance ($p < 0.05$). Noteworthy increases were observed for total bilirubin and γ -GT (SGGT) in 2 subjects for each measure. The increase of total bilirubin with Implanon™ treatment was less than the increase observed with Norplant™, and only reached statistical significance at the 3 month assessment. For ALAT (SGPT), ASAT (SGOT) and alkaline phosphatase, decreases were observed during both treatments. Statistically significantly larger decreases were found in the Implanon™ group for ALAT at month 6 and last measurement and for alkaline phosphatase at month 1 when compared to Norplant™.

Medical Officer's Comments

- **In summary, this reviewer agrees that the LFT results in approximately 545 subjects, obtained from Studies 069001(n=330), 34507(n=129) and 34524(n=86), do not raise a safety concern.**

7.7.4 Parameters of lipid metabolism

Parameters of lipid metabolism were assessed in Studies 34510 (Thailand), 34512, 34514 (UK), 34522, and 069001. The measured parameters were total cholesterol, triglycerides, LDL-cholesterol, HDL-cholesterol, and apolipoproteins A1, A2, and B. Not all parameters were assessed in every study. Study 34510 showed that the changes after treatment were relatively minor for all parameters evaluated (i.e. total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, apolipoprotein A-I, apolipoprotein A-II, apolipoprotein B, HDL/LDL ratio, HDL/total cholesterol ratio, and apolipoprotein A-I/B ratio). The results for Studies 34512, 34522, and 069001 likewise showed that only relatively minor changes from baseline were observed for the evaluated parameters. In Study 34514 (UK) only apolipoprotein was evaluated. Changes from baseline were minor and no significant differences between Implanon™ and Norplant™ treatments were found except for the last measurement of apolipoprotein B. This was due to a decrease of 0.02 mg/dL for the Implanon™ group in comparison to an increase of 0.06 mg/dL for the Norplant™ group.

Medical Officer's Comments

- **The data obtained from the clinical studies of Implanon™ did not reveal any adverse effect on lipid metabolism for both Implanon™ and Norplant™. No special claims can be made in the label based on these studies. Likewise, there are no safety concerns.**

7.7.5 Parameters of Hemostasis

Effects of progestins in combined oral contraceptives on hemostatic function seem to be minimal. Little information is available on the use of etonogestrel as a single agent and its effect on hemostasis. Study 34509 (Sweden and Finland, N=43) was designed to investigate the effects of Implanon™ on hemostasis and liver function in comparison to Norplant™. The period of study was six months. Blood samples were taken at Screen, just prior to implant insertion and at Months 1, 3, and 6. Hemostatic parameters evaluated were as follows:

- Coagulation and coagulation inhibition; activated partial thromboplastic time (APTT), prothrombin time (PT), fibrinogen (factor 1), factor VII activity, factor VIII activity, factor VIII RiCoF (von Willebrand, vWF) activity, factor X, AT-III activity, protein C, protein S free, protein S total
- Fibrinolysis and fibrinolysis inhibition; plasminogen activity, α_2 antiplasmin activity and plasminogen activator inhibitor (PAI-1), fibrin D dimer
- Platelet count and acute phase reactant α_1 -acid glycoprotein (orosomuroid).

In general, changes from baseline of hemostatic parameters were small and well within the normal variation as indicated by the standard deviations observed at baseline. No consistent significant differences were observed between Implanon™ and Norplant™ with regard to coagulation promoters and coagulation inhibitors. Changes from baseline for the coagulation

times APTT and PT were minor during Implanon™ treatment. For APTT no significant treatment differences were found between the Implanon™ group and the Norplant™ group.

Plasminogen activity was slightly and comparably increased in both treatment groups. In both groups a small decrease for α_2 antiplasmin activity was observed, the extent of which was larger in the Norplant™ group at Months 1 and 6. Statistically significant differences in changes of PAI-1 between the treatment groups were not observed at any time-point. This parameter showed a large variation. Several subjects had concentrations of PAI-1 above the upper limit of the reference range of 15 U/mL already at one or both time-points before the start of treatment. Fibrin D-dimer showed a decrease in both treatment groups (except at 1 month in the Norplant™ group), but no statistically significant differences were observed between the treatment groups.

Changes from baseline in platelet count and α_1 -acid glycoprotein were small and similar for both treatment groups.

Medical Officer's Comments

- **This study was performed in 43 women at 4 sites in Sweden and Finland in 1992-93. It is of limited value because of the small number of participants. There were no observed changes in the hemostatic and coagulation parameters that were a signal of concern. In general, there were no major clinical differences between the Implanon™ group and the Norplant™ group.**

7.8 Effects of Treatment on Uterine Bleeding or Spotting

7.8.1 Methods of Analysis

Subjects in the four principal safety and efficacy studies (Studies 069001, 34505, 34507, and 34507 CDN) had to be healthy females who were sexually active, of childbearing potential, and between 18 and 40 years of age. The subjects had to have normal menstrual cycles with a length of 24-35 days and an intra-individual variation of plus or minus 3 days and were not to be currently pregnant or breast feeding. Body weight for inclusion was to be between 80% and 130% of the ideal body weight.

To evaluate the effects of Implanon™ on the menstrual cycle all subjects were given diary cards to record daily occurrences of vaginal bleeding, spotting, and the absence of bleeding or spotting. Data were recorded to perform a reference period (RP) analyses as described by the World Health Organization in which medically relevant bleeding variables were identified and evaluated over consecutive 90-day reference periods. Each 90-day segment represented one reference period, starting with the day of implant insertion as the first day of the first reference period. Data from the Reference-Period-Analyses Group were used to conduct reference period analyses. Reference period analyses included all subjects who had at least 1 evaluable 90-day reference period. A reference period was considered not evaluable and excluded from analysis if diary data with bleeding information were missing for 3 or more consecutive days or if concomitant medications that were not permitted were used. If missing data were spread across 2 reference periods, then both reference periods were excluded. If diary data were missing for less than 2 consecutive days, the missing values were replaced with the same bleeding-spotting response reported on the day immediately preceding the missing values. If the data were missing on the first 1 or 2 days of treatment, then the day immediately following the missing data was used.

Medical Officer's Comments

- **Please see the Medical Officer's Review of IND 42,877/S-000. The proposed Reference-Period-Analysis was acceptable.**

The following definitions were used by the subjects to record daily occurrences of bleeding during the conduct of the clinical trials:

- A "bleeding day" was defined as any day with vaginal discharge containing blood that required more than one sanitary napkin or tampon per day.
- A "spotting day" was defined as any day with vaginal discharge containing blood that did not require more than one sanitary napkin or tampon per day.
- A "bleeding-free day" was defined as a day during which neither bleeding nor spotting was entered in the diary.

The following definitions were used in the analysis of vaginal bleeding patterns in the controlled clinical studies:

- A "bleeding-spotting episode" was defined as one or more consecutive days during which bleeding or spotting was entered in the diary, bounded by bleeding-free days.
- A "bleeding episode" was defined as one or more consecutive days during which bleeding was entered in the diary, bounded by bleeding-free days.
- A "spotting episode" was defined as one or more consecutive days during which spotting was entered in the diary, bounded by bleeding-free days.
- A "bleeding-free interval" was defined as one or more consecutive days during which neither bleeding nor spotting was entered in the diary, bounded by bleeding or spotting days.
- "Amenorrhea" was defined as no bleeding or spotting days throughout the 90-day reference period.
- "Prolonged bleeding" was defined as any bleeding-spotting episode (uninterrupted) lasting more than 14 days in a 90-day reference period.
- "Frequent bleeding" was defined as more than five bleeding-spotting episodes in a 90-day reference period.
- "Infrequent bleeding" was defined as less than three bleeding-spotting episodes in a 90-day reference period, excluding amenorrhea.

Medical Officer's Comments

- **The definitions used to record daily spotting/bleeding events are "standard" and were equally employed across the four principal studies.**

The All-Subjects-Treated Group included all subjects who were treated with Implanon™. The Reference-Period-Analysis Group consisted of all subjects treated who contributed at least one evaluable period for the analysis of vaginal bleeding patterns (period not evaluable if diary data with bleeding information were missing for 3 or more consecutive days or if concomitant medications that were not permitted were used). As shown in Table 30, a total of 1,117 subjects

in Studies 069001, 34505, 34507, and 34507 CDN were treated with Implanon™ and a total of 1,062 subjects (95.1%, 1062 of 1117 subjects) contributed bleeding data for the reference period (RP) analyses.

Table 30 Number of Subjects in the All-Subjects-Treated Group and Reference-Period-Analysis Group for the Four Principal Studies.

Study Number	Number of Subjects Included in the All-Subjects-Treated Group	Number of Subjects Included in the Reference-Period-Analysis Group
U.S. Study		
Study 069001	330	310
Non-U.S. Studies		
Study 34505	100	100
Study 34507	635	603
Study 23407 Canada	52	49
Total: Non-U.S. Studies	787	752
Total: U.S. and Non-U.S. Studies	1117	1062

Source: NDA 21-259, Integrated Summary of Efficacy, Table 7, page 0057.

U.S. Study 069001

At baseline, the mean length of the menstrual cycle in U.S. Study 069001 was 28.3 days (standard deviation [SD] =1.5 days) and the mean duration of bleeding was 4.5 days (SD=1.2 days).

Non-U.S. Studies 34505, 34507 and 34507 CDN

At baseline, the mean length of the menstrual cycle (measured only in Studies 34507 and 34507 CDN) ranged from 28.4 days (SD=1.6 days) to 28.2 days (SD=1.4 days), respectively, and the mean duration of bleeding (measured in all three non-U.S. studies) ranged from 3.8 days in Study 34505 (SD=1.2 days) to 4.9 days in Study 34507 (SD=1.2 days). Study 34507 CDN reported a mean duration of bleeding of 4.6 days (SD=1.1 days).

Clinical Pharmacology Studies

Bleeding data for the clinical pharmacology studies conducted in Europe, Singapore, and Thailand studies were pooled (Studies 34502, 34508, 34509, 34510 [Thailand], 34511, 34512 [UK], 34514, 34515, and 34522). The mean duration of menstrual bleeding at baseline was 4.8 days (SD=1.4 days).

Medical Officer's Comments

- **No significant difference in mean length of menstrual cycle or mean duration of bleeding at baseline is noted across the four adequate and well-controlled studies and the clinical pharmacology studies.**
- **The mean duration of menstrual bleeding at screening was comparable for the U.S. study, the Europe/Thailand studies, and the clinical pharmacology studies (4.5 days, 4.4 days, and 4.8 days, respectively) and appears normal for the study population.**

7.8.2 Integrated Analysis of Vaginal Bleeding Patterns

An integrated analysis of vaginal bleeding patterns was performed to provide an overview of the effect of Implanon™ on the menstrual cycle. Bleeding pattern indices for subjects completed or discontinued during the treatment period were summarized by treatment groups. Because Study 34523 was a lactation study, it was excluded from the bleeding pattern analysis. Data on bleeding patterns are available for a total of 1,372 women who received Implanon™. Table 31 provides an overview of studies included in the integrated analysis of vaginal bleeding patterns.

Table 31 Overview of Studies Included in the Integrated Analysis of Vaginal Bleeding Patterns

Study	Region	Duration (Years)	Implanon™		
			N	Number of RP	
				2-Years	3-Years
069001	N. America	2	330	1674	-
34502	S.E. Asia	5	15	120	165
34505	S.E. Asia	4	100	679	904
34507 ^a	Europe/Chili/N. America	3	687	3803	4326
34508	Europe	3	16	88	110
34509	Europe	2	43	186	187 ^b
34510	S.E. Asia	2	15	109	-
34511	S.E. Asia	2	40	304	-
34512	Europe	2	40	192	-
34514	Europe	3	30	208	252
34515	S.E. Asia	2	10	74	-
34522	Europe/Chile	2	46	308	-
Total			1372	7745	5944

N = Number of subjects in the All-Subjects-Treated Group

RP = 90-Day Reference Period

- = Not available

a. Includes Study 34507 and Study 34507 CDN.

b. Subject 00087 in Study 34509 had an assessment that was outside the window for a final visit at the end of year 2.

Source: Adapted from NDA 21-529, Integrated Summary of Efficacy, Table 36, page 0105.

Discontinuations Due to Bleeding Irregularities (All-Subjects-Treated Group)

Information on discontinuations due to bleeding irregularities in U.S. Study 069001 was derived from the Adverse Experience page of the Case Report Form (CRF). In the non-U.S. Studies 34505 and 34507, the primary reason for discontinuation was categorized based on a pre-defined code list on the Implant Removal form which was part of the CRF. The investigator could choose one of the following bleeding irregularities reasons or amenorrhea: frequent irregular bleeding, heavy menstrual flow, prolonged menstrual flow, spotting, other bleeding problems, or amenorrhea. The same method of classification was used for the clinical pharmacology studies (Studies 34502, 34508, 34509, 34510, 34511, 34512, 34514, 34515, and 34522).

Medical Officer's Comments

- **In U.S. Study 069001, the following “categories” appear on the CRFs for a subject who discontinued due to bleeding irregularities: bleeding and spotting, irregular bleeding/spotting, continuous bleeding/spotting, heavy bleeding, prolonged bleeding/spotting, frequent bleeding, and amenorrhea. These reported bleeding irregularities given as reasons for discontinuation in Study 069001 are similar to or the same as those used in the non-U.S. studies and clinical pharmacology studies. Therefore, little or no differences in reporting bleeding irregularities occurred across the principal studies conducted under NDA 21-259.**

Discontinuations due to bleeding irregularities and amenorrhea in the principal studies and the clinical pharmacology studies combined are presented in Table 32. The number and percentages are displayed for Implanon™-treated subjects.

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Table 32 Number and Percentage of Implanon™ Treated Subjects Who Discontinued Due to Bleeding Irregularities or Amenorrhea as the Primary Reason – Principal and Supportive Clinical Pharmacology Studies Combined

Area	Reason for discontinuation	Specification	Implanon™ n (%)	
Europe and N. America (n = 1070)	Amenorrhea		17	(1.6%)
	Bleeding irregularities	Frequent irregular bleeding	103	(9.6%)
		Heavy menstrual flow	9	(0.8%)
		Prolonged menstrual flow	46	(4.3%)
		Spotting	29	(2.7%)
		Other bleeding problems	7	(0.7%)
	Total bleeding irregularities and amenorrhea		211	(19.7%)
S.E. Asia and Chile (n = 302)	Amenorrhea		1	(0.3%)
	Bleeding irregularities	Frequent irregular bleeding	4	(1.3%)
		Heavy menstrual flow	1	(1.0%)
		Prolonged menstrual flow	3	(1.0%)
		Spotting	3	(1.0%)
		Other bleeding problems	0	(0.0%)
	Total bleeding irregularities and amenorrhea		12	(4.0%)

N = All-Subjects-Treated group size.

n = Number of subjects who discontinued within category.

* = Studies 069001, 34502, 34505, 34507, 34507 CDN, 34508, 34509, 34510, 34511, 34512, 34514, 34515, and 34522.

Source: NDA 21-529, Integrated Summary of Efficacy, Table 37, page 0106.

Based on the individual study reports, there were differences in the rate of discontinuation due to bleeding irregularities and amenorrhea between studies in Europe and North America (19.7%, 211 of 1070 subjects) and Southeast Asia and Chile (4.0%, 12 of 302 subjects).

Medical Officer’s Comments

- **Discontinuations due to bleeding irregularities and amenorrhea in clinical pharmacology comparative studies (Studies 34508, 34509, 34510, 34511, 34512, and 34514 comparing Implanon™ and Norplant™) showed similar Implanon™ results for Europe compared with Southeast Asia as those noted above. In Europe, 30.2% (39 of**

129 subjects) discontinued due to bleeding irregularities and amenorrhea while no subject (0.0%, 0 of 55 subjects) in S.E. Asia discontinued due to bleeding irregularities and amenorrhea. For Norplant™, however, less subjects discontinued in Europe due to bleeding irregularities and amenorrhea than with Implanon™ (22.5%, 29 of 129 subjects) but more discontinued with Norplant™ in S.E. Asia (7.3%, 4 of 55 subjects) (See NDA 21-529, Integrated Summary of Efficacy, Table 38, page 0108).

- In Europe and North America, most of the subjects who discontinued Implanon™ due to bleeding irregularities, discontinued due to frequent irregular bleeding (9.6%, 103 of 1070 subjects) and prolonged menstrual flow (4.3%, 46 of 1070 subjects) while in Southeast Asia and Chile discontinuations due to any cause bleeding irregularity was minimal (4.0%, 12 of 302 subjects).**
- Overall, the reasons for the differences observed in bleeding irregularities and amenorrhea and discontinuation between Europe and N. America and S.E. Asia and Chile are not fully appreciated. It is possible that cultural differences have influenced these findings and that women in Southeast Asia and Chile are more accepting of altered bleeding patterns than women in the U.S. or Europe or are more hesitant to report such occurrences.**
- It is interesting to note, however, that a small percentage of study subjects in Europe and N. America (1.6%, 17 of 1070 subjects) discontinued because of amenorrhea (only one subject in S.E. Asia and Chile gave amenorrhea as the reason for discontinuation). Although this percentage is less than the more common reasons given for discontinuation (for example, frequent irregular bleeding, prolonged bleeding, and spotting), discontinuation due to amenorrhea highlights the “norm” during childbearing years that “predictable” bleeding is better understood and accepted.**

Reference Period Analyses Group

Study populations in the Principal Safety and Efficacy studies had to have normal menstrual cycles with a length of 24-35 days and an intra-individual variation of plus or minus 3 days and were not to be currently pregnant or breast feeding. All subjects were given diary cards to record daily occurrences of vaginal bleeding, spotting, or the absence of bleeding or spotting.

The reference period (RP) analysis defined the subject as the unit of analysis. The reference period analysis divided a subject's bleeding information into 90-day segments. The main reference period analysis in NDA 21-259 is based on the principal non-comparative studies (Studies 069001, 34505, 34507, and 34507 CDN). An additional RP analysis was performed that combined the principal non-comparative studies with the clinical pharmacology non-comparative studies (Studies 34502, 34515, and 34522) since the sample size for the clinical pharmacology non-comparative studies was small (N = 86) and this data is considered supplemental. Reference period analysis for the clinical pharmacology comparative studies (Studies 34508, 34509, 34510, 34511, 34512, and 34514 [UK]) is also provided.

The reference period analyses are based on subjects who completed 2 years of treatment (greater than or equal to 720 days) since 2-year data are available for most studies. In order to assess further changes in bleeding patterns with time, data from the group of subjects who were considered to have completed 3 years is also presented (greater than or equal to 1080 days).

Bleeding patterns over time may be influenced by subjects who discontinue treatment. Therefore, time trends were explored for subjects who were considered to have completed 2 years of treatment. In addition, subjects who discontinued treatment during the first 2 years of treatment were compared to subjects who completed 2 years of treatment in order to investigate the bleeding characteristics of subjects who discontinued. This comparison was based on descriptions of within subject averages and incidences over reference periods 2 through 6 because only a few subjects who discontinued prior to 2 years of treatment contributed data to reference period 7 and none of the subjects who discontinued prior to 2 years contributed data to reference period 8.

For statistical comparisons of bleeding patterns, reference period (RP) one was excluded as implants were inserted during a menstrual period. For the binary bleeding parameters, a Wilcoxon rank sum test on the treatment difference in mean incidence per subject over reference periods 2 through 8 was used for those subjects who completed 2 years of treatment. For the continuous variables, longitudinal analysis of treatment differences over RP 2 through RP 8 was performed for the comparative studies (Studies 34508, 34509, 34510, 34511, 34512, and 34514 [UK] used a Norplant™ comparator treatment group).

Table 33 presents the data for bleeding parameters for those subjects who discontinued prior to completion of 2 years of treatment and those who completed 2 years of treatment in Studies 069001, 34505, 34507, and 34507 CDN combined. Implanon™-treated subjects (completers and non-completers combined) experienced a mean of 18.19 bleeding-spotting days per 90-day reference period. Roughly half of the 18.19 bleeding-spotting days were bleeding days (8.09 days, where more than one sanitary napkin or tampon was used per day). A mean of 2.56 bleeding-spotting episodes (defined as one or more consecutive days of diary recorded bleeding or spotting, bounded by bleeding-free days) was observed over reference period 2 through 6.

Table 33 Bleeding Parameters for Subjects Who Completed or Discontinued for Any Reason During the First 2 Years in the Principal Studies (Reference Period Analysis Group)

Parameters	Implanon™					
	Completed (N = 676)		Discontinued (N = 239)		Total (N = 915)	
	Number of RP	Mean	Number of RP	Mean	Number of RP	Mean
Bleeding-spotting days	3096	17.07	640	23.58	3716	18.19
Bleeding days	3076	7.59	640	10.52	3716	8.09
Bleeding-spotting episodes	3076	2.51	640	2.78	3716	2.56

N = Number of subjects with bleeding-spotting parameters defined for at least one RP.

Completed = 2-year completers (treatment duration ≥ 720 days).

Discontinued = Discontinuation before day 721.

RP = 90-day reference period.

Mean = Mean over all reference periods 2 through 6.

Source: NDA 21-259, Integrated Summary of Efficacy, Table 39 (Studies 069001, 34505, 34507, and 34507 CDN), page 0112.

In the clinical pharmacology comparative studies (Studies 34508, 34509, 34510, 34511, 34512, and 34514), Implanon™-treated subjects who completed or discontinued during the first 2 years of treatment experienced fewer bleeding-spotting days than did subjects who received Norplant™ (19.47 versus 21.24 days, respectively) and fewer bleeding days (7.95 versus 11.80 days, respectively). Also, the mean number of bleeding-spotting episodes was lower in the Implanon™-treated subjects when compared with the Norplant™-treated subjects (2.53 versus 3.24 episodes).

The analyses of bleeding parameters for subjects who completed or discontinued during the first three years of treatment with Implanon™ in the principal studies showed results similar to those observed for subjects during the first two years of treatment for the same studies: a mean of 18.08 bleeding-spotting days per 90-day reference period (RP 2 through 9, N = 448). Less than half of the 18.08 bleeding-spotting days were bleeding days (7.78 days). A mean of 2.44 bleeding-spotting episodes were observed over reference period 2 through 9. Similar results were observed in the principal and clinical pharmacology non-comparative studies combined: 18.11 bleeding-spotting days, 7.76 bleeding days, and 2.43 episodes (N = 470).

Medical Officer's Comments

- **It is well accepted that progestin alone contraception is associated with disruption of bleeding patterns, especially during the first year of use. Unlike the use of cyclic combined estrogen/progestin contraception, the daily progestational impact of progestin alone contraception, the resulting variable suppression of endogenous estrogen, and the absence of exogenous estrogen all contribute to the formation of an unstable endometrium. In addition, the absence of cyclic administration does not allow for predictable vaginal withdrawal bleeding. Consequently, the resulting relatively unstable endometrium sheds at unpredictable intervals.**
- **As shown in Table 33 above, subjects with bleeding irregularities who discontinued experienced an average of 6.51 more days of bleeding-spotting (23.58 days for non-completers versus 17.07 days for completers) and 2.93 more days of bleeding (10.52 days for non-completers versus 7.59 days for completers) per 90-day reference period than completers. These reported differences may have influenced the decision to continue or discontinue study participation.**
- **However, a mean of 18.19 bleeding-spotting days per 90-day reference period is only slightly different from the reported mean duration of bleeding at baseline in the study population. At baseline, the study population in the Principal Studies reported a mean (SD) duration of bleeding of 4.6 ± 1.2 days of bleeding over a mean (SD) 28.3 ± 1.5 days length of the menstrual cycle (roughly a total of 14 days of bleeding over three menstrual cycles). What is different in reported bleeding/spotting in Implanon treated subjects, however, is the absence of "expected" menstrual cycle withdrawal bleeding that has been largely replaced by an increase in unpredictable bleeding.**

An examination of the bleeding pattern indices for subjects in the Principal Safety and Efficacy Studies (Studies 069001, 34505, 34507, and 34507 CDN) that completed or discontinued during the first two years of treatment shows that infrequent bleeding was common (defined as less than three bleeding-spotting episodes in a 90-day reference period, excluding amenorrhea) with an incidence of 32.5% (completers and non-completers combined) while the mean incidence of amenorrhea (defined as no bleeding or spotting days throughout the 90-day reference period) and

prolonged bleeding (defined as any bleeding-spotting episode (uninterrupted) lasting more than 14 days in a 90-day reference period) were similar (19.2% and 18.0%, respectively). Only 7.6% of completers and non-completers combined experienced frequent bleeding. See Table 34.

Table 34 Bleeding Pattern Indices for Subjects Who Completed or Discontinued During the First 2 Years, Principal Safety and Efficacy Studies (Reference Period Analysis Group)

Bleeding pattern indices	Implanon™					
	Completed (N = 676)		Discontinued (N = 239)		Total (N = 915)	
	Number of RP	%	Number of RP	%	Number of RP	%
Amenorrhea	3076	20.2	640	14.4	3716	19.2
Infrequent bleeding	3076	32.2	640	33.9	3716	32.5
Frequent bleeding	3076	7.4	6.4	8.9	3716	7.6
<i>Prolonged bleeding</i>	3076	15.9	640	28.0	3716	18.0

% = Percentage of pattern index occurrence.

N = Number of subjects with bleeding-spotting parameters defined for at least one RP.

Completed = 2-year completers (treatment duration ≥ 720 days).

Discontinued = Discontinuation before day 721.

RP = reference periods 2 through 6.

Source: NDA 21-259, Integrated Summary of Efficacy, Table 41 (Studies 069001, 34505, and 34507), page 0114.

Similar results are noted in Table 35 for the bleeding pattern indices for subjects in the Principal Safety and Efficacy Studies that completed or discontinued Implanon use during the first three years of treatment.

Table 35 Bleeding Pattern Indices for Subjects Who Completed or Discontinued During the First 3 Years, Principal Safety and Efficacy Studies (Reference Period Analysis Group)

Bleeding pattern indices	Implanon™					
	Completed (N = 191)		Discontinued (N = 257)		Total (N = 448)	
	Number of RP	%	Number of RP	%	Number of RP	%
Amenorrhea	1437	20.7	779	18.9	2216	20.1
Infrequent bleeding	1437	34.7	779	32.6	2216	34.0
Frequent bleeding	1437	6.7	779	8.3	2216	7.3
<i>Prolonged bleeding</i>	1437	15.2	779	24.8	2216	18.5

% = Percentage of pattern index occurrence.

N = Number of subjects with bleeding-spotting parameters defined for at least one RP.

Completed = 3-year completers (treatment duration > 1081 days).

Discontinued = Discontinuation before day 1081.

RP = Reference periods 2 through 9.

Source: NDA 21-259, Integrated Summary of Efficacy, Appendix A, Table 6.4 (Studies 069001, 34505, and 34507), page 0151.

Medical Officer's Comments

- **Table 34 and Table 35 above demonstrate the consistency in an increased infrequent bleeding pattern observed for completers and non-completers alike throughout two or three years of treatment (32.2% and 33.9% after two years, respectively; and 34.7% and 32.6% after three years of treatment, respectively). Therefore, no noticeable difference is observed in incidence of infrequent bleeding in women who completed or discontinued during the first two years of treatment or who completed or discontinued following an extension for three years.**
- **The term “infrequent bleeding,” can be misleading as it means according to the Applicant less than 3 bleeding-spotting episodes in a 90-day reference period. Since a bleeding episode can be of any length, a woman could have “infrequent bleeding” and still have a large number of days of bleeding-spotting days (e.g., 2 bleeding-spotting episodes each of 14 days length or 28 days of bleeding-spotting) in a 90-day reference period.**
- **Differences are observed, however, in the prevalence of prolonged bleeding among completers and non-completers at 2 years and 3 years. A higher percentage of subjects who experienced prolonged bleeding discontinued at two years (28.0% discontinued versus 15.9% completers) and at three years (24.8% discontinued versus 15.2 completers). Clearly, the incidence of prolonged bleeding influences the decision to discontinue treatment. The issue of infrequent bleeding and prolonged bleeding should be address in labeling.**

A more in-depth look at the mean number of bleeding-spotting and bleeding days for subjects who completed 2 years of treatment in the principal studies shows that the greatest mean number of bleeding-spotting days and bleeding days was observed during reference period one. This was expected however since Implanon™ was inserted during menstruation. Therefore, reference periods 2 through 8 are more pertinent to assess bleeding parameters over time. See Table 36.

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Table 36 Bleeding Parameters for Subjects Who Completed 2 Years, Principal Safety and Efficacy Studies (Reference Period Analysis Group)

Parameters	Reference Period	Implanon™ Users			
		N	Mean	SD	Median
Number of bleeding-spotting days	1	628	26.79	20.47	22.00
	2	622	18.72	18.61	14.00
	3	624	16.09	15.88	13.00
	4	620	16.52	15.50	14.00
	5	606	16.84	14.95	15.00
	6	604	17.18	14.92	15.00
	7	605	17.48	15.10	15.00
	8	595	18.32	13.90	17.00
Number of bleeding days	1	628	8.37	9.87	5.00
	2	622	6.71	9.53	3.00
	3	624	7.18	9.62	3.00
	4	620	7.89	9.37	6.00
	5	606	8.01	8.94	6.00
	6	604	8.19	8.93	6.00
	7	605	8.45	9.32	6.00
	8	595	9.53	9.47	8.00
Number of bleeding-spotting episodes	1	628	2.91	2.21	2.50
	2	622	2.62	2.13	2.00
	3	624	2.41	2.14	2.00
	4	620	2.49	2.15	2.00
	5	606	2.54	1.99	2.00
	6	604	2.50	1.92	2.00
	7	605	2.56	1.87	3.00
	8	595	2.64	1.70	3.00

N = Number of subjects analyzed within the reference period.

Completed = 2-year completers (treatment duration ≥ 720 days).

RP = 90-day reference period.

Source: NDA 21-259, Integrated Summary of Efficacy, Table 40 (Studies 069001, 34505, and 34507), page 0113.

Medical Officer's Comments

- **Between reference periods 2 through 8 the mean number of bleeding-spotting days and bleeding days for subjects who completed 2 years of treatment ranged between 16.09 and 18.72 days and 6.71 and 9.53 days, respectively. Thus, the number of bleeding-spotting days across RP 2 through 8 remained fairly constant with no significant decrease in the number of bleeding-spotting days or bleeding days over time. Similar results are noted for the clinical pharmacology comparative studies for Implanon™-treated subjects (15.73 and 19.41 days and 5.98 and 8.61 days, respectively) and were consistently lower than that observed for Norplant™ (18.73 and 21.18 days and 10.35**

and 12.39 days, respectively). See NDA 21-259, Integrated Summary of Efficacy, Table 43 and 44 and text, pages 0117-0120 for more details regarding the clinical pharmacology comparative studies.

- In total, 16.2% of subjects (223 of 1372 subjects in the Principal Safety and Efficacy Studies and the Clinical Pharmacology Studies combined) discontinued treatment with Implanon™ due to bleeding irregularities or amenorrhea (see Table 32). Amenorrhea was given as the reason for discontinuation by 1.3% of subjects (18 of 1372 subjects). The remaining subjects who discontinued (14.9%, 205 of 1372 subjects) indicated bleeding irregularities as the reason for discontinuation). Of the 205 subjects who discontinued Implanon™ due to bleeding irregularities, 7.8% experienced frequent irregular bleeding (107 of 1372 subjects) and 3.6% experienced prolonged menstrual flow (49 of 1372 subjects). The remaining 49 subjects (3.6%, 49 of 1372 subjects) experienced heavy menstrual flow, spotting, or other bleeding problems.
- Overall, the vaginal bleeding associated with the use of Implanon™ is characterized by an unpredictable bleeding pattern. Noticeable difference was observed in the effects of prolonged bleeding on completion or discontinuation. A higher percentage of subjects who experienced prolonged bleeding discontinued at two years (28.4% discontinued versus 15.9% completers) and at three years (25.0% discontinued versus 15.3 completers, see Table 34 and Table 35)
- In spite of the unpredictable bleeding pattern observed in subjects who use Implanon for prevention of pregnancy, a review of hematology parameters (hemoglobin, hematocrit, RBC, WBC and differentials, and platelet count) assessed in Studies 069001 and Study 34507 (Austrian site only) shows that none of the subjects in U.S. Study 069001 (N = 327) and only one subject in Study 34507 (N = 8) had a clinically significant low hemoglobin (see section 7.7.1 of this review).

7.9 Implanon™ Insertion and Removal

For all studies an implant was to be placed in the upper arm of each subject and remain in situ for the study duration. At each visit (clinic visit at 3 month intervals) during treatment, the implant site was inspected for complications and the findings were recorded on the CRF.

7.9.1 Implant Insertion

In women with normal cycles (as described under vaginal bleeding), insertion of the implant was to be performed on or between the first and fifth day of the subject's menstrual flow. In post-partum subjects, the implant was to be inserted within 8 weeks after delivery. Implanon™ was inserted on the inside of the upper (non-dominant) arm, 6 to 8 cm above the elbow in the groove between the biceps and triceps (sulus bicipitalis medialis) and remained in situ for the study duration. At each visit (clinic visit at 3 month intervals) during treatment, the implant site was inspected for complications and the findings were recorded on the case report form (CRF).

The mean (SD) insertion time in the U.S./Europe/Thailand studies was 88.2 ± 111.4 seconds with a range of 2 to 900 seconds. Regional differences were observed with longer mean (SD) insertion times observed for subjects from Europe/Thailand compared to the U.S. (112.9 ± 118.0 seconds and 29.3 ± 62.5 seconds, respectively). Similar mean insertion times were observed for the clinical pharmacology studies (68.2 ± 59.4 , range of 4 to 300 seconds)

7.9.2 Implant Removal

The implant was located by palpation. The subject's arm was washed and antiseptic applied. A small amount of 1% lidocaine was applied under the implant. After a 2 mm incision was made, the implant was gently pushed toward the incision until the tip was visible and grasped with forceps and removed. After removal, the incision was closed and bandaged.

The mean (SD) removal time was 266.2 ± 309.1 seconds with a range of 10 to 3600 seconds. Longer mean (SD) removal times were observed for subjects from Europe/Thailand compared to the U.S. (288.3 ± 301.4 and 215.0 ± 321.0 seconds, respectively). Similar mean (SD) removal times were observed for the clinical pharmacology studies (164.1 ± 140.5 , range of 15 to 1200 seconds).

Medical Officer's Comments

- **Summary statistics for implant insertion times in principal and clinical pharmacology studies combined showed a mean (SD) insertion time of 84.3 ± 103.8 seconds and a mean (SD) removal time of 244.1 ± 284.4 seconds. Overall, these findings demonstrate the ease of insertion and removal of Implanon™ under a clinical trial setting.**

7.9.3 Assessment of the Implant Site

The assessment of the condition of the implant site for Implanon™-treated subjects in Studies 069001, 34505, 34507 and 34507 CDN is summarized in Table 37.

Table 37 Condition of Implant Site in Principal Studies

Condition	Implanon™					
	U.S. ^a (N = 330)		Europe/Thailand ^b (N = 787)		Total (N = 1117)	
	n	%	n	%	n	%
Any assessment (N)	327	-	785	-	1112	-
Swelling	0	0.0	4	0.5	4	0.4
Redness	1	0.3	4	0.5	5	0.4
Pain	12	3.7	25	3.2	37	3.3
Hematoma	0	0.0	4	0.5	4	0.4
Expulsion	0	0.0	0	0.0	0	0.0
Last assessment (N)	327	-	785	-	1112	-
Swelling	0	0.0	3	0.4	3	0.3
Redness	0	0.0	3	0.4	3	0.3
Pain	3	0.9	7	0.9	10	0.9
Hematoma	0	0.0	2	0.3	2	0.2
Expulsion	0	0.0	0	0.0	0	0.0

a. Study 069001.

b. Studies 34505, 34507, and 34507 CDN.

Source: NDA 21-529, Integrated Summary of Safety, Table 94, page 0238.

Pain was the most frequently reported condition at any visit (37 subjects, 3.3%) and at last assessment (10 subjects, 0.9%). This finding was the same in the Clinical Pharmacology Studies

34502, 34508, 34509, 34510 (Thailand), 34511, 34514 (UK), 34515, 34522, and 34523. Eleven subjects (3.7%, 11 of 297 subjects) reported pain at any one visit. One subject (0.3%, 1 of 297 subjects) reported pain at last assessment. No complaints related to the site of placement were reported in Study RM04 and only one subject complained of pain at the site of placement at the Month 12 visit in Study RM02.

Medical Officer's Comments

- **Overall, a total of 63 subjects experienced an adverse event at the implant site (including swelling, redness, pain, hematoma, and expulsion) at any one assessment during the 2 year treatment period in the Principal and Clinical Pharmacology studies combined (4.5%, 63 of 1409 subjects). The percentage of subjects experiencing these same abnormalities at last assessment decreased to 1.4% (20 of 1409 subjects). These findings indicate that the majority of Implanon™-treated subjects reported no abnormalities during any of the assessments.**
- **Although pain was the most frequently reported adverse condition at the implant site during any one clinic visit in the Principal and Clinical Pharmacology Studies combined (3.4%, 48 of 1409 subjects), only 10 subjects reported pain at the implant site at the last visit (0.7 %, 10 of 1409 subjects).**
- **No safety concerns arise from these data.**

7.9.4 Complications of Implant Insertion

In studies conducted in U.S./Europe/Thailand, 14 subjects (1.3%, 14 of 1117 subjects) experienced complications at implant insertion. Insertion complications included:

- implant stayed in needle;
- slight bleeding and compression;
- hematoma;
- difficult insertion.

In Clinical Pharmacology Studies 34502, 34508, 34509, 34510 (Thailand), 34511, 34512, 34514 (UK), 34515, 34522, and 34523, only 1 subject experienced a complication at implant insertion (0.3%, 1 of 297 subjects). The implant partially followed the inserter out of the skin.

7.9.5 Complications of Implant Removal

In studies conducted in U.S./Europe/Thailand, 25 subjects (2.3%, 25 of 1117 subjects) experienced complications at implant removal. Removal complications included:

- portion of implant rod broken off
- implant could not be palpated;
- removal difficult due to deep insertion,
- fixed tissue capsule;
- very flexible implant;
- adherences;
- fibrous tissue;
- difficult to find.

In the clinical pharmacology studies, only 2 subjects experienced complications at implant removal (0.7%, 2 of 292 subjects). The two removal complications were due to fibrosis and a broken implant.

In the clinical pharmacology studies that included a comparator product (Norplant™, Studies 34508, 34509, 34510, 34511, 34512, 34514, 34522, and 34523), the incidence of complications at implant removal was higher among the Norplant™ group compared to the Implanon™ group (7.1%, 6 of 84 subjects compared with 0.7%, 2 of 292 subjects). However, the data for the Norplant™ group represents only a subset of subjects as many subjects continued to use Norplant™ after study completion.

Medical Officer's Comments

- **In studies conducted in U.S./Europe/Singapore/Thailand (Principal Safety and Efficacy studies and Clinical Pharmacology Studies combined), a total of 15 subjects (1.1%, 15 of 1414 subjects) experienced complications at implant insertion and 27 subjects (2.0%, 27 of 1381 subjects) experienced complications at implant removal. Overall, these findings do not present safety concerns for Implanon™ insertion or removal. It should be noted, however, that these results are reported for controlled clinical trials in which investigators were well trained in insertion and removal techniques and may not represent insertion and removal complications in general use. The product labeling will need to clearly demonstrate insertion and removal techniques and the Applicant should be encouraged to provide training insertion and removal tools (such as videos and compact discs) to healthcare providers.**

7.10 Additional Safety Assessments

7.10.1 Blood Pressure Changes in Implanon Users

Complete physical examinations were performed at screening and yearly thereafter and at the end of each study. Abnormalities as well as any changes from the last physical examination were recorded on the CRF. Changes in physical examinations were summarized by using the number (and percent) of subjects with changes from normal at baseline to abnormal at the yearly examination and the last assessment. The visit window used for these frequency tables was extended to +/- 3 months, due to a substantial number of subjects with a physical examination done outside the 1.5 months visit window (a 1.5 month [45 days] visit window was allowed for each scheduled assessment on vital signs parameters). The number (percentage) of subjects having one or more clinically significantly abnormal blood pressure value is presented below.

For all studies, measurements were planned at baseline, 3 to 6 month intervals, and at implant removal. In 24 months studies assessment were completed at 3, 6, 12, 18, and 24 months. Study 34505 (Thailand) had additional assessments completed at 9, 15, and 21 months.

The criteria for clinically significantly for systolic and diastolic blood pressure were defined as follows:

- Systolic blood pressure: > 140 mmHg and an increase from baseline greater than 20 mmHg on at least any two visits or at last measurement.
- Diastolic blood pressure: > 90 mm Hg and an increase from baseline greater than 10 mmHg on at least any two visits or at last measurement.

Changes in Blood Pressure.

Using the definitions above, a total of 6 subjects (0.5%, 6 of 1105 subjects) in the four Principal Safety and Efficacy Studies conducted in U.S./Europe/Thailand combined (Studies 069001, 34505, 34507, and 34507 CDN) had a potentially clinically significant increase in systolic blood pressure, and 9 subjects (0.8%, 9 of 1105 subjects) had a potentially clinically significant increase in diastolic blood pressure. Subjects with a baseline blood pressure value and at least one value during treatment were included in the denominator (1105 of 1117 subjects in Studies 069001, 34505, 34507, and 34507 CDN). Subjects with at least one potentially clinically significant value during treatment were included in the numerator (6 subjects had a systolic blood pressure increase and 9 subjects had a diastolic blood pressure increase).

Medical Officer's Comments

- **In 2 of 6 subjects with a potentially clinically significant increase in systolic blood pressure and 3 of 9 subjects with a potentially clinically significant increase in diastolic blood pressure, the clinically significant reading occurred at the last measurement only, without a general increase over time. It is unclear if clinically significant increases in systolic and diastolic blood pressure readings were influenced by the impending removal of the Implanon™ implant.**

The number of subjects who experienced a clinically significant increase in blood pressure were similar for the Implanon™ treatment group in clinical pharmacology studies (Studies 34502, 34508, 34509, 34510 (Thailand), 34511, 34512, 34514 (UK), 34515, 34522, and 34523). A total of 3 subjects (1%, 3 of 297 subjects) had a potentially clinically significant increase in systolic blood pressure, and 2 subjects (0.7%, 2 of 297 subjects) had a potentially clinically significant increase in diastolic blood pressure.

Table 38 shows the mean change from blood pressure baseline values to last assessment in Studies 069001, 34505, 34507, and 34507 CDN (All-Subject-Treated Group). Table 39 shows the mean change from blood pressure baseline values to last assessment in clinical pharmacology studies (All-Subject-Treated Group).

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Table 38 Mean Change from Baseline Blood Pressure to Last Assessment in Principal Studies

Assessment	Implanon™		
	US ^a (N=390)	Europe/Thailand ^b (N=788)	US/Europe/Thailand (N=1118)
Systolic blood pressure			
Baseline (N) Mean +/-SD	(330) 108.8 +/-10.2	(787) 114.5 +/-10.6	(1117) 112.8 +/-10
Last Measurement (N) Mean Change +/-SD	(323) -0.2 +/-10.2	(782) 0.4 +/-12.8	(1105) 0.2 +/-12.1
Diastolic blood pressure			
Baseline (N) Mean +/- SD	(330) 70.1 +/-8.5	(787) 71.8 +/-8.4	(1117) 71.3 +/-8.5
Last Measurement (N) Mean Change +/-SD	(323) -0.4 +/-8.9	(782) 0.1 +/-10.1	(1105) -0.1 +/-9.8

a. Study 069001.

b. Studies 34505, 34507, 34507 CDN.

Source: Adapted from NDA 21-259, Integrated Summary of Safety, Table 60, page 0182.

Medical Officer's Comments

- In general, systolic and diastolic blood pressure showed minimal mean changes from baseline to the last assessment (mean (SD) change of 0.2 (\pm 12.1) and -0.1 (\pm 9.8), respectively) in the principal studies conducted in U.S./Europe/Thailand. The changes observed in systolic and diastolic blood pressure in principal studies pose no safety concerns.

Table 39 Mean Change from Baseline Blood Pressure to Last Assessment in Supportive Clinical Pharmacology Studies

Assessment	Implanon™
	Europe/Singapore/Thailand ^a (N=300)
Systolic blood pressure	
Baseline (N) Mean +/-SD	(297) 114.4 +/-11.1
Last Measurement (N) Mean Change +/-SD	(297) 0.7 +/-11.6
Diastolic blood pressure	
Baseline (N) Mean +/-SD	(297) 71.4 +/-8.4
Last Measurement (N) Mean Change +/-SD	(297) 0.8 +/-9.5

a. Studies 34502, 34508, 34509, 34510 (Thailand), 34511, 34512, 34514 (UK), 34515, 34522, and 34523.

Source: Adapted from NDA 21-259, Integrated Summary of Safety, Table 61, page 0183.

Medical Officer's Comments

- In the clinical pharmacology studies, systolic and diastolic blood pressure showed small increases from baseline to the last assessment, ranging from 1.7 to 2.0 mmHg for

systolic blood pressure and from 0.7 to 0.8 mmHg for diastolic blood pressure. The changes observed in systolic and diastolic blood pressure in clinical pharmacology studies pose no safety concerns.

The mean change from baseline to last assessment blood pressure in the Principal Safety and Efficacy Studies and the Clinical Pharmacology Studies combined is shown in Table 40. In general, systolic and diastolic blood pressure showed minimal mean increases from baseline to last assessment, ranging from 0.1 to 0.3 mmHg for systolic blood pressure and from 0.0 to 0.3 mmHg for diastolic blood pressure.

Table 40 Mean Change from Baseline Blood Pressure Values to Last Assessment in Principal and Clinical Pharmacology Studies Combined

Assessment	Implanon™
	U.S./Europe/Singapore/Thailand ^a (N=1414)
Systolic blood pressure	
Baseline (N) Mean +/-SD	(1413) 113.2 +/-9
Last Measurement (N) Mean Change +/-SD	(1402) 0.3 +/-12
Diastolic blood pressure	
Baseline (N) Mean +/-SD	(1413) 71.3 +/-8.5
Last Measurement (N) Mean Change +/-SD	(1402) 0.1 +/-9.7

a. Studies 069001, 34502, 34505, 34507, 34507 CDN, 34508, 34509, 34510, 34511, 34512, 34514, 34515, 34522, and 34523.

Source: Adapted from NDA 21-259, Integrated Summary of Safety, Table 64, page 0186.

Medical Officer's Comments

- **Overall, the frequency of potentially clinically significant changes in blood pressure for the Principal Studies and Clinical Pharmacology Studies combined was low. A total of 9 subjects (0.6%, 9 of 1402 subjects) in U.S./Europe/Singapore/Thailand studies had a potentially clinically significant increase in systolic blood pressure, and 11 subjects (0.8%, 11 of 1402 subjects) had a potentially clinically significant increase in diastolic blood pressure. In general, mean systolic and diastolic blood pressure showed minimal change from baseline to last assessment, ranging from an increase of 0.1 to 0.3 mmHg for systolic blood pressure and from 0.0 to 0.3 mmHg for diastolic blood pressure. These results do not represent safety concerns for the use of Implanon™.**

7.10.2 Body Mass Index Changes in Implanon Users

The number (percentage) of subjects having one or more clinically significantly abnormal body weight values is presented in the submission. For all studies, body weight measurements were planned at baseline, at 3 to 6 month intervals, and at implant removal. In the four Principal Studies (Studies 069001, 34504, 34507, and 34507 CDN) body weight assessments were completed at 3, 6, 12, 18, and 24 months. Study 34505 (Thailand) had additional assessments at 9, 15, and 21 months.

Body weight was to be between 80% and 130% of the ideal body weight at inclusion. For each weight measurement, the body mass index (BMI) was calculated as $\text{body weight}/\text{height}^2$ (kg/m²),

with body height taken from the baseline assessment, and categorized in groups as follows: (≤ 20 , $>20-22$, $>22-24$, $>24-26$, and >26 kg/m²).

In the U.S. Study 069001, the mean baseline body weight was 63.1 \pm 10.4 kg and the mean baseline body mass index was 23.6 \pm 3.6 kg/m², based on 330 subjects in the All-Subjects-Treated Group. In the three non-U.S. Studies (Studies 34505, 34507 and 34507 CDN), a total of 787 subjects were exposed to Implanon™ (100 subjects in Study 34505, 635 subjects in Study 34507, and 52 subjects in Study 34507 CDN). The pooled mean baseline body weight was 60.4 \pm 9.3 kg, and the mean (SD) baseline body mass index was 22.6 \pm 2.9 kg/m². The mean body mass indexes for the three individual non-U.S. studies were 21.7, 22.7, and 22.8 kg/m², respectively. Baseline BMI values for U.S. Study 069001 and pooled data for Europe/Thailand combined are illustrated below in Table 41 by BMI categorized group (≤ 20 , $>20-22$, $>22-24$, $>24-26$, and >26 kg/m²):

Table 41 Baseline BMI Values (Principal Studies)

BMI Groups	U.S. (N=330)		Europe/Thailand (N=787)	
	n	%	n	%
≤ 20	46	13.9	156	19.8
$>20-22$	84	25.5	194	24.7
$>22-24$	74	22.4	218	27.7
$>24-26$	46	13.9	115	14.6
≥ 26	80	24.2	104	13.2
Mean (SD) BMI Value	23.6 (3.6)		22.6 (2.9)	

Source: Medical reviewer table

In pooled clinical pharmacology studies (Studies 34502, 34508, 34509, 34510 (Thailand), 34511, 34512, 34514 (UK), 34515, and 34522), the mean baseline body weight was 69.7 kg and the mean (SD) baseline body mass index was 22.6 \pm 2.8 kg/m² based on a total of 297 subjects who were exposed to Implanon™. Demographic findings from pooled data for these studies are illustrated below in Table 42 by BMI group (≤ 20 , $>20-22$, $>22-24$, $>24-26$, and >26 kg/m²):

Table 42 Baseline BMI Values (Clinical Pharmacology Studies)

BMI Groups	Europe/Singapore/ Thailand (N=297)	
	n	%
≤ 20	93	31.3
$>20-22$	65	21.9
$>22-24$	62	20.9
$>24-26$	48	16.2
≥ 26	29	9.8
Mean (SD) BMI Value	22.6 (2.8)	

Source: Medical reviewer table

Medical Officer's Comments

- No significant difference in baseline mean body mass index is noted across the four Principal Safety Studies and the nine Clinical Pharmacology Studies (mean BMI of

22.9 ±3.1 and 22.6 ±2.8, respectively). However, it is evident from the data presented that a higher percentage of women in U.S. Study 069001 were > 26 kg/m² (24.2%, 80 of 330 subjects) as compared with 13.2% (104 of 787 subjects) for Europe/Thailand combined and 9.8% (29 of 297 subjects) for the pooled clinical pharmacology studies.

- A greater percentage of subjects were < 20 kg/m² in the pooled Clinical Pharmacology Studies (31.3%, 93 of 297 subjects) than in either the U.S. Study 069001 (13.9%, 46 of 330 subjects) or in Europe/Thailand combined (19.8%, 156 of 787 subjects). These differences are expected, however, as over one-half of the study populations in the Clinical Pharmacology studies are in S.E. Asia and South America and are generally genetically smaller than European women and women in the U.S.
- However, the noted differences in distribution among BMI groups across these studies do not appear to have influenced product efficacy. No pregnancies are reported across all studies with the Implanon™ implant in place.

Body Mass Index Increase

In principal and clinical pharmacology studies, a potentially clinically significant increase in body mass index was defined as an increase of greater than 10% from baseline at least once during treatment. Table 43 shows the number of subjects from these studies conducted under NDA 21-259 who had a clinically significant increase in body mass index.

Table 43 Number (%) of Subject with Potentially Clinically Significant Increases in Body Mass Index Values in Principal and Supportive Clinical Pharmacology Studies

Criteria for clinically significant values of Body Mass Index (kg/m ²)	Implanon™									
	U.S. ^a (N=323)		Europe/Thailand (N=782) ^b		US/Europe/Thailand Combined (N=1105)		Europe/Singapore/ Thailand ^c (n=296)		US/Europe/ Singapore/Thailand Combined (N=1401)	
	n	%	n	%	n	%	n	%	n	%
> 10% increase from baseline at least once during treatment	59	18.3	157	20.1	216	19.5	52	17.6	268	19.1

N = Number of subjects with baseline value and at least one value during treatment.

n = Number of subjects with a clinically significant change in BMI post treatment defined as a as an increase of greater than 10% from baseline at least once during treatment.

a. Study 069001.

b. Studies 34505, 34507, and 34507 CDN.

c. Studies 34502, 34508, 34509, 34510 (Thailand), 34511, 34512, 34514 (UK), 34515, 34522, and 34523.

Source: Adapted from NDA 21-159, Integrated Summary of Safety, Table 65 on page 0187, Table 66 on page 0188, and Table 68 on page 0189.

In the data submitted with NDA 21-259, a gradual increase in body mass index is apparent across the 24-month treatment period in the four Principal Studies with similar results reported for the U.S study population (Study 069001) and the Europe/Thailand study population (Studies 34505, 34507, and 34507 CDN) as shown below in Table 44.

Table 44 Mean Change from Baseline Body Mass Index Over Time in Principal Studies

Visit month	Body mass Index (kg/m ²)					
	U.S. (N = 330)			Europe/Thailand (N = 787)		
	n	Mean	SD	n	Mean	SD
Baseline value	330	23.6	3.6	787	22.6	2.9
Change from baseline:						
Month 3	303	0.2	1.0	741	0.1	1.0
Month 6	272	0.2	1.3	678	0.3	1.3
Month 12	201	0.5	1.7	525	0.4	1.5
Month 18	169	0.6	2.0	486	0.5	1.5
Month 24	165	0.6	2.0	500	0.7	1.6

SD = Standard Deviation

Source: Adapted from NDA 21-529, Integrated Summary of Safety, Table 69, page 0191.

The mean (SD) change from baseline body mass index (kg/m²) for the four principal studies combined was 0.6 ±1.7 kg/m² at 2 years. In Studies 34505 and 34507 (with extensions for 1 or 2 years), the pooled mean (SD) change from baseline body mass index was 0.9 ±1.8 kg/m² at Month 30 (n=180 subjects), 1.1 ±1.9 kg/m² at Month 36 (n=187 subjects), 0.7 ±1.9 kg/m² at Month 42 (n=38), and 1.0 ±2.1 kg/m² at Month 48 (n=42).

A gradual increase in mean body mass index was also noted in the clinical pharmacology studies (Studies 34502, 34508, 34509, 34510 [Thailand], 34511, 34512, 34514 [UK], 34515, 34522, and 34523). The mean (SD) change from baseline was 0.1 ±1.5 kg/m² at Month 12 (n=237 subjects), 0.4 ±1.7 kg/m² at Month 24 (n=203 subjects), and 0.4 ±1.8 kg/m² at Month 36 (n=63 subjects).

Summary statistics of the mean change in body mass index over time for Implanon™-treated subjects in the principal safety and efficacy studies and clinical pharmacology studies combined are shown in Table 45.

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Table 45 Mean Change from Baseline Body Mass Index Values Over Time in Principal Safety and Efficacy Studies and Supportive Clinical Pharmacology Studies Combined

Visit month		Implanon™		
		Body Mass Index (kg/m ²)		
		N	Mean	SD
Baseline value	Baseline	1414	22.9	3.1
Change from baseline	Month 3	1323	0.1	1.0
	Month 6	1195	0.3	1.2
	Month 12	963	0.3	1.5
	Month 18	867	0.5	1.7
	Month 24	868	0.6	1.7
	Month 30	235	0.7	1.8
	Month 36	250	0.9	1.9
	Month 42	47	0.8	2.0
	Month 48	51	1.0	2.1
	Last measure	1401	0.7	1.7

SD = Standard Deviation

Studies 069001, 34502, 34505, 34507, 34507 CDN, 34508, 34509, 34510 (Thailand), 34511, 34512, 34514 (UK), 34515, 34522, 34523.

Source: Adapted from NDA 21-259, Integrated Summary of Safety, Table 72, page 0194.

Looking at the results reported for the clinical pharmacology comparative studies (Studies 34508, 34509, 34510 [Thailand], 34511, 34512, 34514 [UK], 34522, and 34523 with Norplant™ [n=184] or an IUD [n=68]), both the Implanon™ and Norplant™ groups showed an increase in mean body mass index at 2 years, 0.4 kg/m² and 0.8 kg/m², respectively. The number of subjects in each group was too small to make a comparison between groups after two years of treatment. The IUD group had a mean decrease in body mass index (-0.8 kg/m²) after two years of treatment.

In total, 29 subjects (2.6%, 29 of 1117 subjects) principal studies discontinued due to weight increase. In addition, three (3) subjects discontinued due to a weight decrease (0.3%, 3 of 1117 subjects). In the clinical pharmacology studies combined, three subjects discontinued due to a weight increase (1.0%, 3 of 297 subjects). No subjects in the clinical pharmacology studies discontinued due to a weight decrease.

Medical Officer's Comments

- **A gradual increase in body mass index over time was noted in the principal studies and the clinical pharmacology studies. A total of 268 out of 1401 subjects (19.1%) from the principal studies conducted in U.S./Europe/Singapore/Thailand had a clinically significant increase in body mass index (> 10% change from baseline). Overall, the mean number of subjects who experienced a greater than 10% increase in body mass index at any one visit was consistent across all studies submitted under NDA 21-529 and ranged from 17.6% (52 of 297 subjects in combined non-comparative clinical pharmacology studies) to 20.1% (157 of 782 subjects in non-U.S. principal studies).**

- **An analysis of common drug-related adverse events (see section 7.64) demonstrates that weight increase is one of the most frequently occurring individual adverse events (adverse experiences occurring in $\geq 5\%$ of Implanon™-treated subjects) in the principal and clinical pharmacology studies combined.**
- **Overall, 19.1% of subjects (268 of 1401 subjects) experienced body mass index increase of $> 10\%$ from baseline. This information should be included in product labeling.**

7.10.3 Bone Mineral Density (BMD) Changes in Implanon Users

Study 34522 [1994-97, Netherlands, Chile, Finland] was designed to investigate the effects of Implanon™ (N=46) on BMD in comparison to non-medicated IUDs (N=30) in healthy women over a period of two years. The primary sites of BMD measurement were lumbar spine (L2-L4) and femoral neck. The secondary sites were Ward's Triangle, trochanter and distal radius. At Month 24, the Implanon™ group had a significantly greater percent increase from baseline BMD at the lumbar spine (L2-L4) compared to the IUD group (P=0.0224). The secondary sites showed no statistically significant differences between treatment groups. The mean BMD measured at different sites were generally higher than those reported for a reference population in the US and in Europe.

Laboratory values for parameters related to BMD (prolactin, carboxyterminal propeptide for type I procollagen [PICP], and cross-linked carboxyterminal telopeptide of type I collagen [ICTP] were evaluated. Median values for prolactin, PICP, and ICTP during treatment were within the normal range. The median percent increase from baseline prolactin levels at the last measurement was greater in the Implanon™ group compared to the IUD Group. Median PICP values showed a slight increase over time for subjects in the IUD Group, suggesting an increase in bone formation. Median PICP values in the Implanon™ Group decreased at Month 12, but were not notably different from baseline at the last measurement, nor at Month 24. Median values for ICTP, a measure of bone resorption, decreased in both treatment groups. The decrease was somewhat larger in the IUD Group.

An analysis of the relationship of 17β -estradiol levels with the percentage change in BMD values at the lumbar spine and femoral neck after two years of treatment showed that no relationship existed in this study population.

Medical Officer's Comments

- **This comparative study, performed in 3 different countries in 46 women using Implanon™ for two years' duration showed no signs of a negative effect of Implanon use on BMD. The study was performed, in part, because there had been evidence of BMD loss in women using a progestin-only contraception (Depot medroxyprogesterone acetate [DMPA]) for prolonged periods of time. The mechanism of action for BMD loss in users of DMPA is thought to be through suppression of estradiol (E_2), and women of younger age (i.e., adolescents) appear to be more prone to a decrease in BMD .**
- **Although this BMD study had a limited number of subjects, it is reassuring that the Implanon™ group had a significantly greater increase in BMD at the lumbar spine compared to the smaller IUD group and no evidence of a decrease in BMD.**

7.10.4 Acne

Acne was categorized in order of increasing severity as none, occasional, continuously mild, or continuously severe. Among the ImplanonTM- treated subjects from the principal safety studies and clinical pharmacology studies conducted in U.S./Europe/Singapore/Thailand, 147 subjects (13.2%) had a worsening of acne, 162 subjects (14.5%) had an improvement in acne, and 808 subjects (72.3%) had no change in severity of acne between baseline and last measurement. Twelve (12) subjects (1.1%) had continuously severe acne at implant removal. Eleven (11) of the 12 cases of continuously severe acne represented a worsening from baseline: 4 of these subjects had no acne at baseline, 3 subjects had occasional acne at baseline, and 4 subjects had continuously mild acne at baseline.

Medical Officer's Comments

- **In all the U.S./Europe/Singapore/Thailand studies combined, post baseline acne was assessed in the U.S. study and 5 other studies but was not assessed in 7 studies. In the combined 1117 subjects who were assessed for acne, there was essentially the same percentage (13-14%) of women with either an improvement or worsening of their baseline acne and the majority (72%) with no change in the severity of their baseline finding. It is difficult to interpret the 1.1% who had continuously severe acne at the time of implant removal, but it is not a safety concern and may not have any relationship to the drug product.**

7.10.5 Effect on the Eyes and Vision:

A subset of 20 subjects at one site of U.S. Study 069001 was evaluated for ophthalmologic effects. Assessments were made at screen and Months 12 and 24 after implantation. Only two subjects had ocular complaints or abnormalities. Subject No. 05005 had a 1.5 mm ptosis on the left upper eyelid at the screening exam, and an old corneal scar above the visual axis was reported for Subject No. 05018 on Days 357 and 732 of the study. None of these conditions were clinically important and no other clinically significant ophthalmologic abnormalities were observed.

Medical Officer's Comments

- **Because of ophthalmologic abnormalities noted in both clinical and preclinical studies with hormonal contraceptives and other progestin-containing products, the FDA required that this special subset study be performed. The women were evaluated by ocular complaints, visual acuity, refraction, external examination, slit lamp evaluation, lens examination, and ophthalmoscopy. It was carried out in 1994-96 at a single center and demonstrated no safety concerns.**

7.10.6 Effect on the Endometrium:

Studies with long-term progestin-only contraceptive products (NorplantTM and Depo-ProveraTM) have shown no adverse effect on the endometrium. Since ImplanonTM is a progestin-only product that lacks an estrogen component and tends to suppress endogenous estrogen, it was not expected to exert any adverse effects on the endometrium. To confirm this, Study 34514 (UK, N=30) and an endometrial morphology subset study of 22 subjects at one site in U.S. Study 069001 were conducted. Samples were obtained during the non-bleeding phase of the menstrual period at screen and after 12 and 24 months (or end of study).

In Study 34514 (UK), no subjects had hyperplastic or intramucosal neoplastic patterns (category II) during the study. The majority of endometrial patterns were "inactive/weakly proliferative" during the 24 months. No subject had an atrophic pattern at any time (up to 36 months). Simple metaplasias (category III) occurred for two subjects.

In Study 069001, all 22 subjects had a screening biopsy diagnosis of secretory endometrial pattern (no pathology). Post-screen data (Visit Month 24 or last assessment in case of early discontinuation) were available for 19 subjects. Of these 19, eight had inactive/weakly proliferative, five had atrophic, two had secretory, one had early proliferative, one had late proliferative, and one had post-menstrual/early regenerative endometrial changes. None of the subjects were diagnosed with endometrial hyperplasia, neoplasia, or metaplasia.

Medical Officer's Comments

- **In the UK study, there were 8 subjects in each treatment group (Implanon™ and Norplant™) at the 36-month time-point; no abnormal endometrial changes occurred in the third year of treatment. At screening, the (individual) maximum endometrial thickness was similar for both treatment groups with a group mean of 11.3 mm for Implanon™ and 10.6 mm for Norplant™. During treatment, means between 3.2 and 3.6 mm were observed for Implanon™, and means between 4.9 and 5.5 mm were observed for Norplant™. Overall, the endometrium data from the UK study is reassuring and raises no safety concern.**
- **The slightly smaller (non-comparative) 24-month U.S. study confirmed the UK findings on endometrial safety: no subject (N=19) showed changes of endometrial hyperplasia, neoplasia, or metaplasia in 24 months.**

7.10.7 Carbohydrate Metabolism

Parameters of carbohydrate metabolism were evaluated in two studies; a Norplant™ comparative Study 34511, and a subset of the U.S. Study 069001.

In Study 34511, (1992-95, Singapore, N= 40 Implanon, 40 Norplant) there was substantial inter-individual variation in glucose and insulin concentration profiles. For both glucose and insulin, the AUC values observed during treatment were higher than at baseline in both groups. The 2-hour response for glucose at 6 and 12 months of treatment was about 5% higher than at baseline for both groups, while at 24 months an increase from baseline of 10% and 20% was observed for Implanon™ and Norplant™, respectively. The 2-hour response for insulin showed a more pronounced increase with treatment, which at 24 months amounted to about 70% for Implanon™ and 45% for Norplant™. No statistically significant differences between the groups were found.

Fasting glucose levels displayed little inter-individual variation at any time-point and remained fairly stable during either treatment. There was no indication for the existence of differences between groups. Fasting insulin concentrations showed large inter-individual variation at all points. Only the results of the 24-month assessment indicated a mean increase from baseline in both groups. Between-group differences never reached statistical significance. Mean fasting HbA1C was slightly elevated during treatment for both implants.

In the non-comparative U.S. study subset (1994-96, N=25), an oral glucose tolerance test was performed and glucose and blood insulin levels were measured at baseline and at visits at Months 6, 12, 18, and 24. In contrast to the previous study (No. 34511), the mean AUCs for both

plasma glucose and plasma insulin concentrations were lower during treatment compared to baseline, but these differences were not statistically significant. During treatment, no changes from baseline were observed for the glucose concentration following ingestion of glucose, while the insulin response was generally reduced by 20-30%.

In summary, in Study 34511, the fasting levels of glycosylated hemoglobin (HbA1C), glucose, and insulin were constant over time for the Implanon™ and Norplant™ groups, which indicates that overall glycemic control was not affected by either implant. The response to an oral glucose load in Study 34511 was altered during treatment with both Implanon™ and Norplant™, and was characterized by an approximately 50% increase in insulin response, with slightly elevated glucose levels observed during the 2-hour period following glucose intake, indicating mild insulin resistance. Individual values outside the normal laboratory reference range were only occasionally observed. Statistically significant differences between Implanon™ and Norplant™ were not observed. In contrast to Singapore Study 34511, the results from U.S. Study 069001 showed no change from baseline in glucose concentrations, while the insulin concentration was reduced, although not to a statistically significant level.

Medical Officer's Comments

- **The difference in the data from these two studies may reflect a difference in the study populations. These studies were done in a total of 65 Implanon™ users and inter-individual variation was noted. There were no SAEs and no safety signals of concern in these patients. Further glucose metabolic studies are not recommended at this time.**

7.10.8 Pregnancy (Potential for Teratogenesis)

Each year substantial numbers of women accidentally use hormonal contraception in early pregnancy, without realizing that they are pregnant. Although some reports in the 1970s and 1980s suggested the possibility of adverse fetal effects, ranging from spontaneous abortion to birth defects, associated with the older higher-dose pills, these reports have been refuted by better designed studies. These studies concerning the risk of general and specific congenital malformations associated with oral contraceptives used before or during pregnancy have been extensively reviewed and the reviews have generally concluded that no association exists between oral contraceptive use and teratogenic or birth defects. No increased risk of congenital malformations has been documented for progestin-only products used either prior to or during (early) pregnancy^{iv}. Therefore, accidental insertion of Implanon™ during (early) pregnancy or the occurrence of a method failure is not expected to carry a risk of teratogenicity. In the clinical trials, insertion of Implanon™ during pregnancy was generally avoided by inserting the implant on Day 1-5 of the menstrual cycle, although Implanon™ was inserted in 5 women who were already pregnant. Two subjects had induced abortions. No birth defects were reported.

Medical Officer's Comments

- **Based on the clinical trials and a review of the medical literature, there does not appear to be a clearly demonstrated fetal or maternal risk factor should Implanon™ be inadvertently inserted in a pregnant women or should a pregnancy occur after the Implanon™ insertion. The more probable event is insertion of Implanon™ in a woman with an early pregnancy. Routine precautions should be taken to rule out pregnancy before insertion.**

7.10.9 Potential for Ectopic pregnancy:

The absolute rate of ectopic pregnancies is decreased in women using progestin-only regimens compared to the absolute rate in fertile women not using any contraception. However, in the small fraction of women who become pregnant while using the progestin-only pills, the proportion of ectopic pregnancies is possibly increased. Implanon™, in contrast to other progestin-only methods, may inhibit ovulation more effectively. Due to this mechanism of action, not only the absolute pregnancy rate, but also the proportion of ectopic pregnancies may be lower than with other progestin-only contraception. In the Clinical Development Program with Implanon™, there were so few pregnancies that the absolute risk of ectopic pregnancy and the relative risk were not calculable.

Medical Officer's Comments

- **In the worst case scenario, the risk of ectopic pregnancy is extremely small. However, if there are symptoms suggestive of pregnancy or an abnormal pelvic process, the clinician should still consider the possibility of an ectopic pregnancy and use the standard diagnostic methods to make an accurate diagnosis to explain the symptoms.**
- **History of a prior ectopic pregnancy need not be a contraindication, relative or absolute, to the use of Implanon™.**
- **During the postmarketing reporting period (Aug. 1998-Sep. 2003) 20 ectopic pregnancies (out of 1 medically confirmed pregnancies occurred. The proportion of reported ectopic pregnancies relative to reported total pregnancies is higher than the expected proportion in a population of women using either no contraception or a population using hormonal contraceptives other than those that are progestin-only contraceptives. However, the reported proportion of ectopic pregnancies to total pregnancies is similar to that seen with progestin-only contraceptive use. Also, clinicians/women are more likely to report ectopic pregnancies versus normal pregnancies.**

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7.10.10 Effects of Implanon on Lactation and the Breast-fed Baby:

Results of a previous study with an oral desogestrel product at a dose of 0.075 mg/day (Cerazette™) have shown that 3.2% of the maternal daily dose per kg maternal body weight would be ingested by the infant via breast milk. This was based on the maximum etonogestrel serum concentration attained in the mother, the ratio of transfer to breast milk, and an assumed ingested milk volume of 150 mL/kg/day. This quantity is in the same order of magnitude as reported for other progestogens (e.g., 2.8% for levonorgestrel).

Study 34523 [Thailand, 1997-01] compared the effects of Implanon™ (N= 42) and a copper IUD (N= 38) on the volume and composition of breast milk and determined the concentrations of etonogestrel in breast milk and in maternal serum for 4 months. In addition, data concerning the development of the breast-fed children up to 3 years of age was collected. Detailed data on breast milk and serum concentrations of etonogestrel are presented in the Human Pharmacokinetic and Bioavailability Summary section of the NDA.

No statistically significant differences between the Implanon™ and IUD arms were observed for the four studied breast milk parameters (24-hour volume of breast milk ingested, lactose, total protein, and total fat content). Newborn children of lactating mothers who received Implanon™ or an IUD in Study 34523 were compared with regard to the following parameters for a period of

4 months: body length, body weight, biparietal head circumference, abnormalities of psychomotor development, and the presence of abnormalities at physical examination. The newborns in the Implanon™ and IUD groups grew on average 2.51 cm and 2.36 cm, respectively, over the 4-month lactation period. The respective monthly weight increase was 636 g and 617 g, and the increase in biparietal head circumference was 1.17 cm and 1.13 cm. No abnormalities of psychomotor development were reported nor were abnormalities found on physical examination of the newborns in either group.

Medical Officer's Comments

- **There were no serious adverse experiences and no adverse experiences (AEs) leading to discontinuation in this study. Adverse events were reported in 64.3% (27 / 42) of the newborns in the Implanon™ group and in 60.5% (23 / 38) of the newborns in the IUD group. The most frequently reported AE in both treatment groups was upper respiratory tract infection. None of the AEs was considered to be related to the study medications and all were of similar nature and of mild intensity.**
- **In lactating women, treatment with Implanon™ or an IUD for up to 4 months did not differ with regard to the effect on the 24-hour volume of breast milk, the duration of breast feeding or the composition of the breast milk. The mean transfer of etonogestrel to the infant for up to 4 months was highest at Month 1 and amounted to ~20 ng/ kg/ day, which was 1.7% of the maternal daily dose per kg body weight. Concentrations decreased with time. No differences in growth rates were seen between treatment groups, except for a somewhat larger gain in body weight in boys in the Implanon™ group. Incidences and nature of adverse experiences, all non-serious and of mild intensity were similar in the newborns of both treatment groups. It appears that in lactating women, Implanon™ is safe for the newborn and may be labeled as such.**

7.11 Registration History

As of the cutoff date for the original NDA submission (April 30, 2003), Implanon™ had been approved for marketing in 51 countries worldwide (Table 46) and registration applications were pending in 20 other countries (Table 47). According to the Applicant, Implanon™ has not been withdrawn from the market in any country nor has approval been denied for safety or efficacy reasons.

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Table 46 Implanon™ Registration Status Worldwide (Status as of April 30, 2003)

Country	Approval date	Country	Approval date
Australia	01-2000	Luxembourg	03-1999
Austria	03-1999	Mexico	08-2000
Bahrain	10-2001	Netherlands	08-1998
Belgium	05-1999	Netherlands Antilles	09-2001
		New Zealand	06-2002
		Norway	11-2000
Czech Republic	02-2001		
Denmark	03-1999		
	*	Portugal	02-1999
Finland	03-1999	Slovak Republic	10-2000
France	06-1999		
Germany	02-1999	Spain	12-2000
Greece	03-1999	Sweden	02-1999
Hungary	06-2001	Switzerland	08-1999
Iceland	11-2000		
Indonesia	05-1997		
Ireland	03-1999	United Kingdom	06-1999
Italy	11-2000	Vietnam	*

b(4)

* Implanon™ is marketed via the institutional segment, but has not yet received official approval.

Source:

Table 47 Pending Implanon™ Registrations Worldwide (Status as of April 30, 2003)

Country	Submission date	Country	Submission date

b(4)

Source:

Since the 1998 market introduction in several countries outside the US, Organon has collected post-marketing surveillance data from spontaneous safety reporting, published literature, and from a study sponsored by the National Family Planning Coordination Board (BKKN study) of Indonesia. The estimated exposure of Implanon™ based on the sales from market introduction through 30 April 2003 amounted to _____ women.

b(4)

7.12 Post-Marketing Safety Reports (non-U.S.)

7.12.1 Complications with Insertion/Removal - August 1998 through March 2004

Since the market introduction of Implanon™, NV Organon has received complaints of insertion and removal problems. The Dutch Medicines Evaluation Board (DMEB) is the responsible Pharmacovigilance authority for Implanon all European member states. After consulting the DMEB, NV Organon has implemented a system of collecting data referred to as "*Implanon™ Insertion and/or Removal Related Events (IRREs)*". A flow chart in Appendix J in the NDA describes how NV Organon handles these IRREs. NV Organon has a written procedure describing how IRREs should be classified and handled. Data listings of these IRREs are included in the yearly Periodic Safety Update Report (PSUR). In addition, apart from the yearly PSUR, NV Organon produces a separate twice yearly IRRE report (issued every 6 months).

An IRRE is defined as:

- Any event that is related to the insertion- and/or removal of Implanon™, but cannot be classified as being an (S)AE according to the definition for an (S)AE;
- Any event for which it is clear or becomes clear at a stage later than the actual insertion procedure that the woman accidentally had not received Implanon™ due to an insertion failure;
- Any unintended pregnancy for which it is clear or becomes clear at a stage later than the actual insertion procedure that the woman accidentally had not received Implanon™ due to an insertion failure; and
- Any unintended pregnancy for which it is clear that the woman was already pregnant prior to insertion of Implanon™.

There was a revision of the company core data sheet (CCDS), which mainly concerned the sections on the insertion and the removal of Implanon™. Advice was added to inform the doctor, as well as the woman, on proper insertion and instruct them to verify the presence of the implant. *In addition, a text was added to instruct the woman to use condoms until the presence of the implant has been confirmed.* The updated version of the CCDS also contains new text that describes that, in the case an inserted implant cannot be palpated, ultrasound or magnetic resonance imaging should be used to localize the implant. For further clarity, a drawing of the dismantled applicator has also been included in the CCDS

Medical Officer's Comments

- **The information added to the company core data sheet (CCDS) should be added to the label**
- **Organon should develop a phase 4 monitoring program in the U.S. for insertion and removal related events**

The analysis in this report covers the "Total Period" (TP) defined as 28 August 1998 up to 1 March 2004. During this period, the market use, based on sales, was estimated to amount to implants. This TP is subdivided into the following sub-periods:

- <Prior Period (<PP) (28 August 1998 up to 1 March 2003), the **b(4)**
- Prior Period (PP) (1 March 2003 up to 1 September 2003), and the
- Analysis Period (AP) (1 September 2003 up to 1 March 2004).

During the TP, Organon received 1423 reports containing one or more IRREs. A case report can contain more than one IRRE, e.g. when the woman wants Implanon to be removed but Implanon is not palpable and could not be found by ultrasound localization, two codes are added for this case; '*IRRE-palpable presence and IRRE-ultrasound presence*'. The 1423 medically confirmed IRRE reports are divided into two groups:

Group 1: IRREs in association with pregnancies:

this includes 473 pregnancy reports containing 971 IRREs with an average number of 2.1 IRREs/report.

Group 2: IRREs not in association with pregnancies:

this includes 950 reports containing 2285 IRREs with an average number of 2.4 IRREs/report.

7.12.1.1 Complication Related to Insertion of Implanon™

Most frequently reported during the TP were '*IRRE-deep insertion*' (174 occasions), '*IRRE difficult insertion*' (76), '*IRRE-rod bent*' (59) and '*IRRE-broken or cut*' (53). In case the result of the ENG determination was negative, the code '*IRRE-no rod*' was used to store the negative outcome of the ENG level, indicating that Implanon™ was not in situ.

There was a reported small decrease in insertion related adverse events from the PP (115) to the AP (104) of approximately 10%. See Table 48

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Table 48 Insertion related events

IRRE	Reporting by			
	PP	PP	AP	TP
IRRE-BLUE ROD INSERTED	1	0	0	1
IRRE-BROKEN OR CUT	19	16	18	53
IRRE-DEEP INSERTION	82	56	36	174
IRRE-DIFFICULT INSERTION	50	12	14	76
IRRE-NO ROD	29	6	1	36
IRRE-ROD BENT	28	11	20	59
IRRE-MULTIPLE INSERTION	10	10	11	31
IRRE-WRONG PLACE	13	4	4	21
Total	232	115	104	451

Source: Response to information request. 30June04

Medical Officer's Comments

- Problems with insertion of Implanon™ were the major factor that contributed to unintended pregnancies. In particular, these problems concerned ‘wrongly timed insertion’ (notably in pregnant women), ‘non-insertion’, ‘insertion of blue ‘placebo’ training implants’, and ‘difficult insertion’. The consequence of improper insertion resulted in ‘non-palpable Implanon™’, ‘otherwise difficult localization of Implanon™’, ‘broken Implanon™’, and ‘difficult removal of Implanon™’.
- When the obturator is pushed instead of retracting the cannula, this may result in a curled, damaged (broken or cut) or too deeply positioned implant.
- Failed insertions (*‘IRRE-no rod’*) were most likely the result of not keeping the applicator in such a way that the needle is always pointing upwards after removing the needle shield. Directly after insertion, the presence of Implanon™ should always be confirmed by palpation. Furthermore, the needle should always be visually checked for the absence of the implant. In case of doubt of having Implanon™ correctly inserted, the presence of Implanon™ should be confirmed with ultrasound, MRI, or an etonogestrel (ENG) determination to prevent potential multiple insertion. This information should be added to the label.

7.12.1.2 Difficulty with Localization of Implanted Implanon™

Difficult localization of the implant may be caused by using an incorrect insertion technique, inserting the rod in the wrong place (for example, abdomen, and leg) or non-insertion of the implant. Additionally, in some cases, migration of the implant has been reported as a possible reason for difficult localization.

When Implanon™ cannot be palpated at the insertion site, ultrasound is advised to localize Implanon™. If ultrasound does not localize the implant, an MRI-examination can be performed. If this also fails to localize the implant, the patient’s serum etonogestrel level can be determined to provide information on the presence or absence of Implanon™. When serum etonogestrel results were below the limit of quantification of the assay (LOQ<40 pg/ml) the code ‘IRRE-no rod’ was used to indicate that Implanon™ was not in situ. The code ‘IRRE-doubt presence’ was

used to indicate that it has been reported that Implanon™ could not be found/localized, but it was not specified which method (palpation/US/MRI) was used.

In contrast to the previous reporting period, there was a reported greater number of localization related events (uncorrected for number of attempted removals) from the PP (240) to the AP period (295) - 19% increase (see Table 49).

Table 49 Localization related events

IRRE	Result	Reporting period			
		PP	PP	AP	TP
IRRE-PALPABLE PRESENCE	YES	40	14	20	74
	NO	226	94	128	448
	DOUBT	8	2	0	10
IRRE-ULTRASOUND PRESENCE	YES	123	52	34	209
	NO	113	56	76	245
	DOUBT	9	1	5	15
IRRE-MRI PRESENCE	YES	25	5	3	33
	NO	27	14	29	70
	DOUBT	1	2	0	3
Total		572	240	295	1107
IRRE-DOUBT PRESENCE	YES	30	10	23	63

In the above mentioned cases doubt means that, e.g. the result of palpation was doubtful and should therefore not be confused with 'IRRE-doubt presence'.

Source: Response to information request, 30June04

Medical Officer's Comments

- **Difficult localization of Implanon™ may be caused by an incorrect insertion technique, inserting the rod in the wrong place or non-insertion of Implanon™ (IRRE-no rod). Additionally, migration of the implant has been reported as a possible reason for difficult localization**

7.12.1.3 Techniques Used for Localization of non-Palpable Implanon™

Organon did an analysis of implant localization based on all cases in their safety database, in which the presence or absence of Implanon was confirmed. For these cases, the last reported results of palpation, ultrasound and MRI were analyzed.

Ultrasound

Four hundred and eleven (411) cases were used to investigate the accuracy of ultrasound (n=411: 217 –Implanon present; 194 cases Implanon not present). From the 217 cases in which Implanon™ was present, in 127 cases Implanon™ could be localized by ultrasound and in 90 cases ultrasound failed to localize Implanon™ (false negatives). In the 194 cases in which Implanon™ was not present, there were 4 cases in which Implanon™ was localized with ultrasound (false positives) and 190 cases in which ultrasound did not localize the implant.

Localization of Implanon™ by MRI

In 84 cases, the presence or absence of Implanon™ was confirmed (58-Implanon present; 26 Implanon not present). From the 58 cases in which the presence of Implanon™ was

confirmed, 39 cases demonstrated that Implanon™ could be localized by MRI and in 19 cases Implanon™ was not localized by MRI (false negatives). In the 26 cases in which Implanon™ was not present, Implanon™ was not localized in 25 cases; for one case, Implanon™ was localized with MRI (false positive).

The 84 cases where MRI was used to localize Implanon™ in this analysis were relatively low compared to the number of cases where palpation and/or ultrasound (430/411) were used. The limited MRI data may be explained by the fact that in most cases this technique was used when ultrasound was unsuccessful. In addition, this technique was not available everywhere (i.e., not every hospital is equipped with an MRI apparatus).

Medical Officer's Comments

- Palpation/ultrasound/ MRI are not always sufficient as localization techniques for the presence or absence of Implanon™. While a positive finding is reassuring, the higher number of false negative findings may be due to the limited field of view for all three techniques (e.g. the wrong body area is searched).
- Clinical sites that are remote from major medical centers, in both the U.S. and abroad, may not have this costly technology available.

7.12.1.4 Removal Related Adverse Events

A subdivision of the summary of IRREs associated with the removal of Implanon™ is provided in Table 50.

Table 50 Removal related events

IRRE	Result	Reporting period			
		PP	PP	AP	TP
IRRE-ENG POSITIVE, ROD NOT FOUND	YES	3	14	31	48
	YES/closed	11	0	3	14
	YES/comed	1	0	0	1
	YES/continued	4	3	8	15
	YES/removed	16	5	11	32
IRRE-MIGRATION	YES	29	16	15	60
IRRE-REMOVAL PROBLEM	YES	92	51	47	190
IRRE-SUR REMOVAL GEN ANESTHESIA	YES	21	16	8	45
IRRE-SURGICAL INTERVENTION	YES	29	10	7	46
Total		206	115	130	451

Source: Response to information request, 30June04

Medical Officer's Comments

- The numbers of removal related adverse events (unadjusted for the number of removals) were slightly higher in the AP compared to the PP (130 vs. 115).

During the TP, 'IRRE-ENG positive, rod not found' was reported in 110 occasions. This IRRE code is used to indicate that the result of the patient's serum ENG assay was positive, but the

Implanon™ rod could not be localized by palpation and/or US and/or MRI and hence could not be removed.

In 14 reports, the outcome is unknown because no further information can be obtained.

In 1 report, the patient concomitantly used another contraceptive which cross-reacts with the etonogestrel radio immuno assay.

In 15 reports, the patient continued using Implanon after its' presence has been established.

In 32 reports, Implanon was localized and removed. In the remaining 48 reports ('*IRRE-ENG positive, rod not found*'/YES) the final outcome (i.e. implant removed or continued) is pending. Additional information on localization and removal has been requested.

Medical Officer's Comments

- **Forty seven implants out of 110 reports of lost implants were located; this leaves 63 implants/women that were unaccounted for.**
- **Specific information needs to be incorporated into the training program and label to minimize lost implants.**

A global summary of the IRREs for the last two years (from Mar. 1, 2002 up to Mar. 1 2004 is included in Table 51

Table 51 Summary of Implant Insertions/Removal Related Events (March 2002 to March 2004)

Total Events	Mar 02 to Sep 02	Sep 02 to Mar 03	Mar 03 to Sep 03	Sep 03 to Mar 04
Number of Insertion Problems	129	53	115	104
Number of Localizations Needed	327	276	240	295
Number of Removal -Related Events	55	25	115	130

Source: Medical reviewer table: response to information request, 30June04

Medical Officer's Comments

- **Insertion/removal problems occurred despite NV Organon stating that they provided detailed labeling texts, as well as training materials and sessions on Implanon™ insertion, removal and localization to health care providers in all countries where Implanon™ is marketed. Because of complaints of insertion and removal problems, Organon implemented a system of collecting and storing this data.**
- **From the available data, it is not possible to relate precisely the number of IRREs to the number of inserted and removed Implanon™ rods.**
- **When comparing the number of IRREs received in the 6 months ending on Sep 03 with the number of IRREs received in the previous 6 months, a slight *decrease* in the number of insertion related events and a slight *increase* in the number of localization and removal related events was observed. The decrease in insertion related events may be**

related to more training and experience of the clinicians; the increase in removal related events may be explained by an increase incidence of removal of Implanon™. It was expected that after a period of three years from market introduction in August 1998, more Implanon™ rods would be replaced or removed. Furthermore, improvement of the Company Core Data Sheet was expected to encourage physicians to verify the presence of the implant with palpation, ultrasound and MRI.

- Organon is considering the development of a radio-opaque implant to add X-ray visualization as an option for localization, in addition to palpation, ultrasound and MRI techniques. This could significant reduce the number of lost Implanon rods.
- The IRRE data collected for Implanon™ during the period from market introduction in August 1998 up to 1 March 2004 do not give rise to significant concerns about the safety of the product.

7.12.2 Postmarketing Adverse Events Reported in Original NDA Submission

During the period from August 1998 up to and including 30 April 2003, 4015 spontaneous reports were received by NV Organon, describing 5925 adverse events (S)AEs. Approximately 66% of the reports originate from Germany, Austria and Great Britain. A summary listing of the number of (S)AEs reported in this period for all MedDRA system organ classes involved is presented in Table 52.

Table 52 Number of (S)AEs by MedDRA System Organ Class Reported during the Period from August 1998 up to and including 30 April 2003

MedDRA system organ class	Number of (S)AEs
Blood and lymphatic system disorders	29
Cardiac disorders	27
Congenital, familial and genetic disorders	4
Ear and labyrinth disorders	32
Endocrine disorders	21
Eye disorders	17
Gastro-intestinal disorders	127
General disorders and administration site conditions	735
Hepatobiliary disorders	5
Immune system disorders	14
Infections and infestations	53
Injury, poisoning and procedural complications	97
Investigations	312
Metabolism and nutrition disorders	28
Musculoskeletal and connective tissue disorders	42
Neoplasms benign, malignant and unspecified	28
Nervous system disorders	313
Pregnancy, puerperium and preinatal conditions	534
Psychiatric disorders	448
Renal and urinary disorders	5
Reproductive system and breast disorders	2277
Respiratory, thoracic and mediastinal disorders	23
Skin and subcutaneous disorders	659
Vascular disorders	95
Total	5925

Source: Table 129, P306, original ISS 30Sep04

The MedDRA system organ classes which included the most (S)AEs were Reproductive system and breast disorders (2277 events), General disorders and administration site conditions (735 events), Skin and subcutaneous tissue disorders (659 events), Pregnancy, puerperium and perinatal conditions (534 events) Psychiatric disorders (448 events), and Nervous system disorders (313 events), and Investigations (312 events).

Medical Officer's Comments

- **The pattern and frequency of these adverse events did not differ substantially from those observed in the clinical trials.**

7.12.2.1 Selected Serious Adverse Events

7.12.2.2 Thrombotic and Thromboembolic Adverse Events

During the period of August 1998 up to and including 30 April 2003 *twenty-three reports were received describing the occurrence of 25 thromboembolic events (cerebral venous thrombosis (1 report), pulmonary embolism (6 reports), deep vein thrombosis (4 reports), thrombophlebitis (9 reports), thrombophlebitis superficial (4 reports), and thrombosis (1 report)).* These reports originated from Germany (7 reports), France (7 reports), Great Britain (4 reports), Austria (2 reports), Australia (2 reports) and Switzerland (1 report). In 14 of the 23 cases one or more possible risk factors for the development of thromboembolism were identified, i.e. obesity, smoking, varicosis, positive family history, recent airplane flight, age above 35 years old, the occurrence of a thromboembolic event in the medical history and a sports trauma. Eight of the women concerned had more than 1 possible risk factor. As described in Section 7.12.5, one of the patients died (case number 122168).

One case was received during the period of August 1998 up to and including 30 April 2003 describing the event "myocardial infarction". This report originated from Germany. The information provided was limited.

Medical Officer's Comments

- **Women using progestin-only contraception may be at higher risk for spontaneous thromboembolic diseases (not related to use of progestin-only contraception) than combination oral contraceptive users. *Heinemann et. al.* found that they are older, have a higher body mass index, have more often a history of hypertension, high blood pressure during pregnancy, and diabetes, and they are more often smokers, regular drinkers of alcohol, and report more frequently a family history of stroke and myocardial infarction. The presence of (multiple) risk factors in 14 of the 23 patients seems to support the general findings by Heinemann et. al. Although there may be some association between progestin use and thromboembolic disease, there is no evidence of a causal relationship.**

During the period of August 1998 up to and including 30 April 2003, *12 reports describing the event cerebrovascular disorder, (including 3 reports describing the event cerebrovascular accident and 1 report describing the event cerebral hemorrhage) were received.* The reports originate from Germany (5 reports), Great Britain (2 reports), France (2 reports), Denmark (2 reports), and Australia (1 report). In 7 of the 12 reports one or more possible risk factors for the development of cerebrovascular disease were identified, i.e. obesity, diabetes mellitus, migraine,

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hypertension, hypercholesterolemia, possible traumatic dissection, a suspected patent foramen ovale and a history of cavernous angioma hemorrhage.

Medical Officer's Comments:

- It is interesting to note that all 12 reports were from Europe, where the incidence of smoking is higher than many other locations in the world.
- The small number of cerebral vascular accidents reported for Implanon™ is consistent with findings in the literature.
- Taking all of these studies into account, there probably is not an increased risk (compared to no contraception) of thrombosis in women using progestin only contraceptives.

7.12.2.3 Breast Neoplasms - Malignant

During the period from August 1998 up to and including 30 April 2003, *fifteen reports* were received describing the occurrence of breast neoplasia in women while using Implanon™. In 11 cases, the breast neoplasm was diagnosed to be *malignant*. In one case, the neoplasm was assumed malignant, but the pathology report was still pending. In one case, the neoplasm was diagnosed to be benign and in the two remaining cases, it was not clearly reported whether the neoplasm was benign or malignant.

The information provided in the reports was not sufficient to obtain complete insight in most of the cases. Additional data concerning the previous use of contraceptive hormones, the medical history, the absence or presence of concomitant disease, presence of risk factors for the development of breast carcinoma, etc., were not provided in sufficient detail. In 6 out of the 12 cases of malignant breast neoplasm the interval between the start of Implanon™ use and the diagnosis was too short (e.g. 4-10 months) to suggest a causal association.

Medical Officer's Comment

- The risk for breast cancer increases in general with increasing age. During the use of oral contraceptives, the risk of having breast cancer diagnosed is slightly increased. This increased risk disappears gradually within 10 years after discontinuation of OC use and is not related to the duration of use, but to the age of the woman when using the OC.
- The risk in users of contraceptive methods which only contain a progestin such as Implanon™ is possibly of similar magnitude as that associated with COCs. However, it is important to emphasize that for progestin only methods the evidence is less conclusive.

7.12.3 Four Month (120 Day) Safety Update - May 1, 2003 to October 30, 2003

7.12.3.1 Clinical Trial Data

The "120-Day Safety Update" submission provides updated data from two trials (**protocol 34525** and **protocol E-1729-ongoing**) as well as the available post-marketing data up to Oct 30, 2003

Medical Officer's Comment

- **These two studies did not contribute any new information that was different from the Principal Safety and the supportive Clinical Pharmacology Studies submitted in the original NDA. Overall, there are no new safety signals from these two ongoing studies.**

7.12.3.2 Spontaneous Adverse Event Reports

During the four month safety update period, 1655 spontaneous reports were received by Organon, describing 2432 (S) AEs (i.e. SAEs and AEs combined). Overall, the AE patterns were similar to that which was previously reported. Two reports of pulmonary embolism with a fatal outcome were received (see section 7.12.4).

Medical Officer's Comments

- **The postmarketing (S)AEs received during the period from 01 May 2003 up to and including 30 October 2003 show a similar trend as compared to the safety data previously reported for Implanon™ and do not give rise to concern about the safety of the drug.**

7.12.4 Final Postmarketing Safety Update – September 9, 2004

On September 9, 2004, Organon submitted a cumulative listing of all selected postmarketing events from August 1998 – September 1, 2004. The number of implants sold during this period was approximately . Based on this submission, rates of death, pulmonary embolus, cerebrovascular accident, deep vein thrombosis and myocardial infarction worldwide and for Europe only (in number of events per 100,000 woman-years of use) are outlined in Table 53

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Table 53 Cumulative Listing-Selected Postmarketing Events

	Number of events worldwide	Number of events Europe ^a only	Worldwide rates (events per 100,000 woman-years of use) ^b	Europe ^a only rates (events per 100,000 woman-years of use) ^b
Death	5	3	0.15	0.17
Pulmonary embolus	10	7	0.31	0.41
Deep vein thrombosis ^c	18	14	0.55	0.82
(Venous thromboembolic events (VTE)) ^d	(28)	(21)	(0.86)	(1.22)
Cerebrovascular accident (CVA)	14	12	0.43	0.70
Myocardial infarction	1	1	0.03	0.06

^aThe following countries were included for Europe: Austria, Belgium, Denmark, France, Germany, Ireland, Italy, Netherlands, Portugal, Sweden, United Kingdom, Czech Republic, Finland, Malta, Norway, Slovak Republic, Spain, Switzerland, Norway and Iceland.

^bBoth medically confirmed and medically unconfirmed reports are included.

^cSuperficial venous thrombosis is excluded from this analysis. Cases in which it is unclear whether it involves a deep or superficial thrombosis (e.g. only "thrombosis" was reported) are included.

^dVenous thromboembolic events is the total rate of pulmonary embolus and deep vein thrombosis.

Source: Table 5, response 4, information request, 11Oct04

Medical Officer's Comments

- **The rate of individual thromboembolic events is no greater than that which is seen with other hormonal contraceptives.**

7.12.5 Reported Postmarketing Deaths

Since its introduction to the market through September 1, 2004, 5 deaths among Implanon™ users have been reported (4 deaths were in women using the drug, and 1 death was a neonatal death).

One case report originated from Indonesia and described a 35 year old woman, participating in a family planning program, who had Implanon™ inserted by a medical doctor 21 days after delivery. She died 3 or 4 days later. According to the midwife, the patient had preeclampsia during her last pregnancy. She experienced fever and convulsions before her death. A physician suggested that the patient had developed tetanus, an opinion agreed upon by the National Family Planning Coordination Board in Indonesia. According to her family, the patient had a history of liver and heart disease. No local infection was observed at the insertion site. No further information could be obtained.

A second reported case originated from Austria and described a 25 year old woman who presented with abdominal pain and diarrhea 2 months after Implanon™ had been inserted. Her condition worsened and she was hospitalized. She developed tachycardia and cardiac arrest in the evening of the day of admittance and died. Autopsy revealed central and peripheral pulmonary embolism and thrombosis in veins of both lower legs. Possible risk factors for the development of thromboembolism in this patient were smoking, obesity and a positive family history of thromboembolism.

A third case involved a 32 year old Aboriginal woman who presented to an outpatient department with epigastric pain, low blood pressure, tachypnea, peripherally shut down, and paleness. Her jugular venous pressure was elevated and she proceeded to fit and arrest. The patient died. The post mortem showed a massive pulmonary embolism and the coroner's report attributed the death to this pulmonary embolism. It was reported that both the coroner and the doctor did not believe Implanon™ was the cause for this event. The woman's medical history included (alcohol related) epilepsy, hepatitis B, mental impairment, pneumonia, and proteinuria. She had a poor compliance with medications. She had no known allergies and was not diabetic. The woman was a heavy drinker and chewed tobacco. The woman is not known to have been on a long journey. Her nephew (aged 19) died the month after with a presumed severe pneumonia (he had had several episodes). Two clear risk factors for the development of pulmonary embolism could be identified: the patient was a tobacco user (chewed tobacco) and a heavy drinker.

A fourth case was a 35 year old woman who suddenly died from a pulmonary embolism (according to the autopsy). Implanon™ was inserted approximately 22 months earlier. The woman suffered from untreated high blood pressure and untreated hyperthyroidism. No other medical history was reported. She was addicted to tobacco and had a positive family history; her sister presented with a pulmonary embolism at the same age when she was hospitalized for an aggravation of Crohn's disease. The woman had had no recent surgery or immobilization, no varicose veins, no other medically relevant conditions, and no recent long journeys. A search for coagulation disorders was scheduled. The results of these tests have been requested, but so far, no further information has been reported. Three (3) risk factors for the development of a pulmonary embolism could be identified: tobacco addiction, positive family history, and age.

Medical Officer's Comments

- **The four reported deaths described above did not appear to be directly related to Implanon™. There were many contributing factors to these deaths and progestin exposure was unlikely to be one of them.**

7.13 Drug Withdrawal, Abuse, and Overdose

Etonogestrel has not been shown to have any potential for abuse. There is virtually no possibility of overdose since the drug is delivered by an implant that is placed subdermally by a healthcare provider.

7.14 Risk Management Program and Training of Healthcare Providers

The Risk Management Program regarding insertion and removal of Implanon™ consists of the following elements:

7.14.1.1 Committees and Development of Local Experts

A Steering Committee will be formed to develop an effective training program and will consist of Organon's "Thought Leader Consultants". The training program will be piloted in 5 cities in the U.S. to refine it. The 'pilots' will be lead by a Steering Committee member and the attendees will become part of the "Implanon™ Faculty". All attendees will be required to attend a Faculty Development program for training as physicians who will be serving as "Implanon™ Faculty". The training programs will be lead by these faculty members who will be trained 1 month prior to launch by the Steering Committee members. These faculty members will also become the "Local Implanon™ Expert" for difficult cases and referrals.

7.14.1.2 Healthcare Provider Training

Each training session will be a 3-hour program divided into 4 sections:

1. Implanon™ clinical information and data
2. Insertion/Removal/Localization procedures
3. Hands-on training of Insertion and Removal techniques using specially designed model arms
4. Patient Counseling, Ordering, Billing and Coding information

Upon completion of the program the attendees will receive a model arm and practice kit, a CD-ROM reviewing the Clinical Data and Insertion/Removal/Localization procedures, patient information brochures, counseling tools, and other ordering/billing information. Only those healthcare providers who complete the program will be able to order and insert Implanon™.

Approximately 3-4 weeks after the physicians attend the program, they will receive a follow up e-mail survey, which will review key points in the training session and assess the physician's experiences with using the implant. An "Organon Clinical Contact Specialist will meet with the clinicians on a regular basis beginning within 1 week after the training to review the procedures using the model arm, and other relevant information.

Radiologists will receive information on the localization of Implanon with ultrasound and MRI via published journal articles, CD-ROMs, and the Implanon™ web site.

9.3 Data Available or Needed in Other Populations (e.g., Renal or Hepatic Compromised Patients, or Use in Pregnancy)

This drug is contraindicated in pregnancy. The pharmacokinetics of Implanon™ was not evaluated in patients with renal or hepatic impairment. Labeling will address these latter areas.

10. CONCLUSIONS, RECOMMENDATIONS, AND LABELING

10.1 Conclusions Regarding safety and efficacy

10.1.1 Safety

The extent of exposure to Implanon™ in the Applicant's clinical development program in conjunction with more than 5 years of postmarketing safety is adequate to assess the safety of Implanon™ for the prevention of pregnancy. In the principal safety studies and supportive clinical pharmacology studies conducted by GCP criteria, at least 1411 subjects were exposed to Implanon. Among these subjects, 1,112 subjects were exposed to Implanon for at least one year; 789 for at least two years; 214 for at least 3 years; and 47 for at least 4 years.

In the clinical development program, no deaths occurred in any study. There were no serious adverse events of concern (including cardiovascular/thromboembolic events). Bleeding irregularities were the most common reasons for discontinuing Implanon™. Selected common ($\geq 5\%$ incidence) adverse events of Implanon include frequent and prolonged bleeding, headache, weight gain, emotional lability and acne. Laboratory parameters (hematology, blood chemistry, and urinalysis) were assessed in U.S. Study 069001 and in non-U.S. study 34507 (Austria). No clinically meaningful laboratory abnormalities were noted. Parameters of lipid metabolism (studies in the U.S., U.K. and Thailand) did not reveal any adverse effects. In study 069001, analysis of liver function parameters showed a few treatment differences that reached statistical significance; however, these differences were not clinically important. Mean bone mineral density (BMD) values measured at different sites were generally higher in Implanon users at the end of use than those reported for a reference population in the U.S. and in Europe.

Since the start of marketing of Implanon in 1998, more than _____ units have been sold as of 30 April 2003. Selected postmarketing safety data (SAEs) submitted to the FDA on 9 Sep 04, included reports of 4 deaths (3 deaths due to pulmonary embolus; one death due to bacterial infection). Serious cardiovascular adverse events have consisted of 10 reports of pulmonary emboli, 14 reports of CVAs, and 17 reports of DVTs. Implanon has not been withdrawn from any market because of safety issues. The most common significant postmarketing safety issues has related to adequate training of healthcare providers, a problem that was most common following the initial marketing of the product.

b(4)

The Dutch Medicines Evaluation Board (EU Member States) conducted inspections at several European sites because of Organon's findings of violations at the Indonesian sites (see Section 5.4). Several inspections revealed observations, which might have implications for the quality of the trial data. However, it was agreed that there were no reasons for doubts on the safety and efficacy of the product. The Division will need to review the inspection report carefully before approving this product. As such, this reviewer is recommending an approvable action.

10.1.2 Efficacy

There were four trials (Studies 069001(U.S.), 34505(Thailand), 34507(Europe) and 34507(Canada-CDN) with the primary objective of assessing efficacy and safety. These studies are considered principal studies, which provided the basis for evaluating the efficacy of Implanon™ for the indication of prevention of pregnancy.

The assessment of efficacy was based on the occurrence of pregnancies during the treatment period (defined as pregnancies that occurred within 7 days after implant removal). Pregnancies were categorized as those that occurred pre-treatment (prior to implant insertion), in-treatment (with implant in place), and post-treatment (after removal of implant).

The data presented show that a total of 330 subjects in the U.S. controlled clinical study and 787 subjects in the non-U.S. controlled clinical studies had been treated with Implanon™ for up to four years for a total exposure of 475 and 1,580 woman-years (6,198 and 20,600 28-day cycles), respectively.

This reviewer counted four (4) pregnancies, compared to 0 pregnancies counted by the Applicant. A Pearl index of 0.23 (CI 0.006, 0.06) for two years of treatment is well within an acceptable pregnancy rate accrued with other methods of implantable contraception. Both U.S. subjects were Caucasian.

10.1.3 Overall Risk/Benefit Assessment

The benefits of Implanon include the following:

- Compliance non-dependant
- Single rod
- Highly effective (< 1% failure rate)
- Rapid onset of action
- Rapid reversibility and return to fertility

Selected common ($\geq 5\%$ incidence) adverse events of Implanon include frequent bleeding and prolonged bleeding, headache, weight gain, emotional lability and acne. Most risks are reversible, except for potentially very rare cases of implants that are not removable. Weight gain and emotional lability can be a greater risk with pregnancy and can occur with other methods of contraception. The major disadvantages are that a minor surgical procedure is required for use and there is a high discontinuation rate, mainly due to frequent/prolonged vaginal bleeding. These bleeding irregularities are a major nuisance, but do not cause a safety concern.

Implanon is a safe and highly effective method of contraception that does not compromise future fertility. For most women, the benefits outweigh the risks.

10.2 Recommendations on Approvability

10.2.1 Approvability

This reviewer recommends an approvable action for Implanon™ (etonogestrel implant) for the prevention of pregnancy in reproductive age women for three years. Approval is contingent on the following:

- (1) Resolution by Organon of deficiencies identified by the Dutch Medicines Evaluation Board inspectors and the (2) Division's conclusions that the clinical data submitted in NDA 21-529 are sufficient (a) to support the conclusion that Implanon is safe and effective for prevention of pregnancy in women and (b) to allow labeling of Implanon that accurately reflects the safety and efficacy profile of Implanon™.
- A satisfactory inspection report from the Office of Compliance regarding the sterilization facility
- Completion of a final label. b(4)

10.2.2 Basis for Recommendation regarding Approvability (Risk/Benefit Analysis)

Because of potential serious issues concerning (1) the clinical conduct of the principal studies supporting the safety and effectiveness of Implanon and (2) lack of adequate monitoring and oversight by the Applicant of these studies, the accuracy and adequacy of the data submitted to date in NDA 21-529 to support the safety and effectiveness of Implanon™ for prevention of pregnancy in women cannot be assured. Until these issues are resolved, approval cannot be recommended.

If these issues can be satisfactorily resolved, and the data submitted to date in NDA 21-529 are deemed to reflect the safety and effectiveness of Implanon, it can be concluded that Implanon™ is a safe and highly effective method of contraception that does not compromise future fertility. For most women, the benefits would outweigh the risks.

The benefits of Implanon™ include the following:

- Compliance non-dependant
- Single rod
- Highly effective (< 1% failure rate)
- Rapid onset of action
- Rapid reversibility and return to fertility

The major disadvantages are that a minor surgical procedure is required for use and there is a high discontinuation rate, mainly due to frequent/prolonged vaginal bleeding. These bleeding irregularities can be a major nuisance, but do not cause a safety concern

10.2.3 Recommendations on Phase 4 Studies and Risk Management Program

10.2.4 Risk Management Program (Training of Healthcare Providers)

A steering committee will be formed to develop a training program. All attendees will be required to attend a Faculty Development program to become trained as faculty for training other clinicians at their clinical sites. Each training session will include clinical information, insertion/removal/localization procedures, hands on training using model arms, and patient counseling. Upon completion of the program, the attendees will receive a model arm, practice kit and a CD-Rom to review the training. Only those clinicians who complete the program will be able to order and insert Implanon. Effectiveness of the training programs will be monitored in the following ways:

- Evaluation forms and surveys

- The Clinical Contact Specialists to review the skills of clinicians
- The Steering Committee to review issues that have arisen and the progress of the training programs, surveys and evaluations

Organon should develop a Phase 4 monitoring program in the U.S. for insertion and removal related adverse events

10.2.5 Additional Data to Support 3 Years of Use

It is recommended that the Applicant conduct an additional clinical trial(s), or supply additional confirmatory treatment data obtained through an observational study or registry that would further support the 3-year treatment regimen (effectiveness during treatment Year 3 of a single Implanon implant).

10.3 Labeling

The major needed revisions to the originally propose label include the following:

- Relationship of serum concentrations of etonogestrel to body weight
- Use of product in patients with liver disease
- Revision of the Pearl index
- Revision of section on ectopic pregnancies
- Revision of bleeding irregularities section
- Revision of section on insertion/removal issues
- Revision of use during breast feeding
- Revision of incidence of common adverse events

Other revisions are likely to occur during the next review cycle

ⁱ WHO Cardiovascular disease and the use of oral and injectable progestogen-only contraceptives and combined injectable contraceptives; results of an international, multicenter, case- control study. *Contraception* 1998;57:315-324.

ⁱⁱ Heinemann LAJ et. al. Oral progestogen-only contraceptives and cardiovascular risk: results from the Transnational Study on Oral Contraceptives and the Health of Young Women. *EUR J Contracept Reprod Health Care* 1999;4(2):67-73.

ⁱⁱⁱ Vasilakis C et. al. Risk of idiopathic venous thromboembolism in users of progestogens alone. *Lancet* 1999;354:1610-1611.

^{iv} MacCann MF, Potter LS. Progestin-only oral contraception: a comprehensive review. *Contraception* 50, Suppl. 1, S9-S195 1994.

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/s/

Barbara D. Wesley
10/28/04 03:24:39 PM
MEDICAL OFFICER

Scott Monroe
10/29/04 04:01:05 PM
MEDICAL OFFICER

I concur with Dr. Wesley's (1) recommendation that Implanon
cannot be approved at the present time and
(2) recommendations regarding risk management and Phase 4
commitments.

NDA: 21529 _____

**45 Day Filing Meeting Checklist
CLINICAL**

ITEM	YES	NO	COMMENT
1) Is the clinical section of the NDA clearly organized?	X		
2) Is the clinical section of the NDA adequately indexed and paginated?	X		
3) Is the clinical section of the NDA legible?	X		
4) Is there an adequate rationale for selection of dose and dosing schedule?	X		In vitro release rate of 30 µg per day needed to inhibit ovulation
5) Are the requisite number of adequate and well controlled studies submitted in the application?	X		One U.S. study: 6,198 cycles; five non U.S. studies: 45,414 cycles
6) Are the pivotal efficacy studies of appropriate design and duration to assess approvability of this product for its proposed indication?	X		
7) Are electronic data sets (with adequate documentation for their use) provided for pivotal efficacy studies?	X		Information provided by statistician
8) Has the applicant submitted line listings in a format to allow review of individual patient data?	X		
9) Has the applicant submitted a rationale for assuming the applicability of foreign trial results to the U.S. population?		X	Not necessary for this application
10) Has the applicant submitted all required case report forms (i.e., deaths, drop-outs due to ADEs and any other CRFs previously requested by the Division)?	X		
11) If appropriate, have stratified analyses of primary safety and efficacy parameters been conducted for age, gender and race?	X		

ITEM	YES	NO	COMMENT
12) Has the applicant presented the safety data in a manner previously agreed to by the Division?			N/A Standard analysis is presented: AEs, labs, lipids, bleeding patterns, endometrial bx, bone density, etc.
13) If approved in other countries, have a summary and assessment of foreign post-marketing experience been provided?	X		
14) Has draft labeling been submitted?	X		
15) Have all special studies/data requested by the Division during pre-submission discussions with the sponsor been submitted?			N/A
16) From a clinical perspective, is this NDA fileable? If no , please state in item #17 below why it is not.	X		
17) Reasons for refusal to file:			

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Barbara Wesley M.D., M.P.H. 12-11-03 _____
Reviewing Medical Officer / Date

Supervisory Medical Officer/Date

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/s/

Barbara D. Wesley
12/18/03 05:56:25 PM
MEDICAL OFFICER

Scott Monroe
12/24/03 07:40:15 PM
MEDICAL OFFICER