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The US etonogestrel implant mandatory clinical training and active monitoring programs: 6-year experience☆,☆☆,★

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Abstract

Objective: The objective was to monitor the effectiveness of the etonogestrel implant clinical training program through a voluntary active monitoring program (AMP).

Study design: US health care providers underwent mandatory training by the manufacturer on etonogestrel implant insertion, localization and removal. After training, health care providers could enroll in a voluntary AMP to provide outcome data to meet a postmarketing commitment of the manufacturer with the US Food and Drug Administration (FDA). Those who volunteered completed and faxed forms to the manufacturer after implant insertion and removal detailing the procedure and device-related outcomes, including insertion-, localization- or removal-associated events. Experts reviewed outcome data quarterly, which the Sponsor then reported to the FDA.

Results: Among 42,337 health care providers completing the training program, 4294 (10.1%) volunteered to participate in the AMP. The 26,198 forms submitted over 6.4 years included more insertion (n=20,497) forms than removal forms (n=5701). The volunteers reported 646 events on 566 (2.2%) forms related to insertion (n=197), localization (n=34), removal (n=357) and "other" (n=58). Clinically important events included noninsertion (n=4), serum etonogestrel positive but implant not found (n=1), and possible nerve (n=66) or vascular (n=5) injury. The reports did not include any insertion-, localization- or removal-associated hospitalizations. Eight (0.14%) removal reports described referral for surgical implant removal.

Conclusion: Events related to insertion, localization or removal of the etonogestrel implant are uncommon among US providers who received mandatory training in the use of the implant.

Implications: This report presents results from the first mandatory US contraceptive training program. Health care providers volunteered to report information about etonogestrel implant insertion, localization and removal. Although the data do not demonstrate whether a mandatory program improves outcomes, they elucidate the utility and real-life experience that clinical training programs can provide.

Keywords: Contraceptive implant; Etonogestrel; Training; Monitoring

1. Introduction

The etonogestrel implant (Implanon®; Organon USA, Inc. [now Merck & Co., Inc., Kenilworth, NJ, USA]) received US Food and Drug Administration (FDA) approval in July 2006. This single-rod implant is inserted subdermally under local anesthetic in the medial aspect of a patient's upper arm using a specialized needle applicator. The implant provides highly effective contraception for up to 3 years [1–4]. As a condition of etonogestrel implant approval by the

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US FDA, the Sponsor (Organon USA, Inc., now Merck & Co., Inc.) instituted a comprehensive and mandatory clinical training program (CTP) to ensure provider proficiency with insertion and removal procedures. Only CTP-trained health care providers could order etonogestrel implants.

Along with established regulatory pharmacovigilance practices to assess adverse events, the FDA requested additional measures to assess the effectiveness of the etonogestrel CTP, specifically, the monitoring of insertion-, localization- or removal-related events. The specific post-marketing commitment with the FDA was to conduct and submit interim and final study reports for a postmarketing evaluation of insertion and removal complications involving at least 10,000 subjects. The agreement included routine data review and submission of interim and final reports to the FDA. Accordingly, the Sponsor instituted a voluntary active monitoring program (AMP), the first program to monitor the effectiveness of mandatory training for a contraceptive implant, with the primary objective of monitoring the effectiveness of the mandatory CTP. In 2009, the Sponsor added a secondary objective to the AMP to assess the contraceptive efficacy of the etonogestrel implant over time as a function of body weight. The Sponsor submitted the final report for the AMP to the FDA in March 2014, and the FDA deemed the postmarketing commitment as fulfilled in May 2014.

Although not the first contraceptive implant program to offer clinical training, the etonogestrel implant CTP is novel because health care providers could not access the product without completion of mandatory training. This report describes the outcome of the FDA-required CTP and AMP for the etonogestrel implant.

2. Materials and methods

The Sponsor developed the AMP to monitor the effectiveness of the US mandatory CTP by systematically collecting data on insertion-, localization- or removal-related events. Each CTP training session included the following information: (a) etonogestrel implant clinical information and data; (b) procedures for insertion, localization and removal; (c) hands-on training of insertion and removal of training implant rods in purpose-designed models of the human arm; and (d) patient counseling, ordering, billing and coding information [5].

Health care providers who completed the CTP had the option to voluntarily enroll in the AMP. The AMP protocol design intended that an insertion form and a subsequent removal form would be completed by the health care provider for each patient. These forms collected procedure-related information including adverse events as well as any insertion-, localization- or removal-related events and/or pregnancies. The information collected focused on the procedures and not patient or provider characteristics. Health care providers faxed completed forms within 24 h of the insertion or removal procedure to the Sponsor's (Organon USA, Inc., now Merck & Co., Inc.) Global Safety Department. Instructions for participating providers also included that they should report all adverse events and pregnancies related to the etonogestrel implant by calling a toll-free hotline or faxing a report to the Global Safety Department immediately.

The Sponsor added a secondary objective in 2009 to assess the contraceptive efficacy of the etonogestrel implant over time in heavier-weight women (i.e., women who weighed more than 130% of their ideal body weight). In women who became pregnant, health care providers provided information at the time of implant removal on weight, height, the year of etonogestrel implant use in which the pregnancy occurred, and the estimated date of conception. Pregnancy classification included six prespecified categories: presence of pregnancy not confirmed, no active implant present, conception took place outside period of implant use (estimated time of conception before insertion or after removal), contraceptive method failure, reason for pregnancy cannot be determined with complete certainty and improper use. A pregnancy classification of contraceptive method failure only occurred with documentation of the implant as in situ at the time of conception and with a best estimate of fertilization timing at least 10 days after insertion and at least 10 days before removal. A pregnancy occurring when the implant had been in situ for more than 3 years and 10 days received a categorization as due to improper implant use.

The Sponsor extracted data from all submitted insertion and removal forms and classified reported outcomes as insertion-related, localization-related, removal-related or other based on prespecified categories and not based on which type of form the health care provider used to report the event. One patient could present multiple events associated with one implant.

Insertion-related categories included the following: rod was inserted too deeply and located in the muscle or deep in the fat tissue; difficult insertion; training rod inserted; no rod inserted; multiple rods inserted and present at the same time; and rod inserted at the wrong insertion site.

Localization-related events involved the inability to localize the etonogestrel implant. Initial implant localization required palpation followed in unsuccessful cases by ultrasonography and then, if necessary, magnetic resonance imaging. If these methods failed to locate the implant, the Sponsor recommended serum etonogestrel level measurement to confirm presence or absence of the implant. A central Sponsor laboratory performed serum etonogestrel level quantification by radioimmunoassay with a lowest detectable level of 30 pg/mL [6,7].

Removal-related categories included that a rod could not be removed using the normal procedures described in the product labeling [8]; rod migration away from the insertion site; etonogestrel serum level positive without identification of the rod's location; and surgical intervention beyond what has been described in the product labeling or requiring general anesthesia. The Sponsor identified cases that required referrals

Table 1
Insertion-related events reported in the etonogestrel implant AMP[a].

Event	*n* (%)
Difficult insertion	157 (0.77)
Deep insertion[b]	32 (0.16)
No implant inserted (negative serum etonogestrel level[c])	4 (0.02)
Multiple rods inserted at the same time	2 (0.01)
Insertion at the wrong site	2 (0.01)
Total	197 (0.96)

[a] A total of 20,497 insertion evaluation forms were received during the monitoring program from July 2006 through December 2013 (6.4 years).
[b] Deep insertion was considered when the implant was located in the muscle or deep in the fat tissue.
[c] Serum etonogestrel was assessed using a radioimmunoassay with a lower limit of detection of 30 pg/mL.

Table 2
Removal-related events reported in the etonogestrel implant AMP[a].

Event	*n* (%)
Removal problem[b]	338 (5.93)
Implant migration away from insertion site	15 (0.26)
Surgical removal under general anesthesia	3 (0.05)
Serum etonogestrel positive[c] but implant not found	1 (0.02)
Total	357 (6.26)

[a] A total of 5701 removal evaluation forms were received during the monitoring program from July 2006 through December 2013 (6.4 years).
[b] Removal could not be accomplished using the normal procedures described in the product labeling [8].
[c] Serum etonogestrel was assessed using a radioimmunoassay with a lower limit of detection of 30 pg/mL.

to surgeons or interventional radiologists for implant removal, including the categories of successful and unsuccessful surgical removals as well as referrals still pending follow-up.

The Sponsor classified reported events deemed not insertion-, localization- or removal-related as "other," which included rod expulsion, bent rod, cut or broken rod, blunt needle and any other device-related event not otherwise mentioned.

A panel of three expert US obstetricians/gynecologists (M.D.C., A.M.K., P.D.D.) reviewed the etonogestrel implant AMP data quarterly to monitor the AMP-generated data and the progress of the mandatory CTP. A fourth US obstetrician/gynecologist participated in the panel from study inception through April 2011, at which time the physician discontinued involvement due to a conflicting commitment. The original study Sponsor (Organon USA, Inc., now Merck & Co., Inc.) deemed institutional review board review as unnecessary because the study did not include accessing or use of data that would allow patient identification. We present the data as descriptive statistics.

3. Results

The etonogestrel implant CTP commenced in August 2006 with the final program occurring in September 2011. During this period, 42,337 health care providers attended training on implant insertion, localization and removal, 4294 (10.1%) of whom volunteered to participate in the AMP. Active monitoring started in July 2006 (with reports from trainers using the implant) and continued for 6.4 years, ending in December 2013. Health care providers submitted 26,198 AMP forms (20,497 insertion evaluation forms and 5701 removal evaluation forms) of which 566 [2.2%, 95% confidence interval (CI) 2.0%–2.3%] included an insertion-, localization- or removal-related event. The 566 forms included a total of 646 events.

Health care providers reported insertion-related events on 197 (1.0%, 95% CI 0.8%–1.1%) insertion evaluation forms (Table 1) with "difficult insertion," the most frequent insertion-related event, reported in 157 (0.8%, 95% CI 0.6%–0.9%) of the 20,497 insertion reports. Examples of insertion event descriptions reported on the forms included insertion difficult, implant stuck in the applicator, insertion took more time, multiple insertion attempts needed and difficulty withdrawing the cannula.

Health care providers included information concerning localization of the etonogestrel implant in 521 AMP cases. Thirty-four of these 521 cases reported inability to localize the etonogestrel implant, whereas the implant could be localized in the remaining 487 cases.

Among the 5701 removal evaluation forms, health care providers reported 357 (6.3%, 95% CI 5.6%, 6.9%) removal-related events (Table 2). The removal reports included "removal problems" as the most common removal-related event, reported in 338 (5.9%, 95% CI 5.3%–6.5%) of the 5701 reports. Examples of the descriptions of the removal events reported on the forms included attempted removal but no etonogestrel implant found, need for incision enlargement and/or more time needed for removal. Eight (0.1%) of the removal reports described referral to a surgeon or interventional radiologist for removal of an etonogestrel implant. Seven of these eight referrals led to successful surgical implant removal. The reporting health care provider did not provide a final outcome for the eighth case, a referral to a surgeon for removal.

Fifty-eight AMP reports described other events, including 23 broken or cut implant rods, 15 bent rods, 9 expelled rods and 11 describing events in the category "other."

Clinically important outcomes in the reports included noninsertion (n=4; 2 of the noninsertion reports also included pregnancies), localization or removal difficulties in cases with known implant in situ (serum etonogestrel positive) but implant not found (n=1), and possible associated nerve (n=4) or vascular (n=1) injury. None of the reported events required hospitalization. The one report of a positive serum etonogestrel determination with localization or removal difficulties involved a patient who had an insertion reported

Table 3
Etonogestrel implant contraceptive failures in the AMP based on weight and year of use[a].

	<60 kg	60 to <70 kg	70 to <80 kg	80 to <90 kg	90+ kg	Unknown	Total
1st year of use	0	1	1	1	0	0	3
2nd year of use	0	1	1	0	0	1	3
3rd year of use	0	0	0	0	0	0	0
Total	0	2	2	1	0	1	**6**

The denominator for each body weight category is unknown.
[a] A total of 20,497 implant insertions were reported.

as "difficult" due to an initially incomplete insertion for which the health care provider manually pushed in the exposed end of the implant. The health care provider could palpate the implant after placement but requested a serum etonogestrel level the following week, which confirmed the presence of the implant. This patient had no further information submitted.

Nerve and vascular injuries reports occurred infrequently, and not all such reports included associated insertion- or removal-related events. Sixty-two AMP reports described 66 possible nerve injury events and 5 AMP reports included nonserious, medically confirmed possible vascular injury cases. The most frequently occurring nerve injury events included hypoesthesia (39/66 [59.1%]) and paresthesia (15/66 [22.7%]). The majority (n=58, 93.5%) of the 62 possible nerve injury AMP reports did not have an associated insertion- or removal-related event. Four reports of possible nerve injury (two reports of paresthesia, one report of implant site nerve injury, one report of application site anesthesia) did have an associated insertion- or removal-related event (one with removal problem and migration, one with deep insertion and two with fibrosis at the implant site). All four of these cases of possible nerve injury events had unknown outcomes. Five nonserious, medically confirmed possible vascular injury reports occurred, including one "implant site hematoma," one "application site hematoma" and three "injection site hemorrhages." Only one of these five reports (injection site hemorrhage) had an associated insertion- or removal-related event, reported as difficult insertion.

Providers reported 42 pregnancies among the 20,497 women who had implant insertions during the AMP monitoring period (0.20%, 95% CI 0.14%–0.27%). The reports included 1 that had no confirmation of the presence of a pregnancy, 2 with no active implant present, 4 in which conception occurred outside of the period of implant use, 1 related to improper implant use, 28 for whom the reason for the pregnancy could not be determined with complete certainty, and 6 (0.03%, 95% CI 0.01%–0.05%) with true contraceptive method failures. If contraceptive method failures are calculated to include women for whom the reason for the pregnancy could not be determined, the contraceptive method failure rate is 0.17% (0.11%–0.22%).

Table 3 shows the distribution of the six etonogestrel implant contraceptive method failures based on year of use and body weight group. Five of the six women who experienced contraceptive method failure had weight and body mass index (BMI) reported; one had a BMI<25 kg/m^2 (normal weight), two had a BMI of 25–30 kg/m^2 (overweight), and two had a BMI>30 kg/m^2 (obese). Of the six pregnancies due to contraceptive method failure, one woman chose induced abortion, one had a miscarriage, and four had no available follow-up information.

4. Discussion

This AMP report describes outcomes from health care provider volunteers in "real-world" practices with important safety information from over 26,000 clinical reports with the etonogestrel implant. The total number of reported events related to insertion, localization or removal of the etonogestrel implant was extremely low (n=646) in relation to the total number of insertion (n=20,497) and removal (n=5701) evaluation forms received. Even though the number of removal forms was lower than expected, to the authors' knowledge, this represents the largest database concerning experience with the etonogestrel implant, including insertion-, localization- and removal-related events.

One percent of the 20,497 AMP insertion reports included insertion-related events, most frequently "difficult insertion." The types of difficult insertion events reported in the AMP (including implant retained in the applicator needle, slight bleeding, hematoma formation and difficult insertion) agreed with the findings of an integrated analysis of 11 international clinical trials that the FDA used as the basis for the product labeling and served as the source of the clinical information used in the CTP for US health care providers [4]. This integrated analysis reported that 1.0% of women who received an etonogestrel implant had complications with implant insertion [4].

Local migration, while uncommon, is typically no more than 2 cm from the insertion site [9]. The Sponsor encountered infrequent (0.26%) events reporting of migration in the AMP. Although rare cases of migration to the pulmonary artery have been described [10–15], the AMP participants did not report such cases.

The Sponsor received more removal-related event reports (n=357) than insertion-related event reports (n=197), which

is consistent with a previous study reporting that etonogestrel implant removal may require more time and skill to perform than etonogestrel implant insertion [16]. The most common removal-related event, simply reported as "removal problems," comprised 5.9% of the removal reports. The types of events included (breaking the implant, inability to palpate the implant before removal, removal difficulty due to deep insertion, implant fixed by fibrous tissue, implant too flexible for easy removal, implant adherent to underlying tissue and difficulty locating the implant) are similar to those reported in the above-mentioned integrated analysis [4]. However, the overall rate (6.3%) of removal complications is higher than the 1.7% in the integrated analysis. This higher rate may be related to the relatively lower number of removals reported as compared to insertions, which potentially results in more removal-related events reported relative to the actual number of removals.

The Sponsor expected that the number of insertion and removal evaluation forms received would be similar but received four times more insertion than removal forms; thus, not every insertion form had a corresponding removal form. Additionally, some removal forms did not have enough information to enable linkage to the corresponding insertion forms. The Sponsor recognized the lower return of removal forms during the monitoring program and sent a reminder mailing to AMP participants to return these forms. However, despite this mailing, the number of removal forms collected continued to be lower than expected. Likely contributing factors may have included patients changing their addresses and/or health care providers and implant removals being performed by a different health care provider than the one who performed the insertion. Other reasons for not completing or returning removal forms to the Sponsor may include not identifying patients as participating in the AMP and/or removal by health care providers not enrolled in the AMP. Moreover, with the large shift to electronic medical records during the course of the program, many health care providers may not have had access to a removal form.

The AMP reports cannot be used to accurately determine an actual contraceptive failure rate for the etonogestrel implant because the number of women using the method for each of the potential 3 years of use cannot be determined. The product label for the etonogestrel implant provides a Pearl Index over 3 years of use of 0.38 per 100 women-years [14,15]. In the AMP, the conservative contraceptive method failure rate of 0.17%, at a minimum, suggests that the clinical use of the etonogestrel implant is not less effective than stated in the product label.

The number of confirmed contraceptive method failures (n=6) in the AMP is too small to allow meaningful conclusions about possible effects of body weight or BMI. A cohort study with 1168 etonogestrel implant users showed that the effectiveness of the implant did not decrease in overweight or obese women [17]. A recent pharmacokinetic study also demonstrated no significant differences in etonogestrel concentrations between normal-weight and obese women over time, consistent with the clinical effectiveness data [18]. Another report noted that contraceptive effectiveness of most hormonal contraceptives is not reduced in obese women [19].

The AMP had several limitations. As discussed above, the AMP had a relatively lower number of removal compared to insertion forms. It is possible that those providers who volunteered to participate in the AMP may not be representative of the total population of US providers using the etonogestrel implant. Because the AMP obtained data from health care provider volunteers in "real-world" practices, reporting was not as rigorously monitored as in a clinical trial. It was also not possible to determine from the AMP study database the number of patients from whom the insertion and removal evaluation forms were derived. Additionally, the AMP did not collect details about the characteristics of the health care providers trained through the CTP; accordingly, we are only able to report an overall number who volunteered. To improve the linking of insertion and removal events and data capture of removal-related events, any future evaluations will likely require a clinical trial that enrolls and follows women rather than relying on passive provider reporting.

The mandatory CTP provided US health care providers with information regarding etonogestrel implant clinical data and simulated "hands-on" training using a human arm model. The CTP aimed to prepare health care providers to counsel their patients on the benefits and risks of the etonogestrel implant and to perform insertions and removals according to the product labeling. In addition, it helped to identify and minimize potential risks and encouraged reporting of difficulties to the Sponsor. The training in this CTP involved insertions with a different inserter than is currently marketed for the etonogestrel implant (marketed in United States as Nexplanon® as of November, 2011, Organon USA, Inc., now Merck & Co., Inc.). The currently marketed implant also contains small amounts of barium sulfate rendering it radiopaque, which expands the options available to localize the implant. In the AMP, 34 cases (0.2% of insertion reports) included an inability to localize nonpalpable implants with radiologic studies; the presence of barium sulfate may help in these rare situations, but this remains to be determined.

The introduction of the etonogestrel implant in the United States represents the first time a new contraceptive has been accompanied by mandated proficiency training required to prescribe the product. Overall, clinicians infrequently reported insertion-, localization- and removal-related events and rarely (<0.2%) reported serious outcomes such as surgical removal or nerve or vascular injury; no reports included hospitalization. Conclusions regarding whether or not a mandatory clinical training program improves outcomes cannot be determined from this dataset. The results from the AMP provide information concerning the utility and real-life experience of the etonogestrel implant CTP for US health care providers.

Conflicts of interest

Dr. Creinin serves on Advisory Boards for Allergan, Evofem and Merck & Co., Inc., and is a consultant for Danco, Estetra, Femasys, HRA Pharma, Icebreaker Health and Medicines360. The Department of Obstetrics and Gynecology, University of California, Davis, receives research funding for contraceptive clinical trials from Contramed, Medicines360 and Merck & Co., Inc.

Dr. Kaunitz serves on Advisory Boards for Allergan, Bayer, Pfizer and Merck & Co., Inc. The Department of Obstetrics and Gynecology, University of Florida College of Medicine-Jacksonville, receives research funding for contraceptive clinical trials from Agile, Bayer and Merck & Co., Inc.

Dr. Darney serves on an Advisory Board for Merck & Co., Inc. The Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco, receives research funding from Medicines360.

Lisa Schwartz, Tonja Hampton and Hans Rekers are current employees and Keith Gordon is a former employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., and may hold stock/stock options in the company.

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