From: [redacted]
To:
Subject: RE: Essure Contraceptive Implant Tied to Higher Reoperation Rates [SEC=UNCLASSIFIED]
Date: Monday, 19 October 2015 9:42:05 AM
Attachments: SE Brief - October 2015 - Essure Contraceptive Implant - 16 Ocotber 2015 (draft).DOCX
SE Brief - October 2015 - Essure Contraceptive Implant - 16 Ocotber 2015 (draft).tr5
ACSMD 10 - DRAFT - Meeting Statement.DOCX
ACSMD 10 - DRAFT - Meeting Statement.tr5

Hi [redacted]

Sorry, didn't realise that you didn't have a copy or reference to it. I have also attached the draft ACSMD meeting minutes.

Regards
[redacted]

From: [redacted]
Sent: Monday, 19 October 2015 9:26 AM
To: [redacted]
Subject: FW: Essure Contraceptive Implant Tied to Higher Reoperation Rates [SEC=UNCLASSIFIED]
Importance: High

Dear [redacted]
I am very happy to look over the Essure brief. Would you mind forwarding me the link when you get a chance?

Warmest Regards,
[redacted]

[redacted]

Post-market Device Vigilance and Monitoring
Medical Devices Branch
[redacted]

Therapeutic Goods Administration
Department of Health
PO Box 100
Woden ACT 2606 Australia
www.tga.gov.au

From: [redacted] **On Behalf Of** TGA Parliamentary
Sent: Friday, 16 October 2015 9:49 AM
To: [redacted]
Subject: RE: Essure Contraceptive Implant Tied to Higher Reoperation Rates [SEC=UNCLASSIFIED]
Importance: High

Hi [redacted]

We do not have a brief on Essure, nor is it included in any of the medical device briefs currently. I'll draft one up and get it to [redacted] and [redacted] ASAP.

Cheers,

[redacted]

TGA Parliamentary
Ministerial Correspondence / Ministerial Submissions: [redacted]
Ministerial Briefs/QTBs: [redacted]
Divisional Collaboration / Stakeholder Support: [redacted]

Planning, Reporting and Stakeholder Support Section
Regulatory Engagement & Planning Branch
[redacted]

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From: [redacted]
Sent: Friday, 16 October 2015 9:46 AM
To: [redacted]
Cc: GSU PC
Subject: RE: Essure Contraceptive Implant Tied to Higher Reoperation Rates [SEC=UNCLASSIFIED]

GSU

Do we have a brief on Essure? If not can we have one please for Senate Estimates, or update it if we do have one. Thanks

[redacted]

[redacted]
Medical Devices & Product Quality Division
[redacted]

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From: [redacted]
Sent: Friday, 16 October 2015 9:27 AM
To: [redacted]
Subject: Essure Contraceptive Implant Tied to Higher Reoperation Rates [SEC=UNCLASSIFIED]

Medscape re BMJ Essure article

www.medscape.com

Essure Contraceptive Implant Tied to Higher Reoperation

Rates

[redacted]

|October 14, 2015

Implant-based hysteroscopic sterilization may lead to a significantly increased risk for reoperation, according to a new population-based cohort study. The results were published online October 13 in the *BMJ*.

Jialin Mao, MD, from the Department of Health Policy and Research, Weill Medical College of Cornell University, New York City, and colleagues compared the safety and efficacy of hysteroscopic sterilization using the Bayer *Essure* device vs laparoscopic (tubal ligation) sterilization. Using data from the New York State Department of Health Statewide Planning and Research Cooperative System, the researchers identified 8048 women undergoing hysteroscopic sterilization and 44,278 women who underwent laparoscopic sterilization between 2005 and 2013.

One year after surgery, women who had undergone hysteroscopic sterilization had a 10-fold higher risk of requiring reoperation (odds ratio [OR], 10.16; 95% confidence interval [CI], 7.47 - 13.81) compared with women who had undergone laparoscopic sterilization. Reoperation was typically required because of device migration or incompatibility after surgery.

However, hysteroscopic sterilization was associated with a lower risk for iatrogenic complications within 30 days after surgery (OR, 0.35; 95% CI, 0.20 - 0.61), and the rate of unintended pregnancy was similar between the two groups (hysteroscopic, 1.2% vs laparoscopic, 1.1%; $P = 0.66$).

The authors note that compared with women undergoing laparoscopic sterilization, women undergoing hysteroscopic sterilization were more likely to be older (=40 years of age; 25.2% vs 20.5%; $P < .01$) and more likely to have had a history of pelvic inflammatory disease (10.3% vs 7.2%; $P < .01$), a history of major abdominal surgery (9.4% vs 7.9%; $P < .01$), or cesarean section (23.2% vs 15.4%; $P < .01$).

In Subgroup

Subgroup analyses suggested that women with a history of pelvic inflammatory disease may be at lower risk for unintended pregnancy when treated with hysteroscopic sterilization compared with laparoscopic sterilization.

The authors note that the risk for unintended pregnancy among patients undergoing hysteroscopic sterilization was greater than what has been reported in previous studies and suggest this may be because patients with history of pelvic inflammatory disease were underrepresented in those studies.

Approved by the US Food and Drug Administration in 2002, the *Essure* device was the subject of a recent meeting after receiving thousands of reports of adverse events related to its use since approval.

"To the best of our knowledge, our study is the first population cohort based comparative investigation of safety and efficacy of two widely used procedures for permanent birth control," the authors write.

The researchers acknowledge study limitations such as the inability to identify women who experienced complications that did not result in reoperation as well as the possibility of coding errors. They note, however, that "[t]hese data, along with national and regional registries, are key tools for long term evaluation of surgical techniques and device technologies."

The researchers suggest that, given the high number of sterilization procedures performed annually in the United States, complications related to the use of implant-based hysteroscopic sterilization have "a major public health impact."

They conclude, "A registry based study with longer follow-up is warranted to further understand the failure events after device use and improve the safety and efficacy of sterilization procedures."

Funding for this study was provided through a grant from the National Institutes of Health and US Food and Drug Administration. The authors have disclosed no relevant financial relationships.

BMJ. 2015;351:h5162. Full text

[redacted]
Regulatory Services Group
Department of Health
(RSG incorporates Therapeutic Goods, NICNAS and OGTR)

[redacted]

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ESSURE CONTRACEPTIVE DEVICE

RESPONSE:

- We are responsible for the regulation of therapeutic goods in Australia. It is a general requirement under the Therapeutic Goods Act 1989 that medical products to be imported into, supplied in, or exported from Australia be included in the Australian Register of Therapeutic Goods (ARTG).
- To enable the inclusion of a medical device in the ARTG, a manufacturer must be able to demonstrate that both the medical device and the manufacturing processes used to make the device conform to the requirements of the therapeutic goods legislation. Compliance with those regulatory requirements ensures medical devices supplied in Australia are of acceptable quality and perform as intended.
- The Essure birth control device has been approved under this process and is indicated for women who desire permanent birth control (female sterilisation) by bilateral occlusion of the fallopian tubes. The sponsor of Essure is Australasian Medical & Scientific Ltd and it is manufactured in the USA by Bayer.
- The Essure device was involved in clinical trials between 1998 and 2001. The device was first listed as a therapeutic device in 1999 under ARTG number 72090. It is currently included as a Class III medical device under ARTG number 174123.
- There have been some media reports and literature reports (British Medical Journal, October 2015) stating that use of the Essure implant in patients may lead to a higher risk of adverse events and need for reoperation than laparoscopic tubal ligation. The number of unexpected pregnancies is about the same for both procedures.
- We have received 15 adverse event reports associated with the Essure medical device, dating back to 1999.
- Although the majority of the reported adverse events are noted in the Instruction For Use (IFU) document, the TGA has noted an increase in reporting of unusual symptoms including fatigue, weight gain, headache, nausea and alopecia. We are aware of the US FDA consideration of the Essure device and are monitoring any outcomes to review whether any action is required in the Australian context.

Division: Therapeutic Goods Administration
Cleared by: [redacted]
Contact Officer: [redacted]
Phone: [redacted]
Date: October 2015

BACKGROUND

- The Essure contraceptive device is indicated for women who desire permanent birth control (female sterilisation). It is generally used as an alternative to fallopian tube ligation.
- The sponsor of the product is Australasian Medical & Scientific Ltd, and the manufacturer is Bayer Healthcare LLC.
- Since its first availability in Australia in 1999, the Essure system has undergone several changes in sponsor and manufacturer.
- The Essure contraceptive device is the only medical device of its type (Contraceptive, tubal occlusion, Insert) available in Australia. The Essure system consists of permanent implantable micro-inserts; one micro-insert is placed in each fallopian tube. The micro-insert is a dynamically expanding micro-coil that consists of a stainless steel inner coil, a nickel titanium (nitinol) expanding superelastic outer coil, and polyethelene (PET) fibres. According to the Instructions for Use (IFU):
    - When the Essure micro-insert expands on release, it acutely anchors itself in the fallopian tube. Subsequently, the micro-insert elicits an intended benign tissue response, resulting in tissue in-growth into the micro-insert that anchors the micro-insert firmly into the fallopian tube. This benign tissue response is local, fibrotic and occlusive in nature.
- Following deployment using the single-use disposable delivery system and single-use accessory inducer, three to eight expanded outer coils remain trailing into the uterus. The woman must use additional contraception for three months following the procedure, at which time an Essure Confirmation Test (modified hysterosalpingogram (HSG)) is performed to evaluate insert location and fallopian tube occlusion. If bilateral placement and occlusion are satisfactory, the woman can discontinue alternative contraception and rely on the inserts for contraception.
- To enable the inclusion of a medical device in the ARTG, a manufacturer must be able to demonstrate that both the medical device and the manufacturing processes used to make the device conform to the requirements of the therapeutic goods legislation. Compliance with those regulatory requirements ensures medical devices supplied in Australia are of acceptable quality and perform as intended. The Essure birth control device has been approved under this process.
- To further ensure the continued safety of the Australian public, the TGA undertakes post-market monitoring of medical devices after they are included in the ARTG. The primary focus of the TGA is to capture and investigate safety issues related to marketed devices and to ensure appropriate mechanisms are in place to identify safety concerns that may arise once a device receives approval for supply in Australia.
- The TGA has received a very small number of reports for this device. All reports are prioritised according to risk and if necessary an investigation is conducted. The rate of complaints and adverse events remains within expected rates for this device and no advisories or other actions have been undertaken for this device here in Australia or overseas.
- The FDA convened a public meeting to discuss issues with the Essure device on 24 September 2015. The FDA noted that most adverse events are well known and documented in the IFU although there are some events that have been reported for which evidence on their link to the device has not been conclusively determined.

Advisory Committee on the Safety of Medical Devices

Meeting statement

Meeting 10 – 26 August 2015

Role of the Advisory Committee on the Safety of Medical Devices (ACSMD) in the TGA's regulatory decision making process

The ACSMD is a statutory advisory committee established by the Therapeutic Goods Regulations 1990.

The TGA currently has ten statutory advisory committees from which it can obtain independent expert advice on specific scientific and technical matters to aid the TGA's regulatory decision making and other regulatory processes.

The ACSMD provides advice to the TGA on, amongst other things, matters relating to the safety, risk assessment, risk management and performance of medical devices supplied in Australia.

How this statement should be read

The advice provided by the ACSMD is an important element in the undertaking of the regulatory functions of the TGA. However, it forms only one part of the total body of information that is available to, for instance, a TGA delegate making a regulatory decision under the Therapeutic Goods Act 1989 ("the Act"). Therefore, while appropriate consideration will be given to such advice, it is important to note that neither the TGA nor a TGA delegate is obliged to follow it.

It should also be noted that details of the committee's advice may not become publicly available for some time after the committee has provided that advice. The purpose of this Meeting Statement is to describe in general terms the matters considered by the committee at each meeting and for it to be available as soon as reasonably practical after the relevant meeting.

Additionally, following publication of this statement, it is most likely that further work will be undertaken by the TGA to investigate, monitor and / or evaluate the medical devices considered by the ACSMD; and this will continue for some time into the future. It is therefore possible that further information about the medical devices will become publicly available at a later time and this will be pursuant to a regulatory decision under the Act being made and following further consultation with the device's sponsor and / or manufacturer.

Overview of the medical devices referred for advice

At this meeting, the committee's advice was sought on the need for post-market monitoring of the Essure contraceptive device.

Essure contraceptive device

The Essure contraceptive device is indicated for women who desire permanent birth control (female sterilisation) and is the only medical device of its type available in Australia. The device was referred to the ACSMD as the TGA had concerns with the number and types of adverse events being reported. The committee noted that there has been an increase in device incidents reported both in Australia and world-wide since 2013: the TGA received four reports from 1999 to 2012 and nine reports since 2013.

These 13 cases included common and known adverse events such as cramps (most common), pelvic pain, pregnancy, ectopic pregnancy, discharge, perforations, and migration of the device. Although the majority of the reported adverse events are noted in the device's Instructions for Use (IFU) document, the TGA has also observed an increased number of Device Incident Reports (DIR) containing unusual adverse events including fatigue, weight gain, headache, nausea and alopecia.

The committee was asked if it accepted the sponsor's/manufacturer's explanation for the increase in adverse event reports across 2013 and 2014. The committee noted that the sponsor has stated that the increase in adverse event reports since 2013 reflects the implementation of an improved post-market surveillance system internationally, following the change of manufacturer.

The committee also noted that the 13 DIR in Australia were of variable quality. The unusual adverse events were few in number and describe a broad range of generalised symptoms that are difficult to define as being specifically related to the Essure device. It was also noted that such events are also reported for many devices, medicines and placebos. As such, the committee agreed that there was no obvious link between the underlying performance of the device and the number and types of adverse events reported.

The committee noted that the TGA has currently not received any evidence to suggest an issue related to the risk management processes which are in place for the device and advised that the explanation for the increase in adverse event reports across 2013 and 2014 was acceptable.

The committee was asked whether it agreed that additional reporting requirements would be an appropriate method to monitor the rate and pattern of occurrence of adverse events associated with the device. While the committee was not convinced that there was an urgent safety signal that needed to be addressed, the committee advised that additional requirements on the sponsor to regularly report would be an appropriate method to monitor the rate and pattern of occurrence of adverse events associated with the Essure device.

More medically confirmed data will give a more accurate indication of trends. The committee supported the collection of additional information from patients/reporters to assist in the future analysis of the safety of the Essure device and advised that reanalysis should occur in three to five years.

The committee was asked whether it had any additional suggestions on future investigations by the TGA, with regard to both the observed increase in adverse event reports and the increased rate of the more unusual adverse events. The committee suggested that information on the time between insertion of the Essure device and the emergence of an adverse event was relevant to analysis of the data.

The DIR reports did not provide information on how recently the patient had discontinued hormonal contraceptives. The committee highlighted that adverse events attributed to the presence of the device may actually reflect the discontinuation of a hormonal contraceptive. Details on the temporal relationship between this discontinuation, insertion of the device and the emergence of adverse events should be sought from patients/ reporters.

The committee affirmed that insertion of the Essure device should only be performed by a doctor who has completed an approved training program. Regular review of the adequacy of the training program is appropriate to minimise procedural complications and also to optimise counselling practices.

The committee also advised that the sponsor should consider inclusion of follow-up questions that specifically relate to the Essure device and that this may be facilitated via questionnaires that are already in place and being used as required, when incidents are reported.

The committee was asked whether it had any general comments regarding the Essure device and the issues highlighted above. The committee advised that whilst the reported unusual adverse events are hard to explain and could be related to other medical conditions, they should not be entirely discounted. Quality data collection over time should hopefully clarify the picture.

The serious adverse events of pregnancy, including ectopic pregnancy, and perforations are more clinically concerning and the rates of these events should be closely monitored. Health practitioners and the sponsor should be reminded to report these in order to assess how the rates of these events in the 'real world' compare to clinical trial situations. It was commented that generalised symptoms such as fatigue, weight change and rash could be associated with autoimmune disease.

The committee also advised that patient counselling is critical for all contraceptive choices. A patient who does not receive adequate counselling about potential adverse

events is more likely to be worried by such events, should they occur. Any possible effects of simultaneous withdrawal from hormonal contraceptives need to be addressed in patient counselling and in the IFU document.