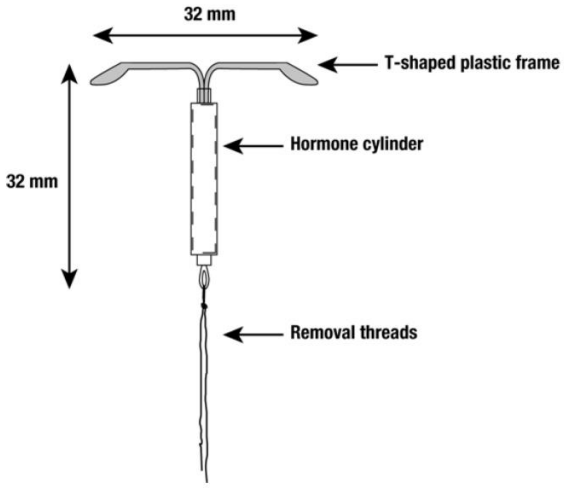
Intrauterine device with levonogestrel Mirena® and device breakage

Introduction

The intrauterine device (IUD) with levonogestrel Mirena® is indicated for *contraception, treatment of enhanced menstrual blood loss or menorrhagia and as progestagen adjuvans to prevent endometrial hyperplasia during estrogen therapy in the peri and post menopause*.
Mirena® is an IUD that contains the progestagen levonogestrel. The levonogestrel is directly delivered in the uterus, in a low daily dose [1].

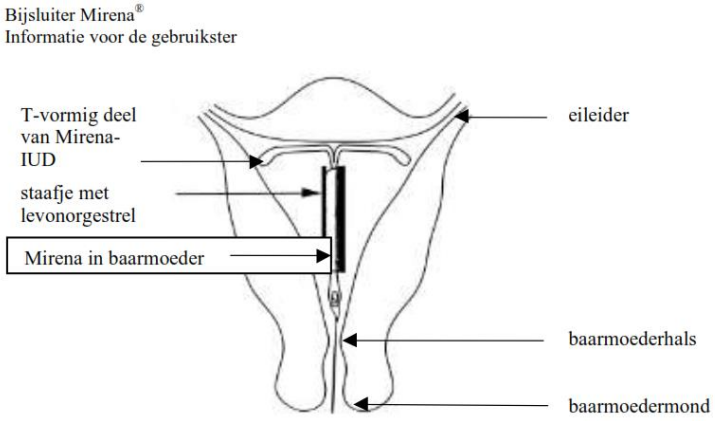
Mirena® consists of the following components:



Schematic drawing of Mirena

[2]

In the body Mirena® is positioned as follows:



[3]

Mirena® was granted marketing authorization in the Netherlands in 1996 [1].

Reports

From 20 September 2011 to 16 May 2018 the Netherlands Pharmacovigilance Centre Lareb received 25 reports of device breakage associated with IUD with progestagen. All 25 reports concerned Mirena®.
One case (NL-BAYER-200911901GPV) was not taken into further account for this Signal, because in this literature report both Mirena® and Essure® were coded as suspect in causing various reactions,

but the reaction wherefore device breakage was coded, concerned specifically Essure® and not Mirena®.
Of the remaining 24 reports, three of these reports were directly received by Lareb, the other 21 reports were received through the MAH. The reports concerned both spontaneous and solicited reports from Mirena® Reimbursements Programmes.

The 24 reports are described here. In some reports perforations, difficulties at insertion or other abnormalities were described. These factors might have resulted in abnormal forces on the IUD, and therefore might have played a major role in the breakage of Mirena®. Therefore, first six reports are described where such factors were not specifically reported, followed by the reports where this was described.

For this Signal, the upper parts of the T-shaped plastic frame of the IUS are referred to as the legs of the IUD. In the reports these were reported as legs, arms or wings of the IUD.

Reports of device breakage at removal without reporting uterine perforation or difficulties at insertion
Lareb received six reports of device breakage during removal in association with Mirena® where it was not reported that the insertion had been difficult or that there had been uterine perforation.
The reports concerned women aged 31-40 years, 51-60 years and 51-60 years, and in three reports ages were unknown. Indications were contraception in one report, menstrual disorder in one report, and not reported in four reports. In three reports Mirena® was removed after five years, in one report in concerned “regular removal” where it was not specifically reported how low the Mirena® was used, and in two reports it was mentioned that Mirena® was removed after a longer period than five years (six years and nine years). In one report (report f), is was reported that in the session in which the Mirena® was inserted also a transcervical myoma was partially removed. It cannot be excluded that this might have played a role in the reaction as well.
Several parts of Mirena® were reported to have broken: The treads (reports a, b and e), the ring to which the threats are attached (report f), the sleeve and left leg (report e), one leg (report c), two legs (report d), different pieces including one leg (report a).
In four reports it was reported that the patient was referred to the gynecologist or that the patient was hospitalized (reports a, c, e, f). In one report (report f) Mirena® was removed. In three reports at the moment of reporting parts of Mirena® still had to be removed (reports a, b, c). In one report (report e) the remaining part was no longer visible and it was unknown whether a small part was still in situ or was lost (report e). In one report (report d), it was not reported whether all parts were removed.
More details on these reports are provided in table 1.

Table 1. Reports of device breakage at removal in association with the use of Mirena® without reporting uterine perforation or difficulties at insertion

Patient, Sex, Age (years), Source	**Drug Indication for use**	**Conco-mitant medica-tion**	**Suspected adverse drug reaction**	**Time to onset, Action with drug Outcome**
a: NL-BAYER-2015-414232, F, unknown, General practitioner	levonorgestrel IUD 52mg Indication not reported		Complication of device removal Device breakage Device difficult to use	5 years Part of Mirena® was removed, the T-part was localized but yet had to be removed
b: NL-BAYER-2016-052812, F, unknown, Gynecologist/ obstetrician	levonorgestrel IUD 52mg Indication not reported Lot number TU0093V		Complication of device removal Device breakage Device difficult to use	Unknown (regular removal) Mirena® was not yet removed, this would be done hysteroscopically at a later moment
c: NL-BAYER-2016-083282, F, 31-40, Gynecologist/ obstetrician	levonorgestrel IUD 52mg Indication not reported		Complication of device removal Device breakage Device difficult to use	5 years Part of Mirena® was removed, the remaining parts yet had to be removed in the surgery room

Patient, Sex, Age (years), Source	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug Outcome
d: NL-BAYER-2017-185375, F, Unknown, General practitioner	levonorgestrel IUD 52mg Indication not reported Batch number TU002L8		Device breakage Device use issue	6 years Mirena® was removed, it was not reported whether all parts were removed
e: NL-LRB-00278391, F, 51-60, Physician	levonorgestrel IUD 52mg Contraception		Device breakage	5 Years Part of Mirena® was removed (regular removal technique was followed by hysteroscopy), the remaining parts were no longer visible at hysteroscopy, ultrasound and curretage, it was unknown whether a small part was still in situ or was lost
f: NL-LRB-174949, F, 51-60, General practitioner	levonorgestrel IUD 52mg Menstrual disorder	Hydrochlorothiazide	Device breakage	9 Years Mirena® was removed during hysteroscopy

<u>Reports of device breakage where uterine perforation, difficulties at insertion or other abnormalities were reported that have played a major role in the device breakage</u>

Lareb received 17 reports of device breakage in association with Mirena® where perforations, difficulties at insertion or other abnormalities were described. These factors might have resulted in abnormal forces on the IUD, and therefore might have played a major role in the breakage of Mirena®. These reports concerned women with ages varying from 25 up to and including 57 years, mean 39 years, median 40 years, and in one report the age of the patient was unknown.

The reported abnormalities that may have played a role in the device breakages were adherence to, embedment in or perforation of the uterine wall in five reports (reports g, v, u, t, w), perforation of the wall of the cervix in one report (report i), cervical location and partly being stuck in the uterine wall in one report (report p), possible insertion in the uterine wall in one report (report j), partial perforation without further specification in one report (report u), problems at insertion and location of Mirena® between uterus and bladder in one report (report h), location in the abdominal cavity in one report (report l), insertion with some difficulty in one report (report k), fibroids and a lot of blood loss as indication in one report (report m), narrow cervix after conization in one report (report o), insertion that did not succeed in one report (report q), possible influence of force and instruments in one report (report n), very shortly (two weeks) after insertion severe abdominal pain and blood loss in one report (report r), and device dislocation without further specification in one report (report s).

The breakages concerned the threads in eight reports (reports g, k, l, m, s, t, u, w), one leg in five reports (reports h, i, r, v, w), lower part and subsequently the legs of Mirena® in one report (report n), the hormonal reservoir in one report (report o), part of the T-piece in one report (report p), and unknown in two reports (reports j, q).

The outcomes were that Mirena® was removed in six reports, where in three reports this occurred via hysteroscopy (reports o, s, u), in one report via laparoscopy (report l), in one report under general anesthesia without further specification (report w), and in one report without a further specified method (report r). At the moment of reporting, there were three reports where parts of Mirena® were removed via hysteroscopy but one leg of the IUD stayed behind (reports h, I, k), one report where parts of Mirena® were removed where the last parts could not be found and probably came out spontaneously (report n), two reports where Mirena® could not be removed hysteroscopically (reports t, v), and one report where except for the threads the IUD was in situ (report m). Outcome was unknown in four reports (reports g, j, p, q).

The case numbers and more extensive details of these reports are provided in the addendum as table 4.

Other report
Lareb received one report (NL-BAYER-200812645GPV) where the breakage became apparent ten months after insertion because of the occurrence of pregnancy. The horizontal part was found in the cervix and was removed, the hormonal bar was not found. The pregnancy continued.

Other sources of information

SmPC

The Dutch SmPC of Mirena® does report that after removal of Mirena® it has to be checked whether Mirena® is still intact. This SmPC does not report device breakage as a possible event [1].

The FDA (Food and Drug Administration in the United States) label of Mirena® reports device breakage as one of the adverse reactions that has been identified during post approval use of Mirena®. It is added that because these reactions that have been identified during post approval use of Mirena® are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure [2].

Literature

No scientific literature was found concerning specifically the breakage of Mirena®.
One case report was described concerning breakage of the Flexi-T® IUD [4] (a copper containing IUD [5]). Ultrasound examinations immediately after insertion and immediately before removal both showed the IUD to be well-positioned. Intramural localization of the IUD was unlikely based on the ultrasound finding and easiness of removal. At removal only a small piece of the IUD was removed though and suction and manual curettage were performed to retrieve the remaining pieces [4].

Database

Table 2. Reports of the PT “Device breakage” associated with Mirena® in the Lareb [6], WHO [7] and Eudravigilance database [8].

Database	MedDRA PT	Number of reports
Lareb	Device breakage	25
WHO	Device breakage	1563
Eudravigilance	Device breakage	1481

RORs were not calculated. The reason was that comparing the number of reports of “Device breakage" for Mirena® to the other drugs in the database where in the majority of drugs “Device breakage” is not applicable, was not considered to be of added value.

Prescription data

Prescription data from the GIP database concern drugs that are used extramurally and reimbursed via the healthcare insurance [9]. Because Mirena® is not reimbursed via the healthcare insurance for all indications, the prescription data cannot be obtained from this database for this drug.

Mechanism

In the cases where a uterine perforation was reported, insertion had been difficult or where there were anatomical abnormalities, unusual forces on the Mirena® might have played a role in the device breakage. On the other hand, material weakness might also be of influence, possibly under influence of the presence in the body for a period of years.

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received 24 reports of device breakage for Mirena®. Lareb received 21 of these reports through the MAH. Of most reports batch numbers were not reported, but the reports were gradually received in a period of seven years. In many of the received reports unusual forces at removal might have played a role in the breakage of Mirena®, for example because of uterine perforation. Lareb also received six reports where such possible influences were not described. It must be noted that in two of these reports Mirena® was in situ for a longer period than five years. The WHO database contains a large amount of 1563 reports of device breakage in association with Mirena®.
The Dutch SmPC of Mirena® does report that after removal of Mirena® it has to be checked whether Mirena® is still intact, but this SmPC does not report device breakage as a separate event which could occur. Nor does the SmPC mention which actions to perform if breakage would occur [1].
Based on the reports received by Lareb, it is suggested that breakage of Mirena® might occur both in situations of mechanical abnormalities caused by for example uterine perforation, as in situations where this is possibly not the case.

References

1. Dutch SmPC Mirena®, IUD 20 microgram/24 uur. (version date: 07-03-2018, access date: 15-05-2018) https://db.cbg-meb.nl/IB-teksten/h16681.pdf.
2. FDA label Mirena® (levonorgestrel-releasing intrauterine system. (version date: 07-2008, access date: 15-05-2018) https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021225s019lbl.pdf.
3. Dutch Bijsluiter [Patient leaflet] Mirena®, IUD 20 microgram/24 uur. (access date: 15-05-2018) https://db.cbg-meb.nl/Bijsluiters/h16681.pdf.
4. Wiebe ER. Broken IUD. J Obstet Gynaecol Can 2012;34(12):1121.
5. KNMP Kennisbank (version date 2018, access date 15-05-2018) https://kennisbank.knmp.nl/article/Informatorium_Medicamentorum/P16424.html.
6. Lareb databank. (version date: 2018, access date: 16-05-2018) www.lareb.nl.
7. WHO Global Individual Case Safety Reports database (Vigilyze). (version date: 2018, access date: 16-05-2018) https://tools.who-umc.org/webroot/ (access restricted).
8. Eudravigilance database. (version date: 2018, access date: 28-05-2018) http://bi.eudra.org (access restricted).
9. College for Health Insurances. GIP database. (version date: 2018, access date: 08-03-2018) http://www.gipdatabank.nl/.

This signal has been raised on August 30, 2018. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbg-meb.nl

Addendum

Table 4. Reports of device breakage in association with the use of Mirena® where uterine perforation, difficulties at insertion or other abnormalities were reported that have played a major role in the device breakage

Patient, Sex, Age (years), Source	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset for the reaction device breakage, Outcome	Remarks, where factors that might have resulted in abnormal forces on the IUD are underlined
g: NL-BAYER-2011-083456, F, 51-60, Physician	levonorgestrel IUD 52mg		Complication of device removal Device breakage Embedded device	Unknown Action and outcome unknown	The threads of Mirena® had broken during removal because the IUD had adhered to the uterine wall (suspected in myometrium).
h: NL-BAYER-2012-016127, F, 21-30, Gynecologist	levonorgestrel IUD 52mg		Complication of device removal Device breakage Device expulsion Embedded device Uterine perforation	About 3 years and 10 moths Part of Mirena® was removed via hysteroscopy, one leg of the IUD stayed behind	The insertion had not gone well. Mirena® had prolapsed into the cervical canal, echo and X-ray showed that the IUD was located between uterus and bladder.
i: NL-BAYER-2012-021778, F, 31-40, Physician	levonorgestrel IUD 52mg Contraception		Device breakage Device breakage Device expulsion Device physical property issue Procedural pain Uterine perforation	2 years (removal because of wish to become pregnant) Part of Mirena® was removed via hysteroscopy, one leg of the IUD stayed behind	Initial attempt of removal was very painful. The IUD was located in the cervix but it seemed one arm had perforated the wall of the cervix.
j: NL-BAYER-2013-032467, F, 41-50, Physician	levonorgestrel IUD 52mg		Complication of device insertion Device breakage Device difficult to use Drug ineffective Embedded device	At insertion Action and outcome unknown	At insertion much resistance was found, the inserter snapped double about 4 cm from distal top and could no longer be used. The IUD possibly inserted in the uterus wall.
k: NL-BAYER-2013-084021, F, 41-50, Gynecologist / obstetrician	levonorgestrel IUD 52mg Menorrhagia Hormone replacement therapy	Conjugated estrogens	Complication of device removal Device breakage Device difficult to use Embedded device Menorrhagia	About 3 years and 9 months Action and outcome unknown	Mirena®was inserted with some difficulty. Mirena® was stuck, threads broke off with firm attempt to extract.
l: NL-BAYER-2014-010043, F, 21-30, General practitioner	levonorgestrel IUD 52mg		Complication of device removal Device breakage Device deployment issue Device difficult to use Uterine perforation	About 1 year because of wish to become pregnant Mirena® was removed from the abdominal cavity via laparoscopy	The treats broke off. At first Mirena® was not visible and it was assumed that Mirena® fell out. Eventually Mirena® was located in the abdominal cavity.
m: NL-BAYER-2014-129074, F, 51-60, Consumer	levonorgestrel IUD 52mg Fibroids Vaginal bleeding		Amenorrhoea Device breakage Device difficult to use Drug ineffective for unapproved indication Device use issue Medical device entrapment Product use issue	About 6 years It was attempted to remove the Mirena® hysteroscopically, but it was encapsulated and removal failed. The IUD was still in situ.	The indication for Mirena® was fibroids and a lot of blood loss. The threads broke off.

Patient, Sex, Age (years), Source	Drug Indication for use	Conco-mitant medication	Suspected adverse drug reaction	Time to onset for the reaction device breakage, Outcome	Remarks, where factors that might have resulted in abnormal forces on the IUD are underlined
n: NL-BAYER-2014-153639, F, 21-30, Gynecologist / obstetrician	levonorgestrel IUD 52mg		Complication of device removal Device breakage Device difficult to use Device expulsion	5 years Parts of Mirena® were removed, the last parts were not found hysteroscopically, they probably came out spontaneously	Initially only the lower part of the Mirena® was removed. Subsequently hysteroscopically the central part was removed but the legs of Mirena® were still inside. Observation of the sample by the MAH gave reason to assume a possible influence of excess force and instruments.
o: NL-BAYER-2015-386035, F, 51-60, Gynecologist	levonorgestrel IUD 52mg Menstrual disorder Headache		Abdominal pain lower Arthralgia Breast cancer Complication of device removal Device breakage Device physical property issue Device use error Dyspareunia Off label use of device Uterine disorder	Mirena® had been in situ for 3 years The remaining parts of Mirena® were hysteroscopically. removed	The patient had a narrow cervix after conization. Because of symptoms including pain, 8 years after removal of Mirena® investigations were performed and the plastic cover / hormone reservoir of Mirena® were located in the uterus.
p: NL-BAYER-2015-449163, F, 41-50, Gynecologist / obstetrician	levonorgestrel IUD 52mg Bleeding menstrual heavy		Abdominal pain Device breakage Embedded device	About 1 year Hysteroscopy was performed, outcome unknown	Mirena® was removed when it was located cervically. Mirena® was partly stuck in the uterine wall and during an inspection a part of the T-piece was missing.
q: NL-BAYER-2015-469020, F, 21-30, General practitioner	levonorgestrel IUD 52mg Contraception		Complication of device insertion Device breakage Device difficult to use Device physical property issue Genital haemorrhage	At insertion Action and outcome unknown	The insertion did not succeed because the portio kept on breaking during latching on. It was very fragile. Device breakage was coded as reaction, but based on the information available to Lareb it was not clear which part of the device broke.
r: NL-BAYER-2016-024796, F, 21-30, Consumer	levonorgestrel IUD 52mg		Abdominal pain Device breakage Genital haemorrhage	2 weeks after insertion Mirena® was removed	2 Weeks after insertion, the patient experienced severe abdominal pain and blood loss. An echo made by the gynecologist, who reported that a foot of the IUD was broken
s: NL-BAYER-2016-195550, F, unknown, Physician	levonorgestrel IUD 52mg Menstrual cycle management Contraception		Complication of device removal Device breakage Device dislocation Genital haemorrhage	Unknown Mirena® was hysteroscopically removed	There was device dislocation. At removal the threads of Mirena® broke off.
t: NL-BAYER-2016-233922, F, 31-40, Physician	levonorgestrel IUD 52mg		Device breakage Device difficult to use Embedded device	About 5 years Mirena® could not be removed hysteroscopically.	The threads broke off during removal of Mirena®. Mirena® was in the uterus wall.
u: NL-BAYER-2017-062617, F, 41-50, Consumer or non-heath professional	levonorgestrel IUD 52mg Contraception		Complication of device removal Device breakage Device deployment issue Device difficult to use Embedded device	Unknown Mirena® was hysteroscopically removed	The threads released during effort to remove Mirena®. Mirena® was stuck in the uterus, there was partial perforation and embedment in cervical position.

Patient, Sex, Age (years), Source	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset for the reaction device breakage, Outcome	Remarks, where factors that might have resulted in abnormal forces on the IUD are underlined
v: NL-LRB-199108, F, 31-40, Consumer	levonorgestrel IUD 52mg Contraception		Complication of device removal Device breakage Embedded device	5.5 years An attempt to hysteroscopically remove Mirena® did not succeed	One leg of the IUD was embedded in the uterus and broke during removal of the Mirena.
w: NL-SHR-NL-2006-012254, F, 31-40, Physician	levonorgestrel IUD 52mg Contraception	ibuprofen paracetamol levocetirizine	Complication of device removal Device breakage Embedded device Foetal death, Foetal distress syndrome Pregnancy with contraceptive device	About 5 Years Mirena® was located behind the bladder and removed under general anaesthesia	The medical history included two myomas. The IUD had been in situ for about 4.5 years. The patient got pregnant. The Mirena® seemed to be situated in the front wall (penetration in the uterine wall) and removal of Mirena® was tried, but the threads broke and the IUD could not be removed. Foetal death occurred (without causality assessment by the reporter regarding the IUD).