The ‘intrauterine ball’ Ballerine®, a intrauterine contraceptive device (IUD) made up of copper beads (copper surface area 300 mm²) has no proven added value over copper IUDs of first choice, such as T-shaped and horseshoe-shaped copper IUDs (with a copper surface area >300 mm²). The supplier claims reliability and safety, but is unable to substantiate this claim. The data from the technical data file that was presented to the Notified Body are not accessible to care providers or patients. In the pre- and postmarketing stages, the manufacturer has had ample opportunity to prove its efficacy and adverse effects in randomised studies. However, the published research collected the data by means of questionnaires, a method that yields insufficiently reliable results. As the IUD is also relatively expensive and offers no added value over existing IUDs, Ge-Bu has given Ballerine a negative ‘drug’ rating.

**Pill verdict: - insufficient**

**Ge-Bu Indication**

- Insufficient data are available to enable a suitable comparison with the current first-choice IUDs.
- Insufficient reliable data are available on the number of pregnancies that arise while wearing the Ballerine, and there are indications that problems like expulsion do not occur less often than with T-shaped or horseshoe-shaped IUDs.
- Based on the currently available studies, the Ballerine offers no proven advantages over existing copper IUDs, with which extensive experience has been gained.

**A new, reliable copper IUD?**

When a new medical device is brought on the market, one may expect that it works at least as well as the existing alternatives, and preferably that it offers advantages over those alternatives. The manufacturer of a new contraceptive copper IUD, which was launched on the Dutch market in 2019, claims: “IUB™ Ballerine® is a new, reliable, hormone-free intrauterine device (IUD). It works in a similar way to other copper IUDs and is effective for 5 years. The Ballerine’s unique and flexible 3D shape makes it an excellent alternative for women who do not respond well to other copper IUDs.”([https://ballerine.nl/professionals/](https://ballerine.nl/professionals/)). However, these claims are not substantiated by research. There have been no direct comparative studies of the risk of pregnancy. Nor are there indications that pain upon insertion, menstrual pain, more severe blood loss during its use, or expulsion are less common than with the coper IUDs which have been on the market for longer periods and with which much experience has been gained. Previous research has shown that a
What is the Ballerine?

The official name of this IUD is ‘IUB™ Ballerine® MIDI’, where IUB stands for ‘intrauterine ball’. The IUD, which consists of 17 copper pearls, unfolds within the uterus into a ball with a 15 mm diameter (Figure 1). The Ballerine IUD is spherical in shape, unlike the usual IUDs, which have a flat frame shaped like a letter T or a horseshoe. The total copper surface area is 300 mm$^2$. The wire along which the beads are strung is made from an alloy of nickel and titanium, and is covered with a layer of polyethylene terephthalate, better known by its acronym ‘PET’. At the lower end, the nickel-titanium wire turns into two monofilament wires made of polypropylene, which must be visible in the vagina in order to enable the IUD to be removed through this applicator tube, after which it unfolds within the uterus.

Copper contraceptive IUDs are regarded as medical devices, in risk class III. For devices of this class, involvement of and assessment by a ‘Notified Body’ is mandatory.

Figure 1. The Ballerine IUD unfolded and inside the applicator tube
Research into the Ballerine IUD

Authorisation research not accessible

Under the current EU legislation on medical devices – which is soon to be replaced – technical data and clinical studies that lead to the certification and introduction of a new medical device are only accessible to the Notified Body, the manufacturer and (in the Netherlands) the Dutch Health and Youth Care Inspectorate (IGJ). The clinical studies on the basis of which the Ballerine has been granted market authorisation are therefore currently not publicly accessible. The new legislation (MDR 2017/745) will make these data partially accessible in the European Databank on Medical Devices (EUDAMED). This databank will only become available in stages as of May 2021. A summary of the clinical data, approved by both the manufacturer and the Notified Body, will become available probably from 2022. An essential component will be the safety and long-term clinical performance of the device.

Certification of the Ballerine

The Ballerine IUD was given EU marketing authorisation in 2014, under the old legislation, by a Notified Body. The clinical data and technical documentation with materials requirements that have led to this certification were not, and still are not, publicly accessible. It is likely that the request for the first assessment and certification referred to the equivalence principle: the new IUD was considered to be equivalent to the other IUDs that had already received marketing authorisation. This is questionable, as the Ballerine is a spherical IUD, unlike the other copper IUDs on the market, and as was mentioned above, any alteration can affect the efficacy or adverse effects.

Recertification

Copper IUDs are Class III medical devices, which means that they need to be recertified every five years after their original certification. From 2021, when the new legislation on medical devices comes into force, this will be changed to annually. The old legislation focused mostly on authorisation on technical grounds, rather than on clinical research, and even less on post-marketing clinical research. Post-marketing research requires all patients involved to be included in a consecutive series (‘real life’ functioning). This procedure involves not only the Notified Body but also national inspectorates (like the IGJ in the Netherlands).

No thorough post-marketing study has so far been undertaken, as this was not a requirement under the old legislation. On the basis of the then available clinical data, a British scientific institute concluded as early as 2019 that data on safety, efficacy and acceptability from robust, independent and comparative studies were lacking for the Ballerine.

As of September 2021, recertification of the Ballerine will be mandatory under the new legislation on medical devices (communication from Titus Health Care). What this will entail is described in the Background Information below.
**Studies of the ballerina in the medical literature**

The medical literature includes a number of studies involving the Ballerine IUD, but not all of these concern the IUD as it has now appeared on the market. Two small-scale randomised studies have been published, but these are not discussed here, as they used IUDs with a different size or copper surface area (12 mm/380 mm$^2$). ClinicalTrials.gov features another randomised trial, carried out by the manufacturer (Ocon Medical Ltd.). However, this trial also compared the smaller 12 mm, 300 mm$^2$ IUD with the TCu380 copper IUD (www.clinicaltrials.gov, 19-10-2020, NCT02036177).

Three retrospective observational studies, sponsored and carried out by the manufacturer of the Ballerine, investigated the IUD as it is currently marketed (Ø15 mm, 300 mm$^2$, Ocon Medical Ltd.). One of these, a post-marketing study of the Ballerine (www.clinicaltrials.gov, 4-11-2020, NCT 02778061), was terminated prematurely due to an insufficient number of enrolments (45 of the required 200; communication from Titus Health Care).

‘Real-world experience’

The authors of the remaining two studies, which are discussed below, use the phrase ‘real-world experience’ in the title of their study. This phrase is here used for a study of user satisfaction, collecting data by means of questionnaires. The level of evidence of these studies is very low.

**First study**

The first study involved presenting a questionnaire to 207 women aged 18 years or over, who had had a Ballerine IUD placed at least 12 months ago. The online survey included questions about the insertion, removal or expulsion of the IUD and about pregnancy. The 153 (73.9%) women who still wore the Ballerine 12 months after insertion were additionally asked questions about their current menstrual pattern, about their physical condition and about their satisfaction with the use of the IUD. There was no control group. The women answered the questions using a 10-point scale (1 = very satisfied, 10 = very dissatisfied).

At the time of the survey, an average of 14 months after the placement, 140 of the 207 (67.6%) women were still wearing the Ballerine IUD. Partial or complete expulsion had occurred in 11 of the 207 (5.3%) women. Thirty-three women (15.9%) had the IUD removed due to heavy menstrual haemorrhages, and 20 (9.7%) had it removed due to severe cramps. In three cases, the IUD was removed because of pregnancy. Ninety-two of the 140 (65.7%) women who still wore the IUD after 12 months were satisfied with its use. This was 44.4% of the total group of women who received the IUD.

Problems during insertion, such as severe pain, were reported by the woman’s doctor. Such problems occurred in 27 of the 207 women (13%). Severe pain during insertion was reported for 4 of the 207 women (1.9%). The figures were comparable in the group of women aged 18 to 25 years (who had in most cases not yet gone through pregnancy). Problems of insertion were reported for 11 of the 44 young women (15.4%), and for 1 of these 44 women (2.6%) this concerned severe pain. Data were collected from notes in the patient file more than a year after the insertion, which implies a high risk of bias in the findings.

**The second study**

The second study used the same design as the first one. It included 175 of 201 women who had a Ballerine placed. At the time of the survey, an average of 17.3 months after the placement, 131 of the 175 women (74.9%) were still wearing the IUD. Thirty-eight IUDs (21.7%) had been removed at the woman’s request. For 14 women, this was due to severe menstrual haemorrhages. Partial or complete expulsion occurred in 6 women (3.4%). One woman had the Ballerine removed because of pregnancy.
Insertion problems, such as severe pain, were reported by the woman’s doctor. Such problems occurred in 23 of the 175 women (13.1%). Severe pain during insertion was reported for 18 of the 175 women (10.3%). The figures were higher in the group of women aged 18 to 25 years (who had in most cases not yet gone through pregnancy). Insertion problems were reported for 9 of the 27 young women (33.3%), and for 7 of these 27 women (25.9%) this concerned severe pain. A striking aspect is that the percentage of women with insertion pain was much higher in this study than in the first study. However, some of the women in the first study used pain killers, for instance the 29 women who had the Ballerine placed after an abortion. Hence, additional research would be required to be able to draw conclusions about the insertion problems.

Comparison with other IUDs

No studies have been published in which the Ballerine IUD was directly compared with other IUDs. Although it is possible to compare the results of different studies, this only yields an indication of the performance of the Ballerine compared to other IUDs.

Protection from pregnancy

The surveys among the women participating in the two studies described above show that after 12 months, the Ballerine was removed in 3 of 207 women and 1 of 175 women, respectively, because of pregnancy. In view of the methods used to obtain these data, it is unclear how complete these data are. The manufacturer’s claim that the Ballerine is effective for 5 years was possibly based on the duration of efficacy of other copper IUDs (www.ballerine.nl). However, the studies of the Ballerine do not provide any information about the efficacy after the first year, and thus cannot substantiate this claim.

Pregnancy in women using copper IUDs with a 2D frame

A Cochrane review found that women using IUDs with a flat frame and a copper surface area of 300 mm$^2$ or more had a cumulative pregnancy rate of 0.1 to 1.0% in the first year. The corresponding rates for IUDs with a flat frame and less than 300 mm$^2$ copper surface area were 0.5 to 2.2%. The patient information leaflet for the Ballerine states that copper IUDs with a copper surface area of at least 300 mm$^2$ have a Pearl Index of 0.1 to 1.4. These figures are based on a literature review, which found this range of Pearl Index values for copper IUDs with a surface area of 300 mm$^2$ or more. It is unclear, however, whether the results of existing IUDs can simply be extrapolated to the Ballerine.

Number of expulsions

A Cochrane review found an expulsion rate for flat-framed IUDs that ranged from 0 to 10.3% (average about 4.7%). The figures found in the two studies of the Ballerine (5.3% and 3.4%) do not suggest that the rates for this IUD will be much worse or better. The question remains, however, how complete and reliable the figures about the Ballerine are, as they are not based on randomized studies.

Background Information

Recertification under the new EU legislation

The new legislation on medical devices sets limits on the equivalence principle. It is no longer allowed to use the equivalence principle for Class III devices. This means that copper IUDs can no longer be certified on the basis of equivalence. Recertification requirements state that the manufacturer must, among other things, provide sufficient clinical evidence to show that the device conforms to the general requirements of safety and performance. This clinical evidence includes three components:

1. A critical evaluation of previously conducted clinical research into existing equivalent devices, where appropriate.
   Since there are no copper IUDs on the market that are fully comparable to the Ballerine, this requirement probably will not apply.
2. A critical evaluation of all available clinical research concerning the manufacturer’s own new device.
3. A review of possible alternative treatment methods. Specifically, this implies that the Ballerine must be compared with a standard IUD in randomised studies. Such a comparative study has not yet taken place.

The post-marketing clinical follow-up will also be subject to stricter requirements. In the Netherlands, percentages relative to the numbers delivered, are calculated on the basis of the number of reports to the manufacturer, the IGJ, the Dutch reporting centre for adverse effects of medical implants (MEBI) and in some cases the Netherlands Pharmacovigilance Centre Lareb. This post-marketing clinical follow-up is passive, in that the so-called opt-in authorisation method means that professionals, the industry and patients report data on a voluntary basis. A general point of criticism on such a method is that this yields incomplete, inaccurate, unverified or biased data. In the longer term, incidents involving medical devices will have to be reported to EUDAMED.

Since copper IUDs are Class III devices, they will as of May 2021 be provided with a barcode and will be included in the unique device identification system (UDI). At present, it is not mandatory in the Netherlands to register IUDs in the Landelijk Implantaten Register (national implant register). The new EU legislation (from 2021) will make reporting of incidents in a register of Class III medical devices mandatory. EUDAMED will be adapted to this.

**Mode of action of a copper IUD**

A copper IUD works by gradually releasing copper into the uterus. Copper kills sperm cells or makes them less motile. In addition, the IUD causes a non-infectious inflammatory reaction and inhibits the implantation of a fertilised egg cell. Copper boosts the inflammatory reaction and also disrupts a number of enzymatic processes, which prevents the uterine mucosa from maturing.

**Gold standard for copper IUDs**

In 2008, Ge-Bu described the TCu380A IUD as “the most effective and safest copper-containing IUD”, although this was then temporarily unavailable in the Netherlands. The conclusion was based on a Cochrane systematic review of randomised trials which concluded that the TCu380A and the TCu380S were the most effective of the IUDs studied. In 2017, the World Health Organization (WHO) summarised the technical specifications. The recent guidelines on contraception issued by the Dutch College of General Practitioners (NHG) and the Netherlands Society of Obstetrics and Gynaecology (NVOG) therefore state: “The general preference is to use a T-shaped IUD (380 mm$^2$ copper) or a horseshoe-shaped IUD (375 mm$^2$ copper).”

**Copper IUDs available in the Netherlands**

**Table 1. Information on copper IUDs available in the Netherlands**
<table>
<thead>
<tr>
<th>Name®</th>
<th>mm² copper</th>
<th>size (mm)</th>
<th>Cost price/ unit* (€) (excl. VAT)</th>
<th>Supplier</th>
<th>Available since</th>
</tr>
</thead>
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<td>300</td>
<td>ø 15</td>
<td>104.17</td>
<td>Titus Health Care</td>
<td>2019</td>
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<tr>
<td>Flexi T 300</td>
<td>300</td>
<td>l 29 b 23</td>
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<td>Will Pharma</td>
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<tr>
<td>MI-DIU sert**</td>
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<tr>
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<td>2010</td>
</tr>
</tbody>
</table>

* Cost price acc. to G-Standaard (Dutch database) October 2020  
** Contains silver as well as copper

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