HUNGARIAN NATIONAL CENTER FOR PUBLIC HEALTH AND PHARMACY

Public Assessment Report

Scientific discussion

Levosert Single-Handed Inserter 20 micrograms/24 hours Intrauterine Delivery System

(levonorgestrel)

HU/H/0580/002/DC

Applicant: Gedeon Richter Plc.

Date: 16.04.2026.

This module reflects the scientific discussion for the approval of Levosert Single-Handed Inserter 20 micrograms/24 hours Intrauterine Delivery System. The procedure was finalised at 21-09-2021 For information on changes after this date please refer to the module 'Update'.

I. Introduction

In accordance with the Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 *on the Community code relating to medicinal products for human use*, an application has been submitted to the reference and competent authorities of the Member State concerned.
This Decentralised Procedure application (Reference member state, RMS: Hungary, concerned member states, CMSs: CZ, LT, LV, PL, SK, CMSs: RO and BG were withdrawn.) concerned a hybrid version of **levonorgestrel 20 micrograms/24 hours Intrauterine Delivery System, under** the trade name **Levosert Single-Handed Inserter 20 micrograms/24 hours Intrauterine Delivery System.**
Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisation for **Levosert Single-Handed Inserter 20 micrograms/24 hours Intrauterine Delivery System.**

The medicinal product is indicated for contraception and treatment of heavy menstrual bleeding.
A comprehensive description of the indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(3) respectively of Directive 2001/83/EC.

The originator product is MIRENA, 52 mg – 20 microgram/24h intrauterine delivery system (Bayer AG), registered and marketed in Europe since 1995.

Since levonorgestrel LNG-releasing intrauterine systems are considered as "locally applied, locally acting" drug products, demonstration of therapeutic equivalence instead of pharmacokinetic bioequivalence was required according to applicable European guidance (CPMP/EWP/239/95).
The application thus relied in part on the results of published preclinical tests and clinical trials of the reference product and in part on new data.
In particular, therapeutic equivalence has been demonstrated in an appropriate clinical study conducted by the applicant.

II. Quality aspects

II.1 Introduction

Gedeon Richter Plc. has applied for Marketing Authorisations via Decentralised Procedure (DCP) for generic products Levonorgestrel 20 microgram/24 h Intrauterine Delivery System containing the known substance levonorgestrel as active ingredient, according to article 10(3) (hybrid application) of consolidated Directive 2001/83/EC of the reference product Mirena Intrauterine Delivery System.

Levonorgestrel is a progestogen used in gynaecology in various ways: as the progestogen component in oral contraceptives, in hormonal replacement therapy or alone for contraception in minipills and subdermal implants. Levonorgestrel can also be administered directly into the uterine cavity as an IUS. This allows a very low daily dosage, as the hormone is released directly into the target organ.

The contraceptive mechanism of action of the levonorgestrel IUS is based mainly on hormonal effects producing the following changes:
- Prevention of proliferation of the endometrium
- Thickening of the cervical mucus thus inhibiting the passage of sperm
- Suppression of ovulation in some women.

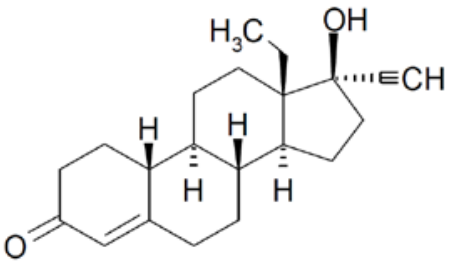
The physical presence of the system in the uterus would also be expected to make a minor contribution to its contraceptive effect.

The reference product is Mirena intrauterine delivery system 52 mg (20 microgram/24 h), Bayer Oy registered since 05-09-1990 in FI.

II.2 Drug Substance

Data on the quality and manufacture of the active substance were provided in the applicant's submission using the CEP procedure with additional data in the marketing authorization dossier. The Quality Overall Summary is adequate.

I.N.N.: Levonorgestrel
Chemical name: 13β-ethyl-17β-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one
Structure:



Levonorgestrel is produced by chemical synthesis. The desired particle size is obtained with a suitable micronization process. Sufficient information regarding the micronization processes has been presented.

The active substance is white or almost white, crystalline powder. It is practically insoluble in water, sparingly soluble in methylene chloride, slightly soluble in alcohol.

The active substance is a well-known compendial-grade material and is tested in accordance with the current European Pharmacopoeia monograph. Additional tests are performed by the finished product manufacturer, which are adequately discussed in the Pharmaceutical development section. The specifications reflect all relevant quality attributes of the active substance and were found to be adequate to control the quality of the drug substance. The limits set are properly justified.

Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch to batch consistency of the production.

Ph. Eur. reference standards used for testing of the active substance. The list of the reference materials has been provided in the documentation.
The packaging materials according to the CEP are double PE bags placed in fiber or aluminium drums. Stability studies have been performed, and appropriate re-test dates have been specified according to the stability results.

Good Manufacturing Practice (GMP) compliance of the API manufacture is demonstrated by the applicant.

II.3 Medicinal Product

The purpose of the development was to develop a levonorgestrel-releasing intrauterine delivery system (IUS), also called intrauterine device. A satisfactory package of data on development pharmaceutics has been presented including a thorough discussion of the drug reservoir and the role of all excipients. In addition, sufficiently detailed information has been presented about the insertion device, as well.

The compositions and the pharmaceutical tests evaluated during development of the final formulation are included in the documentation. As a result of development studies product with the following appearance and composition was obtained:

The product consists of levonorgestrel IUS and an inserter. The inserter is partially preloaded with the levonorgestrel IUS. The IUS consists of a T-shaped polyethylene frame (T-frame) with a drug reservoir around the vertical stem. The drug reservoir is covered by an opaque membrane which regulates the release of levonorgestrel. The T-frame has an eyelet at one end of the vertical stem and two horizontal arms at the other end. A blue removal thread is attached to an eyelet at the end of the vertical stem of the T-frame. The T-frame of contains barium sulphate, which makes it visible in X-ray examination.

The excipients used for manufacturing the drug product are silicone base, tetra-n-propyl silicate, stannous octoate and heptane constituting the reservoir and cured silicone membrane (polydimethylsiloxane membrane), polyethylene T-frame with 20 – 24% barium sulphate, polypropylene thread dyed with copper phthalocyanine blue.

None of the excipients are described in Ph. Eur. However, the material used for inject moulding the Levonorgestrel Intrauterine System (LNG IUS) T-frame has already been widely used in copper IUD. It has been demonstrated that the quality of the excipients is appropriately controlled by the proposed specifications and analytical methods.
Compliance of the product with the general monograph of the European Pharmacopoeia *on the Products with the risk of TSE* has been demonstrated by the applicant.

A description and flow chart of the manufacturing method has been provided. Appropriate in-process controls are included in the manufacturing process. Satisfactory batch formulae were also presented. GMP compliance of the manufacturing site has been demonstrated.

The finished product specification is satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form monograph of the Ph.Eur. and the ICH Q6A guideline. Appropriate control strategy was selected. The test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and complied with the specification. Certificates of analysis for the batches involved in the bioequivalence study are presented.

IUS with the inserter device is individually packed into a thermoformed plastic (PETG) tray with a peelable lid (TYVEK-Polyethylene). Sterile trays are packed into a folding carton. Specifications and quality certificates for all packaging components are enclosed.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results, the following shelf-life and storage condition is approved:
5 years. Store in the original package. This medicinal product does not require any special temperature storage conditions. Keep the sealed tray in the outer carton in order to protect from light.

The Summary of Product Characteristics, patient Information Leaflet and label texts are pharmaceutically acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Conclusion: The product has been shown to meet the current regulatory requirements with regards to its quality and content of the active substance as well as dosage-form characteristics until the end of the approved shelf-life consistently. The manufacture and the quality standards applied adequately support the safe use and efficacy of the product.

III. Non-clinical aspects

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of levonorgestrel are well known. As levonorgestrel is a widely used, well-known active substance, no further studies are required and the applicant provides none. The non-clinical overview is therefore based on a review of data available in several scientific databases or published in relation to the active ingredient, levonorgestrel. Overview based on literature review is appropriate.

III.2 Pharmacology/ Pharmacokinetics/ Toxicology

LNG-IUS is highly effective and highly acceptable form of long acting contraception, which can be used across the entire reproductive lifecycle, and it is also an effective and well tolerated treatment option for idiopathic menstrual bleeding.

LNG or D-(-)-13β-ethyl-17β-hydroxy-18, 19-dinor-l7α-pregn-4-en-20-yn-3-one is a very potent synthetic progestin which produces secretory endometrial transformation and possesses antigonadotropic and anti-estrogenic activity. The local hormone delivery causes high LNG levels in the endometrial tissue but low levels in the systemic circulation. This leads to strong endometrial suppression and, in many cases, a dramatic reduction in menstrual blood loss. LNG has already been approved as a contraceptive. Its contraceptive efficacy is well documented through extensive international clinical research using different routes of administration, including oral route, intrauterine route and sub-dermal route

Locally, its actions on the endometrium growth and on the amount and viscosity of cervical fluids during the menstrual cycle are believed to contribute to the main efficacy of a contraceptive regimen. Menstrual bleeding is decreased by 75% and it is attributed to the progestin-induced decidualization and suppression of the endothelium; 20 to 50% of users become amenorrheic within the first 2 years after insertion. Alternatives to oral administration allow bypassing the hepatic first pass metabolism, enabling to decrease the dose of drug required to achieve therapeutic levels, and therefore causing less undesirable side effects.

LNG has undergone thorough toxicological evaluation. Early studies using the oral route of administration to support safety as an oral contraceptive were supplemented with additional studies using the parenteral route of administration. No unusual toxicity was noted in studies in rodents, dogs and monkeys. LNG was not genotoxic in in vitro and in vivo tests and did not induce tumours that have not been seen before with other contraceptive progestogens in long term carcinogenicity studies. Seven-year studies in beagles demonstrated that a high dose of LNG could elicit a significant tumourigenic response. However, results from high-dose carcinogenicity studies in dogs probably have no relevance to humans. LNG had no adverse effects on fetal development despite its known androgenicity.
Extensive toxicity studies were performed on all the components of the LNG-IUS, principally from Mirena® but also from Levosert®: LNG itself, the unfilled polymer, the LNG-releasing polydimethylsiloxane reservoir, the polydimethylsiloxane membrane tubing, the polyethylene T-body and the polypropylene removal thread. All these tests, conducted in accordance with Good Laboratory Practice and relevant guidelines, allow concluding that Levosert® is safe.
In particular, a study was undertaken in rats to evaluate the sub-chronic systemic toxicity of the reservoir and membrane (without drug) of the device after subcutaneous implantation for 3 months. The study was conducted by LEMI (Martillac, France), in accordance with the guideline ISO 10993-11 (Biological Evaluation of Medical Devices - Part 11: Tests for Systemic Toxicity) and OECD guidelines for Testing of Chemicals N°408 (Sub-Chronic Oral Toxicity - Rodent: 90 Day Study). Under the experimental conditions tested, the placebo of the device implanted subcutaneously for 91 days was well tolerated. It did not induce specific changes indicative of systemic toxicity. No local tissue reactions were observed to the contact of the implant or in its direct vicinity.

In conclusion, Levosert® (levonorgestrel-releasing intrauterine device [52 mg - 20 µg/24 h]), used in its claimed indication, i.e. contraception and treatment of idiopathic menorrhagia, has a favourable benefit-to-risk profile. The hazard associated with LNG-IUS appears to be low and acceptable when considered in relation to the therapeutic benefits that largely prevail over the safety concerns.

III.3 Ecotoxicity/environmental risk assessment (ERA)

The ERA has been considered appropriate. The submitted Phase II fate and effects assessment did not show any unacceptable risks to aquatic or terrestrial compartments from the use of Levosert One Intrauterine system with a Single-hand Inserter. Based on Tier A analysis, it can be acceptable that Phase II Tier B testing is not necessary.
According to the Phase II Tier A assessment levonorgestrel does not present an increased risk to the environment from the use of Levosert One Intrauterine system with a Single-hand Inserter, given that is essentially a substitution of Mirena®.
The risk mitigation measures for Mirena® and Levosert One Intrauterine System with Single-hand Inserter are equivalent as detailed in the SmPC 6.6 Sections.

III.4 Discussion on the non-clinical aspects

Pharmacodynamics, pharmacokinetics and toxicology of levonorgestrel are well-known. As Levosert Single-Handed Inserter 20 micrograms/24 hours Intrauterine Delivery System is a generic product there is no need for further excessive non-clinical studies.
The non-clinical part of the application is thus acceptable.

IV. Clinical aspects

IV.1 Introduction

Levosert® is a levonorgestrel LNG-releasing intrauterine system (LNG-IUS) containing 52 mg of LNG in a cylindrical-shaped silastic reservoir. The reservoir is mounted on the vertical arm of a T-shaped polyethylene frame and is covered with a release rate controlling polydimethylsiloxane membrane. The T-body has a loop at one end and two arms at the other end. Removal threads are attached to the loop.
Levosert is loaded at the tip of an inserter. The inserter components are an insertion tube, plunger, flange, body and slider. Both Levosert and inserter are supplied in a sterile pack that should not be opened until required for insertion. After insertion in the uterus, the product is capable of releasing LNG directly and continuously for up to 5 years.
Levosert requires a physician/health care professional to insert and remove the system from the uterus.
Different types of inserter were developed for the placement of the product into the uterine cavity, an original two-handed inserter (THI-001) (THI-002, intended for EU market) and a subsequent single-handed inserter (SHI-001).

Safety and efficacy of the present formulation is based on the safety and efficacy of the already approved reference product.
The clinical aspects of the SmPC are in line with the SmPC of the reference product Mirena.

To support the application, the Applicant has submitted results from four clinical trials (M360-L102, M360-L103, M360-L104 and Levosert-20):

To evaluate long-term reversible contraception with Levosert use Medicine360 is conducting M360-L102, an ongoing, multicenter, open-label, Phase 3 study. The Phase 3 study, M360-L102, was initiated using a two- handed inserter (THI-001) for insertion. However, after 760 patients were treated using this inserter, enrollment into M360- L102 was suspended due to investigator reported difficulty in insertion.

While enrollment was suspended, Medicines360 developed a single handed inserter (SHI-001) and tested this inserter in a Phase 1 clinical study (M360-L103).

In addition to the pivotal study on contraception (Study M360-L102), this Phase 1 study (Study M306-L103) was conducted with the objective to define the ease of use of the one-handed inserter (SHI-001, which was developed primarily for US market) which was also used during the latter part of the Phase 3 trial.

The SHI-001 inserter was thereafter used in 991 subjects in the M360-L102 pivotal Phase 3 study. After enrollment into M360-L102 was completed, in preparation for a new drug application submission, Medicines360 decided to use a modified two-handed inserter designed for the European market as the proposed to-be-marketed inserter. The modified two-handed inserter (THI-002) is a redesign of the THI-001 inserter with design improvements.

Due to the above, another Phase 1 study (Study M306-L104) was conducted with the objective to define the ease of use of the optimized, two-handed inserter (THI-002, intended for EU market).
The M360-L104 study was conducted to assess the performance of the THI-002 inserter in placing the LNG IUS.

In support of the other indication – heavy menstrual bleeding (HMB) – the Applicant submitted the data of the phase 3 Study Levosert-20 in patients at least 18 years of age with menorraghia (compared to the originator product, Mirena) to provide efficacy, safety and PK data for Levosert.

IV.2 Pharmacokinetics

The pharmacokinetics of levonorgestrel itself have been extensively investigated and reported in the literature. A half-life of 20 hours is considered the best estimate although some studies have reported values as short as 9 hours and others as long as 80 hours. Another important finding, although one in agreement with experience with other synthetic steroids, has been marked differences in metabolic clearance rates among individuals, even when administration was by the intravenous route. Levonorgestrel is extensively bound to proteins (mainly sex hormone binding globulin [SHBG]) and extensively metabolised to a large number of inactive metabolites.

The initial in vivo release rate of 19.5 micrograms/day levonorgestrel from Levosert Single-Handed Inserter 20 micrograms/24 hours Intrauterine Delivery System decreases to 17.0 micrograms/day during the first year and 9.8 micrograms/day at the fifth year. Levonorgestrel is delivered directly into the uterine cavity with low plasma concentrations (252 ± 123 pg/mL 7 days after insertion and 113 ± 50 pg/mL after 5 years) resulting in only minor systemic effects.
There should be no reason to expect that release of LNG from successfully inserted Levosert is influenced by the inserter type per se.

IV.3 Pharmacodynamics

Levonorgestrel is a progestogen used in gynaecology in various ways: as the progestogen component in oral contraceptives, in hormonal replacement therapy or alone for contraception in minipills and subdermal implants. Levonorgestrel can also be administered directly into the uterine cavity as an IUS. This allows a very low daily dosage, as the hormone is released directly into the target organ.
The contraceptive mechanism of action of the levonorgestrel IUS is based mainly on hormonal effects producing the following changes:

- Prevention of proliferation of the endometrium
- Thickening of the cervical mucus thus inhibiting the passage of sperm
- Suppression of ovulation in some women.

The physical presence of the system in the uterus would also be expected to make a minor contribution to its contraceptive effect.

IV.4 Clinical efficacy

In the **Levosert-20 study** the results demonstrated the therapeutic equivalence between Mirena and Levosert in the treatment of menorrhagia. The evaluation of secondary efficacy endpoints also confirmed similar efficacy of the two treatments: the results showed similar residual levels of levonorgestrel in both group for up to three years and the serum levels of Levonorgestrel were also similar in both the Levosert and Mirena groups, suggesting similar PK characteristics up to three years.

Study M360-L102: Three on-treatment pregnancies occurred in subjects placed with the THI-001 inserter and 6 occurred in subjects placed with the SHI-001 inserter. The cumulative PI and life table-derived pregnancy rates by inserter type for the Levosert MITT population did not differ significantly between the two inserter sub-groups
In Study M360-L102, the contraceptive efficacy of Levosert was high in the overall MITT population (as assessed in previous applications) and was similar regardless of the inserter type used. For the first study year (where it would in particular be expected that any potential difference in contraceptive efficacy due to inserter type would become apparent), one on-treatment pregnancy occurred in each inserter group. These single pregnancies resulted in a cumulative Pearl Index point estimate and 95% confidence intervals.

IV.5 Clinical safety

In the **Levosert-20 study** the adverse events were comparable in both the Levosert and Mirena group. The most frequently reported adverse event was metrorrhagia (intermenstrual bleeding and spotting). The most frequent reason for discontinuation was expulsion of the IUD.
Overall the safety profile was similar for both treatments. Only one case of pregnancy was reported but it was considered unrelated to study treatment as no IUS was present. It was concluded that Levosert and Mirena had similar therapeutic efficacy and safety profiles in patients with functional menorrhagia. There were no data regarding the inserter type.

Study M360-L102
Levosert was placed with the THI-001 inserter for the first 760 women enrolled and was inserted with the single-handed SHI-001 inserter for the 991 subsequently enrolled women.
The number of Levosert IUSs placed with the SHI-001 in the Efficacy Group was 952 subjects compared to 648 with the THI-001 inserter. In contrast, only one-third of the subjects in the Non-Efficacy group were placed with the SHI-001 inserter (39 compared to 112 subjects) because at the time of the enrollment pause the majority of this limited protocol population (N=150) had already been enrolled. These differences, like the difference in the exposure, also can influence the results.

With the THI-001 inserter 96.2% (731 of 760) of Levosert subjects had successful placements, with a first attempt success rate of 90.9% and a second attempt success rate of 87.5%.
With the SHI-001 inserter 99.2% (983 of 991) of Levosert subjects had successful placements, with a first attempt success rate of 96.3% and a second attempt success rate of 96.7%.

A total of 3 uterine perforation was observed in the Levosert subjects, all in the Efficacy Group with use of the THI-001 inserter.

Use of cervical anesthesia during any placement was generally comparable with somewhat higher overall rates of use for the SHI-001 inserter (38.7%) compared to the THI-001 inserter (29.7%). In both inserter groups, the majority of subjects received anesthesia as prophylaxis.
The proportion of cervical anesthesia when it was used out of clinical necessity was also similar (14.2% for the THI-001 inserter and 12.0% for the SHI-001 inserter).

Dilation was more frequently required when the THI-001 inserter was used. For the THI-001 inserter, cervical dilation rates during the first and second attempts were 20.6% and 43.8%, respectively. For the SHI-001 inserter, these rates were 11.8% and 26.7%, respectively.

Combined, placement was classified by the Investigator as difficult in 11.6% of first attempts and 32.9% of second attempts. For the THI-001 inserter, these rates were 17.2% and 37.0%, respectively. With the SHI-001 inserter, the rates were 7.3% and 26.7%, respectively.

Heavy bleeding during the placement procedure was rare and reported in only 2 (0.1%) Levosert subjects, both in the Efficacy Group with use of the THI-001 inserter. Moderate placement-related bleeding was reported in 4.2% (32/760) of women in the THI-001 inserter group and in 2.9% (29/991) of women in the SHI-001 inserter group.

Some level of cramping was reported in 80.6% of first placement attempts with the THI-001 inserter, of which 11.2% were severe in intensity. Some level of cramping was reported in 85.2% of first attempts with the SHI-001 inserter, of which 9.3% were severe in intensity.

Expulsions occurred in 32 (4.2%) subjects with the THI-001 and 31 (3.1%) with the SHI-001 inserter, rates that are similar given the difference in time of exposure between the two groups. Among the 63 total expulsions, 10 (15.9%) occurred in the first 30 days and 50 (79.4%) by the first 12 months. Of the 10 expulsions with onset ≤30 days after insertion, 4 occurred for the THI-001 inserter (incidence rate =0.5% (4/760)) and 6 occurred for the SHI-001 inserter (incidence rate =0.6% (6/991)).

In summary, ease of placement was more frequently designated as ”difficult” and clinically necessary cervical anaesthesia, cervical dilation and ultrasound guidance was more frequently employed by the investigator when using the THI-001 inserter compared to the SHI-001 inserter regardless of parity. No uterine perforation was reported for SHI-001. These safety results overall support the choice of the SHI-001 for the present application. Only small differences in placement-related bleeding were apparent when comparing the two inserters, with the two cases of heavy bleeding both reported with use of the THI-001 inserter. IUS expulsions within 30 days of Levosert insertion were rare, with an incidence rate of approximately 0.5% for both inserters. Small differences in cramping/pain were apparent between the two inserters.

In conclusion, for the inserter-related outcomes presented by inserter type from Study M360-L102, there were no concerning safety signals for the SHI-001 inserter.

The long-term, reversible contraceptive efficacy and safety - including succesful placement with both THI-001 and SHI-001 - of Levosert has previously been granted based on intermediate results from a pivotal, Phase 3 study (M360-L102).
Although there is no direct clinical comparison between the one-handed SHI-001 inserter and the currently marketed two-handed THI-002 inserter, an appropriate presentation has been made to demonstrate the safe use of the SHI-001 insert in clinical study M360-L102 performed by the Applicant.

In the Levosert Efficacy Group, during the first 90 days following IUS placement, incidence of AEs of moderate or higher severity was comparable between inserter types.
Since the inserter has no further contact with Levosert subjects after its removal following placement of the IUS, there should be no basis upon which to expect that long-term safety profile of Levosert following the IUS placement procedure would be conditioned on the type of inserter used.

Study M360-L103
This phase I study, Study M360- L103 was conducted to assess the ease of use, the subject tolerance and performance of the SHI-001 inserter in placing the Levosert IUS, see above for further details of the study.

The 96% rate of succesful insertion in Study M360-L103 is in line with the successful placement rate of 96.3% for the first attempt with the SHI-001 inserter in the pivotal phase 3 trial Study M360-L102.
Local anaesthesia applied to the cervix was employed in 28 (56.0%) subjects with only 3 (6.0%) subjects (all nulliparous) requiring additional anaesthesia for discomfort related to sounding or IUS placement.
Cervical dilatation during placement was performed in 3 subjects (6.0%),
Levosert placement was rated as "easy" in 44 (88.0%) subjects while the placement was considered "difficult" in four (8.0%).
No IUS expulsion was evaluated in the 48 subjects who had successful insertion. No IUS expulsions occurred after placement.
Some level of cramping and/or pain was reported in 47 of the 50 subjects (94.0%) who underwent the IUS placement procedure. Thirty-two (64.0%) subjects (16 parous, 16 nulliparous) experienced only mild pain. Moderate and severe pain was reported in 11 (22.0%) and 4 (8.0%) subjects, respectively. The 2 subjects who had unsuccessful placement reported mild pain.
Nearly half of subjects treated (42.0%) experienced no bleeding during IUS placement. Bleeding was observed during IUS placement in 29 subjects (58.0%) with 16 subjects (32.0%) experiencing only spotting and 10 subjects (20.0%) experiencing light bleeding. Only 3 (6.0%) subjects experienced moderate or heavy bleeding
Although due to the short time period of only 5-15 minutes between IUS placement and removal the information of IUS expulsion is limited, overall, the data regarding IUS placement with the SHI-001 inserter in Study M360-L103 demonstrate acceptable safety results.
In conclusion, for the inserter-related outcomes from Study M360-L103, there were no concerning safety signals for the SHI-001 inserter.
At least one TEAE was reported by 12 (24.0%) subjects
All AEs were mild with the exception of three events rated as moderate (back pain,
presyncope, and dyspareunia) in two subjects.
Nine subjects (18.0%) experienced AEs related to Levosert placement, with metrorrhagia being the most frequently reported placement-related event (5 subjects, 10.0%).
No SAE was observed in this study, and no subject discontinued the procedure because of an AE.

Study M360-L104
The Company chose to market Levosert with a modified two-handed inserter THI-002, the currently marketed Levosert inserter in a number of EEA countries.
As the THI-002 inserter was not used in the primary efficacy trial, and as per U.S. regulatory request, the Applicant conducted an additional Phase 1 clinical study (M360-L104) in order to characterize the ease of use and safety of the THI-002 inserter.
IUS placement with the THI-002 inserter was completed in 99 of 100 women enrolled in Study M360-L104 (including 95% with successful first placement attempt).
Local cervical anaesthesia administration was used prophylactically according to Investigator preference in 44 (44%) subjects, but no subjects required cervical anaesthesia for clinical reasons related to the placement procedure.
Cervical dilation for IUS placement was performed during first placement attempts in a total of 18 (18%) subjects.
Levosert placement was considered "easy" or "neutral" in a majority (81) of subjects, which means that 19% of the insertions were rated as difficult by the Investigator.
No perforations or IUS expulsions occurred.
Bleeding was observed during Levosert placement in 59.0% of subjects with 31.0% experiencing only spotting, 20.0% light bleeding and 8.0% moderate bleeding; there was no heavy bleeding noted.
Cramping/pain during the IUS placement procedure was reported in 87 (87.0%) of the 100 subjects; 36.0% mild, 46.0% moderate and 5.0% severe.
Cramping pain in between the procedures or during the follow-up period after IUS removal was experienced by 25.0% of all subjects; mild 11.0% and moderate 14.0%.

The findings regarding bleeding and cramping/pain associated with Levosert placement using the THI-002 inserter or IUS removal in Study M360-L104 resemble the results reported from Study M360-L103 (phase 1 study of the single-handed SHI-001 inserter) and are not considered to raise any safety concern.

There were no reports of heavy bleeding, and only 5.0% of subjects experienced severe cramping/pain in connection with the insertion procedure.
Reported AEs in Study M360-L104 were unexceptional, and there were no treatment-related SAEs.

Overall, there does not appear to be any cause for concern regarding the safety of Levosert Single-Handed Inserter.
The proposed indication and posology are generally in line with the innovator's SmPC and are acceptable with the requested amendments.

IV.6 Pharmacovigilance

Product's name: Levosert Single-Handed Inserter 20 micrograms/24 hours Intrauterine Delivery System
Active substance: levonorgestrel;
Applicant/MAH: Gedeon Richter Plc
Reference number: HU/H/0580/002/DC

1. Summary of Pharmacovigilance System

The Applicant has submitted a signed Summary of the Applicant's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation 520/2012 and as detailed in the relevant GVP module, the Summary is considered acceptable.

2. Risk Management Plan (Version number: 10.1 dated on 08.05.2023 accepted in the HU/H/0580/001-002/II/40 procedure on 16.12.2023)

2.1 Summary of safety concerns

Summary of safety concerns	
Important identified risks	Uterine perforation
	Ectopic pregnancy
	Expulsion of device
Important potential risks	Off-label use (use in other indication, prolonged use)
	Medication error (product confusion)
Missing information	None

2.2 Pharmacovigilance Plan

Routine pharmacovigilance activities:
As routine pharmacovigilance activities beyond adverse reactions reporting and signal detection a Specific adverse reaction follow-up questionnaire is in place in the case of the reference product for the adverse reaction "Uterine perforation", so Applicant introduced it in to Part III.1 and Annex 4 as well. In addition, Applicant performs regular analysis on expulsion/dislocation frequency based on the number of cases received as other forms of routine pharmacovigilance activities for expulsion of device (important identified risk).

Additional pharmacovigilance activities:
Not applicable, since no additional pharmacovigilance studies/activities are conducted or planned.

2.2 Risk Minimisation Measures

Routine risk minimisation is not sufficient in the case of the risk of ectopic pregnancy and off-label use/medication error and additional risk minimisation activities are proposed by the applicant, which is endorsed.
As additional minimisation measures educational materials should be distributed all prescribing health care professionals.
Educational material consists of Prescriber checklist, Patient reminder card and Combined healthcare professional brochure

Key elements for the Prescriber checklist (part of the SmPC/PIL):

- Indications approved and duration of use
- Conditions of use
- Description of the device
- Method of insertion including preparation phase
- Warning regarding signs of uterine perforation

Key elements for the Patient Reminder Card (part of the package material):

- IUD brand name (and active substance)
- Indication
- Day of insertion
- Latest date of removal
- Next appointments
- LOT number
- HCP contact details
- Link to the latest product information (local NCA-homepage)

Key elements of Combined healthcare professional brochure (way of distribution to be elaborated with other LNG-IUD MAHs, especially with the originator):

- The risk of ectopic pregnancy in case of contraceptive failure
- Information concerning the background incidence for ectopic pregnancies
- Signs and symptoms of ectopic pregnancy
- Influence on the patient's fertility
- Risk factors for ectopic pregnancies
- Advice to hand over the product information leaflet and the completed patient reminder card to the patient before insertion of the IUD
- The need to thoroughly counsel a woman regarding the risk, signs and symptoms and monitoring of ectopic pregnancy
- Distinctive characteristics of the products (e.g. size, colour of threads) including pictures (detailing whether there is a silver ring or not)
- Different indications and durations of use of the products and
- How to recognize them via ultrasound (2D and 3D imaging) and X-ray.
- Information on different insertion techniques

3. PSUR

PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.

IV.7 Discussion on the clinical aspects

The application concerns a hybrid version of levonorgestrel 20 micrograms/24 hours Intrauterine Delivery System, under Levosert Single-Handed Inserter.
Levosert Single-Handed Inserter 20 micrograms/24 hours Intrauterine Delivery System is indicated for contraception and treatment of heavy menstrual bleeding, which are approvable.

The application relied in part on the results of published preclinical tests and clinical trials of the reference product and in part on new data.
Therapeutic equivalence has been demonstrated in an appropriate clinical study conducted by the applicant.

There were no objections against granting the marketing authorization from a clinical point of view.

V. Overall conclusion, benefit/risk assessment and recommendation

The risk/benefit ratio is currently estimated as positive.
The application contains an adequate review of published clinical data.
Approval is recommended from the clinical point of view.

Modul 6
Steps taken after the initial procedure with an influence on the Public Assessment Report

Procedure number	Type of modification [1]	Date of start of the procedure	Date of end of procedure	Approval/non approval
HU/H/0580/002/IB/038	C.I.3.z). Other variation	2022.05.25	2022.06.24	Approved
HU/H/0580/002/II/039/G	B.I.b).1.c). Addition of a new specification parameter to the specification with its corresponding test method B.I.b).1.f). Change outside the approved specifications limits range for the active substance B.I.b).2.a). Minor changes to an approved test procedure B.III.1.a).2. Updated certificate from an already approved manufacturer	2023.02.14	2023.04.15	Approved
HU/H/0580/002/II/040	C.I.6.a). Addition of a new therapeutic indication or modification of an approved one An updated version of the RMP (version 10.0) was also submitted.	2023.03.22	2023.12.16	Approved
HU/H/0580/002/IB/041	C.I.2.a). Implementation of change(s) for which no new additional data is required to be submitted by the MAH	2023.07.14	2023.09.28	Approved
HU/H/0580/002/P/001		2024.06.25	2024.09.23	Approved
HU/H/0580/002/IB/042	C.I.2.a). Implementation of change(s) for which no new additional data is required to be submitted by the MAH	2024.08.12	2024.11.07	Approved

HU/H/0580/002/IA/043	A.5.a). The activities for which the manufacturer/importer is responsible include batch release	2024.10.21	2024.11.20	Positive
HU/H/0580/002/IA/045/G (DK/H/xxxx/IA/371/G)	Type IA E.5 - Deletion of manufacturing site for an active substance due to commercial reasons (Gedeon Richter Plc.) Type IA Q.III.1.a.2 - Update of an approved certificate of suitability (CEP) (Levonorgestrel manufactured by Industriale Chimica s.r.l; CEP 2003-127 - Rev 03)	2026.02.14	2026.03.16	Negative