DATA SHEET

1. MICROLUT®

Microlut 30 micrograms tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains 30 micrograms levonorgestrel.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sugar-coated tablets

The tablets are white, biconvex, round and 5.7 mm in diameter.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Oral contraception.

4.2. Dose and method of administration

The pregnancy rate of progestogen-only pills is slightly higher than that of combined oral progestogen-oestrogen combinations. Combined oral contraceptives, when taken correctly, have a failure rate of approximately 1% per year. The failure rate may increase when pills are missed or taken incorrectly.

The dosage of MICROLUT is one tablet daily without any break, taken at the same time each day with some liquid as needed.

How to take MICROLUT

Tablets must be taken in the order directed on the package for the full 28 days without regard to bleeding. This means that after the first pack has been finished, the next should be started without interruption. The days of the week are printed on the pack for convenience.

It is important to maintain an interval of exactly 24 hours between tablets. This interval should by no means be exceeded by more than 3 hours. If, for example, the patient chooses 7 a.m. as the time for taking her tablets, she should try to always take them at this time. Whenever this is impossible, the tablet must be taken by 10 a.m. at the very latest, otherwise protection against conception may decline. The greatest possible reliability of MICROLUT can be assured only by adhering as closely as possible to the 24-hour-intervals.

How to start MICROLUT

No preceding hormonal contraceptive use (in the past month)

Tablet taking has to start on the first day of the menstrual bleeding.

Changing from a combined oral contraceptive (COC)

The woman should start with MICROLUT immediately on the day after the last hormonal tablet of her previous COC and omit the pill-free interval of this COC.

Changing from another progestogen-only method (Minipill, injection or implant)

When switching from another progestogen-only Minipill, the woman may start with MICROLUT on any day, without any break between tablets.

The woman may switch from an implant on the day of its removal, from an injectable when the next injection would be due, but should in both cases be advised to additionally use a barrier contraceptive method for the first 7 days of tablet taking.

Following abortion

The woman may start immediately.

Following delivery

For breast-feeding women, Microlut may be initiated 6 weeks post-partum, (see section 4.6). Women who are not breast-feeding should be advised to start in the fourth week after delivery. When starting later, the woman should be advised to additionally use a barrier contraceptive method for the first 7 days of tablet taking. However, if intercourse has already occurred, pregnancy should be excluded before starting MICROLUT use or the woman has to wait for her first menstrual period.

Management of missed tablets

If even 1 tablet is taken late (i.e. if it is more than 27 hours since the last tablet was taken, i.e. more than three hours later than it should have been taken) or if even 1 tablet is missed, protection against conception may be impaired. The user should take the last missed tablet as soon as she remembers, even if this means taking 2 tablets at the same time. She then continues to take tablets at her usual time. In addition, a barrier method should be used for the next 7 days. If intercourse took place in the preceding 7 days, the possibility of a pregnancy should be considered. The more tablets are missed, the higher the risk of a pregnancy.

Advice in case of vomiting or diarrhoea

If vomiting and/or diarrhoea occur within 3 - 4 hours after tablet taking, absorption may not be complete and additional contraceptive measures should be taken. In such an event, the advice concerning missed tablets is applicable. If the woman does not want to change her normal tablet-taking schedule, she has to take the extra tablet(s) needed from another pack.

4.3. Contraindications

MICROLUT should not be used in the presence of any of the conditions listed below. Should any of the conditions appear during the use of Microlut, the use of the preparation must be discontinued immediately.

- Known or suspected pregnancy
- Active venous thomboembolic disorder

- Presence or history of arterial and cardiovascular disease (e.g. myocardial infarction, cerebrovascular accident, ischaemic heart disease)
- Diabetes mellitus with vascular involvement
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal
- Presence or history of liver tumours (benign or malignant)
- Presence or history of cancer of the breast or genital organs, if sex steroid-influenced
- Undiagnosed vaginal bleeding
- Hypersensitivity to any of the components of MICROLUT

4.4. Special warnings and precautions for use

If any of the conditions/risk factors mentioned below is present, the benefits of using Microlut should be weighed against the possible risks for each individual woman and discussed with the woman before she decides to start using it. In the event of aggravation, exacerbation or first appearance of any of these conditions or risk factors, the woman should contact her physician. The physician should then decide on whether Microlut should be discontinued.

Circulatory Disorders

From epidemiological studies there is little evidence for an association between progestogen-only pills and an increased risk of myocardial infarction and cerebral thromboembolism. The risk of cardiovascular and cerebral events is rather related to increasing age, hypertension and smoking. In women with hypertension the risk of stroke may be slightly enhanced by progestogen-only pills.

Some studies indicated that there may be a slightly, but not statistically significant increased risk of venous thromboembolism (deep venous thrombosis, pulmonary embolism) associated with the use of progestogen-only pills. Generally recognized risk factors for venous thromboembolism (VTE) include a positive personal or family history (VTE in a sibling or a parent at a relatively early age), age, obesity and prolonged immobilisation, major surgery or major trauma. In case of long-term immobilisation, it is advisable to discontinue the use of MICROLUT (in the case of elective surgery at least four weeks in advance) and not to resume until two weeks after complete remobilisation.

The increased risk of thromboembolism in the puerperium must be considered.

Treatment should be stopped at once if there are symptoms of an arterial or venous thrombotic event or suspicion thereof.

Tumours

A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently using COCs mainly using oestrogen-progestogen preparations. The excess risk gradually disappears during the course of the 10 years after cessation of COC use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the overall risk of breast cancer. The risk of having breast cancer

diagnosed in progestogen-only pill users is possibly of similar magnitude to that associated with COC. However, for progestogen-only preparations, the evidence is based on much smaller populations of users and so is less conclusive than that for COCs. These studies do not provide evidence for causation. The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in COC users, the biological effects of OCs or a combination of both. The breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users.

In rare cases, benign, and even more rarely, malignant liver tumours have been reported in users of oral contraceptives. In isolated cases, these tumours have led to life-threatening intra-abdominal haemorrhages. A hepatic tumour should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal haemorrhage occur in women taking MICROLUT.

Other conditions

Progestogen-only pills generally do not appear to affect blood pressure in normotensive women. However, if a sustained clinically significant hypertension develops during the use of MICROLUT, it is advisable to withdraw MICROLUT and treat the hypertension.

Recurrence of cholestatic jaundice and/or pruritus which occurred first during pregnancy or previous use of sex steroids necessitates the discontinuation of MICROLUT.

An increase in frequency or severity of headaches during MICROLUT use, in particular the onset of migraine which may be prodromal of a cerebrovascular event, may be a reason for immediate discontinuation of MICROLUT.

Although MICROLUT may have a slight effect on peripheral insulin resistance and glucose tolerance, there is generally no need to alter the therapeutic regimen in diabetics using progestogen-only pills. However, diabetic women and those with a history of gestational diabetes mellitus should be carefully observed while taking MICROLUT.

Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation whilst taking MICROLUT.

Pregnancies that occur among users of progestogen-only pills are more likely to be ectopic than are pregnancies among users of COCs. In women with a history of extrauterine pregnancy or an impairment of tube function, the use of MICROLUT should be decided on only after carefully weighing the benefits against the risks. If lower abdominal pain occurs together with an irregular cycle pattern (amenorrhoea or amenorrhoea followed by persistent bleeding), an ectopic pregnancy must be considered.

Persistent ovarian follicles (often referred to as functional ovarian cysts) may occur during the use of MICROLUT. Most of these follicles are asymptomatic, although some may be accompanied by pelvic pain or dyspareunia. In most cases, the enlarged follicles disappear spontaneously during 2 - 3 months of observation.

Medical examination/consultation

A complete medical history and physical examination should be taken prior to the initiation or reinstitution of MICROLUT, guided by section 4.3 and section 4.4. This should be repeated at least annually during the use of MICROLUT. The frequency and nature of these assessments should be based on established practice quidelines and adapted to the individual woman, but should generally include special reference to blood pressure, breasts, abdomen and pelvic organs and should also include cervical cytology.

Women should be advised that oral contraceptives do not protect against HIV infections (AIDS) and other sexually transmitted diseases.

Reduced efficacy

The efficacy of MICROLUT may be reduced in the event of missed tablets, vomiting and/or diarrhoea, or concomitant medication.

Reduced cycle control

Menstrual bleeding

Menstrual bleeding occurs at normal intervals and is of normal duration and intensity in the majority of cases. However, both shortened and lengthened intervals are observed.

For this reason the possibility of such changes in menstrual rhythm should, as a precaution, be pointed out to the patient before the start of tablet taking. The changes occur mainly during the first few months of use, but with continuing treatment the cycle pattern tends to stabilise, and in most cases an individual pattern is established. The patient should be encouraged to keep a record of bleeding on the calendar contained in each pack.

Procedure in the event of intermenstrual bleeding

Intermenstrual bleeding of varying intensity may occur, particularly during the first few months. It is not a medical reason to stop tablet taking, as long as organic causes for such bleeding can be ruled out by means of adequate diagnostic measures.

It is inadvisable to attempt to influence cycle disturbances by the additional administration of an oestrogen. This would only serve to reverse the changes brought about by MICROLUT in the cervical mucus, thereby considerably jeopardising the contraceptive effect.

Absence of withdrawal bleeding

Amenorrhoea may occur in some women, in most cases only for one or two menstrual periods. In rare cases bleeding may fail to occur at longer intervals.

If no menstrual bleeding has occurred within 6 weeks after the last menstrual bleeding, pregnancy must be excluded before tablet taking is continued.

Use in Children

Microlut is only indicated after menarche.

Use in the Elderly

Microlut is not indicated after menopause.

Patients with Hepatic Impairment

Microlut is contraindicated in women with severe hepatic disease as long as liver function values have not returned to normal (see section 4.3).

Patients with Renal Impairment

Microlut has not been specifically studied in renally impaired patients.

4.5. Interaction with other medicines and other forms of interaction

Note: The data sheet of concomitant medications should be consulted to identify potential interactions.

Effects of other medicinal products on Microlut

Interactions can occur with drugs that induce microsomal enzymes, which can result in increased clearance of sex hormones which may lead to changes in the uterine bleeding profile and/or contraceptive failure.

Women on treatment with any of these drugs should temporarily use a barrier method in addition to MICROLUT or choose another method of contraception. The barrier method should be used during the time of concomitant drug administration and for 28 days after their discontinuation.

Substances increasing the clearance of levonorgestrel (diminished efficacy of Microlut by enzyme-induction), e.g.:

Hydantoins, barbiturates, primidone, carbamazepine, rifampicin and possibly also griseofulvin, oxcarbazepine, topiramate, felbamate, rifabutin and products containing St John's Wort (*Hypericum perforatum*).

Enzyme induction can already be observed after a few days of treatment. Maximal enzyme induction is generally seen within a few weeks. After the cessation of drug therapy, enzyme induction may be sustained for about 4 weeks.

Substances with variable effects on the clearance of levonorgestrel

When co-administered with sex hormones, many HIV/HCV protease inhibitors and non-nucleoside reverse transcriptase inhibitors can increase or decrease plasma concentrations of the progestin.

These changes may be clinically relevant in some cases.

Substances decreasing the clearance of levonorgestrel (enzyme inhibitors)

Strong and moderate CYP3A4 inhibitors such as azole antifungals (e.g. fluconazole, itraconazole, ketoconazole, voriconazole), verapamil, macrolides (e.g. clarithromycin, erythromycin), diltiazem and grapefruit juice can increase plasma concentrations of the progestin.

Effects of Microlut on other medicinal products

Oral contraceptives may affect the metabolism of certain other drugs. Accordingly, plasma and tissue concentrations may be affected (e.g. cyclosporin).

Other forms of Interaction

Laboratory tests

The use of preparations like MICROLUT may influence the results of certain laboratory tests, including biochemical parameters of liver, thyroid, adrenal and renal function, plasma levels of (carrier) proteins, e.g. corticosteroid binding globulin and lipid/lipoprotein fractions, parameters of carbohydrate metabolism and parameters of coagulation and fibrinolysis. Changes generally remain within the normal laboratory range.

4.6. Fertility, pregnancy and lactation

Use in Pregnancy (Category B3)

Microlut is not indicated during pregnancy. If pregnancy occurs during treatment with Microlut, further intake must be stopped. However, extensive extensive epidemiological studies have revealed neither an increased risk of birth defects in children born to women who used OCs prior to pregnancy, nor a teratogenic effect when OCs were taken inadvertently during early pregnancy. See also section 4.3.

Use in Lactation

Hormonal contraceptives are not recommended as the contraceptive method of first choice during lactation, but progestogen-only methods are considered to comprise the next choice category after non-hormonal methods. There appears to be no adverse effect on infant growth or development when using any progestogen-only method after 6 weeks postpartum. Progestogen-only methods do not appear to affect the quantity or quality of breast milk; however, minute amounts of the active substance are excreted with the milk.

4.7. Effects on ability to drive and use machines

There are no observed effects.

4.8. Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions with progestogen-only pills including Microlut are uterine/vaginal bleeding including spotting, menorrhagia and/ or metrorrhagia and amenorrhea. They occur in ≥ 1% of users.

Tabulated list of adverse reactions

Serious undesirable effects of MICROLUT have been referred to in section 4.3 and section 4.4.

In addition, the following undesirable effects have been reported in users of progestogen-only pills, although the causal relationships have not been confirmed:

System Organ Class	Common (≥ 1/100 and < 1/10)	Rare (< 1/1000)
Immune system disorders		Hypersensitivity reaction
Psychiatric disorder		Depressed mood Libido decreased Libido increased
Nervous system disorders		Headache, dizziness

Eye disorders		Contact lens intolerance
Gastrointestinal disorders		Nausea, vomiting
Skin and subcutaneous tissue disorders		Skin disorder Acne Hirsutism
Reproductive system and breast disorders	Uterine/ Vaginal bleeding including Spotting, Menorrhagia and/ or Metrorrhagia, Amenorrhea	Breast tenderness Vaginal discharge
Investigations		Weight increased Weight decreased

The most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9. Overdose

There have been no reports of serious deleterious effects from overdose.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

Symptoms

Symptoms that may occur in this case are nausea, vomiting and slight vaginal bleeding.

Treatment

There are no antidotes and further treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Progestogens, levonorgestrel

ATC Code: G03AC03

MICROLUT contains the oral progestogen levonorgestrel in a very low dose. The continuous daily ingestion of 0.03mg levonorgestrel prevents conception in several independent ways. Mainly, there are changes in the cervical mucus which make the migration and ascent of sperm difficult or block this. Furthermore, changes in the endometrium throughout the cycle can be considered as having the effect of rendering nidation difficult. Ovulation is not inhibited in the majority of women, but

MICROLUT can impair the midcycle gonadotrophin peaks and the corpus luteum function which may contribute to the contraceptive action.

5.2. Pharmacokinetic properties

Absorption

Orally administered levonorgestrel is rapidly and completely absorbed. Peak serum concentrations of 0.8 ng/ml are reached about 1 hour after single ingestion of MICROLUT. The absolute bioavailability of levonorgestrel from MICROLUT is about 82%.

Distribution

Levonorgestrel is bound to serum albumin and to sex hormone-binding globulin (SHBG). Only about 1.5% of the total serum drug concentrations is present as free steroid and about 65% is specifically bound to SHBG. The relative distribution (free, albumin-bound, SHBG-bound) depends on the SHBG concentrations in the serum. Under MICROLUT treatment, a slight decline in the SHBG serum levels could occur which in turn might have minor effects on the relative distribution of levonorgestrel with respect to the two binding proteins. The apparent volume of distribution of levonorgestrel is about 106 l.

Levonorgestrel distributes into mother's milk and about 0.1% of the maternal dose can be transferred to the breast-fed infant.

Metabolism

Levonorgestrel is completely metabolised by the known pathways of steroid metabolism. No pharmacologically active metabolites are known. The metabolic clearance rate from serum is between 1 and 1.5ml/min/kg.

Elimination

Levonorgestrel serum levels decrease in two phases which are characterised by half-lives of about 1 hour and about 20 hours, respectively. Levonorgestrel is not excreted in unchanged form. Its metabolites are excreted at about equal parts via urine and faeces. The half-life of metabolite excretion is about 1 day.

Steady-state conditions

Following daily repeated administration of levonorgestrel, drug serum levels reach steady-state after about 2-3 weeks, when SHBG levels achieve steady-state. The pharmacokinetics of levonorgestrel is influenced by serum levels of SHBG. The daily ingestion of 0.15mg levonorgestrel (corresponding to 5 times the daily dose of MICROLUT) led to a 50% decrease in SHBG serum levels and thus, a 40% reduction in levonorgestrel trough levels after 2 - 3 weeks. A similarly directed effect of MICROLUT should account, however, for a decrease of only about 10% in both parameters.

5.3. Preclinical safety data

Acute toxicity studies did not indicate a risk of acute adverse effects in case of inadvertent intake of a multiple of the daily contraceptive dose.

In animal studies on systemic tolerance with repeated oral administration, including tumourigenic studies, no systemic intolerance reactions were observed which would

cause concern regarding the dosages required for contraception. However, it should be borne in mind that sex steroids might stimulate the growth of hormone-dependent tissues and tumours.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Calcium carbonate, glycol montanate, lactose monohydrate, macrogol 6000, magnesium stearate, maize starch, povidone, purified talc, sucrose.

Microlut is gluten free.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

5 years

6.4. Special precautions for storage

Store below 25^{o}C.

6.5. Nature and contents of container

PVC/Aluminium blisters. Pack sizes of 1 x 28 or 3 x 28 tablets.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Bayer New Zealand Limited
3 Argus Place
Hillcrest
North Shore
AUCKLAND 0627

Free Phone: 0800 233 988

9. DATE OF FIRST APPROVAL

08 February 1973

10. DATE OF REVISION OF THE TEXT

21 March 2017

Summary table of changes

Section changed	Summary of new information
All sections	Change to Data Sheet format. Included and amended information as appropriate.
4.2	Minor editorial change
4.4	Rewording of section and editorial change. Additional information on use in special populations.
4.5	Editorial changes and new interactions added.
4.6	Reworded section and provided further information for healthcare providers.
4.7	Added the section “Summary of the safety profile”.
6.1	Rearranged excipients alphabetically and renamed excipients according to Medsafe product detail