PROPOSED PROFESSIONAL INFORMATION FOR KLIOGEST®

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

Kliogest® 2 mg/1 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains: Estradiol hemihydrate equivalent to anhydrous estradiol 2 mg, and norethisterone acetate 1 mg.

Excipients with known effect:

Contains sugar: Each tablet contains 36,3 mg lactose monohydrate.

For the full list of excipients, see section 6 .1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

White, film-coated, biconvex tablets engraved with NOVO 281 on one side. Diameter 6 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hormone replacement therapy (HRT) for estrogen deficiency symptoms in women more than one year after menopause.

- To reduce the risk of bone loss in postmenopausal women.

Kliogest® has no contraceptive effect.

4.2 Posology and method of administration

Kliogest® is a continuous combined hormone replacement product intended for use in women with an intact uterus. One tablet should be taken orally once a day without interruption, preferably at

the same time every day. Treatment with Kliogest® should preferably be initiated not earlier than one year after the menopause.

For treatment of postmenopausal symptoms, the lowest effective dose should be used. Kliogest® should only be continued as long as the benefit in alleviation of severe symptoms outweighs the risk.

In women with amenorrhoea and not taking HRT or women in transition from another continuous combined HRT product, treatment with Kliogest® may be started on any convenient day. However, when women switch from a sequential HRT product to Kliogest® it is recommended to start treatment after the bleeding episode, i.e. the same day as the start of a new treatment cycle with sequential HRT was planned.

If the patient has forgotten to take one tablet, the forgotten tablet is to be discarded. Forgetting a dose may increase the likelihood of breakthrough bleeding and spotting.

4.3 Contraindications

- Known hypersensitivity to estradiol or norethisterone acetate or to any of the excipients of Kliogest® (see section 6.1).
- Not for use during pregnancy or lactation.
- Known, past history (personal and/or family) or suspected breast cancer.
- Known, past or suspected estrogen-dependent neoplasia such as endometrial carcinoma, ovarian cancer or other hormone-dependent tumours.
- Active liver disease. Acute or chronic liver disease or a history of liver disease as long as liver function tests have failed to return to normal.
- Liver tumours.
- Undiagnosed vaginal bleeding.
- Untreated endometrial hyperplasia.
- Endometriosis.

- Previous or current venous thromboembolism (deep venous thrombosis, pulmonary embolism).
- Active or previous arterial thromboembolic disease (e.g. angina, myocardial infarction).
- Inherited thrombophilia or known thrombophilic disorders (e.g. protein C, protein S or antithrombin deficiency (see section 4.4).
- Cardiovascular disease.
- Use with caution in patients with hypertension.
- Porphyria.
- Patients with known inherited genetic mutations: BRCA1 and BRCA2 genes.
- Early menstrual periods (before the age of 12 years).
- History of non-cancerous breast diseases (atypical hyperplasia or lobular carcinoma *in situ*).
- Previous treatment using radiation therapy to the chest or breast.
- Previous exposure to diethylstilbestrol (DES).

Consult the doctor if in doubt about any of these or other diseases in connection with estrogen therapy.

4.4 Special warnings and precautions for use

The experience of treating women older than 65 years is limited.

For the treatment of postmenopausal symptoms, Kliogest® should only be initiated for symptoms that adversely affect quality of life. In all cases, a careful appraisal of the risks and benefits should be undertaken at least annually and Kliogest® should only be continued as long as the benefit outweighs the risk.

Evidence regarding the risks associated with HRT in the treatment of premature menopause is limited.

Due to the low level of absolute risk in younger women, however, the balance of benefits and risks for these women may be more favourable than in older women.

Medical examination/follow-up:

Before initiating or re-instituting Kliogest®, a complete personal and family medical history should be taken. Physical (including pelvic and breast) examination should be guided by this and by the contraindications and warnings for use. During treatment periodic check-ups are recommended of a frequency and nature adapted to the individual women. Women should be advised of what changes in their breast should be reported to their doctor. Investigations, including appropriate imaging tools, e.g. mammography, should be carried out in accordance with currently accepted screening practices and modified to the clinical needs of the individual.

A careful appraisal of the risks and benefits should be undertaken over time in women treated with hormone replacement therapy.

Women with an intact uterus with abnormal genital bleeding of unknown aetiology or women with an intact uterus who have previously been treated with unopposed estrogens should be examined with special care in order to disclose a possible hyperstimulation/malignancy of the endometrium before initiation of treatment with Kliogest®.

Conditions which need supervision:

If any of the following conditions are present, have occurred previously, and/or have been aggravated during pregnancy or previous hormone treatment, the patient should be closely supervised.

Conditions that may recur or be aggravated during treatment with Kliogest® (see section 4.3):

- Leiomyoma (uterine fibroids) or endometriosis.
- A history of or risk factors for venous or arterial thromboembolic disorders.
- Risk factors for estrogen-dependent tumours, e.g. 1st degree heredity for breast cancer.
- Hypertension.
- Liver disorders (e.g. liver adenoma).
- Diabetes mellitus with or without vascular involvement.

- Cholelithiasis.
- Migraine or (severe) headache.
- Systemic lupus erythematosus.
- A history of endometrial hyperplasia.
- Epilepsy.
- Asthma.
- Otosclerosis.
- Cardiac failure.

Endometrial hyperplasia and carcinoma:

In women with an intact uterus, the risk of endometrial hyperplasia and carcinoma is increased when estrogens are administered alone for prolonged periods. The reported increase in endometrial cancer risk among estrogen-only users varies from 2- to 12-fold greater compared with non-users, depending on the duration of treatment and estrogen dose (see section 4.8). After stopping treatment, the risk may remain elevated for at least 10 years.

The addition of a progestagen cyclically for at least 12 days per month/28-day cycle or in a continuous combined manner reduces, however it does not eliminate, this risk in non-hysterectomised women.

Breakthrough bleeding and spotting may occur during the first months of treatment. If breakthrough bleeding or spotting continues after the first months of treatment, appears after some time on therapy, or continues after treatment has been discontinued, the reason should be investigated, which may include endometrial biopsy to exclude endometrial malignancy.

Breast cancer:

Hormone replacement therapy, including Kliogest®, contains estrogen and progestagen which, on prolonged use, may increase the risk of developing breast cancer. A meta-analysis of prospective epidemiological studies from 1992 to 2018 reported a significant increase in the risk of developing

breast cancer in 55 575 women 40 – 59 years of age who used menopausal hormone therapy (MHT). The risk increased steadily with duration of use and was slightly greater for estrogen-progestagen than estrogen-only preparations, and the risk persisted for more than 10 years after stopping the treatment. The relative risk (RR) to develop breast cancer for estrogen-progestagen preparations was 1,60 at 1 – 4 years and RR = 2,08 at 5 – 14 years, while that for estrogen-only preparations were 1,17 at 1 – 4 years and 1,33 at 5 – 14 years. There was no risk to develop breast cancer in women who started MHT at 60 years of age.

All women on Kliogest® should receive yearly breast examinations by a health care provider and perform monthly breast self-examinations. Mammography evaluations should be done based on the patient's age, risk factors, and prior mammogram results.

Kliogest® increases the density of mammographic images which may adversely affect the radiological detection of breast cancer.

Venous thromboembolism:

HRT, such as Kliogest®, is associated with a higher relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism.

The occurrence of such an event is more likely in the first year of HRT use, than later. Generally recognised risk factors for VTE include use of estrogens, older age, major surgery, prolonged immobilisation, a personal history or family history, severe obesity (body mass index > 30 kg/m^2), pregnancy/postpartum period, systemic lupus erythematosus (SLE), and cancer. There is no consensus about the role of varicose veins in VTE.

In women with no personal history of VTE but with a first-degree relative with a history of venous thromboembolism at a young age, screening may be offered after careful counselling regarding its limitations (only a proportion of thrombophilic defects are identified by screening).

If a thrombophilic defect is identified which segregates with venous thromboembolism in family members or if the defect is "severe" (e.g. antithrombin, protein S, or protein C deficiencies or a combination of defects), HRT is contraindicated (see section 4.3).

Patients with a history of VTE or known thrombophilic states have an increased risk of VTE; Kliogest® may add to this risk. Personal or strong family history of thromboembolism, or recurrent spontaneous abortion, should be investigated in order to exclude a thrombophilic predisposition. Until a thorough evaluation of thrombophilic factors has been made or anticoagulant treatment initiated, use of Kliogest® in such patients should be viewed as contraindicated. Those women already on anticoagulant treatment require careful consideration of the benefit-risk of use of Kliogest®.

The risk of VTE may be temporarily increased with prolonged immobilisation, major trauma or major surgery. Scrupulous attention should be given to prophylactic measures to prevent VTE following surgery.

Where prolonged immobilisation is liable to follow elective surgery, particularly abdominal or orthopaedic surgery to the lower limbs, consideration should be given to temporarily stopping Kliogest® four to six weeks earlier, if possible. Treatment should not be restarted until the woman is completely mobilised.

If VTE develops after initiating therapy, Kliogest® should be discontinued. Patients should be told to contact their doctors immediately when they are aware of a potential thromboembolic symptom (e.g. painful swelling of a leg, sudden pain in the chest, dyspnoea).

Ovarian cancer:

Ovarian cancer is much rarer than breast cancer.

Epidemiological evidence from a large meta-analysis suggests a slightly increased risk in women taking estrogen-only or combined estrogen-progestagen HRT, which becomes apparent within 5 years of use and diminishes over time after stopping.

Some other studies, including the WHI trial, suggest that use of combined HRTs is associated with a similar or slightly similar risk (see section 4.8).

Coronary artery disease (CAD):

There is no evidence from randomised controlled trials of protection against myocardial infarction in women with or without existing CAD who received combined estrogen-progestagen or estrogen-only HRT.

The relative risk of CAD during use of combined estrogen-progestagen HRT, such as Kliogest®, is slightly increased. As the baseline absolute risk of CAD is strongly dependent on age, the number of extra cases of CAD due to estrogen-progestagen use is very low in healthy women close to menopause, but will rise with more advanced age.

Ischaemic stroke:

Combined estrogen-progestagen and estrogen-only therapy are associated with an up to 1,5-fold increase in risk of ischaemic stroke. The relative risk does not change with age or time since menopause. However, as the baseline risk of stroke is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age (see section 4.8).

Hypothyroidism:

Patients who require thyroid hormone replacement therapy should have their thyroid function monitored regularly while on HRT to ensure that thyroid hormone levels remain in an acceptable range.

Angioedema:

Estrogens may induce or exacerbate symptoms of angioedema, in particular in women with hereditary angioedema.

Depressed mood, depression and risk of suicidality:

Depressed mood and depression are well-known undesirable effects of hormonal contraceptive use (see section 4.8). Depression can be serious and is a well-known risk factor for suicidal behaviour and suicide. Women should be advised to contact their medical practitioner in case of mood changes and depressive symptoms, including shortly after initiating the treatment.

Other conditions:

Estrogen such as the estradiol in Kliogest® may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed. Patients with terminal renal insufficiency should be closely observed, since it is expected that the level of circulating active ingredients in Kliogest® will increase.

Kliogest® is contraindicated in patients with active liver disease (acute or chronic liver disease or a history of liver disease as long as liver function tests have failed to return to normal) (see section 4.3).

Women with pre-existing hypertriglyceridaemia should be followed closely during estrogen replacement or HRT such as Kliogest®, since cases of large increases of plasma triglycerides leading to pancreatitis have been reported with estrogen therapy in this condition.

Estrogens increase thyroid binding globulin (TBG), leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 levels (by column or by radioimmunoassay) or T3 levels (by radioimmunoassay). T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered. Other binding proteins may be elevated in serum, i.e. corticoid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased circulating corticosteroids and sex steroids, respectively. Free or biologically active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-I-antitrypsin and ceruloplasmin).

Kliogest® use does not improve cognitive function. There is some evidence of increased risk of probable dementia in women who start using continuous combined or estrogen-only HRT after the age of 65.

Duration of treatment:

Estrogens should not be prescribed for longer than one year without another physical examination, including a gynaecological examination, being performed.

The long-term prevention of bone mineral content loss should be restricted to women at increased risk of developing fractures.

Reasons for immediate withdrawal:

Therapy should be discontinued in case a contraindication is discovered and in the following situations:

- Venous thromboembolic disorders.
- The appearance of jaundice or deterioration of liver function.
- The emergence of migraine-type headache.
- Sudden visual disturbances.
- Significant increase in blood pressure.
- Pregnancy.

Lactose monohydrate:

Kliogest® tablets contain lactose monohydrate. Patients with hereditary problems of galactose intolerance e.g. galactosaemia, total lactase deficiency or glucose-galactose malabsorption should not take Kliogest®.

4.5 Interaction with other medicines and other forms of interaction

The metabolism of estrogens and progestagens may be increased by concomitant use of substances known to induce medicine-metabolising enzymes, specifically cytochrome P450

enzymes such as anticonvulsants (e.g. phenobarbital, phenytoin, carbamazepine) and anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz). Ritonavir, telaprevir and nelfinavir, although known as strong inhibitors, by contrast exhibit inducing properties when used concomitantly with steroid hormones. Herbal preparations containing St John's wort (*Hypericum perforatum*) may induce the metabolism of estrogens and progestagens.
Clinically, an increased metabolism of estrogens and progestagens may lead to decreased effect and changes in the uterine bleeding profile.

Some laboratory tests may be influenced by estrogen therapy, such as tests for glucose tolerance or thyroid function.

Medicines that inhibit the activity of hepatic microsomal medicine-metabolising enzymes, e.g. ketoconazole and itraconazole, may increase circulating levels of the active substances in Kliogest®.

Concomitant administration of ciclosporin may cause increased blood levels of ciclosporin, creatinine and transaminases due to decreased metabolism of ciclosporin in the liver.

Hormone contraceptives containing estrogens have been shown to significantly decrease plasma concentrations of lamotrigine when co-administered due to induction of lamotrigine glucuronidation. This may reduce seizure control. Although the potential interaction between hormone replacement therapy and lamotrigine has not been studied, it is expected that a similar interaction exists, which may lead to a reduction in seizure control among women taking both medicines together.

4.6 Fertility, pregnancy and lactation

Pregnancy

Kliogest® is contraindicated during pregnancy (see section 4.3).
If pregnancy occurs during medication with Kliogest®, treatment should be withdrawn immediately.

Clinically, data on a limited number of exposed pregnancies indicate adverse effects of norethisterone on the fetus. At doses higher than those normally used in oral contraceptive and HRT formulations, masculinisation of female fetuses was observed.
The results of most epidemiological studies to date, relevant to inadvertent fetal exposure to combinations of estrogens and progestagens, indicate no teratogenic or fetotoxic effect.

Lactation

Kliogest® is contraindicated during lactation (see section 4.3).

4.7 Effects on ability to drive and use machines

Some side effects e.g. headache or visual disturbances can occur and may affect the ability to drive or use machines. Caution is advised until the effects of Kliogest® are known.

4.8 Undesirable effects

The most frequently reported adverse events in clinical trials with Kliogest® were vaginal bleeding and breast pain or tenderness, reported in approximately 10 % to 30 % of patients.

Vaginal bleeding occurred in the first months of treatment.
Bleeding may continue in some postmenopausal women and in these cases, consideration should be given to change to an alternative therapy.
Breast pain usually disappears after a few months of therapy.

All adverse events observed in the randomised clinical trials with a higher frequency in patients treated with Kliogest® or similar HRT products when compared to placebo and which on an overall judgement are possibly related to treatment, are presented in the table below:

System organ class	**Very common ≥ 1/10**	**Common ≥ 1/100 – < 1/10**	**Uncommon ≥ 1/1 000 – < 1/100**	**Rare ≥ 1/10 000 – < 1/1 000**

Infections and infestations		Genital candidiasis or vaginitis (see also "Reproductive system and breast disorders")		
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)			Breast cancer (see section 4.4)	
Immune system disorders			Hypersensitivity (see also "Skin and subcutaneous tissue disorders")	
Metabolism and nutrition disorders		Fluid retention (see also "General disorders and administration site conditions")		
Psychiatric disorders		Depression or depression aggravated	Nervousness	
Nervous system disorders		Headache, migraine or migraine aggravated		
Vascular disorders			Superficial thrombophlebitis	Pulmonary embolism, deep thrombophlebitis
Gastrointestinal disorders		Nausea, abdominal pain, abdominal distention or	Flatulence or bloating	

		abdominal discomfort		
Skin and subcutaneous tissue disorders			Alopecia, hirsutism or acne, pruritus or urticaria	
Musculoskeletal and connective tissue disorders		Back pain, leg cramps		
Reproductive system and breast disorders	Breast pain or breast tenderness, irregular menstruation or vaginal haemorrhage	Breast oedema or breast enlargement, uterine fibroids aggravated or uterine fibroids recurrence or uterine fibroids		
General disorders and administration site conditions		Peripheral oedema	Medicine ineffective	
Investigations		Increased body mass		

Post-marketing experience:

Neoplasms benign and malignant (including cysts and polyps): Endometrial cancer.

Immune system disorders: Generalised hypersensitivity reactions (e.g. anaphylactic reaction/shock).

Psychiatric disorders: Insomnia, anxiety, libido decreased, libido increased.

Nervous disorders: Dizziness, stroke.

Eye disorders: Visual disturbances.

Vascular disorders: Hypertension aggravated.

Cardiac disorders: Myocardial infarction.

Gastrointestinal disorders: Dyspepsia, vomiting.

Hepatobiliary disorders: Gall bladder disease, cholelithiasis, cholelithiasis can be aggravated, cholelithiasis recurrence.

Skin and subcutaneous tissue disorders: Seborrhoea, rash, angioedema.

Reproductive system and breast disorders: Endometrial hyperplasia, vulvovaginal pruritus.

Investigations: Body mass decreased, blood pressure increased.

Other adverse reactions have been reported in association with estrogen/progestagen treatment:

- Skin and subcutaneous tissue disorders: Chloasma, erythema multiforme, erythema nodosum, vascular purpura.
- There may be alterations in liver function, jaundice, a decrease in glucose tolerance and decrease in tolerance of contact lenses.
- Dry eyes.
- Tear film composition.
- Probable dementia over the age of 65 years.
- Severe depression with a higher risk of suicidal thoughts/behaviour and suicide.

If any side effects persist or intensify, the patient should inform the medical practitioner.

Ovarian cancer risk

Use of estrogen-only or combined estrogen-progestagen HRT has been associated with a slightly increased risk of having ovarian cancer diagnosed (see section 4.4).

A meta-analysis from 52 epidemiology studies reported an increased risk of ovarian cancer in women currently using HRT compared to women who have never used HRT (RR 1,43, 95 % CI 1,31 – 1,56). For women aged 50 to 54 years taking 5 years of HRT, this resulted in about 1 extra case per 2 000 users. In women aged 50 to 54 who are not taking HRT, about 2 women in 2 000 will be diagnosed with ovarian cancer over a 5-year period.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of Kliogest® is important. It allows continued monitoring of the benefit/risk balance of Kliogest®. Healthcare providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc-org) found on SAHPRA's website.

4.9 Overdose

Symptoms of overdosage with oral estrogens are breast tenderness, nausea, vomiting and/or metrorrhagia. Overdosage of progestagens may lead to a depressive mood, fatigue, acne and hirsutism.

There is no specific antidote and treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 21.8.2 Progesterones with estrogens.

Pharmacotherapeutic group: Progestagens and estrogens, fixed combinations

ATC code: G03FA01

Estradiol: The active ingredient, synthetic 17β-estradiol, is chemically and biologically identical to endogenous human estradiol.

Estrogens prevent bone loss following menopause or ovariectomy.

Norethisterone acetate is a progestagen which reduces but does not eliminate the estrogen-induced risk of endometrial hyperplasia in non-hysterectomised women.

5.2 Pharmacokinetic properties

Following oral administration of 17β-estradiol in micronised form, rapid absorption from the gastrointestinal tract occurs. It undergoes extensive first-pass metabolism in the liver and other enteric organs and reaches a peak plasma concentration of approximately 44 pg/mL (range 30 –

53 pg/mL) within 6 hours. It circulates bound to sex hormone-binding globulin (SHBG) (37 %) and to albumin (61 %), while only approximately 1 – 2 % is unbound. Metabolism of 17β-estradiol occurs mainly in the liver and the gut but also in the target organs and involves the formation of less active or inactive metabolites, including oestrone, catecholestrogens and several estrogen sulphates and glucuronides. Estrogens are excreted with the bile, hydrolysed and reabsorbed (enterohepatic circulation), and mainly eliminated in the urine in biologically inactive form.
After oral administration, norethisterone acetate is rapidly absorbed and transformed to norethisterone (NET). It undergoes first-pass metabolism in the liver and other enteric organs, and reaches a peak plasma concentration of approximately 9 ng/mL (range 6 – 11 ng/mL) within 1 hour after intake of 1 mg. The terminal half-life of NET is about 10 hours. NET binds to SHBG (36 %) and to albumin (61 %). The most important metabolites are isomers of 5α-dihydro-NET and of tetrahydro-NET, which are excreted mainly in the urine as sulphate or glucuronide conjugates.

The pharmacokinetics of estradiol is not influenced by norethisterone acetate.
The pharmacokinetics in patients above 70 years old has not been studied.

5.3 Preclinical safety data

The toxicity profiles of estradiol and norethisterone acetate are well known. There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the professional information.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydroxypropylcellulose (E463)

Hypromellose (E464)

Lactose monohydrate

Maize starch

Magnesium stearate (E572)

Talc (E553b)

Triacetin (E1518).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

Store at or below 25 °C.

6.4 Special precautions for storage

Do not refrigerate.

Keep the container in the outer carton until required for use.

Do not use this product after the expiration date marked on the label of the calendar-dial pack and/or carton.

6.5 Nature and contents of container

Kliogest® is supplied in a calendar dial pack each containing 28 tablets.

The calendar dial pack with 28 tablets consists of the following 3 parts:

- The base made of coloured non-transparent polypropylene.
- The ring-shaped lid made of transparent polystyrene.
- The centre dial made of coloured non-transparent polystyrene.

6.6 Special precautions for disposal and other handling

None.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Novo Nordisk (Pty) Ltd

90 Grayston Drive

Sandton

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2196

Tel no: +27 11 202 0500

8. REGISTRATION NUMBER

Y/21.8.2/230

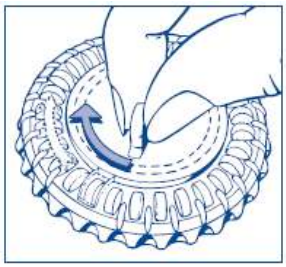
9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11 March 1996

10. DATE OF REVISION OF THE TEXT

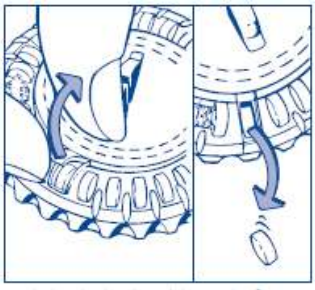
14 August 2025

How to use the calendar dial pack



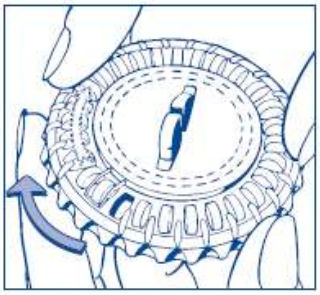
1. Set the day reminder:

Turn the inner disc to set the day of the week opposite the little plastic tab.



2. Take the first day's tablet:

Break the plastic tab and tip out the first tablet.



3. Move the dial every day:

On the next day simply move the transparent dial clockwise one space as indicated by the arrow.

Tip out the next tablet. Remember to take only one tablet once a day.

You can only turn the transparent dial after the tablet in the opening has been removed.