

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Flexyess 0.02 mg/3 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 0.020 mg ethinylestradiol (as betadex clathrate) and 3 mg drospirenone.

Excipient with known effect: lactose 46 mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets

The tablets are light pink, round with convex faces, one side embossed with the letters “DS” in a regular hexagon.

The tablets have a diameter of 6 mm and a thickness of 3 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Oral contraception

The decision to prescribe Flexyess should take into consideration the individual woman’s current risk factors, particularly those for venous thromboembolism (VTE), and how the risk of VTE with Flexyess compares with other Combined Hormonal Contraceptives (CHCs) (see sections 4.3 and 4.4).

4.2 Posology and method of administration

Method of administration: oral use

Posology

How to take Flexyess

Flexyess can only be used in combination with the Clyk tablet dispenser. The tablet dispenser will guide the user through the regimen.

The Instructions for Use for the Clyk tablet dispenser should be read carefully before use and kept for future reference.

For instructions on how to prepare the Clyk tablet dispenser for use and how to dispense a tablet, see section 6.6.

One tablet must be taken every day at about the same time, if necessary with a little liquid. Tablets must always be taken continuously for a minimum of 24 days.

Flexyess tablets can be taken continuously for up to 120 days, after which a 4-day tablet free interval must be taken.

The tablet taking consists of two phases:

1. A mandatory phase (Day 1 to Day 24):

When starting Flexyess, tablets must be taken continuously for a minimum of 24 days.

The Clyk dispenser indicates whether a 4-day tablet-free interval can be taken. During the first 24 days (mandatory phase), the tablet dispenser does not allow for initiation of a 4-day tablet-free interval.

2. A flexible phase (Day 25 to Day 120):

During days 25-120, the tablets can be taken continuously up to a maximum of 120 days. Within this period, the woman may decide herself to take a 4-day tablet-free interval or not.

This 4-day tablet-free interval should only be started if tablet taking has been continuous for 24 days.

During the flexible phase, the Clyk tablet dispenser allows the user to initiate a 4-day tablet-free interval at any time.

A 4-day tablet-free interval should never be later than after 120 days of continuous tablet intake.

A tablet-free interval should never be longer than 4 days.

The Clyk dispenser automatically initiates a 4-day tablet-free interval after 120 days of continuous tablet intake.

During the 4-day tablet-free interval, bleeding usually occurs and may not have finished before the next tablet has to be taken.

After each 4-day tablet-free interval, a new intake cycle of a minimum of 24 days to a maximum of 120 days starts.

After the 4-day tablet-free interval the Clyk tablet dispenser automatically reminds the user that a new cycle starts and that again a tablet has to be taken every day.

It is never allowed to take a 4-day tablet-free interval in the mandatory phase where tablets have to be taken for a minimum of 24 days.

If continued bleeding and/or spotting for three consecutive days occurs in the flexible phase (days 25-120), it is advisable to take a 4-day tablet-free interval. This may reduce the total number of days with bleeding.

This 4-day tablet-free interval should only be taken if tablet taking has been continuous for at least 24 days minimum.

How to start Flexyess

- No preceding hormonal contraceptive use (in the past month)

Tablet-taking has to start on day 1 of the woman's natural cycle (i.e. the first day of her menstrual bleeding). Starting on days 2-5 is allowed, but during the first cycle a barrier method is recommended in addition for the first 7 days of tablet-taking.

- Changing from a combined hormonal contraceptive (combined oral contraceptive (COC), vaginal ring or transdermal patch)

The woman should start with Flexyess preferably on the day after the last active tablet (the last tablet containing the active substances) of her previous COC, but at the latest on the day following the usual tablet-free or hormone-free tablet interval of her previous COC. In case a vaginal ring or transdermal patch has been used the woman should start using Flexyess preferably after removal, but at the latest when the next application would have been due.

- Changing from a progestogen-only-method (progestogen-only pill, injection, implant) or from a progestogen-releasing intrauterine system (IUS)

The woman may switch any day from the progestogen-only pill (from an implant or the IUS on the day of its removal, from an injectable when the next injection would be due) but should in all of these cases be advised to additionally use a barrier method for the first 7 days of tablet-taking.

- Following first-trimester abortion

The woman may start immediately. When doing so, she need not take additional contraceptive measures.

- Following delivery or second-trimester abortion

Women should be advised to start at day 21 to 28 after delivery or second-trimester abortion. When starting later, the woman should be advised to additionally use a barrier method for the first 7 days of tablet-taking. However, if intercourse has already occurred, pregnancy should be excluded before the actual start of COC use or the woman has to wait for her first menstrual period.

For breastfeeding women see section 4.6.

Management of missed tablets

If the user is **less than 24 hours** late in taking any tablet, contraceptive protection is not reduced. The woman should take the tablet as soon as she remembers and should take further tablets at the usual time.

If she is **more than 24 hours** late in taking any tablet, contraceptive protection may be reduced. The management of missed tablets can be guided by the following two basic rules:

1. the recommended tablet-free interval is 4 days, tablet-taking must never be discontinued for longer than 7 days
2. 7 days of uninterrupted tablet-taking are required to attain adequate suppression of the hypothalamic-pituitary-ovarian-axis.

Accordingly the following advice can be given in daily practice:

- Day 1-7

The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. In addition, a barrier method such as a condom 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 and the closer they are to the tablet-free interval, the higher the risk of a pregnancy.

- Day 8-24

The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. Provided that the woman has taken her tablets correctly in the 7 days preceding the first missed tablet, there is no need to use extra contraceptive precautions. However, if this is not the case or if she has missed more than 1 tablet, the woman should be advised to use extra precautions until she has taken tablets continuously without interruption for at least 7 days.

- Day 25-120

The risk of reduced reliability may be imminent because of the possibility of a forthcoming hormone-free interval. However, by adjusting the tablet-intake schedule, reduced contraceptive protection can still be prevented. By adhering to either of the following two options, there is therefore no need to use extra contraceptive precautions, provided that in the 7 days preceding the first missed tablet the woman has taken all tablets correctly. If this is not the case, the woman should be advised to follow the first of these two options and to use extra precautions for the next 7 days as well.

1. The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time until she has taken at least 7 tablets in a row without interruption.
2. The woman may also decide to have a tablet-free interval of 4 days, including the days she missed tablets, in order to induce the withdrawal bleeding and subsequently start a new intake cycle of Flexyess.

If the woman missed tablets and subsequently has no withdrawal bleed in the following tablet-free interval, the possibility of a pregnancy should be considered.

Advice in case of gastro-intestinal disturbances

In case of severe gastro-intestinal disturbances (e.g., vomiting or diarrhoea), absorption may not be complete and additional contraceptive measures should be taken.

If vomiting occurs within 3-4 hours after taking a tablet the advice concerning missed tablets, as given in section 4.2, is applicable. If the woman does not want to change her tablet-taking schedule, she has to take the extra tablet(s) needed from the tablet dispenser.

Additional information on special populations

Children and adolescents

Flexyess is only indicated after menarche.

Geriatric patients

Not applicable. Flexyess is not indicated after menopause.

Patients with hepatic impairment

Flexyess is contraindicated in women with severe hepatic diseases. See also sections 4.3 and 5.2.

Patients with renal impairment

Flexyess is contraindicated in women with severe renal insufficiency or acute renal failure. See also sections 4.3 and 5.2.

4.3 Contraindications

Combined hormonal contraceptives (CHCs) should not be used in the following conditions. Should any of the conditions appear for the first time during CHC use, the product should be stopped immediately.

- Presence or risk of venous thromboembolism (VTE)
 - Venous thromboembolism – current VTE (on anticoagulants) or history of (e.g. deep venous thrombosis [DVT] or pulmonary embolism [PE])
 - Known hereditary or acquired predisposition for venous thromboembolism, such as APC-resistance, (including Factor V Leiden), antithrombin-III-deficiency, protein C deficiency, protein S deficiency
 - Major surgery with prolonged immobilisation (see section 4.4)
 - A high risk of venous thromboembolism due to the presence of multiple risk factors (see section 4.4)
- Presence or risk of arterial thromboembolism (ATE)
 - Arterial thromboembolism – current arterial thromboembolism, history of arterial thromboembolism (e.g. myocardial infarction) or prodromal condition (e.g. angina pectoris)
 - Cerebrovascular disease – current stroke, history of stroke or prodromal condition (e.g. transient ischaemic attack, TIA)
 - Known hereditary or acquired predisposition for arterial thromboembolism, such as hyperhomocysteinaemia and antiphospholipid-antibodies (anticardiolipin-antibodies, lupus anticoagulant)
 - History of migraine with focal neurological symptoms
 - A high risk of arterial thromboembolism due to multiple risk factors (see section 4.4) or to the presence of one serious risk factor such as:
 - diabetes mellitus with vascular symptoms
 - severe hypertension
 - severe dyslipoproteinaemia
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal
- Severe renal insufficiency or acute renal failure
- Presence or history of liver tumours (benign or malignant)
- Known or suspected sex-steroid influenced malignancies (e.g. of the genital organs or the breasts)
- Undiagnosed vaginal bleeding
- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Warnings

If any of the conditions or risk factors mentioned below is present, the suitability of Flexyess should be discussed with the woman.

In the event of aggravation, or first appearance of any of these conditions or risk factors, the woman should be advised to contact her doctor to determine whether the use of Flexyess should be discontinued.

In case of suspected or confirmed VTE or ATE, CHC use should be discontinued. In case anti-coagulant therapy is started, adequate alternative contraception should be initiated because of the teratogenicity of anticoagulant therapy (coumarins).

- Circulatory Disorders

Risk of venous thromboembolism (VTE)

The use of any combined hormonal contraceptive (CHC) increases the risk of venous thromboembolism (VTE) compared with no use. **Products that contain levonorgestrel, norgestimate or norethisterone are associated with the lowest risk of VTE. Other products such as Flexyess may have up to twice this level of risk. The decision to use any product other than one with the lowest VTE risk should be taken only after a discussion with the woman to ensure she understands the risk of VTE with Flexyess, how her current risk factors influence this risk, and that her VTE risk is highest in the first ever year of use. There is also some evidence that the risk is increased when a CHC is re-started after a break in use of 4 weeks or more.**

In women who do not use a CHC and are not pregnant about 2 out of 10,000 will develop a VTE over the period of one year. However, in any individual woman the risk may be far higher, depending on her underlying risk factors (see below).

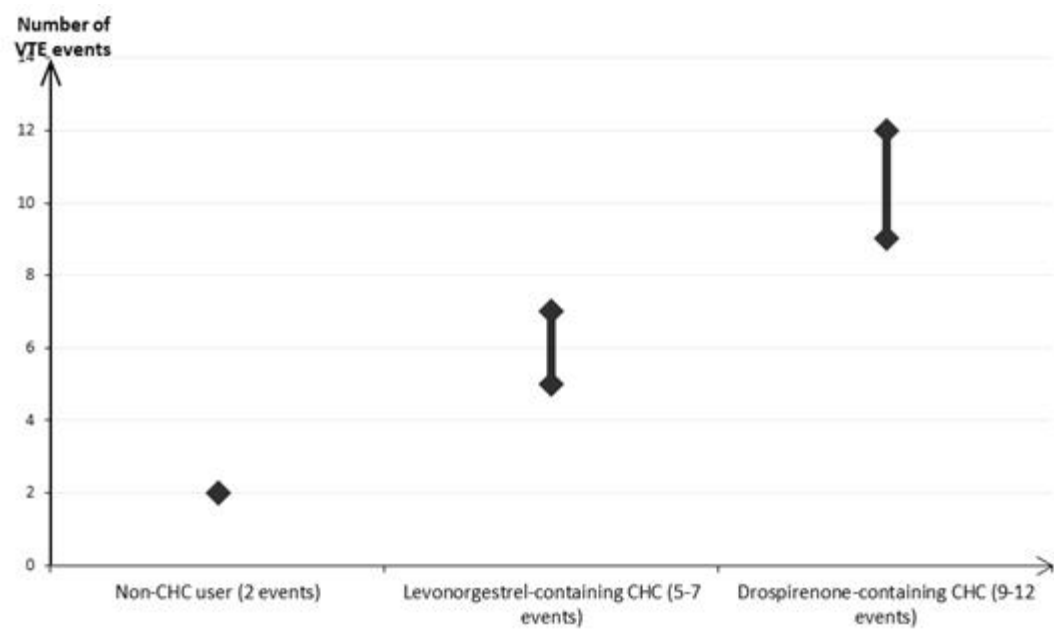
It is estimated¹ that out of 10,000 women who use a CHC containing drospirenone between 9 and 12 women will develop a VTE in one year; this compares with about 6² in women who use a levonorgestrel-containing CHC.

In both cases, the number of VTEs per year is fewer than the number expected during pregnancy or in the postpartum period. VTE may be fatal in 1-2% of the cases.

¹ These incidences were estimated from the totality of the epidemiological study data, using relative risks for the different products compared with levonorgestrel-containing CHCs.

² Mid-point of range of 5-7 per 10,000 WY, based on a relative risk for CHCs containing levonorgestrel versus non-use of approximately 2.3 to 3.6

Number of VTE events per 10,000 women in one year



Extremely rarely, thrombosis has been reported to occur in CHC users in other blood vessels, e.g. hepatic, mesenteric, renal or retinal veins and arteries.

Risk factors for VTE

The risk for venous thromboembolic complications in CHC users may increase substantially in a woman with additional risk factors, particularly if there are multiple risk factors (see table).

Flexyess is contraindicated if a woman has multiple risk factors that put her at high risk of venous thrombosis (see section 4.3). If a woman has more than one risk factor, it is possible that the increase in risk is greater than the sum of the individual factors – in this case her total risk of VTE should be considered. If the balance of benefits and risks is considered to be negative a CHC should not be prescribed (see section 4.3).

Table: Risk factors for VTE

Risk factor	Comment
Obesity (body mass index over 30 kg/m²)	Risk increases substantially as BMI rises. Particularly important to consider if other risk factors also present.
Prolonged immobilisation, major surgery, any surgery to the legs or pelvis, neurosurgery, or major trauma Note: temporary immobilisation including air travel >4 hours can also be a risk factor for VTE, particularly in women with other risk factors	In these situations it is advisable to discontinue use of the pill (in the case of elective surgery at least four weeks in advance) and not resume until two weeks after complete remobilisation. Another method of contraception should be used to avoid unintentional pregnancy. Antithrombotic treatment should be considered if Flexyess has not been discontinued in advance.
Positive family history (venous thromboembolism ever in a sibling or parent especially at a relatively early age e.g. before	If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any CHC use

50).	
Other medical conditions associated with VTE	Cancer, systemic lupus erythematosus, haemolytic uraemic syndrome, chronic inflammatory bowel disease (Crohn’s disease or ulcerative colitis) and sickle cell disease
Increasing age	Particularly above 35 years

There is no consensus about the possible role of varicose veins and superficial thrombophlebitis in the onset or progression of venous thrombosis.

The increased risk of thromboembolism in pregnancy, and particularly the 6 week period of the puerperium, must be considered (for information on “Pregnancy and lactation” see section 4.6.

Symptoms of VTE (deep vein thrombosis and pulmonary embolism)

In the event of symptoms women should be advised to seek urgent medical attention and to inform the healthcare professional that she is taking a CHC.

Symptoms of deep vein thrombosis (DVT) can include:

- o unilateral swelling of the leg and/or foot or along a vein in the leg;
- o pain or tenderness in the leg which may be felt only when standing or walking,
- o increased warmth in the affected leg; red or discoloured skin on the leg.

Symptoms of pulmonary embolism (PE) can include:

- o sudden onset of unexplained shortness of breath or rapid breathing;
- o sudden coughing which may be associated with haemoptysis;
- o sharp chest pain;
- o severe light headedness or dizziness;
- o rapid or irregular heartbeat.

Some of these symptoms (e.g. “shortness of breath”, “coughing”) are non-specific and might be misinterpreted as more common or less severe events (e.g. respiratory tract infections).

Other signs of vascular occlusion can include: sudden pain, swelling and slight blue discoloration of an extremity.

If the occlusion occurs in the eye symptoms can range from painless blurring of vision which can progress to loss of vision. Sometimes loss of vision can occur almost immediately.

Risk of arterial thromboembolism (ATE)

Epidemiological studies have associated the use of CHCs with an increased risk for arterial thromboembolism (myocardial infarction) or for cerebrovascular accident (e.g. transient ischaemic attack, stroke). Arterial thromboembolic events may be fatal.

Risk factors for ATE

The risk of arterial thromboembolic complications or of a cerebrovascular accident in CHC users increases in women with risk factors (see table). Flexyess is contraindicated if a woman has one serious or multiple risk factors for ATE that puts her at high risk of arterial thrombosis (see section 4.3). If a woman has more than one risk factor, it is possible that the increase in risk is greater than the sum of the individual factors - in this case her total risk should be considered. If the balance of benefits and risks is considered to be negative a CHC should not be prescribed (see section 4.3).

Table: Risk factors for ATE

Risk factor	Comment
Increasing age	Particularly above 35 years
Smoking	Women should be advised not to smoke if they wish to use a CHC. Women over 35 who continue to smoke should be strongly advised to use a different method of contraception.
Hypertension	
Obesity (body mass index over 30 kg/m ²)	Risk increases substantially as BMI increases. Particularly important in women with additional risk factors
Positive family history (arterial thromboembolism ever in a sibling or parent especially at relatively early age eg. below 50).	If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any CHC use
Migraine	An increase in frequency or severity of migraine during CHC use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation
Other medical conditions associated with adverse vascular events	Diabetes mellitus, hyperhomocysteinaemia, valvular heart disease and atrial fibrillation, dyslipoproteinaemia and systemic lupus erythematosus.

Symptoms of ATE

In the event of symptoms women should be advised to seek urgent medical attention and to inform the healthcare professional that she is taking a CHC.

Symptoms of a cerebrovascular accident can include:

- o sudden numbness or weakness of the face, arm or leg, especially on one side of the body;
- o sudden trouble walking, dizziness, loss of balance or coordination;
- o sudden confusion, trouble speaking or understanding;
- o sudden trouble seeing in one or both eyes;
- o sudden, severe or prolonged headache with no known cause;
- o loss of consciousness or fainting with or without seizure.

Temporary symptoms suggest the event is a transient ischaemic attack (TIA).

Symptoms of myocardial infarction (MI) can include:

- o pain, discomfort, pressure, heaviness, sensation of squeezing or fullness in the chest, arm, or below the breastbone;
- o discomfort radiating to the back, jaw, throat, arm, stomach;
- o feeling of being full, having indigestion or choking;
- o sweating, nausea, vomiting or dizziness;
- o extreme weakness, anxiety, or shortness of breath;
- o rapid or irregular heartbeats.

- Tumours

An increased risk of cervical cancer in long-term users of COCs (> 5 years) has been reported in some epidemiological studies, but there continues to be controversy about the extent to which this finding is attributable to the confounding effects of sexual behaviour and other factors such as human papilloma virus (HPV).

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. 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. 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 COCs 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 liver tumours, and even more rarely, malignant liver tumours have been reported in users of COCs. 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 COCs.

With the use of the higher-dosed COCs (50 µg ethinylestradiol) the risk of endometrial and ovarian cancer is reduced. Whether this also applies to lower-dosed COCs remains to be confirmed.

- Other conditions

The progestin component in Flexyess is an aldosterone antagonist with potassium sparing properties. In most cases, no increase of potassium levels is to be expected. In a clinical study, however in some patients with mild or moderate renal impairment and concomitant use of potassium-sparing medicinal products serum potassium levels slightly, but not significantly, increased during drospirenone intake. Therefore, it is recommended to check serum potassium during the first treatment cycle in patients presenting with renal insufficiency and a pretreatment serum potassium in the upper reference range, and particularly during concomitant use of potassium sparing medicinal products. See also section 4.5.

Women with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs.

Although small increases in blood pressure have been reported in many women taking COCs, clinically relevant increases are rare. Only in these rare cases an immediate discontinuation of COC use is justified. If, during the use of a COC in preexisting hypertension, constantly elevated blood pressure values or a significant increase in blood pressure do not respond adequately to antihypertensive treatment, the COC must be withdrawn. Where considered appropriate, COC use may be resumed if normotensive values can be achieved with antihypertensive therapy.

The following conditions have been reported to occur or deteriorate with both pregnancy and COC use, but the evidence of an association with COC use is inconclusive: jaundice and/or pruritus related to cholestasis; gallstones; porphyria; systemic lupus erythematosus; haemolytic uremic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss.

In women with hereditary angioedema exogenous estrogens may induce or exacerbate symptoms of angioedema.

Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal. Recurrence of cholestatic jaundice and/or cholestasis-related pruritus which previously occurred during pregnancy or during previous use of sex steroids necessitates the discontinuation of COCs.

Although COCs may have an effect on peripheral insulin resistance and glucose tolerance, there is no evidence for a need to alter the therapeutic regimen in diabetics using low-dose COCs (containing < 0.05 mg ethinylestradiol). However, diabetic women should be carefully observed, particularly in the early stage of COC use.

Worsening of endogenous depression, of epilepsy, of Crohn's disease and of ulcerative colitis has been reported during COC use.

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 COCs.

Each tablet of this medicinal product contains 46 mg lactose per tablet. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption who are on a lactose-free diet should take this amount into consideration.

Medical examination/consultation

Prior to the initiation or reinstitution of Flexyess a complete medical history (including family history) should be taken and pregnancy must be ruled out. Blood pressure should be measured and a physical examination should be performed, guided by the contra-indications (see section 4.3) and warnings (see section 4.4). It is important to draw a woman's attention to the information on venous and arterial thrombosis, including the risk of Flexyess compared with other CHCs, the symptoms of VTE and ATE, the known risk factors and what to do in the event of a suspected thrombosis.

The woman should also be instructed to carefully read the user leaflet and to adhere to the advice given. The frequency and nature of examinations should be based on established practice guidelines and be adapted to the individual woman.

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

Reduced efficacy

The efficacy of COCs may be reduced in the event of e.g. missed active tablets (see section 4.2), gastro-intestinal disturbances during tablet taking (see section 4.2) or concomitant medication (see section 4.5).

Reduced cycle control

The flexible regimen is designed to delay menstruation. In many women, delay of menstruation is limited by the occurrence of spotting or breakthrough bleeding. The onset of this type of bleeding is unscheduled and cannot be predicted. Only the hormonal withdrawal bleeding which follows the 4-day tablet-free interval can be scheduled. The flexible regimen of Flexyess allows scheduling of the withdrawal bleeding during the flexible phase between day 25 and 120 of the intake cycle.

As with all COCs, irregular bleeding (spotting or breakthrough bleeding) may occur, even during the fixed phase of the intake cycle between days 1-24, especially during the first months of use. Therefore, the evaluation of any irregular bleeding is only meaningful after an adaptation interval of about three months.

If bleeding irregularities persist even after induction of withdrawal bleeding, i.e. if bleeding episodes after the 4-day break are markedly prolonged or increased in intensity above the usual, then non-hormonal causes should be considered and adequate diagnostic measures are indicated to exclude malignancy or pregnancy. These may include curettage.

In some women withdrawal bleeding may not occur during the tablet-free interval. If the COC has been taken according to the directions described in section 4.2, it is unlikely that the woman is pregnant. However, if the COC has not been taken according to these directions prior to the first missed withdrawal bleed or if two withdrawal bleeds are missed, pregnancy must be ruled out before COC use is continued.

Withdrawal bleeding under treatment with Flexyess does not necessarily occur every 4 weeks but at a reduced frequency with intervals of up to 120 days (depending on when the user decides to take a 4-day tablet-free interval). Therefore, the absence of withdrawal bleeding cannot be used as a sign of an unexpected pregnancy and as such, unexpected pregnancy may be difficult to recognize. This may be of particular importance to women using teratogenic drugs. Although pregnancy is unlikely if Flexyess is taken as directed, if for any reason, pregnancy is suspected, a pregnancy test should be performed.

4.5 Interaction with other medicinal products and other forms of interaction

Note: The prescribing information of concomitant medications should be consulted to identify potential interactions.

- Effects of other medicinal products on Flexyess

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

Management

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.

Short-term treatment

Women on treatment with enzyme inducing drugs should temporarily use a barrier method or another method of contraception in addition to the COC. The barrier method must be used during the whole time of the concomitant drug therapy and for 28 days after its discontinuation.

During the period when the barrier method is used, tablet taking should not be interrupted by a tablet-free interval.

Long-term treatment

In women on long-term treatment with hepatic enzyme-inducing active substances, another reliable, non-hormonal, method of contraception is recommended.

The following interactions have been reported in the literature.

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

Barbiturates, bosentan, carbamazepine, phenytoin, primidone, rifampicin, and HIV medication ritonavir, nevirapine and efavirenz and possibly also felbamate, griseofulvin, oxcarbazepine, topiramate and products containing the herbal remedy St. John's Wort (*hypericum perforatum*).

Substances with variable effects on the clearance of COCs:

When co-administered with COCs many combinations of HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors, including combinations with HCV inhibitors can increase or decrease plasma concentrations of estrogen or progestins. The net effect of these changes may be clinically relevant in some cases.

Therefore, the prescribing information of concomitant HIV/HCV medications should be consulted to identify potential interactions and any related recommendations. In case of any doubt, an additional barrier contraceptive method should be used by women on protease inhibitor or non-nucleoside reverse transcriptase inhibitor therapy.

Substances decreasing the clearance of COCs (enzyme inhibitors):

The clinical relevance of potential interactions with enzyme inhibitors remains unknown.

Concomitant administration of strong CYP3A4 inhibitors can increase plasma concentrations of the estrogen or the progestin or both.

In a multiple dose study with a drospirenone (3 mg/day) / ethinylestradiol (0.02 mg/day) combination, co-administration of the strong CYP3A4 inhibitor ketoconazole for 10 days increased the AUC(0-24h) of drospirenone and ethinylestradiol 2.7-fold and 1.4-fold, respectively.

Etoricoxib doses of 60 to 120 mg/day have been shown to increase plasma concentrations of ethinylestradiol 1.4 to 1.6-fold, respectively when taken concomitantly with a combined hormonal contraceptive containing 0.035 mg ethinylestradiol.

- Effects of Flexyess on other medicinal products

COCs may affect the metabolism of certain other active substances. Accordingly, plasma and tissue concentrations may either increase (e.g. ciclosporin) or decrease (e.g. lamotrigine).

Based on in vivo interaction studies in female volunteers using omeprazole, simvastatin or midazolam as marker substrate, a clinically relevant interaction of drospirenone at doses of 3 mg with the cytochrome P450 mediated metabolism of other active substances is unlikely.

Clinical data suggests that ethinylestradiol is inhibiting the clearance of CYP1A2 substrates leading to a weak (e.g. theophylline) or moderate (e.g. tizanidine) increase in their plasma concentration.

- Other forms of interactions

In patients without renal insufficiency, the concomitant use of drospirenone and ACE-inhibitors or NSAIDs did not show a significant effect on serum potassium. Nevertheless, concomitant use of Flexyess with aldosterone antagonists or potassium-sparing diuretics has not been studied. In this case, serum potassium should be tested during the first treatment cycle. See also section 4.4.

- Laboratory tests

The use of contraceptive steroids 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. Drospirenone causes an increase in plasma renin activity and plasma aldosterone induced by its mild antimineralocorticoid activity.

4.6 Fertility, pregnancy and lactation

Pregnancy

Flexyess is not indicated during pregnancy. The possibility of pregnancy should be considered in any patient who may be experiencing symptoms of pregnancy, especially if she has not adhered to the prescribed schedule. If pregnancy occurs during use of with Flexyess, the preparation should be withdrawn immediately. Extensive epidemiological studies have revealed neither an increased risk of birth defects in children born to women who used COCs prior to pregnancy, nor a teratogenic effect when COCs were taken inadvertently during pregnancy.

Animal studies have shown undesirable effects during pregnancy and lactation (see section 5.3). Based on these animal data, undesirable effects due to hormonal action of the active compounds cannot be excluded. However, general experience with COCs during pregnancy did not provide evidence for an actual adverse effect in humans.

The available data regarding the use of Flexyess during pregnancy are too limited to permit conclusions concerning negative effects of Flexyess on pregnancy, health of the foetus or neonate. To date, no relevant epidemiological data are available.

Withdrawal bleeding under treatment with Flexyess normally does not occur every 4 weeks but at a reduced frequency with intervals of up to 120 days. Unexpected pregnancy may be difficult to recognize. If for any reason pregnancy is suspected in a woman using Flexyess, a pregnancy test should be performed.

The increased risk of VTE during the postpartum period should be considered when re-starting Flexyess (see section 4.2 and 4.4).

Breast-feeding

Lactation may be influenced by COCs as they may reduce the quantity and change the composition of breast milk. Therefore, the use of COCs should generally not be recommended until the breast-feeding mother has completely weaned her child. Small amounts of the contraceptive steroids and/or their metabolites may be excreted with the milk during COC use. These amounts may affect the child.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. No effects on ability to drive and use machines have been observed in users of COCs.

4.8 Undesirable effects

Summary of safety profile

The most commonly reported adverse reactions with Flexyess are nausea and breast pain. They occur in > 3 % of users.

Serious adverse reactions are arterial and venous thromboembolism, breast cancer and focal nodular hyperplasia.

Tabulated summary of adverse reactions

The frequencies of ADRs of the table below include the labeled ADRs of YAZ which are combined with the ADRs reported in clinical trials with Flexyess(N=2623). In those cases where ADRs were reported in studies of both clinical development programs, and the frequency under Flexyess was higher, the frequency under Flexyess is shown.

System Organ Class (MedDRA version 9.1)	common (≥1/100 to <1/10)	uncommon (≥1/1,000 to <1/100)	rare (≥1/10,000 to <1/1,000)	not known (cannot be estimated from the available data)
Infections and infestations			Candidiasis	
Blood and lymphatic system disorders			Anemia Thrombocythemia	
Immune system disorders			Allergic reaction	Hypersensitivity
Endocrine disorders			Endocrine disorder	
Metabolism and nutrition disorders			Increased appetite Anorexia Hyperkalemia Hyponatremia	
Psychiatric disorders	Emotional lability Depression Libido decreased	Nervousness Somnolence	Anorgasmia Insomnia	
Nervous system disorders	Headache	Dizziness Paresthesia	Vertigo Tremor	
Eye disorders			Conjunctivitis Dry eye Eye disorder	
Cardiac disorders			Tachycardia	
Vascular disorders	Migraine	Varicose vein Hypertension	Phlebitis Vascular disorder Epistaxis Syncope Venous thrombo-embolism (VTE) Arterial thrombo-embolism (ATE)	
Gastrointestinal disorders	Nausea	Abdominal pain Vomiting Dyspepsia Flatulence Gastritis Diarrhea	Abdomen enlarged Gastrointestinal disorder Gastrointestinal fullness Hiatus hernia Oral candidiasis Constipation Dry mouth	
Hepatobiliary disorders			Biliary pain Cholecystitis	
Skin and subcutaneous tissue disorders		Acne Pruritus Rash	Chloasma Eczema Alopecia Dermatitis acneiform Dry skin Erythema nodosum	Erythema multiforme

			Hypertrichosis Skin disorder Skin striae Contact dermatitis Photosensitive dermatitis Skin nodule	
Musculoskeletal and connective tissue disorders		Back pain Pain in extremity Muscle cramps		
Reproductive system and breast disorders	Breast pain Metrorrhagia* Amenorrhea	Vaginal candidiasis Pelvic pain Breast enlargement Fibrocystic breast Uterine / Vaginal bleeding* Genital discharge Hot flushes Vaginitis Menstrual disorder Dysmenorrhea Hypomenorrhea Menorrhagia Vaginal dryness Papanicolaou smear suspicious	Dyspareunia Vulvovaginitis Postcoital bleeding Withdrawal bleeding Breast cyst Breast hyperplasia Breast neoplasm Cervical polyp Endometrial atrophy Ovarian cyst Uterine enlargement	
General disorders and administration site conditions		Asthenia Sweating increased Edema (Generalized edema, Peripheral edema, Face edema)	Malaise	
Investigations		Weight increase	Weight decrease	

* bleeding irregularities usually subside during continued treatment

For venous thromboembolic events (deep vein thrombosis, pulmonary embolism) and arterial thromboembolic events (myocardial infarction, cerebrovasculair accident), breast cancer, focal nodular hyperplasia (benign liver tumors) and migraine see also sections 4.3 and 4.4.

Description of selected adverse reactions

An increased risk of arterial and venous thrombotic and thrombo-embolic events, including myocardial infarction, stroke, transient ischemic attacks, venous thrombosis and pulmonary embolism has been observed in women using CHCs, which are discussed in more detail in section 4.4.

Adverse reactions with very low frequency or with delayed onset of symptoms which are considered to be related to the group of combined oral contraceptives are listed below (see also sections 4.3 and 4.4):

Tumours

- The frequency of diagnosis of breast cancer is very slightly increased among COC users. As breast cancer is rare in women under 40 years of age the excess number is small in relation to the overall risk of breast cancer. Causation with COC use is unknown.
- Liver tumors (benign and malignant)

Other conditions

- Erythema nodosum, erythema multiforme
- Women with hypertriglyceridemia (increased risk of pancreatitis when using COCs)
- Hypertension
- Occurrence or deterioration of conditions for which association with COC use is not conclusive: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; hemolytic uremic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss
- In women with hereditary angioedema exogenous estrogens may induce or exacerbate symptoms of angioedema
- Liver function disturbances
- Changes in glucose tolerance or effect on peripheral insulin resistance
- Crohn's disease, ulcerative colitis.
- Chloasma
- Hypersensitivity (including symptoms such as rash, urticaria)

Interactions

Breakthrough bleeding and/or contraceptive failure may result from interactions of other drugs (enzyme inducers, some antibiotics) with oral contraceptives (see section 4.5).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL – Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

There has not yet been any experience of overdose with Flexyess. On the basis of general experience with combined oral contraceptives, symptoms that may possibly occur in case of taking an overdose of hormone containing tablets are: nausea, vomiting and, in young girls, slight vaginal bleeding. There are no antidotes and further treatment should be symptomatic.

5 PHARMACOLOGICAL PROPERTIES**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group (ATC): Progestogens and estrogens, fixed combinations
ATC Code: G03AA12

In clinical trials performed with Flexyess in the European Union/Canada and in the USA the following Pearl Indices were calculated:

EU/Canada: Pearl Index for method failure: 0.59 (upper two-sided 95 % confidence limit: 1.22). Overall Pearl Index (method failure + patient failure): 0.63 (upper two-sided 95% confidence limit: 1.24).

USA: Overall Pearl Index (method failure + patient failure): 1.65 (upper two-sided 95% confidence limit: 2.65).

The contraceptive effect of Flexyess is based on the interaction of various factors, the most important of which are seen as the inhibition of ovulation and the changes in the endometrium.

Flexyess is a COC with ethinylestradiol and the progestogen drospirenone. In a therapeutic dosage, drospirenone also possesses antiandrogenic and mild antimineralocorticoid properties. It has no estrogenic, glucocorticoid and antiglyucocorticoid activity. This gives drospirenone a pharmacological profile closely resembling the natural hormone

progesterone.

There are indications from clinical studies that the mild antimineralocorticoid properties of YAZ result in a mild antimineralocorticoid effect.

Flexyess is a COC with a flexible extended regimen based on the conventional COC YAZ, therefore the minimum continuous tablet intake is 24 days and the length of the tablet-free interval is 4 days.

A multicenter open randomized parallel group study (EU/Canada) comparing Flexyess with YAZ demonstrated that the flexible regimen, when used to achieve a maximum length of bleeding-free intervals, was able to reduce the total number of days of menstrual bleeding per year from a mean of 66 days (YAZ) to a mean of 41 days (Flexyess).

Two multicenter, double blind, randomized, placebo controlled studies were performed to evaluate the efficacy and safety of YAZ in women with moderate acne vulgaris.

After six months of treatment, in comparison with placebo, YAZ showed a statistically significantly greater reduction of 15.6% (49.3% versus 33.7%) in inflammatory lesions, 18.5% (40.6% versus 22.1%) in non-inflammatory lesions, and 16.5% (44.6% versus 28.1%) in total lesion counts. In addition, a higher percentage of subjects, 11.8% (18.6% versus 6.8%), showed a 'clear' or 'almost clear' rating on the Investigator's Static Global Assessment (ISGA) scale.

5.2 Pharmacokinetic properties

- Drospirenone

Absorption

Orally administered drospirenone is rapidly and almost completely absorbed. Maximum concentrations of the active substance in serum of about 38 ng/ml are reached at about 1-2 h after single ingestion. Bioavailability is between 76 and 85 %. Concomitant ingestion of food has no influence on the bioavailability of drospirenone.

Distribution

After oral administration, serum drospirenone levels decrease with a terminal half-life of 31 h. Drospirenone is bound to serum albumin and does not bind to sex hormone binding globulin (SHBG) or corticoid binding globulin (CBG). Only 3 - 5 % of the total serum concentrations of the active substance are present as free steroid. The ethinylestradiol-induced increase in SHBG does not influence the serum protein binding of drospirenone. The mean apparent volume of distribution of drospirenone is 3.7 ± 1.2 l/kg.

Biotransformation

Drospirenone is extensively metabolized after oral administration. The major metabolites in plasma are the acid form of drospirenone, generated by opening of the lactone ring, and the 4,5-dihydro-drospirenone-3-sulfate, formed by reduction and subsequent sulfatation. Drospirenone is also subject to oxidative metabolism catalyzed by CYP3A4.

In vitro, drospirenone is capable to inhibit weakly to moderately the cytochrome P450 enzymes CYP1A1, CYP2C9, CYP2C19 and CYP3A4.

Elimination

The metabolic clearance rate of drospirenone in serum is 1.5 ± 0.2 ml/min/kg. Drospirenone is excreted only in trace amounts in unchanged form. The metabolites of drospirenone are excreted with the faeces and urine at an excretion ratio of about 1.2 to 1.4. The half-life of metabolite excretion with the urine and faeces is about 40h.

Steady-State Conditions

During a treatment cycle, maximum steady-state concentrations of drospirenone in serum of about 70 ng/ml are reached after about 8 days of treatment. Serum drospirenone levels accumulated by a factor of about 2-3 as a consequence of the ratio of terminal half-life and dosing interval.

Special Populations

Effect of renal impairment

Steady-state serum drospirenone levels in women with mild renal impairment (creatinine clearance CL_{cr}, 50-80 mL/min) were comparable to those of women with normal renal function. The serum drospirenone levels were on average 37 % higher in women with moderate renal impairment (CL_{cr}, 30 - 50 mL/min) compared to those in women with normal renal function. Drospirenone treatment was also well tolerated by women with mild and moderate renal impairment. Drospirenone treatment did not show any clinically significant effect on serum potassium concentration.

Effect of hepatic impairment

In a single dose study, oral clearance (CL/F) was decreased approximately 50 % in volunteers with moderate hepatic impairment as compared to those with normal liver function. The observed decline in drospirenone clearance in volunteers with moderate hepatic impairment did not translate into any apparent difference in terms of serum potassium concentrations. Even in the presence of diabetes and concomitant treatment with spironolactone (two factors that can predispose a patient to hyperkalemia) an increase in serum potassium concentrations above the upper limit of the normal range was not observed. It can be concluded that drospirenone is well tolerated in patients with mild or moderate hepatic impairment (Child-Pugh B).

Ethnic groups

No clinically relevant differences in the pharmacokinetics of drospirenone or ethinylestradiol between Japanese and Caucasian women have been observed.

- Ethinylestradiol

Absorption

Orally administered ethinylestradiol is absorbed rapidly and completely. Peak serum concentrations of about 33 pg/ml are reached within 1 - 2 hours after single oral administration. Absolute bioavailability as a result of presystemic conjugation and first-pass metabolism is approximately 60 %. Concomitant intake of food reduced the bioavailability of ethinylestradiol in about 25 % of the investigated subjects while no change was observed in the others.

Distribution

Serum ethinylestradiol levels decrease in two phases, the terminal disposition phase is characterized by a half-life of approximately 24 hours. Ethinylestradiol is highly but non-specifically bound to serum albumin (approximately 98.5 %), and induces an increase in the serum concentrations of SHBG and corticoid binding globulin (CBG). An apparent volume of distribution of about 5 l/kg was determined.

Biotransformation

Ethinylestradiol is subject to significant gut and hepatic first-pass metabolism. Ethinylestradiol is primarily metabolized by aromatic hydroxylation but a wide variety of hydroxylated and methylated metabolites are formed, and these are present as free metabolites and as conjugates with glucuronides and sulfate. The metabolic clearance rate of ethinylestradiol is about 5 ml/min/kg.

In vitro, ethinylestradiol is a reversible inhibitor of CYP2C19, CYP1A1 and CYP1A2 as well as a mechanism based inhibitor of CYP3A4/5, CYP2C8, and CYP2J2.

Elimination

Ethinylestradiol is not excreted in unchanged form to any significant extent. The metabolites of ethinylestradiol are excreted at a urinary to biliary ratio of 4:6. The half-life of metabolite excretion is about 1 day.

Steady-state conditions

Steady-state conditions are reached after approximately 14 days of continued daily tablet intake. Serum levels of ethinylestradiol accumulate by a factor of about 1.5 to 2.3.

5.3 Preclinical safety data

In laboratory animals, the effects of drospirenone and ethinylestradiol were confined to those associated with the

recognised pharmacological action. In particular, reproduction toxicity studies revealed embryotoxic and fetotoxic effects in animals which are considered as species specific. At exposures exceeding those in users of Flexyess, effects on sexual differentiation were observed in rat fetuses but not in monkeys.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Lactose monohydrate
Maize starch
Magnesium stearate (E470b)

Tablet film-coating:

Hypromellose (E464)
Talc (E553b)
Titanium dioxide (E171)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.
In-use stability: 40 days.

6.4 Special precautions for storage

This medical product does not require any special storage conditions.

As soon as the cartridge has been taken out of the blister, the cartridge has to be inserted into the tablet dispenser and tablets have to be used immediately.

6.5 Nature and contents of container

Starter Pack:

1x30 film-coated tablets and a tablet dispenser

Refill Packs:

1x30 film-coated tablets
3x30 film-coated tablets
4x30 film-coated tablets
12x30 film-coated tablets

The film-coated tablets are provided in a cartridge. Each cartridge contains 30 light pink tablets and is packed in a coldforming blister made of a two multilayer foils (OPA/Al/PE).

The cartridges are white/transparent and composed of methyl methacrylate / acrylonitrile / butadiene / styrene polymer (MABS), polybutylene terephthalate (PBT) and polyoxymethylene (POM).

The tablet dispenser (only in Starter Pack) housing is made of MABS with soft handles based on styrene / ethylene / butylene / styrene block copolymers (SEBS).

The cartridge slides into a tube part of the inner housing construction made of a polyarylamide compounded with glass fibers.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Flexyess can only be used in combination with the Clyk dispenser.

The instructions for use of the dispenser should be carefully read before and during use of the tablet dispenser.

Dispenser overview:



- Soft sides**
This is where you squeeze to release a pill.
- Cartridge release**
Ejects the cartridge
- Pill drop area**
This is where the pills will come out.

Reference Time indicator

Indicates the time when you should take a pill.

Display

Shows the home screen and associated MENU screens.

MENU button

Moves you through the MENU screens.

OK button

Performs confirming actions, such as starting a 4-day-break and changing the reminder sound status.

Most Important Functions:

The most important functions of the Clyk dispenser are explained in a short scheme in the Quick Reference Card.

Activating the new tablet dispenser:

The cartridge (containing 30 tablets) is removed from its packaging and should IMMEDIATELY be inserted into the tablet dispenser. This is done by inserting the narrow end of the cartridge into the dispenser so that the window of the dispenser (as well as the tablets in the cartridge) can be seen (see Fig 1). The cartridge MUST be pushed all the way in.

Fig 1: Preparing the tablet dispenser for use



The dispenser will automatically record the moment of the first tablet release by setting this time as the reference time. Therefore, the user has to

- make sure she only unpacks and inserts the cartridge on the day she wants to start her pill intake
- be sure to release her first pill at a time that will be convenient for her to take her pill every day.

Every 24 hours the dispenser window will show that it is time for the next tablet intake.

Dispensing a tablet:

The two soft sides of the dispenser are to be squeezed simultaneously with one hand to release a tablet which will be dispensed on the other hand.

Replacing a cartridge:

In routine use, a cartridge can only be removed when it is empty. By pressing the cartridge release button, the empty cartridge will be released. The dispenser keeps all information about the current cycle, and a new full cartridge can be inserted as described above.

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

7 MARKETING AUTHORISATION HOLDER

Bayer Limited
The Atrium,
Blackthorn Road,
Dublin 18,
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1410/065/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 8th March 2013

10 DATE OF REVISION OF THE TEXT

August 2015