ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORM, STRENGTH OF THE MEDICINAL PRODUCTS, ROUTE OF ADMINISTRATION, APPLICANT, MARKETING AUTHORISATION HOLDER IN THE MEMBER STATES

Member state	Marketing authorisation Holder	Applicant	Invented name	Strength	Pharmaceutical form	Route of administration
Austria		Medimpex France S.A.	Rigevidon	0.03 mg Ethinylestradiol 0.150 mg Levonorgestrel	Coated tablets	Oral Use
Belgium		Medimpex France S.A.	Rigevidon	0.03 mg Ethinylestradiol 0.150 mg Levonorgestrel	Coated tablets	Oral Use
Denmark	Medimpex France S.A.		Rigevidon	0.03 mg Ethinylestradiol 0.150 mg Levonorgestrel	Coated tablets	Oral Use
Germany		Medimpex France S.A.	Rigevidon	0.03 mg Ethinylestradiol 0.150 mg Levonorgestrel	Coated tablets	Oral Use
Greece		Medimpex France S.A.	Rigevidon	0.03 mg Ethinylestradiol 0.150 mg Levonorgestrel	Coated tablets	Oral Use
Ireland		Medimpex France S.A.	Rigevidon	0.03 mg Ethinylestradiol 0.150 mg Levonorgestrel	Coated tablets	Oral Use
Italy		Medimpex France S.A.	Rigevidon	0.03 mg Ethinylestradiol 0.150 mg Levonorgestrel	Coated tablets	Oral Use
Luxemburg		Medimpex France S.A.	Rigevidon	0.03 mg Ethinylestradiol 0.150 mg Levonorgestrel	Coated tablets	Oral Use
The Netherlands		Medimpex France S.A.	Rigevidon	0.03 mg Ethinylestradiol 0.150 mg Levonorgestrel	Coated tablets	Oral Use
Norway		Medimpex France S.A.	Rigevidon	0.03 mg Ethinylestradiol 0.150 mg Levonorgestrel	Coated tablets	Oral Use
Portugal		Medimpex France S.A.	Rigevidon	0.03 mg Ethinylestradiol 0.150 mg Levonorgestrel	Coated tablets	Oral Use
Spain		Medimpex France S.A.	Rigevidon	0.03 mg Ethinylestradiol 0.150 mg Levonorgestrel	Coated tablets	Oral Use
Sweden		Medimpex France S.A.	Rigevidon	0.03 mg Ethinylestradiol 0.150 mg Levonorgestrel	Coated tablets	Oral Use
United Kingdom		Medimpex France S.A.	Rigevidon	0.03 mg Ethinylestradiol 0.150 mg Levonorgestrel	Coated tablets	Oral Use

ANNEX II

SCIENTIFIC CONCLUSIONS PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF RIGEVIDON (see Annex I)

Inadequate exposure to the active components of a combined oral contraceptive (COC) may lead to therapeutic failure, i.e. pregnancy, which has a large impact on people's life. Inadequate exposure could also lead to disruption of cycle control and increase the occurrence of breakthrough bleeding, which may affect compliance and cause discontinuation of COC use.

However, a review of the literature suggests that effects on ovarian function and the endometrium occur at doses that are considerably lower than those in currently approved COCs and does not support the view that COCs in general have a narrow therapeutic margin in terms of efficacy/safety parameters. Furthermore, high contraceptive efficacy has been demonstrated with lower doses in marketed products than those found in Rigevidon and high contraceptive efficacy has also been shown for progestogen-only methods with considerably lower doses than those found in COCs.

COCs generally exhibit wide variation with regard to pharmacokinetics. The intra-individual and interindividual variability in pharmacokinetics of COCs is significant. Hence, from a pharmacokinetic point of view there is no evidence to suggest that a COC such as Rigevidon should be categorised as a narrow therapeutic index product. Thus, the current prerequisite for bioequivalence, i.e. the demonstration of bioequivalence within 80 – 125%, is considered appropriate for Rigevidon as it will sufficiently prove its performance as an essentially similar product in terms of rate and extent of absorption.

Based on the finding that:
⇒   Adequate contraceptive efficacy has been demonstrated with COCs even containing lower doses than Rigevidon and with lower dosed progestogen-only products,

⇒   Rigevidon has been on the market in some member states without any signal of insufficient efficacy or safety,

⇒   Despite wide inter- and intra-individual variations of steroid plasma concentrations, high contraceptive efficacy is consistently demonstrated in COC's with 0.030 mg ethinylestradiol and 0150 mg levonorgestrel,

⇒   There is a poor correlation between plasma steroid levels and contraceptive efficacy,

⇒   The pharmacokinetics of progestogens and EE do not adequately reflect safety parameters, such as endometrial bleeding or common adverse events nor rare effects such as risk of thromboembolic disease,

⇒   There are no safety issues placing COCs with 0.030 mg ethinyloestradiol and 0.150 mg levonorgestrel in the category of narrow therapeutic index drugs.

The conclusion is that bioequivalence studies with narrower acceptance limits would not contribute to the ability to extrapolate safety and efficacy data for Rigevidon. Thus, the current prerequisite for bioequivalence, i.e. the demonstration of bioequivalence within 80 – 125%, is considered appropriate for Rigevidon.

Therefore the CHMP has recommended that there are no objections for the granting of the Marketing Authorisation for Rigevidon.

ANNEX III

**SUMMARY OF PRODUCT CHARACTERISTICS
OF THE REFERENCE MEMBER STATE**

Note: This SPC is the one that was Annexed to the Commission Decision on this Article 29 referral for levonogestrel and ethinylestradiol containing medicinal products. The text was valid at that time.

After the Commission Decision, the Member State competent authorities will update the product information as required. Therefore, this SPC may not necessarily represent the current text.

1.   **NAME OF THE MEDICINAL PRODUCT**

Rigevidon coated tablets.

2.   **QUALITATIVE AND QUANTITATIVE COMPOSITION**

One tablet contains 150 micrograms levonogestrel and 30micrograms ethinylestradiol.
For excipients, see section 6.1.

3.   **PHARMACEUTICAL FORM**

Coated tablet
White, biconvex, circular tablets

4.   **CLINICAL PARTICULARS**

4.1   Therapeutic indications

Oral contraception.

4.2   Posology and method of administration

How is Rigevidon taken ?
The tablets must be taken in the order given on the blister pack, every day at approximately the same
time point.
One tablet is taken daily for 21 consecutive days. Every subsequent blister pack is started after a 7 day
tablet-free interval during which time a withdrawal bleed usually occurs. This bleeding will usually start
on the 2nd or 3rd day after the last tablet has been taken and it may not have stopped, before the next
blister pack is started.

How to start Rigevidon
No preceding hormonal contraceptive use in the past month.
The tablets should be started on day 1 in the woman's normal cycle (i.e. on the first day the woman has
a menstrual bleed). It is acceptable to start the tablets on day 2-5, but during the first cycle the
concomitant use of a barrier method for the first 7 days is recommended.

*Changing from another combined hormonal contraceptive (combined oral pills, vaginal ring or
transdermal patch):*
The woman should start with Rigevidon on the day after she took the last active tablet in her previous
blister pack of contraceptive pills (or removed the vaginal ring or transdermal patch) but, no later than
on the day after the usual tablet-free (or placebo, patch-free or ring-free) interval with her previous
contraceptive.

Changing from a progestogen-only method (progestogen-only or mini-pills, injection, implant)
The woman may switch from progestogen-only pills on any day (from an implant on the day the implant
is removed or from injection, when the next injection should have been given). In all these cases the
woman should be advised to use a concomitant barrier method for the first 7 days of the tablet intake.

After abortion in 1st trimester
The woman may start the tablet intake immediately. In this case, it is not necessary to take further
contraceptive precautions.

After delivery or abortion in 2nd trimester
For lactating women – see section 4.6.

The woman should be advised to start on day 21-28 after delivery or abortion in the 2nd trimester, because there is an increased risk of thromboembolic disorders during the post partum period. If she starts later than this, she should be advised to use a concomitant barrier method during the first 7 days of tablet intake. However, if she already has had intercourse, pregnancy must be excluded, before she starts the tablets, or she should wait for her first menstrual bleed.

Missed tablets
If the woman has forgotten tablet intake for less than 12 hours, the contraceptive protection is not reduced. The woman should take the tablet as soon as she remembers this, and the remaining tablets should be taken as usual.

If the delay exceeds 12 hours, the contraceptive protection may be reduced. Handling of missed tablets may be managed by the following two basic rules:

1.   Tablets should never be delayed for longer than 7 days.
2.   Seven days of uninterrupted tablet taking is required to maintain adequate suppression of the hypothalamus-pituitary-ovarian-axis.

Thus, the following advice may be given in daily practice:

Week 1:
The woman should take the last missed tablet as soon as she remembers this, even if this means that she has to take 2 tablets at the same time. Hereafter, she continues taking the tablets at the usual time point. She should use a barrier method concomitantly, e.g. a condom, for the next 7 days. If intercourse has taken place during the previous 7 days, the possibility of pregnancy must be considered. The more forgotten tablets, and the closer to the usual tablet-free interval this takes place, the greater the risk of pregnancy.

Week 2:
The woman should take the last missed tablet as soon as she remembers this, even if this means that she has to take 2 tablets at the same time. Hereafter, she continues taking the tablets at the usual time point. Provided that the tablets have been taken correctly during the 7 days preceding the forgotten tablet, it is not necessary to take further contraceptive precautions. However, if this is not the case, or if more than 1 tablet has been forgotten, the woman should be advised to use another contraceptive method for 7 days.

Week 3:
The risk of contraceptive failure is imminent because of the ensuing tablet-free interval. The reduced contraceptive protection may, however, be prevented by adjusting the tablet intake. Therefore, by following one of the following two alternatives, it is not necessary to take further contraceptive precautions, provided that all tablets have been taken correctly during the 7 days preceding the forgotten tablet. If this is not the case, the woman should be advised to follow the first of the two alternatives and use another contraceptive method concomitantly for the next 7 days.

1.   The woman should take the last missed tablet as soon as she remembers this, even if this means that she has to take 2 tablets at the same time.Thereafter, she should continue to take the tablets at the usual time point. She should start on the next blister pack immediately after taking the last tablet in the current blister pack, i.e. there will be no tablet-free interval between the blister packs. A withdrawal bleed is unlikely until the end of the second blister pack, but she may experience spotting or break through bleeding on the days she is taking tablets.
2.   The woman may also be advised to stop taking tablets from the current blister pack. In this case, she should keep a tablet-free interval of up to 7 days, including the days she forgot to take her tablets, and thereafter continue with the next blister pack.

If the woman has missed tablets and does not get a withdrawal bleed during the first, normal tablet-free interval, the possibility of pregnancy must be considered.

Advice in the case of vomiting/diarrhoea
If vomiting occurs within 3-4 hours after tablet taking, absorption may not be complete. In this case the advice concerning missed tablets, described above should be followed. Diarrhoea may reduce the efficacy by preventing full absorption. If the woman does not want to change her usual tablet intake, she should take the required extra tablet(s) from another blister pack.

How to delay or shift a period:
In order to delay a period, the woman should continue the next blister pack of Rigevidon, after taking the last tablet in the current pack, without. a tablet-free interval. The extension can be carried on for as long as desired until the end of the second blister pack. During the extension the woman may experience break through bleeding or spotting. Regular intake of Rigevidon is resumed after the usual 7 days tablet-free interval.

To shift her period to another day of the week, rather than the one the woman is used to with the present tablet intake, she may be advised to shorten the forthcoming tablet-free interval by as many days as she likes. The shorter the interval, the greater the risk that she will not have a withdrawal bleed and she may have break through bleeding or spotting during the second blister pack (which is also the case when delaying a period). It is important to emphasise that the tablet-free interval should not be extended.

4.3 Contraindications

Combined contraceptives must not be used in the presence of the conditions mentioned below. If such a condition should occur for the first time during use of oral contraceptives, the use of oral contraceptives must be discontinued immediately:

- Venous thromboembolism or medical history of venous thromboembolism (deep venous thrombosis, pulmonary embolism) with or without risk factors (see section 4.4)
- Arterial thromboembolism or medical history of arterial thromboembolism, in particular myocardial infarction, cerebrovascular disorder (see section 4.4)
- Considerable or multiple risk factors for venous or arterial thrombosis (see section 4.4)
- Previous prodromal symptoms of thrombosis (e.g. transient cerebral ischaemia, angina pectoris)
- Pregnancy or suspected pregnancy (see section 4.6)
- Cardiovascular disorders, i.e. cardiac diseases, valvulopathy, arrhythmic disturbances
- Severe hypertension
- Diabetes, complicated with micro or macro angiopathy
- Ocular disorder of vascular origin
- Malignant tumours in the breast
- Malignant endometrial tumours or other known or suspected estrogen-dependent neoplastic disorder
- Serious or recent hepatic disorders, in which liver function tests are not normalised
- Present or previous benign or malignant liver tumours
- Undiagnosed vaginal bleeding
- Migraine with focal neurological symptoms
- Hypersensitivity to the active substances or to any of the excipients

4.4 Special warnings and special precautions for use

Assessment and examination prior to starting combined oral contraceptives
Before the start or resumption of treatment with oral contraceptives a complete personal and family medical history must be obtained and a physical examination performed, in accordance with the contraindications (see section 4.3) and warnings (see "Warnings" in this section). This should be repeated at least once a year during oral contraceptive use. Periodic medical assessments are also important since contraindications (e.g. transient cerebral ischaemia) or risk factors (e.g. hereditary venous or arterial thrombotic disorders) may occur for the

first time during oral contraceptive use. The frequency and nature of these assessments should be adapted to the individual woman, but should, in general, include special reference to blood pressure, breasts, abdomen and abdominal organs, including cervical cytology and relevant laboratory tests.

Warnings

Women should be advised that oral contraceptives do not protect against HIV (AIDS) or other sexually transmitted infections (STI). If there is risk of STI/HIV the correct and consistent use of condoms is recommended, either alone or with another contraceptive method.

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with the extent of smoking and is particularly marked in women over 35 years of age. All women who use oral contraceptives should be strongly advised not to smoke. Other methods of contraception should be considered for those women over 35 years old who smoke.

If any of the risk factors below is present in any individual woman,the benefits of combined oral contraception must be weighed against possible risks in each individual case and discussed with the woman before combined oral contraception is commenced. In the event of aggravation, exacerbation or first appearance of any of these conditions or risk factors the woman should be advised to contact her physician. The physician must then decide, whether the use of oral contraceptives should be discontinued.

1.Circulatory disorders

Epidemiological studies indicate a relationship between the use of oral contraceptives and an increased risk of arterial and venous thrombosis and thromboembolic disorders, such as myocardial infarction, stroke, deep venous thrombosis (DVT) and pulmonary embolic disorders.

The treatment must cease if symptoms indicating imminent complications occur: serious abnormal headache, visual disturbances, increased blood pressure, clinical signs of deep venous thrombosis or pulmonary embolic disorders.

Venous thromboembolism (VTE), manifesting itself as deep venous thrombosis and/or pulmonary embolic disorder, may occur with any oral contraceptive. The approximate occurrence of VTE in users of oral contraceptives with a low content of estrogen (less than 50 microgram ethinylestradiol) is up to 4/10,000 woman years compared to 0.5-1/10,000 woman years in non-users. The occurrence of VTE during oral contraceptive use is, however, much lower than the occurrence related to pregnancy (i.e. 6/10,000 woman years).

Thrombosis in other blood vessels has very rarely been reported, i.e. hepatic, mesenteric, renal or retinal veins and arteries, in users of oral contraceptives. There is no consensus, whether the occurrence of these cases is related to use of oral contraceptives.

The risk for development of thromboembolism (venous and/or arterial) increases with:
- Age.
- Smoking (women over 35 should be warned not to smoke if they wish to use combined oral contraceptives).
- Hereditary predisposition (e.g. venous or arterial thromboembolism in siblings or parents at a relatively young age). In the case of suspected hereditary predisposition, the woman should be referred to a specialist before she decides to use oral contraception.
- Obesity (body mass index above 30 kg/m²).
- Dyslipoproteinaemia.
- Hypertension.
- Valvular disorder.
- Atrial fibrillation.
- Prolonged immobilisation, major surgery, surgery on the legs or major trauma. In such cases, it is recommended that treatment with oral contraceptives be discontinued (in the case of elective surgery

at least 4 weeks prior to the operation) and should not be resumed until 2 weeks after complete remobilisation.

There is no consensus concerning the possible role of varicose veins and superficial thrombophlebitis in venous thromboembolism.

The increased risk of thromboembolism during the puerperal period should be taken into consideration (for further information - see section 4.6).

Other medical conditions which have been related to circulatory disorders, include diabetes mellitus, systemic lupus erythematosus, haemolytic uraemic syndrome, chronic inflammatory bowel disease (Crohn's disease or colitis ulcerosa) and sickle cell anaemia.
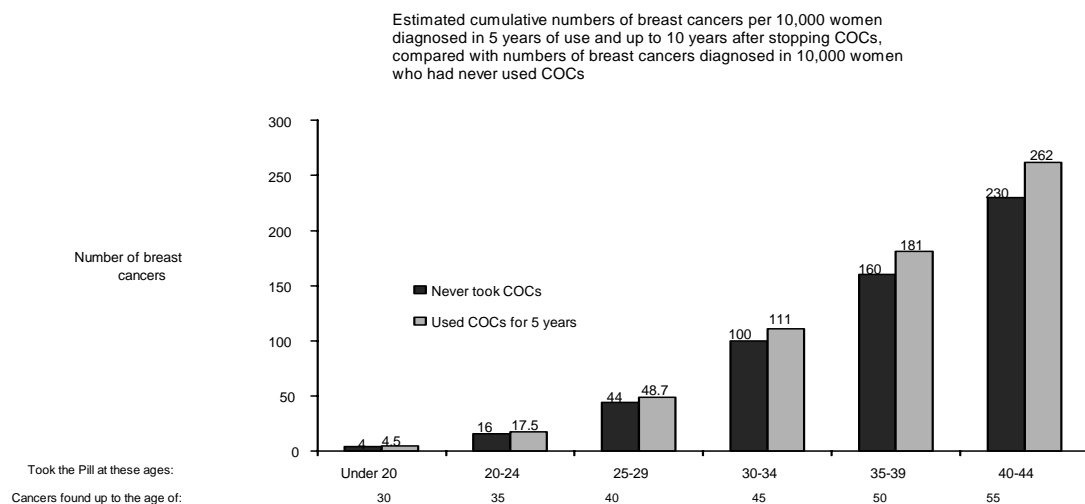
An increase in the frequency or severity of migraine (which may be prodromal for a cerebrovascular condition) during use of oral contraceptives must lead to consideration of immediate discontinuation of oral contraceptives.

Biochemical factors indicating hereditary or acquired predisposition for venous or arterial thrombosis, include activated protein C (APC) resistance, hyperhomocysteinaemia, antithrombin III deficiency, protein C deficiency, protein S deficiency, antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant).

2. Tumours:
In some epidemiological studies an increased risk of cervical cancer has been reported in longterm users of oral contraceptives, but it is still not clear to which extent this finding may be influenced by impacts of sexual behaviour and other factors, such as human papilloma virus (HPV).

A meta-analysis from 54 epidemiological studies has shown that women using combined oral contraceptives have a slightly increased relative risk (RR=1.24) of having breast cancer diagnosed. This increased risk gradually declined over 10 years following cessation of oral contraception. Since breast cancer is a rare condition in women below 40 years of age, the increase in number of diagnosed cases of breast cancer in current and previous users of oral contraceptives is small compared to the risk of breast cancer during their entire life time.

Estimated cumulative numbers of breast cancers per 10,000 women diagnosed in 5 years of use and up to 10 years after stopping COCs, compared with numbers of breast cancers diagnosed in 10,000 women who had never used COCs

Took the Pill at these ages:	Under 20	20-24	25-29	30-34	35-39	40-44
Never took COCs	4	16	44	100	160	230
Used COCs for 5 years	4.5	17.5	48.7	111	181	262
Cancers found up to the age of:	30	35	40	45	50	55

Number of breast cancers

These studies do not present evidence for a causal relationship. The observed pattern of an increased risk may be caused by an earlier diagnosing of breast cancer in users of oral contraceptives, the biological effects of oral contraceptives or a combination of both. The diagnosed cases of breast cancer in users of oral contraceptives, have a tendency to be clinically less advanced, compared to the diagnosed cases of breast cancer in non-users.

Benign and malignant liver tumours have been reported in users of combined oral contraceptives. These tumours have, in isolated cases, lead to life threatening, intra-abdominal haemorrhage. A liver tumour must be taken into consideration as a differential diagnosis when severe pain occurs in the upper abdomen, if there is hepatomegaly, or if there are signs of intra-abdominal haemorrhage in women taking oral contraceptives.

3. Other conditions
Women with hypertriglyceridaemia, or a family history thereof, may be at increased risk of pancreatitis when taking oral contraceptives.

In the case of acute or chronic impairment of liver function the use of the preparation should be stopped until liver function tests return to normal. Steroid hormones may be poorly metabolised in patients with impaired liver function.

Hyperlipidaemic women should be closely monitored if they choose to use contraceptive pills.

Even though slight increases in blood pressure have been reported in many women taking oral contraceptives, clinically important increases in blood pressure are rare. If persistent clinical hypertension develops during treatment with oral contraceptives they should be discontinued and the hypertension treated. Oral contraception may be resumed if appropriate, when normotensive values are reached with antihypertensive therapy.

It has been reported that the following conditions may occur, or worsen both during pregnancy and during use of oral contraceptives, but the evidence of a relationship with use of oral contraceptives is inconclusive: Jaundice and/or pruritus in connection with cholestasis; development of gallstones; porphyria; systemic lupus erythematosus; haemolytic uraemic syndrome; Sydenham's chorea; herpes gestationis; loss of hearing due to otosclerosis.

Oral contraceptives may have an influence on the peripheral insulin resistance and glucose tolerance. Therefore, diabetics should be monitored closely during use of oral contraceptives.

Rigevidon contains lactose and sucrose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption or with rare hereditary problems of fructose intolerance should not take this medicinal product.

Crohn's disease and colitis ulcerosa have been associated with the use of combined oral contraceptives.

Chloasma may occasionally occur, in particular in women with a medical history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to sunlight or ultraviolet radiation while taking oral contraceptives.

Ocular Lesions
There have been case reports of retinal thrombosis with the use of oral contraceptives. Oral contraceptives should be discontinued if there is unexplained partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions.

Women who get severely depressed during the use of contraceptive pills should stop taking the pills and be advised to use an alternative contraceptive method while trying to determine if the symptoms are due to the oral contraceptive preparation. Women who have previously suffered from depression should be closely monitored and stop the use of the oral contraceptive preparation if the symptoms of depression relapse.

Herbal preparations containing St John's wort (Hypericum perforatum) should not be used while taking Rigevidon due to the risk of decreased plasma concentrations and reduced clinical effects of Rigevidon (see section 4.5).

Reduced efficacy
The efficacy of oral contraceptives may be reduced in the case of missed tablets or vomiting (see section 4.2) or concomitant use of other medicinal product (see section 4.5).

Reduced cycle control
With all combined oral contraceptives, irregular bleeding (spotting or break through bleeding) may occur, especially during the first months. Hence, the evaluation of any irregular bleeding should be considered after a period of adaptation of approximately 3 cycles.

If bleeding irregularities persist or occur after previously regular cycles, then non-hormonal causes should be considered, and adequate diagnostic measures are indicated to exclude malignancy or pregnancy. If non-hormonal causes are excluded, oral contraceptives with a higher hormonal content may need to be considered.

Occasionally withdrawal bleeding during the tablet-free interval may not occur at all. If the tablets have been taken according to the instructions described in section 4.2, it is unlikely that the woman is pregnant. However, if the oral contraceptive has not been taken according to the instructions, before the first absent withdrawal bleed, or if two withdrawal bleeds are overdue, pregnancy should be excluded before the oral contraceptive is continued.

4.5 Interactions with other medicinal products and other forms of interaction

Drug interactions resulting in an increased clearance of sexual hormones may lead to break through bleeding and contraceptive failure. This has been demonstrated with hydantoins (e.g. phenytoin, barbiturates, primidone, carbamazepine and rifampicin. Other active substances suspected of having the capacity to reduce the efficacy of oral contraceptives include oxcarbazepine, topiramate, and griseofulvin. The mechanism of action seems to be based on the liver enzyme inducing properties of these active substances. Maximal enzyme induction is generally not observed until 2-3 weeks after start of treatment, but may then persist for at least 4 weeks after cessation of treatment. Contraceptive failure has also been reported with antibiotics such as ampicillin and tetracyclines, although the mechanism of action is unclear.

For short-term use of any of these enzyme-inducing active substances, additional use of barrier methods is recommended from the time of commencing the concurrent active substance, during treatment and for 4 weeks after cessation of treatment. Women on short term treatment with these antibiotics must temporarily use a barrier method concomitantly with the contraceptive pills, i.e. during the period of other concomitant active substance intake and for 7 days after cessation of this active substance. If these extra precautions overrun the end of the pack, the next pack should be started without a break. In this case, a withdrawal bleed should not be expected until the end of the second pack. If the patient does not have a withdrawal bleed at the end of the second pack, she must return to her doctor to exclude the possibility of pregnancy.

For long-term users of these medicinal products, use of other contraceptives should be advised.

Hypericum perforatum (St. John's wort)
The herbal preparation St John's wort (Hypericum perforatum) should not be taken concomitantly with this medicine as this could potentially lead to a loss of contraceptive effect. Breakthrough bleeding and unintended pregnancies have been reported. This is due to induction of drug metabolising enzymes by St John's wort. The inducing effect may persist for at least 2 weeks after cessation of treatment with St John's wort.

Concomitant use of ritonavir may also induce the liver enzymes with a similar negative effect on contraceptive efficacy.

Rigevidon may increase the plasma concentration of cyclosporin and diazepam (and other benzodiazepines that are hydroxylated), possibly via inhibiting hepatic elimination.

Rigevidon may increase the bioavailability of imipramin leading to an increased risk of toxicity.

Laboratory tests

The use of contraceptive steroids may have an influence on the results of certain laboratory tests, including biochemical parameters for liver, thyroid, adrenal and renal function; on the plasma levels for (transport)-proteins, e.g. corticosteroid-binding globulin and lipid/lipoprotein fractions; on parameters for carbohydrate metabolism and parameters for coagulation and fibrinolysis. Changes usually remain within the normal laboratory reference range.

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

4.6   Pregnancy and lactation

Rigevidon is not indicated during pregnancy. If pregnancy occurs during medication with Rigevidon, treatment should be withdrawn immediately.
Clinically, data on a limited number of exposed pregnancies indicate no adverse effects of levonorgestrel alone on the fetus.
The results of most epidemiological studies to date neither show an increased risk of birth defects in children born to women taking contraceptive pills before pregnancy, nor any teratogenic or fetotoxic effect in case of inadvertent fetal exposure to combinations of estrogens and progestagens.

Lactation may be influenced by COCs as they may reduce the amount and change the composition of human milk. Hence, the use of oral contraceptives cannot generally be recommended until the lactating mother has completely weaned off the child. Small amounts of contraceptive steroids and/or their metabolites may be excreted with the milk.

4.7   Effects on ability to drive and use machines

Rigevidon has no or negligible influence on the ability to drive and use machines.

4.8   Undesirable effects

Relatively rare but serious events that demand interruption of treatment:
 – arterial thromboembolic disorders (in particular myocardial infarction, cerebrovascular disorder)
 – venous thromboembolic disorders (phlebitis, pulmonary embolism)
 – arterial hypertension, coronapathies
 – hyperlipidaemia (hypertriglyceridaemia and/or hypercholesterolaemia), diabetes
 – serious mastodynia, benign mastopaty
 – pituitary adenoma with prolactinoma (rarely accompanied by galactorrhoea)
 – serious, abnormal headache, migraine, dizziness, visual disturbances
 – worsening of epilepsy
 – hepatic adenoma, cholestatic jaundice
 – chloasma.

More frequent but smaller events that usually do not demand interruption of treatment, but in which a change to another combined oral contraceptive may be considered:
 – nausea, mild headache, weight increase, irritability, heavy feeling in legs
 – breast tenderness, spotting, oligomenorrhoea, amenorrhoea, changes in libido
 – ocular irritation when wearing contact lenses.

Rarely:
 – acne, seborrhoea, hypertricosis
 – depressions;
 – vomiting;
 – allergic reactions.

Other: cholelithiasis**.**

Effect at cessation of treatment:

– postterapeutic amenorrhoea.

Amenorrhoea with anovulation (more frequent in women with irregular cycles in medical history) may be observed at termination of treatment It usually disappears spontaneously. If it is of longer duration, it should be examined for pituitary disorders , before further prescription.

4.9   Overdose

No serious, harmful effects after overdose have been reported. The symptoms which may occur in connection with overdose are: Nausea, vomiting, and in young girls a slight vaginal bleeding. There is no antidote, and further treatment should be symptomatic.

5.   PHARMACOLOGICAL PROPERTIES

5.1   Pharmacodynamic properties

Pharmacotherapeutic group: Progestogens and estrogens, fixed combinations
ATC code: G 03 AA 07

The contraceptive effect of Rigevidon is based on the interaction between various factors, the most important of which are the inhibition of ovulation and changes in the cervical mucus.

The Pearl Index (number of pregnancies/100 woman years) for combined low-dose monophasic oral contraceptives containing 0.15 mg levonorgestrel and 0.03 mg ethinylestradiol is 0.1 (method failure).

5.2.   Pharmacokinetic properties

Levonorgestrel

Absorption:
Levonorgestrel is rapidly and completely absorbed after oral administration of Rigevidon. The bioavailability is approximately 100% and levonorgestrel is not subject to first-pass metabolism.

Distribution:
Levonorgestrel is to a large extent bound to albumin and SHBG (Sex Hormon Binding Globulin) in plasma.

Metabolism:
Metabolism is mainly by reduction of the Δ4-3-oxo group and hydroxylation at the positions 2α, 1β and 16β, followed by conjugation. The majority of the metabolites circulating in the blood are sulphates of 3α, 5β-tetrahydro-levonorgestrel, while excretion mainly takes place as glucuronides. Some of the original levonorgestrel is also circulating as 17β-sulphate. Metabolic clearance is subject to marked inter-individual variation which may partly explain the wide variation in the concentrations of levonorgestrel observed among patients.

Elimination:
Levonorgestrel is eliminated with a mean T½ of approximately 36 hours at steady state. Levonorgestrel and its metabolites are primarily excreted in the urine (40%-68%) and approximately 16%-48% is excreted in the faeces.

Ethinylestradiol

Absorption:

Ethinylestradiol is rapidly and completely absorbed, and peak plasma levels are reached after 1.5 hours. Following presystemic conjugation and first-pass metabolism, the absolute bioavailability is 60%. The area under curve and Cmax may over time be expected to increase slightly.

Distribution:
Ethinylestradiol is to 98.8% bound to plasma proteins, almost entirely to albumin.

Metabolism:
Ethinylestradiol undergoes presystemic conjugation both in the small intestinal mucosa and in the liver. Hydrolysis of the direct conjugates of ethinylestradiol by the intestinal flora gives ethinylestradiol, which can be re-absorbed, thereby creating an enterohepatic circulation. The primary route of metabolism of ethinylestradiol is cytochrome P-450-mediated hydroxylation, where the primary metabolites are 2-OH-Ethinylestradiol and 2-methoxy-Ethinylestradiol. 2-OH-Ethinylestradiol is further metabolised to chemically reactive metabolites.

Elimination:
Ethinylestradiol disappears from plasma with a T½ of approximately 29 hours (26-33 hours), plasma clearance varies from 10-30 l/hour. The excretion of conjugates of ethinylestradiol and its metabolites takes place via urine and faeces. (ratio 1:1)

5.3. Preclinical safety data

Acute toxicity of ethinylestradiol and levonorgestrel is low. Because of marked species differences preclinical results possess a limited predictive value for the application of estrogens in humans.
In experimental animals estrogens displayed an embryolethal effect already at relatively low doses; malformations of the urogenital tract and feminisation of male fetuses were observed. Levonorgestrel displayed a virilising effect in female fetuses. Reproduction toxicology studies in rats, mice and rabbits revealed no hint for teratogenicity beyond the effect on sexual differentiation.
Preclinical data based on conventional studies of repeated dose toxicity, genotoxicity and carcinogenic potential revealed no particular human risks beyond those discussed in other sections of the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
- silica, colloidal anhydrous
- magnesium stearate
- talc
- maize starch
- lactose monohydrate

Coating:
- sucrose
- talc
- calcium carbonate
- titanium dioxide (E171)
- copovidone K90
- Macrogol 6000
- silica, colloidal anhydrous
- povidone K30
- carmellose sodium

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

4 years.

6.4. Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5. Nature and contents of container

Aluminium-PVC/PVDC blister

Pack sizes: 1×21 and 3×21 coated tablets
Not all pack size may be marketed.

6.6. Instructions for use and handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Medimpex France SA
1-3 rue Caumartin
75009 Paris
France

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

10. DATE OF REVISION OF THE TEXT