National Institute of Pharmacy
Directorate
of the National Institute for Quality- and Organizational Development in Healthcare and Medicines
Budapest, Hungary

GYEMSZI
Gyógyszerészeti és Egészségügyi Minőség- és Szervezetfejlesztési Intézet

Public Assessment Report

Name of the Product:

Mistral Continuous

2 mg/0.03 mg film-coated tablets

(dienogest/ethinyl estradiol)

Procedure number:
HU/H/0332/001/DC

Marketing authorisation holder: Richter Gedeon Nyrt.

Date: 29 January 2014

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LAY SUMMARY

After careful assessment of its quality and therapeutic benefit/risk ration, the National Institute of Pharmacy Directorate of the National Institute for Quality- and Organizational Development in Healthcare and Medicines, the national competent authority for Human medicinal products, together with the competent authorities of the member states concerned, decided to issue the marketing authorisation of the medicinal product Mistral Continuous 2 mg/0.03 mg film-coated tablets. The marketing authorisation was granted in a decentralised procedure with Hungary as reference member state. The national competent authorities of member states concerned in this procedure: Bulgaria, Estonia, Slovenia and Romania did agree.

The product name in Bulgaria is Sibilla 28, in Estonia Sibilla Plus, in Slovenia Sibilla, in Romania Sibilla Zilnic.

The holder of the marketing authorisation is Richter Gedeon Nyrt., Hungary.

Mistral Continuous film-coated tablets are a combined oral contraceptive, one of a group of drugs often referred to as the pill.

Each of the 21 white active tablets contains two types of female hormones: a progestogen, dienogest and an oestrogen, ethinyl estradiol.

The 7 green tablets contain no active substances and are also called placebo tablets.

The Mistral Continuous 2 mg/0.03 mg film-coated tablets are packaged in white PVC/PE/PVDC// Aluminium blisters. The tablets are marked with number 1 to 28 on the blister. The first tablet is marked with “1 Start”, the last one is marked with ”28”. There are arrows between the numbers on the blister which help you to follow the order of the numbers. The blisters are packed into folding box with patient leaflet and etui storage bag is enclosed in each box.

Each blister package of the Mistral Continuous film-coated tablets contains 21 round white active film-coated tablets (tablets 1-21) and 7 green placebo film-coated tablets which are larger (tablets 22-28). The active tablets are white or almost white, round, biconvex film-coated tablets with the engraving on one side: “G53”; the other side is without engraving.

The active coated tablets contain the active substances dienogest and ethinyl estradiol. Each film-coated tablet contains 2 mg dienogest and 0.03 mg ethinyl estradiol.

The other ingredients are:
- tablet core: lactose monohydrate, maize starch, hypromellose type 2910, talc, polacrilin potassium and magnesium stearate;
- film-coating: poly(vinyl alcohol), titanium dioxide (E171), Macrogol 3350 and talc.

The placebo tablet is green, round, biconvex film-coated tablet, without engraving.

Composition of the placebo coated tablets is, as follows:
- tablet core: cellulose, microcrystalline type 12, lactose anhydrous, starch, pre-gelatinised, magnesium stearate and silica, colloidal anhydrous;
- film-coating: poly(vinyl alcohol), titanium dioxide (E171), Macrogol 3350, talc, Indigo Carmine Aluminum Lake (E132), Quinoline Yellow Aluminum Lake (E104), Iron oxide, black (E172) and Sunset Yellow FCF Aluminum Lake (E110).

The combined contraceptive pill protects women against getting pregnant in three ways:
1. stop the ovary from releasing an egg each month (ovulation)
2. also thicken the fluid (at the neck of the womb) making it more difficult for the sperm to reach the egg
3. alter the lining of the womb to make it less likely to accept a fertilised egg.

Mistral Continuous film-coated tablets belong to the group of drugs often referred to as "micro pills" due to its low hormone content, "combined pills" due to the two types of hormones in the pill and monophasic oral contraceptives due to the identical composition of each tablet.

Mistral Continuous film-coated tablets alleviate pimples (acne) in women caused by the excessive quantity of male sex hormones called "androgens" that are present in every woman.

What women need to know before taking Mistral Continuous film-coated tablets

General information

There are some cases listed below when taking Mistral Continuous film-coated tablets should be stopped or the effectiveness of the pill may be reduced. In these cases their users either should not have sex, or use extra non-hormonal contraceptive precautions (such as condoms or another barrier method) during intercourse to ensure effective contraception. Do not use the calendar method or measurement of body temperature on waking because oral contraceptives may influence body temperature and the cyclical change of composition of the mucus of the neck of the womb.

It should be kept in mind that combined oral contraceptive pills like Mistral Continuous film-coated tablets will not protect their users against sexually-transmitted diseases (such as AIDS). Only condoms can help to do this.

Do not take Mistral Continuous film-coated tablets, who
- are allergic to dienogest or ethinyl estradiol or any of the other ingredients of this medicine;
- have or have had in the past a blood clot (thrombosis) in a blood vessel of the leg, lung (embolus) or other organs;
- have or have had in the past a heart attack or stroke;
- or any member of whose close family have any medical condition which makes you more at risk of developing blood clots;
- have or have had in the past a disease that can be a predictor of a heart attack (for example, angina pectoris, which causes severe pain in the chest) or of a stroke (for example, a transient slight stroke with no residual effects);

- have diabetes with damaged blood vessels;
- have severe high blood pressure;
- have blood-fat (lipid) disorders;
- have hereditary or acquired predisposition for venous or arterial thrombosis, such as APC-resistance, antithrombin-III-deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinaemia and antiphospholipid-antibodies (anticardiolipin-antibodies, lupus anticoagulant);
- have or ever had severe liver disease, yellowing of the skin (jaundice). Jaundice or itching of the whole body can be the signs of liver disease;
- have liver tumours or if you have ever had these;
- have or may have breast cancer or other cancer, for example ovarian cancer, cervical cancer, or cancer of the uterus (womb);
- have unusual bleeding from your vagina;
- have or have ever had migraine with disorders of perception, sensation, or movement.

Patients recognising any of the above conditions while taking Mistral Continuous film-coated tablets stop taking the pills and contact their doctor immediately. In the meantime, use another, non-hormonal method of contraception.

Warnings and precautions

In certain cases combined oral contraceptives should be taken under strict medical supervision. Patients who do have any of the following conditions must consult their doctor before taking Mistral Continuous film-coated tablets. The doctor will then explain the risk factors of the following conditions:

- diabetes;
- considerable overweight (obese);
- high blood pressure;
- a heart valve disorder or a certain heart rhythm disorder;
- cases of inflammation of a vein (usually in the legs) (thrombophlebitis);
- varicose veins;
- the patient or any member of her close family have any medical condition which places her more at risk of developing blood clots;
- migraine;
- the movement disorder called Sydenham's chorea;
- the patient or any member of her close family have a disorder of blood-fat (lipid) metabolism, or other very rare blood disorders;
- liver and/or gall bladder disease (yellowing of the skin, gallstones);
- Crohn's disease or ulcerative colitis (chronic inflammatory bowel diseases);
- jaundice or itching of your whole body;
- have systemic lupus erythematosus - SLE (an inflammatory disease which can affect many parts of the body, including the skin, joints and internal organs);
- a blood disorder called haemolytic uraemic syndrome - HUS (a disorder where blood clots cause the kidneys to fail);
- the inherited disease called porphyria;
- having had the rash known as herpes gestationis;

- the inherited form of deafness known as otosclerosis;
- brown patches on the face and body (chloasma), which can be reduce by staying out of the sun and not using sunbeds or sunlamps;
- smoking: in smokers combined oral contraceptives increase the risk of severe cardiovascular conditions (such as myocardial infarction, stroke); the risk increases with age and the number of cigarettes smoked.

Women over 35 years should be strongly advised not to smoke if they wish to use a COC. If the woman would not quit smoking, other method of contraception should be used, especially when concomitant risk factors are also present.

Mistral Continuous film-coated tablets and thrombosis

The use of any combination pill, including Mistral Continuous film-coated tablets, increases women's risk of developing a venous blood clot (venous thrombosis) compared with women who do not take any contraceptive pill. The excess risk of venous thromboembolism is highest during the first year a woman initially starts using pill or when she restarts pill use after a pill-free interval of at least a month.

The risk of venous blood clot in users of combination pills increases:
- with increasing age;
- with overweight;
- if one of the close relatives had a blood clot in the leg, lung (pulmonary embolism), or other organ at a young age;
- former surgery, a serious accident or if the patient is immobilized for a long time. It is important to inform the doctor in advance on using Mistral Continuous film-coated tablets as the treatment may have to be stopped. The doctor will decide when to start Mistral Continuous film-coated tablets again. This is usually about two weeks after the patient recovered.

The chances of having a blood clot are increased by taking the Mistral Continuous film-coated tablets (the Pill) as follows:
- of 100,000 women who are not on the Pill and not pregnant, about 5-10 may have a blood clot in a year;
- of 100,000 women taking a Pill like Mistral Continuous film-coated tablets, 30-40 may have a blood clot in a year, the exact number is unknown;
- of 100,000 women who are pregnant, around 60 may have a blood clot in a year.

A blood clot in the veins may travel to the lungs and may block blood vessels (called a lung embolus). Formation of blood clots in the veins may be fatal in 1-2% of cases.
The use of combination pills has been connected with an increase of the risk of an arterial blood clot (arterial thrombosis), for example, in the blood vessels of the heart (heart attack) or the brain (stroke).

The risk of an arterial blood clot in users of combination pills increases with
- smoking. It is strongly advised to stop smoking when using Mistral Continuous film-coated tablets, especially for those who are older than 35 years;
- increasing age;

- high levels of blood cholesterol or triglycerides;
- overweight;
- having a close relative who had a heart attack or stroke at a young age;
- high blood pressure;
- suffering from migraine;
- heart problems (valve disorder, a disturbance of the cardiac rhythm).

Those who notice possible signs of blood clot have to stop taking Mistral Continuous film-coated tablets and contact their doctor immediately. The signs may comprise:

- severe pain and/or swelling in one of the legs;
- sudden severe pain in the chest which may reach the left arm;
- sudden breathlessness;
- sudden cough without an obvious cause;
- any unusual, severe or long-lasting headache or worsening of migraine;
- partial or complete blindness or double vision;
- difficulty in speaking or inability to speak;
- giddiness or fainting;
- seizures;
- weakness, strange feeling, or numbness in any part of the body;
- movement disturbances;
- severe pain in the abdomen (known as acute abdomen).

Mistral Continuous film-coated tablets and cancer

Breast cancer has been observed slightly more often in women using combination pills, but it is not known whether this is caused by the treatment. For example, it may be that more tumours are detected in women on combination pills because they are examined by their doctor more often. The occurrence of breast tumours becomes gradually less after stopping the combination hormonal contraceptives. It is important to regularly check the breasts and when feeling any lump the doctor should be contacted immediately.

In rare cases, benign liver tumours, and in even fewer cases malignant liver tumours have been reported in Pill users. Experiencing unusual severe abdominal pain the doctor should be contacted.

Other medicines and Mistral Continuous film-coated tablets

Some medicines may stop the pill from working properly, i.e. they may reduce contraceptive efficacy. The signs of reduced efficacy can be the occurrence of breakthrough bleeding. These medicines are for example:

- medicines used to treat epilepsy, such as phenytoin, phenobarbital, primidone, carbamazepine, oxcarbazepine, topiramate, felbamate;
- rifampicin (to treat tuberculosis);
- antibiotics to treat certain infections (such as ampicillin, tetracycline, griseofulvin);
- ritonavir, rifabutin, efavirenz, nevirapine, nelvinafir;
- the herbal remedy commonly known as St John's wort (Hypericum perforatum);

- Mistral Continuous film-coated tablets may decrease the efficacy of other medicines, e.g. medicines containing cyclosporin, or the anti-epileptic lamotrigine (this could lead to an increased frequency of seizures).

Before the prescription of any other medicine, patients must be sure to inform the prescribing doctor or dentist on taking Mistral Continuous film-coated tablets. The doctor or dentist can explain then whether extra contraceptive precautions should be practised and for how long.

If taking any of these medicines in the short term, women will also need to use an extra method of contraception (e.g. condoms) during taking the other medicine and for 7 days after stopping it.

For women on treatment with rifampicin, a barrier method should be used in addition to the COC during the time of rifampicin administration and for 28 days after its discontinuation. If concomitant medicinal product administration runs beyond the end of the active tablets in the blister pack of Mistral Continuous film-coated tablets, the next pack of Mistral Continuous film-coated tablets should be started without the usual placebo tablet phase.

If taking drugs with so called liver enzyme inducing effects in the long term, the doctor should be informed as Mistral Continuous film-coated tablets may not be suitable for such patients. In certain cases a non-hormonal method of contraception should be chosen.

Pregnancy and breast-feeding

Those who are pregnant or breast-feeding, think they may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Pregnant women must not use Mistral Continuous film-coated tablets. Those who become pregnant or think they might be pregnant, stop taking Mistral Continuous film-coated tablets and consult their doctor immediately.

Women taking Mistral Continuous film-coated tablets while they are breast-feeding, the tablet may reduce the quantity and change the composition of breast milk. Small amounts of the contraceptive steroids and/or their metabolites may be excreted with the milk. These amounts may affect the child. Therefore, Mistral Continuous film-coated tablets should not be taken during breast-feeding.

Driving and using machines

Mistral Continuous film-coated tablets have no influence on the ability to drive and use machines.

Mistral Continuous film-coated tablets contain lactose, Sunset Yellow FCF Aluminium Lake and Quinoline Yellow Aluminum Lake

In the Mistral Continuous film-coated tablets the white active film-coated tablets contain 45.28 mg of lactose (as lactose monohydrate) while the green inactive ones contain 37.26 mg of lactose (as lactose anhydrous). Those who have been told by their doctor that may have intolerance to some milk sugar, consult the doctor before taking this medicinal product.

In Mistral Continuous film-coated tablets the green inactive film-coated tablets contain 0.003 mg of Sunset Yellow FCF Aluminum Lake (E110) and 0.0177 mg of Quinoline Yellow Aluminum Lake (E104). They may cause allergic reactions.

How to take Mistral Continuous film-coated tablets

Each blister pack of Mistral Continuous film-coated tablets contains 28 film-coated tablets. The blister pack has been designed to help the patients to remember how to take the pills.

Patients should try to take the pill at about the same time each day; if necessary with a little liquid, in the order shown on the blister pack. One tablet is to be taken daily, starting with the 21 white, active pills in the pack. The first tablet to be taken is marked with “Start”. To keep the order, follow the direction of the arrows on the pack. Then take the 7 green, placebo tablets. During taking the 7 green placebo tablets, on day 2 or 3, menstruation-like withdrawal bleeding, i.e. the monthly period will occur.

Start the next pack following the 7 green placebo tablets straightaway (so there is no gap between two blister packs) – even if the bleeding has not yet ended. As long as taking Mistral Continuous film-coated tablets correctly, each new pack will always be started on the same day of the week, and the monthly period will also occur on the same day of the week.

Those who take the pills correctly will have contraceptive protection at once.

Starting the first pack

If no oral contraception has been used during the preceding cycle

Take the first pill on the first day of your period. This is the first day of your cycle - the day when bleeding starts. Take the first pill marked with “Start”.

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

Start taking Mistral Continuous film-coated tablets on the day after you take the last active pill (the last tablet containing active substances) from the strip of your previous contraceptive, but at the latest on the day after the tablet-free days of your previous pill finish (or after the last inactive tablet of your previous pill).

When changing from a vaginal ring or transdermal patch, follow the advice of your doctor.

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

You can switch from pills only containing progestogen any time, and start taking Mistral Continuous film-coated tablets the next day at the usual time, from an implant or IUS on the day of its removal, from an injectable when the next injection would be due, but in all of these cases you must use extra protective measures (for example, a condom) for the first 7 days of tablet-taking.

Starting after miscarriage in the first three months of pregnancy

Follow the advice of your doctor.

Starting after having a baby or abortion during the second three months of pregnancy

After having a baby or second-trimester abortion, you can start Mistral Continuous film-coated tablets between 21 and 28 days later. If you start later than day 28, you must use a so-called barrier method (for example, a condom) during the first seven days of Mistral Continuous film-coated tablets use. If, after having a baby, you have had intercourse before starting Mistral Continuous film-coated tablets (again), you must first be sure that you are not pregnant or you must wait until the next menstrual bleed.

What to do when taking more Mistral Continuous film-coated tablets than prescribed

No data are available on the overdose with Mistral Continuous film-coated tablets. The acute oral toxicity of an overdose with other combined oral contraceptives in adults and children is low. Symptoms that may possibly occur in this case are: nausea, vomiting and, in young girls, slight vaginal bleeding. In general there is no need of special treatment; if necessary, treatment should be symptomatic.

Having noticed that a child has taken one or more tablets, consult a doctor.

What to do when taking Mistral Continuous film-coated tablets was forgotten

Green placebo tablets (22-28)

The last seven film-coated tablets in the strip are placebo film-coated tablets. If taking one of these film-coated tablets is forgotten, this will not have any effect on the efficacy of Mistral Continuous film-coated tablets. Discard the forgotten placebo film-coated

tablet to avoid prolonging the placebo week, which would have a negative effect on the efficacy of Mistral Continuous film-coated tablets.

White active tablets (1-21)

Those who are late less than 12 hours in taking the Pill:

- They are still protected against pregnancy if take the late Pill as soon as recognising the forgetfulness, and keep taking the next pills at the usual time. This may mean taking two pills in one day.

Those who are late more than 12 hours in taking the Pill:

- Their protection against pregnancy might be reduced. The risk of a pregnancy is higher if taking the Pill was forgotten at the start of a pack or before the end of the white, active tablets. In this case the following rules should be followed:
    - if taking of *more than one Pill* was forgotten: the doctor should be consulted and it should be remembered that the contraceptive protection is failed;
    - if taking the Pill was missed *in the first week*: the last missed tablet must be taken as soon as the failure was recognised, even if this means that 2 Pills are taken at the same time. Thereafter, taking the Pills should continue tablets at the usual time of the day. A barrier method of contraception should also be used, e.g. a condom, for the next 7 days. If intercourse has taken place during the preceding 7 days, the possibility of pregnancy must be considered and the doctor contacted for advice as soon as possible;
    - if taking the Pill was missed in *the second week*, take the last missed tablet as soon as it was recognised even if this means that 2 Pills are taken at the same time. Thereafter, taking the Pills should continue tablets at the usual time of the day. Provided that the tablets have been taken in a correct manner during the 7 days preceding the missed tablet, it is not necessary to take further contraceptive measures;
    - if taking the Pill was missed *in the third week*, provided that all former Pills have been taken correctly during the 7 days preceding the missed one *and* one of the two alternatives below id followed, it is not necessary to take further contraceptive precautions:
        - take the last missed tablet as soon as realising the mistake, even if it means that 2 Pills are taken at the same time. Thereafter, continue taking the tablets at the usual time of the day. Start then the next pack immediately after taking the last tablet in the current pack, i.e. without a placebo tablet phase between the packs. Withdrawal bleeding is unlikely until the end of the second pack, but there may be some spotting, or breakthrough bleeding, on the days you are taking tablets;
        - taking of the white active tablets may also be stopped, going directly to the green placebo tablets. Before this placebo week, notice the day when taking of the active Pill was forgotten to remember the first day of the hormone-free period, which can never be longer than 7 days, including that day when the Pill was forgotten. Thereafter continue with the next strip. If you

want to start a new strip on the day when you always start, make the placebo tablet period *less than 7 days*.

If missing a Pill and then do not get a withdrawal bleeding in the first normal placebo tablet phase, the possibility of pregnancy must be considered. In this case the doctor must be consulted before you starting the next pack.

What to do having a stomach upset

Having been sick or having diarrhoea within 3-4 hours after taking an active Pill, the active substances in the tablet may not be fully absorbed into the body. In this case the advice concerning missed pills, described above should be followed. Take another active pill as soon as possible, *not later than within 12 hours*. If more than 12 hours have elapsed, follow the instructions in section "If you forget to take Mistral Continuous film-coated tablets".

What to do if you want to delay your period

If you want to delay your period, you should continue the next pack of Mistral Continuous film-coated tablets, after taking the last white, active tablet in the current pack, without a placebo tablet period. When you use the second pack, you may have breakthrough bleeding or spotting. After the usual placebo film-coated tablet period of 7 days, continue with the first active film-coated tablet of the following strip.

What to do if you want to shift your period

If you take Mistral Continuous film-coated tablets correctly, you will always have your monthly period on the same day of the week. If you want to shift your period to another day of the week, rather than the one you are used to with the present pill intake, you may shorten (but never lengthen) the forthcoming placebo pill phase by as many days as you like. For example, if your monthly period usually starts on Friday and you want it to start on Tuesday (i.e. three days earlier), you should start the next pack of Mistral Continuous film-coated tablets three days earlier. The shorter the placebo tablet phase, the greater the possibility that you will not have a withdrawal bleeding, and that you may have breakthrough bleeding or spotting during the second pack.

If you have bleeding between periods

A few women may have a little breakthrough bleeding or spotting while taking the pill, especially during the first few months. Normally, this bleeding is nothing to worry about, and will stop in a day or two. You may need to have a sanitary pad or tampon, but keep taking the pills as usual, and the problem should disappear after the first few packs.

If the bleeding keeps on returning, is annoying or long-lasting, consult your doctor.

If you miss a period

If you have taken all your pills correctly, and you have not had a stomach upset, or used other medicines, then you are very unlikely to be pregnant. Continue to take Mistral Continuous film-coated tablets as usual.

If you have missed your period twice in a row, then you might be pregnant and you should see your doctor immediately. You are only allowed to continue taking the pill after doing a pregnancy test and on your doctor's advice.

Stopping taking Mistral Continuous film-coated tablets

Taking Mistral Continuous film-coated tablets may be stopped any time. Those who do not want to become pregnant straight away, consult their doctor for another reliable contraceptive method.

Possible side effects

Like all medicines, Mistral Continuous film-coated tablets can cause side effects, although not everybody experiences them.

COC use increases the risk of arterial and venous thromboembolism (e.g. venous thrombosis, pulmonary embolism, stroke, myocardial infarct). This risk is higher in case of smoking, high blood pressure, blood clotting or fat metabolism disorders, varicosity, late stage phlebitis and thrombosis.

Serious adverse reactions

Some women have had serious reactions to contraceptive pills. These side effects are listed in section "Warnings and precautions". If necessary, the doctor should be consulted immediately.

Other possible side effects

The adverse drug reactions of the dienogest and ethinyl estradiol combination are listed below according to their frequency. These are the frequencies of adverse drug reactions for which a causal relationship was probable, as observed in clinical trials on altogether 3590 women with the dienogest and ethinyl estradiol combination. Because all adverse drug reactions were less frequent than 1/10, none of them could be graded as "very common".

The following adverse drug reactions have been reported during the combined use of dienogest and ethinyl estradiol in clinical studies:

- common (may affect up to 1 in 10 people): headache, stomach pain, breast pain, breast tenderness.
- uncommon (may affect up to 1 in 100 people):
  - migraine, nervousness,

  - nausea, vomiting,
  - infection in urinary system,
  - acne, skin rash, a tan discoloration of the face (chloasma), hypersensitivity skin reactions, loss of hair, increased appetite,
  - vaginal disorders (fungal infection of the vagina, vaginal infections),
  - increased or decreased blood pressure, varicose veins,
  - fatigue/malaise, weight increase, swelling of the extremities (oedema),
  - menstrual bleeding disturbances, painful bleeding, breast enlargement, ovarian cysts, painful sexual intercourse, changes of the vaginal secretion,
  - mood disturbances (including depression).
- rare (may affect up to 1 in 1,000 people):
  - anaemia,
  - rapid heart beat,
  - visual disturbances, inflammation of the eye,
  - asthma, inflammation of the windpipe, inflammation of one of the paranasal sinuses,
  - hearing loss,
  - diarrhoea,
  - skin disorders, excessive hair growth and other male secondary sex characteristics in a female (virilism), itching,
  - decreased appetite,
  - vein disturbances (inflammation of superficial veins, blood clot inside a blood vessel (thrombosis)), haematoma, embolism in the lungs, disorders of blood flow of the arteries and veins,
  - flu-like symptoms, allergic reactions,
  - inflammation of the breast, fibrocystic breast, breast discharge, benign tumour of the muscle of the uterus, inflammation of the uterus and the fallopian tubes, menstrual disorders,
  - anorexia, agressivity, changes in sexual desire, apathy.

The following serious adverse events have been reported in women using combined oral contraceptives, which are discussed in section “Warnings and precautions”:
- blood clots;
- high blood pressure;
- liver tumours;
- brown patches on your face and body (chloasma);
- occurrence or deterioration of conditions for which association with COC use is not conclusive:
  - Crohn's disease,
  - ulcerative colitis,
  - porphyria,
  - systemic lupus erythematosus,
  - herpes gestationis,
  - Sydenham's chorea,
  - haemolytic uraemic syndrome,
  - cholestatic jaundice.

The frequency of diagnosis of breast cancer is very slightly increased among OC 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.

Effects on the formation of breast cancer

Breast cancer is a hormone-dependent tumour. Due to change in hormonal environment (e.g. use of hormonal contraceptives) the susceptibility of the mammary glands can increase towards other factors, i.e. development of breast cancer. Epidemiological studies indicate a possible causal relationship between long-term COC use started at young age and the development of breast cancer at middle age. However, COC use is only one of the multiple potential risk factors.

For further information, see sections "Do not take {Mistral Continuous film-coated tablets}" and "Warnings and precautions".

How to store Mistral Continuous film-coated tablets

Store them in the original packaging in order to protect from light. Store below 25 ºC.

Keep this medicine out of the sight and reach of children.

Scientific discussion

during the initial procedure

This module reflects the scientific discussion for the approval of Mistral Continuous 2 mg/0.03 mg film-coated tablets. The procedure was finalised at 16 July 2013. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

In accordance to the Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 *on the Community code relating to medicinal products for human use*, implemented by the Act CXV of 2005 *on Medicinal Products for Human Use and on the Amendment of Other* R*egulations Related to Medicinal Products* as well as by the Decree 52/2005 (IX. 18.) of the Minister of Health *on placing medicinal products for human use on the market* in Hungary, an application has been submitted to the reference and competent authorities of the Member State concerned.

With Hungary as the Reference Member State (RMS) in this Decentralised Procedure, Gedeon Richter Gedeon Nyrt. (Plc.) applied for the marketing authorisations for Mistral Continuous 2mg/0,03mg film-coated tablet in Bulgaria, Estonia, Romania and Slovenia.

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Mistral Continuous 2 mg/0.0.3 mg (in Bulgaria: Sibilla 28, in Estonia: Sibilla Plus, in Slovenia: Sibilla, in Romania: Sibilla Zilnic 2 mg/0.0.3 mg) film-coated tablets, from Richter Gedeon Nyrt., Budapest.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC claiming to be generic medicinal products of Celimona (Valette) coated tablets by Jenapharm GmbH & Co. KG, having marketing authorisation granted since 2000 in Germany.

The active principles of the product are dienogest in a dose of 2 mg and ethinyl estradiol in a dose of 0.03 mg (30 μg). It contains 28 active plus 7 placebo tablets.

A similar product of the same marketing authorisation holder containing 2 mg dienogest and 0.03 mg ethinyl estradiol has been authorised under the name Mistral in a formed decentralised procedure, the Concerned Member States were the Czech Republic, Estonia, Latvia, Lithuania, Poland Romania and Slovakia while Hungary acted as Reference Member State. The procedure was finalized on 25 February 2012 successfully.

Since the active ingredients of dienogest and ethinyl estradiol 2 mg/0.03 mg are the same in these medicinal products, the only difference is the presence of placebo tablets in the same pack in the present preparation, the data submitted and assessed in the formal procedure are considered relevant for the present procedure as well.

Mistral Continuous 2mg/0,03mg film-coated tablets are combined oral contraceptive with anti-androgenic effect, containing ethinyl estradiol as estrogen and dienogest, a synthetic steroid hormone having progestagenic and not significant androgen, mineralocorticoid or glucocorticoid effects.

Mistral Continuous 2mg/0.03mg film-coated tablet is administered daily for 21 days followed by the inert (placebo) tablets for 7 days.

The product is indicated:

- for oral contraception
- in the treatment of acne with moderate severity in women without contraindications for oral contraceptives and in whom topical treatment was ineffective

A comprehensive description of the indications and posology is given in the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

The chemical-pharmaceutical assessment report concerns the application of Mistral Continuous 2mg/0.03 mg film-coated tablets *via* a decentralized procedure according to Article 10(1) of Directive 2001/83/EC (i.e. a generic application).

Mistral Continuous 2mg/0,03mg film-coated tablets, developed by Richter Gedeon Plc., contain dienogest in a dose of 2 mg and ethinyl estradiol in a dose of 0,03mg. The product is administered daily for 21 days followed by placebo tablets for 7 days.

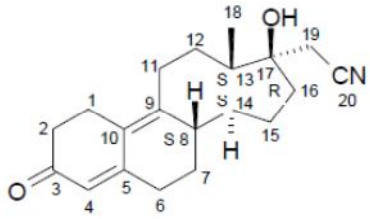
As reference product for bioequivalence Valette coated tablet (Jenapharm GmbH & Co. KG, DE, containing 2 mg dienogest and 0.03 mg ethinyl estradiol as active ingredients was used.

II.2 Drug Substances

II.2.1 Dienogest (micronized)

Data on the quality and manufacture of the active substance were provided in the submission using the Active Substance Master File (ASMF) procedure with additional data in the marketing authorization dossier. The Quality Overall Summary is adequate.

INN name: dienogest
Chemical name: (17α)-17β-hydroxy-3-oxo-19-norpregna-4,9-diene-21-nitrile
Structure:



The active substance is white or almost white crystalline powder, practically insoluble in water, slightly soluble in ethanol and ethyl acetate, sparingly soluble in acetone and methanol, freely soluble in dimethyl sulfoxide. Dienogest has four chiral centres. The possible number of the optical isomers is 16; the manufacturer consistently produces the correct isomer.

The ASMF holder presented complete details of the manufacturing process. Description of the manufacturing process of the active pharmaceutical ingredient (API) including the micronization process is adequate.

Evidence of the structure has been confirmed by ^{1}H-and ^{13}C-NMR, IR and MS. According to the scientific literature and the manufacturer's experience there is no evidence of

polymorphic modifications of dienogest. It was proven by consistent TG-, DSC-, IR- and X-ray powder diffraction data. Additionally, no morphological change occurs during the micronization procedure.

Dienogest is not official in the European Pharmacopoeia (Ph. Eur.); therefore, an in-house specification has been set for the active substance. This specification includes the following tests: appearance, identification by IR and melting point, loss on drying, sulphated ash, specific optical rotation, metal residue, related substances, residual solvents, assay, particle size distribution.

The specification is in accordance with the International Conference on Harmonisation (ICH) Q6A guideline. It reflects all relevant quality attributes and has been judged to be adequate for the control the quality of the drug substance. The limits set are properly justified.

The test methods are adequately described and sufficiently validated. Reference materials used by the active substance manufacturers and the drug product manufacturer for the control of the substance are adequately characterised.

The substance complies with the requirements of the European Medicines Agency (EMA) guideline on genotoxic impurities.

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

Stability studies have been performed with the drug substance. According to the presented stability data a re-test period of 4 years is acceptable with the storage condition "store it in the original package in order to protect from light".

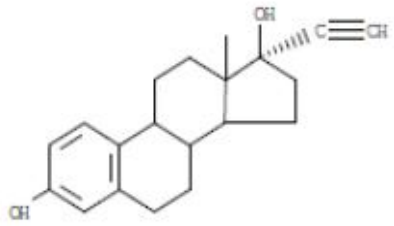
Good Manufacturing Practice (GMP) compliance of the active substance manufacture is demonstrated by the applicant.

II.2.2 Ethinyl estradiol (micronized)

Data on the quality and manufacture of the crystalline ethinyl estradiol were provided in the applicant's submission using the Ph. Eur. Certificate of Suitability (CEP) procedure with additional data in the marketing authorization dossier. The Quality Overall Summary is adequate.

INN name: ethinyl estradiol
Chemical name: 19-nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol

Structure:



The active substance is white or slightly yellowish-white crystalline powder, practically insoluble in water, freely soluble in ethanol (96 per cent). It dissolves in dilute alkaline solutions. It shows polymorphism, the manufacturer consistently produces the same polymorphic form.

The description of the manufacturing process of the micronization of the active substance is adequate.

The substance is specified according to the requirements of the current Ph. Eur. monograph; additional specification has only been set for residual solvents, particle size distribution and microbial impurities.
The Ph. Eur. specification includes the following tests for ethinyl estradiol: appearance, identification by IR and TLC, loss on drying, related substances, and assay.

The presented specification is in accordance with the Ph. Eur. general monograph on *Substances for Pharmaceutical Use* and the ICH Q6A guideline. It reflects all relevant quality attributes and has been judged to be adequate to control the quality of the drug substance. The limits set are properly justified.

Testing methods not described in details in the Ph. Eur. are adequately drawn up and sufficiently validated. Reference materials used by the active substance manufacturer and the drug product manufacturer for the control of the substance are adequately characterised.

The substance complies with the requirements of the EMA guideline on genotoxic impurities.

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

A retest period of 3 years and the packaging material (double polyethylene bags placed in a metal can or a fibre drum) have been specified in the CEP for crystalline ethinyl estradiol.

Stability studies have been performed with the micronized drug substance. According to the presented stability data a re-test period of 2 years is acceptable in the same packaging material mentioned on the CEP with the storage condition “store it in airtight container, protect from light and humidity”.

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

II.3 Medicinal Products

II.3.1 Active tablets

The aim of the pharmaceutical development was to produce film-coated tablets containing dienogest and ethinyl estradiol as drug substances in 2 mg and 0.03 mg doses, respectively which are pharmaceutically equivalent and bioequivalent to the reference medicinal product Valette 2 mg/0.03 mg coated tablets produced by Schering, Jenapharm.

A satisfactory package of data on development pharmaceutics has been presented. Brief discussion on reasons for inclusion and quantity of excipients has been provided.

As regards dissolution and impurity profile the product is shown to be similar to the reference product.

The compositions and the pharmaceutical tests evaluated during development of the final formulation are included in the documentation.

As a result of development studies a product with the following appearance, composition and packaging was obtained: white or almost white, round, biconvex film-coated tablets, with “G53” engraving on one side, and without engraving on the other side.

The excipients used in the finished product are lactose monohydrate, hypromellose type 2910, talc, magnesium stearate, polacrilin potassium, maize starch, macrogol 3350, titanium dioxide (E171), poly(vinyl alcohol) and talc. All excipients used comply with their respective Ph. Eur. monographs with the exception of the polacrilin potassium which complies with USP/NF. Compliance of the product with the general monograph of the Ph. Eur. on the *Products with the risk of TSE* has been demonstrated by the applicant.

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

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

II.3.2 Placebo tablets

The objective of the development was to formulate film-coated tablets without active substances to improve the patient compliance. A satisfactory package of data on development pharmaceutics has been presented. Brief discussion on reasons for inclusion and quantity of excipients has been provided.

The placebo tablets are green, round, biconvex film-coated tablet, with the diameter about 6 mm and without engraving.

The excipients used in the placebo film-coated tablets are lactose anhydrous, microcrystalline cellulose type 12, pregelatinised starch, magnesium stearate, colloidal anhydrous silica, macrogol 3350, titanium dioxide, poly(vinyl alcohol), talc, black iron oxide, Sunset yellow FCF aluminium lake, indigo carmine aluminium lake and quinoline yellow aluminium lake. All excipients used comply with their respective Ph. Eur. monograph with the exception of colouring agents which comply with the European Commission Directive 2008/128/EC. Compliance of the product with the general monograph of the Ph. Eur. on the *Products with the risk of TSE* has been demonstrated by the applicant.

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

The finished product specification is satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form monograph of the Ph. Eur. and the ICH Q6A guideline.

Appropriate control strategy was selected. The test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and complied with the specification.

II.3.3 Active and Placebo tablets

The placebo tablets will be marketed packaged together with the hormone containing tablets.

The container closure system of the product is white PVC/PE/PVDC // aluminium blisters. The tablets are marked with number 1 to 28 on the blister. The first tablet is marked with ”1 Start”, the last one is marked with ”28”. Tablets 1 to 21 represent the active while those marked 22 to 28 the placebo ones. There are arrows between the numbers on the blister which help patients to follow the order of the numbers.

Specifications and quality certificates for all packaging materials are enclosed.

Finished product stability studies have been conducted in accordance with the current guidelines in the final package. Based on the results, a shelf-life of 3 years with the stor-

age conditions "store below 25 ºC, store in the original packaging in order to protect from light" is approved.

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

II.4 Discussion on chemical, pharmaceutical and biological aspects

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

From quality aspects the product is approvable.

III. NON-CLINICAL ASPECTS

III.1 Introduction

The pharmaco-toxicological properties of both dienogest and ethinyl estradiol as well as those and of their combination are well known. The legal basis of this application was "generic", i.e. it was based on the establishment of the bioequivalence with a marketed medicinal product. The non-clinical overview is therefore based on a review of data available in several scientific databases or published in relation to dienogest and ethinyl estradiol.

III.2 Pharmacology

No specific new non-clinical studies have been performed, which is acceptable for this type of application. The submitted overview is satisfactory.

III.3 Pharmacokinetics

No specific new non-clinical studies have been performed, which is acceptable for this type of application. The submitted overview is satisfactory.

III.4 Toxicology

No specific new non-clinical studies have been performed, which is acceptable for this type of application. The submitted overview is satisfactory.

III.5 Ecotoxicity/environmental risk assessment

Since Mistral Continuous 2mg/0,03mg film-coated tablets are intended to substitute the innovator product, its storage, distribution, use and disposal will not result in an increase of risk to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

The pharmacodynamic, pharmacokinetic and toxicological properties of dienogest and ethinyl estradiol are well known.

No new non-clinical data have been supplied with this application and none are required for applications of this type. The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

There are no objections to the approval of the product from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction

Pharmacodynamic and pharmacokinetic properties of dienogest and ethinyl estradiol are well known. As this fixed combination comprises widely used active substances and the application was based on the establishment of the bioequivalence with a marketed medicinal product, no further clinical trials except the bioequivalence study are required and the applicant provides none. The submitted overview based on literature review is, thus, appropriate.

IV.2 Pharmacokinetics

IV.2.1 Literature data

Dienogest

It is rapidly and completely absorbed after oral administration. The peak plasma concentration of 51 ng/ml is reached within 2.5 hours. The absolute bioavailability when co-administered with ethinyl estradion is 96%.

Dienogest is bound to serum albumin and does not bind to SHBG or corticosteroid binding globulin (CBG). The fraction of the free dienogest in plasma is 10%, whilst 90% is non-specifically bound to albumin. Dienogest has an apparent volume of distribution of 37-45 l.

Dienogest is mainly metabolized by hydroxylation and alternatively by glucuronidation. Its metabolites are inactive and rapidly eliminated from plasma; thus metabolites cannot be detected in significant quantities in plasma besides unchanged dienogest. The total clearance after single-dose administration (Cl/F) is 3.6 l/h.

The half-life of dienogest is approximately 9 hours. The fraction of unchanged dienogest renally eliminated is not significant. After an oral dose of 0.1 mg/kg, the elimination with the faeces and urine has an excretion ratio of about 3.2. After oral administration approximately 86% is eliminated within 6 days, 42% of this being eliminated within the first 24 hours, predominantly in urine.

As for steady-state conditions, pharmacokinetics of dienogest is not influenced by the plasma levels of SHBG. Serum levels of dienogest are accumulated by a factor of about 1.5 and steady-state is reached within 4 days.

Ethinyl estradiol

It is rapidly and completely absorbed after ingestion. After the intake of the product, peak plasma concentrations of 67 pg/ml are reached at 1.5-4 hours. Ethinyl estradiol

undergoes an extensive first-pass effect and is extensively metabolized. The absolute bioavailability is approximately 44%.

Ethinyl estradiol is extensively but not specifically is bound to serum albumin (approx. 98%). It increases plasma levels of sex hormone binding globulin (SHBG). The apparent volume of distribution of ethinyl estradiol is 2.8-8.6 l/kg.

Ethinyl estradiol is conjugated in the enteric mucosa and liver. Its main metabolic pathway is represented by aromatic hydroxylation, but its metabolism results also in a wide range of hydroxilated and metylated metabolites, which are present in free, glucuronidated and sulfatated form. The clearance is approximately 2.3-7 ml/min/kg.

Plasma levels of ethinyl estradiol decrease in two phases, with half-lives of 1 and 10-20 hours. It is not excreted in unchanged form to any significant extent. The metabolites of ethinyl estradiol are excreted at a urinary to biliary ratio of 4:6. The half-life of metabolite excretion is about 1 day.

Steady-state conditions are reached during the second half of a treatment cycle and serum levels of ethinyl estradiol accumulated by a factor of about 2.

IV.2.2 Bioequivalence study

To support the submission, the applicant has submitted one bioequivalence study. It was a single-dose, randomised, 2-way crossover study in fasting conditions. As reference product for bioequivalence Valette coated tablets (Jenapharm GmbH & Co. KG, DE, containing 2 mg dienogest and 0.03 mg ethinyl estradiol as active ingredients were used.

Two tablets of the reference (R) or the test (T) product were administered in each study period. Healthy, female volunteers with childbearing potential were enrolled and dosed in the study.

For the determination of ethinyl estradiol and dienogest plasma concentrations two separate, validated LC-MS-MS methods were applied.

The following pharmacokinetic primary parameters were calculated for each subject and treatment, both for ethinyl estradiol and dienogest: $AUC_{0\text{-tlast}}$, $AUC_{0\text{- inf}}$, C_{max} and T_{max}.

For concluding bioequivalence for ethinyl estradiol and dienogest the pre-determined condition was that the 90% geometric confidence intervals of the ratio (A/B) of least-squares means from the ANOVA of the ln-transformed $AUC_{0\text{-last}}$, and C_{max} fall within the 80% to 125% interval.

The results are summarised in two Tables as follows.

Dienogest

Parameter	$AUC_{0-tlast}$	AUC_{0-inf}	C_{max}
Ratio T/R, %	99.1	98.7	100.5
90% Geometric confidence interval, %	95.9 – 101.8	95.6 – 101.6	97.2 – 103.9

Ethinyl estradiol

Parameter	$AUC_{0-tlast}$	AUC_{0-inf}	C_{max}
Ratio T/R, %	99.8	100.6	97.4
90% Geometric confidence interval, %	96.7 – 102.9	97.7 – 103.7	92.9 – 102.0

Results show that the test product, i.e. the Mistral Continuous 2 mg/0.03 mg (active) film-coated tablets manufactured by Richter Gedeon PLC, Hungary) is bioequivalent to the reference product with respect to rate and extent of availability under single-dose fasting conditions.

IV.3 Pharmacodynamics

The contraceptive effect of Mistral Continuous 2mg/0,03mg film-coated tablets 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.

The anti-androgenic effect of the dienogest/ethinyl estradiol combination is based mainly on the decrease of plasma androgen levels. In one multicentric study, this combination improved the symptoms of mild-to-moderate acne, and had beneficial effects on the symptoms of seborrhoea.

Dienogest is a norethisterone derivate, which has 10 - 30 fold lower affinity to progesterone receptor *in vitro* as compared to other synthetic progestogens. Dienogest does not have significant androgen, mineralocorticoid or glucocorticoid effects *in vivo*.

IV.4 Clinical efficacy

No new efficacy data have been submitted and none are required for this type of application.

IV.5 Clinical safety

No new clinical safety data have been submitted and none are required for this type of application.

During the bioequivalence study no new unexpected adverse effect occurred. Having the bioequivalence proven, the clinical safety of the Mistral Continuous 2mg/0,03mg film-coated tablets should be the same as that of the marketed reference product.

IV.6 Discussion on the clinical aspects

Abridged, such as generic applications are not needed to be supported by repeated clinical efficacy trials on humans. For these applications the bioequivalence studies are pivotal. The study carried out concluded that Mistral Continuous 2mg/0.03mg film-coated tablets manufactured by Richter Gedeon Plc., Hungary are bioequivalent to the reference product (Valette coated tablets, Jenapharm GmbH & Co. KG, DE) under fasting conditions.

Thus, from clinical aspects, the product is approvable.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The present applications concerns Mistral Continuous 2 mg/0.0.3 mg film-coated tablets. The applicant and the future holder of authorisation has been Richter Gedeon Nyrt., Hungary.

The active principles of the product are dienogest in a dose of 2 mg and ethinyl estradiol in a dose of 0.03 mg (30 µg). It contains 28 active plus 7 placebo tablets.

The application was submitted according to Article 10(1) of Directive 2001/83/EC (generic application).

Mistral Continuous 2mg/0,03mg film-coated tablets are combined oral contraceptive with anti-androgenic effect, containing ethinyl estradiol as estrogen and dienogest, a synthetic steroid hormone having progestagenic and not significant androgen, mineralocorticoid or glucocorticoid effects.

The applicant successfully demonstrated bioequivalence to the reference medicinal product Celimona (Valette) coated tablets by Jenapharm GmbH & Co. KG, having marketing authorisation granted since 2000 in Germany.

The submitted documentation is administratively adequate and scientifically sound. The quality of the product is satisfactory. There were no non-clinical or clinical concerns raised. The therapeutic benefit/risk assessment is, therefore, positive.

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Mistral Continuous 2 mg/0.0.3 mg (in Bulgaria: Sibilla 28, in Estonia: Sibilla Plus, in Slovenia: Sibilla, in Romania: Sibilla Zilnic 2 mg/0.0.3 mg) film-coated tablets.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

V.1 Conditions for the marketing authorisation

Requirements for specific post-marketing obligations

Not needed.

Pharmacovigilance system

The marketing authorisation holder submitted detailed description of the Pharmacovigilance System intended to be used, which fulfils the requirements and provides adequate evidence that the marketing authorisation holder has the services of qualified persons responsible for pharmacovigilance in all member states concerned and

has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management Plan

The applicant stated that no Risk Management Plan, as per the provisions of Volume 9A of *The Rules Governing Medicinal Products in the European Union* (March 2007) needed to be submitted, for the application concerned a generic product, with no more safety concerns identified for the reference product. Both the reference and the concerned member states accepted this statement.

Periodic Safety Update Report (PSUR)

No PSURs are requested for products referred to in Articles 10(1) of Directive 2001/83/EC as amended, the legal basis used for granting the marketing authorisation of the Mistral Continuous 2 mg/0.0.3 mg film-coated tablets.

Legal status

Prescription-only medicine.

V. 2 Summary of Product Characteristics (SmPC)

The SmPC is, from both pharmaceutical and medical aspects, acceptable.

V.3 Package Leaflet and user testing

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the patient information leaflet was Hungarian.

The results show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

VI. Upgrade: steps taken after the initial procedure with an influence on the Public Assessment Report

This module reflects the procedural steps and scientific information after the finalisation of the initial procedure.

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval or non approval	Assessment report attached