Public Assessment Report

Name of the Product:

Arankelle Continuous
3 mg/0.02 mg film-coated tablets

(Drospirenone/Ethinylestradiol)

Procedure number: HU/H/0356/001/DC

Marketing authorisation holder: Richter Gedeon Plc.

Date: 7 January 2015

CONTENT

LAY SUMMARY

After careful assessment of its quality and therapeutic benefit/risk ratio, the member states have granted the marketing authorisation of the Arankelle Continuous 3 mg/0.02 mg film-coated tablets (in Belgium and Luxemburg Arankellecont, in Finland MaitalonCont, in Romania Daylla Zilnic). The holder of the marketing authorisation is Gedeon Richter Plc.

The active substances are 3 mg drospirenone and 0.02 mg ethinylestradiol in each white tablet. The 7 green tablets contain no active substances and are also called placebo tablets.

The other ingredients are:
- active film-coated tablets:
    - tablet core: lactose monohydrate, maize starch, pregelatinised maize starch, macrogol poly(vinyl alcohol) grafted copolymer and magnesium stearate;
    - film-coating: polyvinyl alcohol partially hydrolyzed, titanium dioxide (E171), talc, macrogol 3350 and lecithin (soya);
- placebo film-coated tablets:
    - tablet core: microcrystalline cellulose, lactose anhydrous, pregelatinised maize starch, magnesium stearate and colloidal anhydrous silica;
    - film-coating: polyvinyl alcohol partially hydrolyzed, titanium dioxide (E171), macrogol 3350, talc, indigo carmine aluminium lake (E132), quinoline yellow aluminium lake (E104), iron oxide black (E172) and sunset yellow FCF aluminium lake (E110).

The active film-coated tablet is white or almost white, round, biconvex film-coated tablet. Engraving on one side: “G73”, other side is without engraving.

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

The film-coated tablets are packed in PVC/PE/PVDC-Al blister packs. The blisters are packed into folding box with patient leaflet and etui storage bag enclosed in each box.

Contraceptive pills that contain two hormones are called „combination” pills.

What one needs to know before you use Arankelle Continuous film-coated tablets

Before a patient can start taking Arankelle Continuous film-coated tablets, the doctor will ask some questions about the personal health history and that of the close relatives. The doctor will also measure the blood pressure, and depending upon the patient’s personal situation, may also carry out some other tests.

There may be several situations where using Arankelle Continuous film-coated tablets should be stopped, or where the reliability of Arankelle Continuous film-coated tablets may be decreased. In such situations one should either have no sex or should take extra non-hormonal contraceptive precautions, e.g., use a condom or another barrier method.

The use of rhythm or temperature methods is not encouraged. These methods can be unreliable because Arankelle Continuous film-coated tablets alter the monthly changes of body temperature and of the cervical mucus.

Arankelle Continuous film-coated tablets, like other hormonal contraceptives, do not protect against HIV infection (AIDS) or any other sexually transmitted disease.

Arankelle Continuous film-coated tablets should not be used in any of the conditions listed below (the doctor should be consulted and the doctor will decide what other form of birth control would be more appropriate:

- allergy to ethinylestradiol or drospirenone, or any of the other ingredients of this medicine. This may cause itching, rash or swelling;
- having (or ever had) a blood clot in a blood vessel of the legs (deep vein thrombosis, DVT), of the lungs (pulmonary embolus, PE) or in another organs;
- having (or ever had) a heart attack or stroke;
- having (or have ever had) angina pectoris (a condition that causes severe chest pain and may be a first sign of a heart attack) or transient ischaemic attack (TIA – temporary stroke symptoms);
- having any of the following diseases that may increase the risk of a clot in the arteries:
  - severe diabetes with blood vessel damage,
  - very high blood pressure,
  - a very high level of fat in the blood (cholesterol or triglycerides),
  - a condition known as hyperhomocystinaemia;
- having a disorder affecting the blood clotting – for instance, protein C deficiency, protein S deficiency, antithrombin-III deficiency, Factor V Leiden or antiphospholipid antibodies;
- needing an operation or if having been off the feet for a long time (see section 'Blood clots');
- having (or have ever had) a type of migraine called 'migraine with aura';
- having (or have ever had) a liver disease and the liver function is still not normal;
- if the kidneys are not working well (renal failure);
- having (or have ever had) a tumour in the liver;
- having (or have ever had) or suspected of having breast cancer or cancer of the genital organs;
- experiencing any unexplained bleeding from the vagina.

Warnings and precautions

Those who notice possible signs of a blood clot that may mean a blood clot in the leg (i.e. deep vein thrombosis), a blood clot in the lung (i.e. pulmonary embolism), a heart attack or a stroke (see 'Blood clots' section below) must seek urgent medical attention. For a description of the symptoms of these serious side effects see the section "How to recognise a blood clot".

When any of the following conditions apply the doctor must be contacted for in some situations the patients need to take special care while using Arankelle Continuous film-coated tablets or any other combination pill, and may need to regular medical examination. If the following condition develops, or gets worse while using Arankelle Continuous film-coated tablets, the doctor must be consulted:

- a close relative has or has ever had breast cancer;
- a disease of the liver or the gallbladder;
- diabetes;
- depression;
- Crohn's disease or ulcerative colitis (chronic inflammatory bowel disease);
- haemolytic uraemic syndrome (HUS – a disorder of blood clotting causing failure of the kidneys);
- sickle cell anaemia (an inherited disease of the red blood cells);
- epilepsy (see "Other medicines and Arankelle Continuous film-coated tablets");
- systemic lupus erythematosus (SLE – a disease affecting the natural defence system);
- having a disease that first appeared during pregnancy or earlier use of sex hormones, for example, hearing loss, a blood disease called porphyria, skin rash with blister during pregnancy (gestational herpes), a nerve disease causing sudden movements of the body (Sydenham's chorea);
- having (or have ever had) chloasma (a discolouration of the skin, especially of the face or neck known as "pregnancy patches"). If so, direct sunlight or ultraviolet light should be avoided;
- hereditary angioedema, products containing oestrogens may cause or worsen symptoms. The doctor must be consulted immediately if symptoms of angioedema such as swollen face, tongue and/or throat and/or difficulty swallowing or hives together with difficulty breathing are experienced;
- elevated levels of fat in the blood (hypertriglyceridaemia) or a positive family history for this condition. Hypertriglyceridaemia has been associated with an increased risk of developing pancreatitis (inflammation of the pancreas);
- those who have just given birth are at an increased risk of blood clots. They should ask the doctor how soon after delivery taking Arankelle Continuous film-coated tablets may be started;
- an inflammation in the veins under the skin (superficial thrombophlebitis);
- varicose veins;
- those who need an operation, or are off your feet for a long time (see in section 2 'Blood clots').

Blood clots

Using a combined hormonal contraceptive such as Arankelle Continuous film-coated tablets increases the risk of developing a blood clot compared with not using one. In rare cases a blood clot can block blood vessels and cause serious problems.

Blood clots can develop in the
- veins (referred to as a 'venous thrombosis', 'venous thromboembolism' or VTE),
- arteries (referred to as an 'arterial thrombosis', 'arterial thromboembolism' or ATE).

Recovery from blood clots is not always complete. Rarely, there may be serious lasting effects or, very rarely, they may be fatal.

It is important to remember that the overall risk of having a harmful blood clot due to any Arankelle Continuous film-coated tablets is small.

How to recognise a blood clot

Those who notice any of the following signs or symptoms must seek urgent medical attention:

Experiencing any of these signs	Possibly suffering from

• Swelling of one leg or along a vein in the leg or foot especially when accompanied by:
  • pain or tenderness in the leg which may be felt only when standing or walking
  • increased warmth in the affected leg
  • change in colour of the skin on the leg e.g. turning pale, red or blue
	Deep vein thrombosis

• Sudden unexplained breathlessness or rapid breathing; • sudden cough without an obvious cause, which may bring up blood; • sharp chest pain which may increase with deep breathing; • severe light headedness or dizziness; • rapid or irregular heartbeat • severe pain in your stomach; It should be kept in mind that some of these symptoms such as coughing or being short of breath may be mistaken for a milder condition such as a respiratory tract infection (e.g. a 'common cold').	Pulmonary embolism
Symptoms most commonly occur in one eye: • immediate loss of vision or • painless blurring of vision which can progress to loss of vision	Retinal vein thrombosis (blood clot in the eye)
• Chest pain, discomfort, pressure, heaviness • sensation of squeezing or fullness in the chest, arm or below the breastbone; • fullness, indigestion or choking feeling; • upper body discomfort radiating to the back, jaw, throat, arm and stomach; • sweating, nausea, vomiting or dizziness; • extreme weakness, anxiety, or shortness of breath; • rapid or irregular heartbeats	Heart attack
• Sudden weakness or numbness of the face, arm or leg, especially on one side of the body; • sudden confusion, trouble speaking or understanding; • sudden trouble seeing in one or both eyes; • sudden trouble walking, dizziness, loss of balance or coordination;	Stroke

• sudden, severe or prolonged headache with no known cause; • loss of consciousness or fainting with or without seizure. Sometimes the symptoms of stroke can be brief with an almost immediate and full recovery, but you should still seek urgent medical attention as you may be at risk of another stroke.	
• Swelling and slight blue discolouration of an extremity; • severe pain in your stomach (acute abdomen).	Blood clots blocking other blood vessels.

Blood clots in the vein

What can happen if a blood clot forms in a vein?

- The use of combined hormonal contraceptives has been connected with an increase in the risk of blood clots in the vein (venous thrombosis). However, these side effects are rare. Most frequently, they occur in the first year of use of a combined hormonal contraceptive.
- If a blood clot forms in a vein in the leg or foot it can cause a deep vein thrombosis (DVT).
- If a blood clot travels from the leg and lodges in the lung it can cause a pulmonary embolism.
- Very rarely a clot may form in a vein in another organ such as the eye (retinal vein thrombosis).

When is the risk of developing a blood clot in a vein highest?
The risk of developing a blood clot in a vein is highest during the first year of taking a combined hormonal contraceptive for the first time. The risk may also be higher if restarting taking a combined hormonal contraceptive (the same product or a different product) after a break of 4 weeks or more.

After the first year, the risk gets smaller but is always slightly higher than not using a combined hormonal contraceptive.

Stopping the use of Arankelle Continuous film-coated tablets the risk of a blood clot returns to normal within a few weeks.

How big is the risk of developing a blood clot?

The risk depends on the person's natural risk of VTE and the type of combined hormonal contraceptive you are taking but the overall risk of a blood clot in the leg or lung (DVT or PE) with Arankelle Continuous film-coated tablets is small.

- Out of 10,000 women who are not using any combined hormonal contraceptive and are not pregnant, about 2 will develop a blood clot in a year.

- Out of 10,000 women who are using a combined hormonal contraceptive that contains levonorgestrel, norethisterone, or norgestimate about 5-7 will develop a blood clot in a year.
- Out of 10,000 women who are using a combined hormonal contraceptive that contains drospirenone such as Arankelle Continuous film-coated tablets between about 9 and 12 women will develop a blood clot in a year.
- The risk of having a blood clot will vary according to the personal medical history (see "Factors that increase your risk of a blood clot" below).

	Risk of developing a blood clot in a year
Women who are not using a combined hormonal pill/patch/ring and are not pregnant	About 2 out of 10,000
Women using a combined hormonal contraceptive pill containing levonorgestrel, norethisterone or norgestimate	About 5-7 out of 10,000
Women using Arankelle Continuous film-coated tablets	About 9-12 out of 10,000

Factors that increase the risk of a blood clot in a vein
The risk of a blood clot with Arankelle Continuous film-coated tablets is small but some conditions will increase the risk. The risk is higher for those who:
- are very overweight (body mass index or BMI over 30 kg/m^2);
- in their immediate family have had a blood clot in the leg, lung or other organ at a young age (e.g.. below the age of about 50). In this case it is a hereditary blood clotting disorder;
- need to have an operation, or are off your feet for a long time because of an injury or illness, or have the leg in a cast. The use of Arankelle Continuous film-coated tablets may need to be stopped several weeks before surgery or while the person is less mobile. Those who need to stop Arankelle Continuous film-coated tablets should ask their doctor when to start using it again;
- get older (particularly above about 35 years);
- gave birth less than a few weeks before.

The more of the above conditions are valid the higher is the risk of developing a blood clot.

Air travel (>4 hours) may temporarily increase the risk of a blood clot, particularly if some of the other factors listed occurs.

Blood clots in an artery

What can happen if a blood clot forms in an artery?
Like a blood clot in a vein, a clot in an artery can cause serious problems. For example, it can cause a heart attack or a stroke.

Factors that increase your risk of a blood clot in an artery
It is important to note that the risk of a heart attack or stroke from using Arankelle Continuous film-coated tablets is very small but can increase:

- with increasing age (beyond about 35 years);
- with smoking. When using a combined hormonal contraceptive like Arankelle Continuous film-coated tablets, it is advisable to stop smoking. If someone is unable to stop smoking and are older than 35, the doctor may advise to use a different type of contraceptive;
- with overweight;
- with high blood pressure;
- if a member of the immediate family has had a heart attack or stroke at a young age (less then about 50). In this case family members could also have a higher risk of having a heart attack or stroke;
- if someone in the immediate family, have a high level of fat in the blood (cholesterol or triglycerides);
- with migraines, especially migraines with aura;
- with a problem with the heart (valve disorder, disturbance of the rhythm called atrial fibrillation);
- with have diabetes.

Having more than one of these conditions or if any of them are particularly severe the risk of developing a blood clot may be increased even more.

Arankelle 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 contacting the doctor if feeling any lump.

In rare cases, benign liver tumours, and in even fewer cases malignant liver tumours have been reported in pill users. Those who have unusually severe abdominal pain must contact their doctor.

Bleeding between periods

During the first few months when taking Arankelle Continuous film-coated tablets, unexpected bleeding (bleeding outside the week when you are taking the green tablets) can occur. If this bleeding occurs for more than a few months, or if it begins after some months, the doctor must identify what is wrong.

What to do if no bleeding occurs in the placebo days

Having taken all the white active tablets correctly, experiencing no vomiting or severe diarrhoea and taken no other medicines, the pregnancy is highly unlikely.

If the expected bleeding does not happen twice in succession, the pregnancy is likely. The doctor must be contacted immediately. The next strip should not be started until having been sure that pregnancy is excluded.

Other medicines and Arankelle Continuous film-coated tablets

The doctor who prescribes Arankelle Continuous film-coated tablets should know which medicines or herbal products the patient is already using. Other doctor or dentist who prescribes another medicine (or the pharmacist compounding non-prescription medicines) should also know that the patient uses Arankelle Continuous film-coated tablets. This way they can tell if additional contraceptive precautions (for example condoms) and if so, for how long.

Certain medicines can decrease the efficacy of the Arankelle Continuous film-coated tablets in preventing pregnancy, or can cause unexpected bleeding. These include:

- medicines used for the treatment of
  - epilepsy (e.g. primidone, phenytoin, barbiturates, carbamazepine, oxcarbazepine),
  - tuberculosis (e.g. rifampicin),
  - HIV infections (ritonavir, nevirapine) or other infections (antibiotics such as griseofulvin, penicillin, tetracycline),
  - high blood pressure in the blood vessels in the lungs (bosentan);
- the herbal remedy St. John's wort.

Moreover, Arankelle Continuous film-coated tablets may influence the effect of other medicines, e.g.

- medicines containing ciclosporin,
- the anti-epileptic lamotrigine (this could lead to an increased frequency of seizures).

Laboratory tests

Those who need a blood test, tell their doctor or the laboratory staff that they are taking the pill, because hormone contraceptives can affect the results of some tests.

Taking Arankelle Continuous film-coated tablets with food and drink

Arankelle Continuous film-coated tablets may be taken with or without food, if necessary with a small amount of water.

Pregnancy and breast-feeding

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

not take Arankelle Continuous film-coated tablets. Those who become pregnant while taking Arankelle Continuous film-coated tablets, should stop it immediately and contact their doctor. Those who want to become pregnant, can stop taking Arankelle Continuous film-coated tablets at any time (see also "If you want to stop taking {Arankelle Continuous film-coated tablets}".

Use of Arankelle Continuous film-coated tablets is generally not advisable when a woman is breast-feeding. Those want to take the pill while breast-feeding should contact their doctor for advice.

Driving and using machines

There is no information suggesting that use of Arankelle Continuous film-coated tablets affects the ability for driving or use of machines.

Arankelle Continuous film-coated tablets contains lactose, soya lecithin and sunset yellow

In Arankelle Continuous film-coated tablets the white active film-coated tablets contain 48.53 mg of lactose monohydrate and the green inactive ones contain 37.26 mg of lactose anhydrous per film-coated tablet. Those who have been told by their doctor that they have an intolerance to milk sugar, contact their doctor before taking this medicinal product.

Arankelle Continuous film-coated tablets contains soya lecithin. Those who are allergic to peanut or soya, do not use this medicinal product.

The ingredient sunset yellow may cause allergic reactions.

How to take Arankelle Continuous film-coated tablets

A strip contains 28 tablets. Each blister contains 21 active white tablets and 7 green placebo tablets. The two differently coloured tablets of Arankelle Continuous film-coated tablets are arranged in order.

Take one tablet of Arankelle Continuous film-coated tablets every day, if necessary with a small amount of water. The tablets may be taken with or without food, but they should be taken every day around the same time.

The tablets should not be confused: take a white tablet for the first 21 days and then a green tablet for the last 7 days. Then a new strip should be started straightaway (21 white and then 7 green tablets). Thus, there is no gap between two strips.

Because of the different composition of the tablets, it is necessary to begin with the first tablet at position 1 on the strip which is marked with "Start" and taking the tablets every day. For the correct order, the direction of the arrows and the numbering on the strips should be followed.

Preparation of the strip

The procedure described in the patient information leaflet (Package Leaflet) should be followed.

When to start with the first strip?

- If no contraceptive with hormones was used in the previous month
  Begin with Arankelle Continuous film-coated tablets on the first day of the cycle (i.e. the first day of the period). Those who start taking Arankelle Continuous film-coated tablets on the first day of their period are immediately protected against pregnancy. Taking the tablets may also begin on day 2-5 of the cycle, but then extra protective measures (for example a condom) must be used for the first 7 days.
- Changing from a combination hormonal contraceptive, or combination contraceptive vaginal ring or patch
  Taking Arankelle Continuous film-coated tablets preferably may be started on the day after the last active tablet (the last tablet containing active substances) of the previous pill, but at the latest on the day after the tablet-free days of the previous pill (or after the last inactive tablet of the previous pill). When changing from a combination contraceptive vaginal ring or patch, the advice of the doctor should be followed.
- Changing from a progestogen-only method (progestogen-only pill, injection, implant or a progestogen-releasing IUD)
  The switch is possible any day from the progestogen-only pill (from an implant or an IUD, on the day of its removal, from an injectable when the next injection would be due), but in all of these cases extra protective measures (for example, a condom) should be used for the first 7 days of tablet-taking.
- After a miscarriage
  The doctor's advice should be followed.
- After having a baby
  Starting Arankelle Continuous film-coated tablets is possible between 21 and 28 days after having a baby. Starting later than day 28, a so-called barrier method (for example, a condom) should be used during the first 7 days of Arankelle Continuous film-coated tablets use. However, having sex after having had a baby before starting Arankelle Continuous film-coated tablets (again), pregnancy must be excluded or the tablet taking must be delayed until the next period.
- Breastfeeding and wanting to start Arankelle Continuous film-coated tablets (again) after having a baby
  Consult the section on "Pregnancy and breast-feeding".

What happens if more Arankelle Continuous film-coated tablets were taken than prescribed

There are no reports of serious harmful results of taking too many Arankelle Continuous film-coated tablets. However, taking several tablets at once may cause symptoms of nausea or vomiting. Young girls may have bleeding from the vagina.

If too many Arankelle Continuous film-coated tablets were taken, or it is discovered that a child has taken some, the doctor or the pharmacist must be consulted for advice.

What to do if taking of the Arankelle Continuous film-coated tablets was forgotten

The last seven tablets of the strip are placebo tablets. If one of these tablets was forgotten, this has no effect on the reliability of Arankelle Continuous film-coated tablets. The forgotten placebo tablet should simply be thrown away.

If taking a white active tablet from the strip (film-coated tablets 1-21) was missing, the following should be done:

- If less time than 12 hours elapsed since taking a tablet, the protection against pregnancy is not reduced. The tablet should be taken as soon as soon as possible and then the following tablets again at the usual time.
- If more time than 12 hours elapsed since taking a tablet, the protection against pregnancy may be reduced. The greater the number of tablets forgotten to take, the greater is the risk of becoming pregnant.

The risk of incomplete protection against pregnancy is greatest on the first or on the third week of taking the white, active tablets. Therefore, the following rules (explained also in a diagram in the Package Leaflet) should be followed:

- More than one tablet forgotten in this strip
  Contact the doctor.
- One tablet forgotten in week 1
  The forgotten tablet should be taken as soon as possible, even if that means taking two tablets at the same time. Taking the tablets should be continued at the usual time and extra precautions should be used for the next 7 days, for example a condom. If there was sex in the week before forgetting the tablet pregnancy is possible. In that case the doctor should be contacted.
- One tablet forgotten in week 2
  The forgotten tablet should be taken as soon as possible, even if that means taking two tablets at the same time. Taking the tablets should be continued at the usual time. The protection against pregnancy is not reduced, and no take extra precautions are needed.
- One tablet forgotten in week 3
  One of the two possibilities below must be chosen:
  - The forgotten tablet should be taken as soon as possible, even if that means taking two tablets at the same time. Taking the tablets should be continued at the usual time. Start the next strip instead of taking the green placebo tablets on this strip, throw them away.

Most likely it will result in a period at the end of the second strip, while taking the green placebo tablets, but light or menstruation-like bleeding during the second strip is possible.

- It is also possible to stop taking the active, white tablets going directly to the 7 green placebo tablets (before taking the placebo tablets, the day on which the tablet was forgotten should be recorded). If you want to start a new strip on the day when always started, take the placebo tablets for less than 7 days.

If one of these two recommendations have been followed, there remains protection against pregnancy.

If taking any of the tablets in a strip is forgotten, moreover, there is no bleeding during the normal placebo days, it may mean pregnancy. The doctor must be contacted before starting the next strip.

What to do in the case of vomiting or severe diarrhoea

If vomiting within 3-4 hours after taking an active white tablet or having severe diarrhoea, there is a risk that the active substances in the pill will not be fully taken up by the body. The situation is almost the same as forgetting a tablet. After vomiting or diarrhoea, another white tablet should be taken from a reserve strip as soon as possible. If possible, it should be taken within 12 hours of when the pill is normally taken. If that is not possible or 12 hours have passed, the advice given under "What to do if taking of the Arankelle Continuous film-coated tablets was forgotten" should be followed.

Delaying the period: important information

Even though it is not recommended, the period can be delayed by not taking the green placebo tablets (tablets 22-28) and going straight to a new strip of Arankelle Continuous film-coated tablets and finishing it. Light or menstrual-like bleeding may be experienced while using this second strip. This second strip should be finished by taking the 7 green tablets from the end of the row (tablets 22-28). Then the next strip is to be started.

Changing the first day of the period: important information

If the tablets are taken according to the instructions, the period will begin during the placebo week. If this day is to be changed, the number of placebo days should be reduced – when the green placebo tablets are taken (but they should never be increased – 7 is the maximum!). For example, if taking the placebo tablets starts normally on a Friday, and this is intended to be changed to a Tuesday (3 days earlier), a new strip should be started 3 days earlier than usual. If the placebo period is made very short (for example, 3 days or less), no bleeding may be experienced during these days. Then light or menstrual-like bleeding may occur.

If taking Arankelle Continuous film-coated tablets is intended to be stopped

Taking Arankelle Continuous film-coated tablets can be stopped whenever it is intended. If pregnancy is to be avoided, the doctor will give an advice about other reliable methods of birth control.

If pregnancy is intended, taking Arankelle Continuous film-coated tablets should be stopped.

Possible side effects

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

An increased risk of blood clots in the veins (venous thromboembolism VTE) or blood clots in the arteries (arterial thromboembolism ATE) is present for all women taking combined hormonal contraceptives.

The following is a list of the side effects that have been linked with the combined use of drospirenone and ethinylestradiol.

Common side effects (may affect up to 1 in 10 people):
- mood swings,
- headache,
- abdominal pain (stomach ache),
- acne,
- breast pain, breast enlargement, breast tenderness, painful or irregular periods,
- weight gain.

Uncommon side effects (may affect up to 1 in 100 people):
- Candida (fungal infection),
- cold sores (herpes simplex),
- allergic reactions,
- increased appetite,
- depression, nervousness, sleep disorder,
- feeling of ‘pins and needles’, giddiness (vertigo),
- problems with vision,
- irregular heart beat or unusually fast heart rate,
- a blood clot (thrombosis) in a vessel of the leg or the lungs (pulmonary embolism), high blood pressure, low blood pressure, migraine, varicose veins,
- sore throat,
- nausea, vomiting, inflammation of stomach and/or intestine, diarrhoea, constipation,
- sudden swelling of the skin and/or mucous membranes (e.g. tongue or throat), and/or difficulty swallowing or hives together with difficulty breathing (angioedema), hair loss (alopecia), eczema, itching, rashes, dry skin, oily skin disorders (seborrheic dermatitis),
- neck pain, limb pain, muscle cramps,

- bladder infection,
- breast lump (benign and cancer), milk production while not pregnant (galactorrhea), ovarian cysts, hot flushes, absence of periods, very heavy periods, vaginal discharge, vaginal dryness, lower abdominal (pelvic) pain, abnormal cervical smear (Papanicolaou or Pap smear), decreased interest in sex,
- fluid retention, lack of energy, excessive thirst, increased sweating,
- weight loss.

Rare side effects (may affect up to 1 in 1,000 people):
- harmful blood clots in a vein or artery for example: in a leg or foot (i.e. DVT), in a lung (i.e. PE), heart attack, stroke, mini-stroke or temporary stroke-like symptoms, known as a transient ischaemic attack (TIA), blood clots in the liver, stomach/intestine, kidneys or eye. (The chance of having a blood clot may be higher if the patient has any other conditions that increase this risk),
- asthma,
- hearing impairment,
- blockage of a blood vessel by a clot formed elsewhere in the body,
- erythema nodosum (characterised by painful reddish skin nodules),
- erythema multiforme (rash with target-shaped reddening or sores).

Dietary soya-products are known to cause allergic reactions including severe anaphylaxis in persons with soya allergy. Patients with known allergy to peanut protein carry an enhanced risk for severe reactions to soya preparations.

How to store Arankelle Continuous film-coated tablets

Do not store them above 25 °C. Store them in the original package in order to protect from light.

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 Arankelle Continuous 3 mg/0.02 mg film-coated tablets. The procedure was finalised at 27 May 2014. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

This Decentralised Procedure application (Reference member state, RMS: Hungary, concerned member states, CMS: Belgium, Finland, Luxemburg and Romania) application has been submitted in accordance with Article 10(1) of Directive 2001/83/EEC (i.e. generic application), based on a claim of essential similarity to Yasminelle film-coated tablets of drospirenone and ethinylestradiol active ingredients, products of Bayer Schering Pharma A.G., Germany. The first marketing authorisation for drospirenone/ethinylestradiol combination was granted in 2000 for the product Yasmin (Bayer Pharma A.G.).

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisation for Arankelle Continuous 3 mg/0.02 mg film-coated tablets (in Belgium and Luxemburg Arankellecont, in Finland MaitalonCont, in Romania Daylla Zilnic) from Gedeon Richter Plc.

The product is indicated for the prevention of pregnancy in women who select to use an oral contraceptive.

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

Drospirenone/ethinylestradiol is a combined oral contraceptive indicated for prevention of pregnancy in women. Its therapy consists in a single dose of 3 mg/0.02 mg once daily for 21 consecutive days per cycle followed by placebo tablet for 7 days.

The contraceptive effect of drospirenone 3 mg + ethinylestradiol 0.02 mg 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.

Ethinylestradiol is a potent synthetic estrogen, closely related to the human estrogen, estradiol. It exerts its action by binding to the estrogen receptor, which is present in many different tissues. Drospirenone is an analogue of the antimineralocorticoid spironolactone with antimineralocorticoid, progestogenic and antiandrogenic activity

II. QUALITY ASPECTS

II.1 Introduction

This chemical-pharmaceutical assessment report concerns the application of Arankelle Continuous 3 mg/0.02 mg film-coated tablets via a decentralized procedure according to Article 10.1 of Directive 2001/83/EC (i.e. a generic application). The products have been developed by Gedeon Richter Plc.

The reference product is Yasminelle (containing 3 mg of drospirenone and 0.02 mg ethinylestradiol as active ingredients) which was the original products of Bayer Schering Pharma AG.

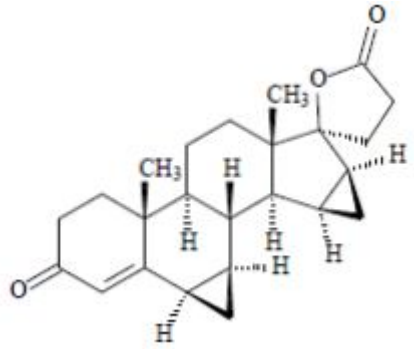
Each blister contains 21 white active film-coated tablets and 7 green film-coated placebo tablets. The blisters are packed into cardboard box with a patient leaflet, and etui storing bag is enclosed in each box.

II.2 Drug substances

II.2.1 Drospirenone

Data on the quality and manufacture of the active substance were provided in the applicant's submission using the Certificate of European Pharmacopoeia (CEP) procedure with additional data in the marketing authorization dossier. The Quality Overall Summary is adequate.

INN name: drospirenone
Chemical name: 3-Oxo-6α,7α,15α,16α-tetrahydro-3'*H*,3"*H*-dicyclopropa[6,7:15,16]-17α-pregn-4-en-21,17-carbolactone
Structure:



The active substance is white or almost white crystalline powder, practically insoluble in water, freely soluble in methylene chloride, soluble in methanol and sparingly soluble in ethanol (96 per cent). The molecule of drospirenone has 10 asymmetric centers. The active substance has only one optical isomer. It shows polymorphism, the manufacturer consistently produces the correct isomer and the same polymorphic form.

The substance is specified according to the requirements of the current European Pharmacopoeia (Ph. Eur.) monograph. Additional specification has only been set for loss on drying for the measurement of residual solvent.

The Ph. Eur. specification includes the following tests for drospirenone: appearance, identification (specific optical rotation, IR spectrum), related substances (HPLC), loss on drying, microbiological purity and assay.

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 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.

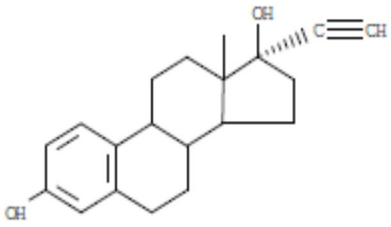
The retest period and the packaging material (double polyethylene bag placed in a paper bag) have been described in the CEP.

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

II.2.2 Ethinylestradiol

Data on the quality and manufacture of the active substance were provided in the applicant's submission using the CEP procedure with additional data in the marketing authorization dossier. The Quality Overall Summary is adequate.

INN name: ethinylestradiol
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 and freely soluble in ethanol (96 per cent). It dissolves in dilute alkaline solutions. The molecule has five asymmetric carbon atoms in the steroid skeleton, consequently it has isomers.

The substance is specified according to the requirements of the current Ph. Eur. monograph. Additional specification has only been set for a residual solvent.

The Ph. Eur. specification includes the following tests for ethinylestradiol: appearance, identification (IR, TLC), related substances (HPLC), loss on drying, microbiological purity and assay. The CEP contains additional tests: particle size distribution, residual solvents.

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 testing methods and demonstrate the batch to batch consistency of the production.

A retest period for the crystalline substance and the packaging material (double polyethylene bag placed in a metal can or fiber drum) have been described in the CEP.

Stability studies have been performed with the micronized drug substance. According to the presented stability data a re-test period of 2 years is in the same packaging mentioned above acceptable with storage condition ‘protect from light and humidity, in an airtight container’.

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

II.3 Medicinal products

II.3.1 Active tablets

The aim was to develop film-coated tablets containing drospirenone in 3 mg and ethinylestradiol as drug substances in 0.02 mg doses, pharmaceutically equivalent and bioequivalent equivalent to the reference medicinal product Yasminelle film-coated tablets, the branded original products of Bayer Schering Pharma AG.

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 has been 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:

Arankelle Continuous 3mg/0.02mg film-coated tablets were white or almost white, round, biconvex ones, one side engraved with G73, the other side without engraving.

The excipients used in the finished product are lactose monohydrate, maize starch, pregelatinised starch (maize), macrogol poly(vinyl alcohol) grafted copolymer and magnesium stearate. All excipients used comply with their respective Ph. Eur. monograph. 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. Certificates of analysis for the batches involved in the bioequivalence study are presented.

The container closure system of the product is transparent PVC/PE/PVDC//Al blister. Specifications and quality certificates for all packaging components are enclosed.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results, a shelf-life of 2 years with ‘Do not store above 25°C’ and ‘Store in the original package in order to protect from light’ conditions is approved. The Summary of Product Characteristics, patient Information Leaflet and label texts are pharmaceutically acceptable.

II.3.2 Placebo tablets

The objective of the development was to formulate a film-coated tablet without oral contraceptive hormones 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 compositions and the pharmaceutical tests evaluated during development of the final formulation are included in the documentation. As a result of development studies product with the following appearance, composition and packaging was obtained.

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

The excipients used in the finished product are lactose anhydrous, microcrystalline cellulose (type 12), pregelatinised starch (maize), colloidal anhydrous silica, magnesium stearate and Opadry II Green. All excipients used comply with their respective Ph. Eur. monograph, except the film-coating agent Opadry II Green but its components also comply with the Ph. Eur. 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.

The container closure system of the product is transparent PVC/PE/PVDC//Al blister. Specifications and quality certificates for all packaging components are enclosed.

Finished product stability studies have been conducted in accordance with the current guidelines. The stability study of the placebo tablets was carried out with transparent PVC/PVDC//Al packaging. The three-layer PVC/PE/PVDC//Al gives more protection than the two-layer PVC/PVDC//Al, so the difference is acceptable. Based on the results, a shelf-life of 2 years with 'Do not store above 25°C' and 'Store in the original package in order to protect from light' conditions is approved.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The product has been shown to meet the current regulatory requirements with regards to its quality and content of the active substance as well as 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 chemical and pharmaceutical points of view the product is approvable.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This assessment report concerns the application of Arankelle Continuous 3 mg/0.02 mg film-coated tablets via a decentralized procedure according to Article 10.1 of Directive 2001/83/EC (i.e. a generic application). The products have been developed by Gedeon Richter Plc.

The reference product is Yasminelle (containing 3 mg of drospirenone and 0.02 mg ethinylestradiol as active ingredients) which was the original products of Bayer Schering Pharma AG.

The non-clinical part of the dossier contains literature summaries.

III.2 Pharmacology

Combination oral contraceptives act by suppression of gonadotropins. Although the primary mechanism of this action is inhibition of ovulation other alterations include changes in cervical mucus and endometrium increasing the difficulty of sperm entry into the uterus and reducing the likelihood of implantation, respectively.

Drospirenone has progestational, antiandrogenic and antimineralocorticoid activity. It does not show any significant androgenic, estrogenic or glucocorticoid activity.

Ethinylestradiol is a synthetic steroid prepared from estron. It acts via estrogen receptors. It stimulates proliferation and differentiation in the fallopian tube, and increase the tubal muscular activity. Ethinylestradiol also increases the water content of cervical mucus and favours contraction of the uterine myometrium.

III.3 Pharmacokinetics

Following oral administration, absorption of drospirenone was rapid and almost complete in mice, rats, rabbits and monkeys. Metabolic clearance and volume of distribution are after intravenous dose of 1 mg/kg in rats, and 0.5 mg/kg in rabbits and monkeys. Excretion was primarily in the faeces of rats (75-90%), mice (65%) and monkeys (57-61%). In rabbits it was 50 % in faeces and 40 % in urine.

Ethinylestradiol is rapidly and completely absorbed form the gastrointestinal tract. The ethinyl substitution in the C17 position inhibits first-pass metabolism. Bioavailability of ethinylestradiol was found to be 40%. It is extensively bound to plasma proteins, mainly to albumin. Its peak plasma concentrations occur initially at 2 to 3 hours after oral ingestion. A second, 12-hour peak is thought to represent extensive enterohepatic circulation. Biological half-life is approximately 7.7 hours following a single oral therapeutic dose. Elimination half-life is established between 13 and 27 hours.

III.4 Toxicology

In laboratory animals, the effects of drospirenone and ethinylestradiol were confined to those associated with the recognised pharmacological action. In particular, reproduction toxicity studies revealed embryotoxic and fetotoxic effects in animals which are considered as species specific. At exposures exceeding those in users of drospirenone/ethinylestradiol, effects on sexual differentiation were observed in rat foetuses but not in monkeys.

III.5 Ecotoxicology/environmental risk assessment (ERA)

Since Arankelle Continuous film-coated tablets are intended for generic substitution, this will not lead to an increased exposure 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 drospirenone and ethinylestradiol are well known. As drospirenone and ethinylestradiol are well-known active substances, no further new non-clinical data are required and the applicant has not provided any.

Abridged applications avoid the need for repetitive tests on animals and humans.

IV. CLINICAL ASPECTS

IV.1 Introduction

This decentralized application concerns a generic version of drospirenone and ethinylestradiol 3 mg and 0.02 mg, under name of Arankelle Continuous. The originator product is Yasminelle film-coated tablet (Bayer Schering Pharma A.G., Germany.) has been authorised in Hungary since 2006.

Essential similarity to Yasminelle has been demonstrated for Arankelle Continuous film-coated tablets by the required bioequivalence study, and comparative tests on dissolution. As Arankelle Continuous film-coated tablets contain no new chemical entity, and this application is based on the claim for essential similarity, instead of further clinical studies conducted by the marketing authorisation applicant published scientific literature is summarised.

IV.2 Pharmacokinetics

To support the application, the applicant has submitted the report of one randomised two-treatment, two-period, two-sequence, single dose bioequivalence study with Arankelle Continuous 3 mg/0.02 mg film-coated tablets (test product, T) compared with Yasminelle from Bayer Schering Pharma A.G (reference, R), performed in healthy female subjects under fasting conditions.

The preparations were administered after an overnight fast with water.

Both drospirenone and ethinylestradiol were measured by high performance liquid chromatography coupled to tandem mass spectrometry. Full analytical validation reports are provided.

The following pharmacokinetic parameters were:

- primary variables: AUC_{0-t}, C_{max};
- secondary variables: AUC_{0-inf}, residual area, T_{max}, K_{el} and $T_{1/2\ el}$.

Pharmacokinetic parameters were summarized by treatment. Plasma concentrations were summarized by treatment and time point. Individual and mean plasma concentrations, as well as the plots of the plasma levels for all subjects *versus* time were graphically displayed for the two treatments. ANOVA was performed on ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} and untransformed K_{el} and $T_{1/2el}$. A non-parametric test (Wilcoxon's Signed-Rank test) was carried out to compare the T_{max} between treatments. Ratios of least-squares means and 90% geometric confidence intervals were calculated for ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max}. Inter- and intra-subject CVs were also calculated. Bioequivalence was to be concluded if the 90% geometric confidence intervals of the ratio (T/R) of least-squares means for ln-transformed AUC_{0-t} and C_{max} were within the acceptable range of 80% to 125% drospirenone and ethinylestradiol.

Results

Ratios, 90% geometric confidence intervals and intra-subject CVs (%) for AUC_{0-t}, AUC_{0-inf}, and C_{max} for drospirenone:

	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	102.82%	103.55%	96.60%
90 % Geometric C.I.[2]	100.25 % to 105.45 %	100.73 % to 106.45 %	92.52 % to 100.86 %
Intra-Subject CV	5.31 %	5.81 %	9.08 %

[1] Calculated using least-squares means according to the formula: $e^{(\text{Drospirenone-Ethinyl Estradiol (A) - Yasminelle Film-Coated Tablet (B)})} \times 100$
[2] 90% Geometric Confidence Interval using ln-transformed data

Ratios, 90% geometric confidence intervals and intra-subject CVs (%) for AUC_{0-t}, AUC_{0-inf}, and C_{max} for ethinylestradiol:

	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	104.64%	102.40%	108.17%
90 % Geometric C.I.[2]	100.91 % to 108.50 %	99.01 % to 105.91 %	102.81 % to 113.80 %
Intra-Subject CV	7.49 %	6.95 %	10.49 %

[1] Calculated using least-squares means according to the formula: $e^{(\text{Drospirenone-Ethinyl Estradiol (A) - Yasminelle Film-Coated Tablet (B)})} \times 100$
[2] 90% Geometric Confidence Interval using ln-transformed data

Based on these results, it can be concluded that the test Arankelle Continuous 3 mg/0.02 mg film-coated tablets are bioequivalent with the reference Yasminelle film-coated tablets under fasting conditions.

IV.3 Pharmacodynamics

The clinical pharmacology of drospirenone and ethinylestradiol is well known. No novel pharmacodynamic data are supplied or required for this application.

Mechanism of action and pharmacodynamic effects are as follows. The contraceptive effect of Arankelle Continuous 3 mg/ 0.02 mg 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.

Ethinylestradiol is a potent synthetic estrogen, closely related to the human estrogen, estradiol. It exerts its action by binding to the estrogen receptor, which is present in many different tissues. Drospirenone is an analogue of the antimineralocorticoid spironolactone with antimineralocorticoid, progestogenic and antiandrogenic activity

IV.4 Clinical efficacy

No new efficacy data have been submitted or required for these types of applications.

IV.5 Clinical safety

No new safety data have been submitted or required for these types of applications.

IV.6 Risk Management Plan

A Risk Management Plan for Arankelle Continuous 3 mg/0.02 mg film-coated tablets has been submitted by the applicant and accepted during the procedure.

Summary of safety concerns	
Important identified risk	Venous thromboembolism Arterial thromboembolism Breast cancer Benign and malignant liver tumours Disturbances of liver function Pancreatitis Increased blood pressure Induction or exacerbation of the symptoms of hereditary angioedema
Important potential risk	Cervical cancer Worsening of depression Worsening of Crohn's disease and ulcerative colitis Insulin resistance Hyperkalemia
Missing information	None

On-going and planned additional pharmacovigilance studies/activities

At present, no additional pharmacovigilance studies/activities are on-going.

Gedeon Richter Plc., working together with the other marketing authorisation holders concerned with this issue, agreed to participate in a joint survey to measure the effectiveness of the proposed additional risk minimisation activities (i.e. the success of providing and understanding all core communication and educational materials) regarding the safety concerns of venous

thromboembolism and arterial thromboembolism. Details of the joint survey-based study will be discussed with the National Competent Authorities in a further phase.

Summary of post-authorisation efficacy development plan

Not applicable, since no post-authorisation efficacy studies/activities are conducted or proposed.

Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Venous thromboembolism	Appropriate labelling (SmPC and Package Leaflet, PIL) Text in the SmPC: • Warnings in Section 4.1 regarding prescription for woman with current risk factors. • Prescence or risk of venous thromboembolism is listed as contraindication in Section 4.3. • Warnings and precaution measures regarding the development of venous thromboembolism in Section 4.4. • Venous thromboembolic disorders are also listed in Section 4.8. Prescription only medicine	• Direct Healthcare Professional Communication (DHPC)* • Questions & Answers for women** • Checklist for prescribers** • Information card for women** *The necessity and details of re-sending the DHPC letters will be agreed individually with each National Competent Authority if the products under the current marketing authorisation procedure of **Hiba! A hivatkozási forrás nem található.** are put on the market more than one year after the distribution of the initial DHPC letter in the given country **The need for the re-distribution of this material and details of this activity will be discussed individually with each National Competent Authority
Arterial thromboembolism	Appropriate labelling (SmPC and PIL) Text in the SmPC: • Warnings in Section 4.1 regarding prescription for woman with current risk factors. • Presence or risk of arterial thromboembolism is listed as contraindication in Section 4.3. • Warnings and precaution measures regarding the development of arterial thromboembolism in Section 4.4. • Arterial thromboembolic disorders are also listed in Section 4.8. Prescription only medicine	• Direct Healthcare Professional Communication (DHPC)* • Questions & Answers for women** • Checklist for prescribers** • Information card for women** * The necessity and details of re-sending the DHPC letters will be agreed individually with each National Competent Authority if the products under the current marketing authorisation procedure of **Hiba! A hivatkozási forrás nem található.** are put on the market more than one year after the distribution of the initial DHPC letter in the given country **The need for the re-distribution of this material and details of this activity will be dis-

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
		cussed individually with each National Competent Authority
Breast cancer	Appropriate labelling (SmPC and PIL) Text in the SmPC: • Known or suspected sex-steroid influenced malignancies of the breast are listed as contraindications in Section 4.3. • Section 4.4 contains epidemiological data regarding the occurrence of breast cancer. • Breast cancer is listed in Section 4.8. Prescription only medicine	No additional risk minimisation activities are planned
Benign and malignant liver tumours	Appropriate labelling (SmPC and PIL) *Text in SmPC:* Presence or history of liver tumours is highlighted as contraindication in ***Section 4.3.*** ***Section 4.4*** contains data regarding development of liver tumours. Liver tumour is listed in ***Section 4.8.*** Prescription only medicine	No additional risk minimisation activities are planned

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Disturbances of liver function	Appropriate labelling (SmPC and PIL) Text in SmPC: • Presence or history of severe hepatic disease is highlighted as contraindication in Section 4.3. • Warnings in Section 4.4 regarding liver function disturbances. • Acute or chronic disturbances of liver function are listed in Section 4.8. • Section 5.2 contains pharmacokinetic data regarding subjects with hepatic impairment. Prescription only medicine	No additional risk minimisation activities are planned
Pancreatitis	Appropriate labelling (SmPC and PIL) Text in SmPC: Section 4.4 contains data regarding the development of pancreatitis. Prescription only medicine	No additional risk minimisation activities are planned
Increased blood pressure	Appropriate labelling (SmPC and PIL) Text in SmPC: • Severe hypertension is listed as contraindication in Section 4.3. • Warnings in Section 4.4 regarding blood pressure increase in women taking CHCs. • Hypertension is also listed in Section 4.8. Prescription only medicine	No additional risk minimisation activities are planned

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Induction or exacerbation of the symptoms of hereditary angioedema	Appropriate labelling (SmPC and PIL) Text in SmPC: • Warnings in Section 4.4 regarding possible induction or exacerbation of the symptoms of hereditary angioedema. • Angioedema and induction or exacerbation of hereditary angioedema is listed in Section 4.8. Prescription only medicine	No additional risk minimisation activities are planned
Cervical cancer	Appropriate labelling (SmPC and PIL) Text in SmPC: • Known or suspected sex-steroid influenced malignancies or undiagnosed vaginal bleeding are listed as contraindication in Section • Section 4.4 contains epidemiological data regarding the occurrence	No additional risk minimisation activities are planned
	of cervical cancer. • Suspicious Papanicolaou smear is listed in Section 4.8. Prescription only medicine	
Worsening of depression	Appropriate labelling (SmPC and PIL) Text in SmPC: • Warning in Section 4.4 regarding the possibility of worsening of depression during COC use. • Depression, nervousness, emotional lability and sleep disorder are listed in Section 4.8. Prescription only medicine	No additional risk minimisation activities are planned

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Worsening of Crohn's disease and ulcerative colitis	Appropriate labelling (SmPC and PIL) Text in SmPC: • Warning in Section 4.4 regarding worsening of Chron's disease and ulcerative colitis. • Worsening of Chron's disease and ulcerative colitisare are listed in Section 4.8. Prescription only medicine	No additional risk minimisation activities are planned
Insulin re-sistance	Appropriate labelling (SmPC) Text in SmPC: warnings in Section 4.4 regarding peripherial insulin re-sistance, glucose tolerance and treat-ment of diabetic women. Prescription only medicine	No additional risk minimisation activities are planned
Hyperkalemia	Appropriate labelling (SmPC and PIL) Text in SmPC: • Severe renal insufficiency or acute renal failure is listed as con-traindication in Section 4.3. • Warnings in Section 4.4, Section 4.5 and Section 5.2 regarding pa	No additional risk minimisation activities are planned
	tients with renal impairment and the concomitant admin-istration of this product with potassium sparing medicines. Prescription only medicine	

IV.7 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

Abridged applications avoid the need for repetitive tests on animals and humans. For these applications the bioequivalence studies described in Section IV.2 are pivotal.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

V.1 Summary

The present applications concerns Arankelle Continuous (drospirenone/ethinylestradiol) 3 mg/0.02 mg film-coated tablets. The applicant and the future holder of authorisation is Gedeon Richter Plc.

The product is indicated for the prevention of pregnancy in women who select to use an oral contraceptive.

The application was submitted in accordance with Article 10(1) of Directive 2001/83/EEC (i.e. generic application), proving the bioequivalence with Yasminelle film-coated tablets of drospirenone and ethinylestradiol active ingredients, products of Bayer Schering Pharma A.G., Germany. The application contains also an adequate review of published non-clinical and clinical data.

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 (Hungary as RMS, Belgium, Finland, Luxemburg and Romania as CMSs) have granted marketing authorisation for Arankelle Continuous 3 mg/0.02 mg film-coated tablets (in Belgium and Luxemburg Arankellecont, in Finland MaitalonCont, in Romania Daylla Zilnic) from Gedeon Richter Plc.

V.2 Legal status

Prescription-only medicine.

V.3 Package Leaflet and user consultation

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*.

National Institute of Pharmacy
Directorate of GYEMSZI
Budapest, Hungary

Public Assessment Report Number:
HU/H/0150/003/DC

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