Public Assessment Report

Name of the Product:

Voriconazole Richter

50 mg, 200 mg film-coated tablets

(voriconazole)

Procedure number: HU/H/0365/001-002/DC

Marketing authorisation holder: Gedeon Richter Plc.

Date: 4 August 2015
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UPGRADE: STEPS TAKEN AFTER THE INITIAL PROCEDURE WITH AN INFLUENCE ON THE PUBLIC ASSESSMENT REPORT
LAY SUMMARY

After careful assessment of its quality and therapeutic benefit/risk ratio, the member states have granted the marketing authorisation of the Voriconazole Richter 50 mg and 200 mg film-coated tablets. The holder of the marketing authorisation is Gedeon Richter Plc. in Hungary, Czech Reupublic, Slovakia, Bulgaria, Latvia and Lithuania, Gedeon Richter Polska Sp. z o.o. in Poland and Gedeon Richter România S.A. in Romania.

The active substance is voriconazole. Each tablet contains either 50 mg or 200 mg voriconazole.

The other ingredient are:
- core: lactose monohydrate, pregelatinized maize starch, croscarmellose sodium, povidone K-25 and magnesium stearate;
- coating: hypromellose E5, lactose monohydrate, triacetin and titanium dioxide (E171).

The 50 mg film-coated tablets are white to off white, round, approximately 7.0 mm in diameter, debossed with 'V50' on one side and plain on the other side.

The 200 mg film-coated tablets are white to off white, oval, approximately 15.6 mm in length and 7.8 mm in width, debossed with 'V200' on one side and plain on the other side.

In case of both strengths, 10 or 14 film-coated tablets are packed in clear PVC / Aluminium blisters pack comprises clear transparent PVC film and hard tampered aluminium foil as lidding foil. One, two or three blisters are packed in a carton along with package leaflet.

Voriconazole is an antifungal agent. It works by killing or stopping the growth of the fungi that cause infections.

Voriconazole Richter film-coated tablets are used for the treatment of patients (adults and children aged 2 years and above) with:
- invasive aspergillosis (a type of fungal infection due to Aspergillus sp.),
- candidaemia (another type of fungal infection due to Candida sp.) in non-neutropenic patients (patients without abnormally low white blood cells count),
- serious invasive Candida sp. infections when the fungus is resistant to fluconazole (another antifungal medicine),
- serious fungal infections caused by Scedosporium species or Fusarium species (two different groups of fungi).

Voriconazole Richter tablets are intended for patients with worsening, possibly life-threatening, fungal infections.

Their indication comprises also prevention of fungal infections in high risk bone marrow transplant recipients.

This product should only be taken under the supervision of a doctor.
What patients need to know before taking Voriconazole Richter?

Those who are allergic to voriconazole or any of the other ingredients of this medicine should not take it.

It is very important that patients inform their doctor if taking or have taken any other medicines, even those that are obtained without a prescription, or herbal products.

The medicines in the following list must not be taken during the course of Voriconazole Richter treatment:
- terfenadine (used for allergy),
- astemizole (used for allergy),
- cisapride (used for stomach problems),
- pimozide (used for treating mental illness),
- quinidine (used for irregular heart beat),
- rifampicin (used for treating tuberculosis),
- efavirenz (used for treating HIV) in doses of 400 mg and above once daily,
- carbamazepine (used to treat seizures),
- phenobarbital (used for severe insomnia and seizures),
- ergot alkaloids (e.g., ergotamine, dihydroergotamine; used for migraine),
- sirolimus (used in transplant patients),
- ritonavir (used for treating HIV) in doses of 400 mg and more twice daily,
- St. John’s Wort (herbal supplement for the treatment of depression).

Warnings and precautions

Patients should talk to their doctor before taking Voriconazole Richter if:
- they have had an allergic reaction to other azoles;
- they are suffering from, or have ever suffered from liver disease. If the patient has liver disease, the doctor may prescribe a lower dose of voriconazole and should also monitor the liver function while the patient is being treated with Voriconazole Richter by doing blood tests;
- they are known to have cardiomyopathy, irregular heartbeat, slow heart rate or an abnormality of electrocardiogram (ECG) called ‘long QTc syndrome’.

The patients should avoid any sunlight and sun exposure while being treated. It is important to cover sun exposed areas of skin and use sunscreen with high sun protection factor (SPF), as an increased sensitivity of skin to the sun’s UV rays can occur. These precautions are also applicable to children.

While being treated with Voriconazole Richter, the patient should inform the doctor immediately developing:
- sunburn,
- severe skin rash or blisters,
- bone pain.

If the patient develops skin disorders as described above, the doctor may refer him/her to a
A dermatologist, who after consultation may decide that it is important for the patient to be seen on a regular basis. There is a small chance that skin cancer could develop with long-term use of Voriconazole Richter.

The doctor should monitor the function of the liver and kidney by doing blood tests.

**Children and adolescents**

Voriconazole should not be given to children younger than 2 years of age. Since the recommended dose regimen of voriconazole initiates the therapy with intravenous loading dose regimen in children below the age of 12, this medicinal product is not suitable alone for the treatment of this subset of the paediatric population. Young teenagers aged 12 to 14 years may be treated with Voriconazole Richter if their body weight is 50 kg or more. Adolescents older than 14 years should take the same dose as adults.

**Other medicines and Voriconazole Richter**

Patients should inform their doctor if they are taking, have recently taken or might take any other medicines. Certain medicines, when taken at the same time as Voriconazole Richter, may affect the way voriconazole works. Similarly, Voriconazole Richter may affect the way they work.

Patients should inform their doctor if taking the following medicine, as treatment with Voriconazole Richter at the same time should be avoided if possible: ritonavir (used for treating HIV) in doses of 100 mg twice daily.

Patients should inform their doctor if taking any of the following medicines, as treatment with Voriconazole Richter at the same time should be avoided if possible, and a dose adjustment of voriconazole may be required:
- rifabutin (used for treating tuberculosis). If the patient is already being treated with rifabutin, the blood counts and side effects to rifabutin will need to be monitored;
- phenytoin (used to treat epilepsy). If the patient is already being treated with phenytoin, the blood concentration of phenytoin will need to be monitored during the treatment with Voriconazole Richter and its dose may be adjusted.

Patients should inform their doctor if taking any of the following medicines, as a dose adjustment or monitoring may be required to check that the medicines and/or Voriconazole Richter still have the desired effect:
- warfarin and other anticoagulants (e.g., phenprocoumon, acenocoumarol; used to slow down clotting of the blood),
- ciclosporin (used in transplant patients),
- tacrolimus (used in transplant patients),
- sulphophylureas (e.g., tolbutamide, glipizide, and glyburide, used for diabetes),
- statins (e.g., atorvastatin, simvastatin, used for lowering cholesterol),
- benzodiazepines (e.g., midazolam, triazolam, used for severe insomnia and stress),
- omeprazole (used for treating ulcers),
- oral contraceptives (if taking Voriconazole Richter whilst using oral contraceptives, the
patient may get side effects such as nausea and menstrual disorders),
- Vinca alkaloids (e.g., vincristine and vinblastine, used in treating cancer),
- indinavir and other HIV protease inhibitors (used for treating HIV),
- non-nucleoside reverse transcriptase inhibitors (e.g., efavirenz, delavirdine, nevirapine, used for treating HIV, certain doses of efavirenz can NOT be taken at the same time as Voriconazole Richter),
- methadone (used to treat heroin addiction),
- alfentanil, fentanyl and other short-acting opiates such as sufentanil (painkillers used for surgical procedures),
- oxycodone and other long-acting opiates such as hydrocodone (used for moderate to severe pain),
- non-steroidal anti-inflammatory drugs (e.g., ibuprofen, diclofenac, used for treating pain and inflammation),
- fluconazole (used for fungal infections),
- everolimus (used for treating advanced kidney cancer and in transplant patients).

**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.

Voriconazole Richter must not be taken during pregnancy, unless indicated by the doctor.

Effective contraception must be used in women of childbearing potential. Women has to contact their doctor immediately if they become pregnant while taking Voriconazole Richter.

**Driving and using machines**

Voriconazole Richter may cause blurring of vision or uncomfortable sensitivity to light. While affected, patients must not drive or operate any tools or machines. Whenever experiences this, the doctor should be contacted.

**Voriconazole Richter contains milk sugar (lactose)**

Those who have been told by their doctor that they have an intolerance to some sugars, should consult their doctor before taking this medicinal product.

**How to take Voriconazole Richter?**

The tablet should be taken at least one hour before, or one hour after a meal, swallowing it whole with some water.

The doctor will determine the dose depending on the weight and the type of infection the patient has.

The recommended dose for adults (including elderly patients) is as follows:
### Tablets

<table>
<thead>
<tr>
<th></th>
<th>Patients 40 kg and above</th>
<th>Patients less than 40 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose for the first 24 hours</strong> (Loading dose)</td>
<td>400 mg every 12 hours for the first 24 hours</td>
<td>200 mg every 12 hours for the first 24 hours</td>
</tr>
<tr>
<td><strong>Dose after the first 24 hours</strong> (Maintenance dose)</td>
<td>200 mg twice a day</td>
<td>100 mg twice a day</td>
</tr>
</tbody>
</table>

Depending on the response to the treatment, the doctor may increase the daily dose to 300 mg twice a day.

The doctor may decide to decrease the dose if the patient has mild to moderate cirrhosis.

**Use in children and adolescents**

The recommended dose for children and teenagers is as follows:

<table>
<thead>
<tr>
<th></th>
<th>Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose for the first 24 hours</strong> (Loading dose)</td>
<td>Children aged 2 to less than 12 years and teenagers aged 12 to 14 years weighing less than 50 kg: The treatment will be started as an infusion. Teenagers aged 12 to 14 years weighing 50 kg or more; and all teenagers older than 14: 400 mg every 12 hours for the first 24 hours</td>
</tr>
<tr>
<td><strong>Dose after the first 24 hours</strong> (Maintenance dose)</td>
<td>9 mg/kg twice a day (a maximum dose of 350 mg twice daily)</td>
</tr>
</tbody>
</table>

Depending on the response to the treatment, your doctor may increase or decrease the daily dose.

Tablets must only be given if the child is able to swallow tablets.

If the patient (either an adult or a child) takes Voriconazole Richter for prevention of fungal infections, the doctor may stop giving it if the patient develops treatment-related side effects.

**What to do if more Voriconazole Richter tablets have been taken than it should be?**

Having taken more tablets than prescribed (or if someone else takes the patient’s tablets) he/she must seek medical advice or go to the nearest hospital casualty department immediately taking the box of Voriconazole Richter with him/her. Taking more Voriconazole Richter than prescribed the patient may experience abnormal intolerance to light.

**What to do if taking Voriconazole Richter has been forgotten?**

It is important to take Voriconazole Richter tablets regularly at the same time each day. If the
patient forgets to take one dose, the next dose should be taken when it is due. No double dose should be taken to make up for a forgotten dose.

*May taking Voriconazole Richter be stopped by the patient?*

It has been shown that taking all doses at the appropriate times may greatly increase the effectiveness of this medicine. Therefore, unless the doctor instructs the patient to stop treatment, it is important to keep taking Voriconazole Richter correctly, as described above.

Consequently, patients should continue taking these medicine until the doctor tells to stop. Patients should not stop treatment early because the infection may not be cured this way. Patients with a weakened immune system or those with difficult infections may require long-term treatment to prevent the infection from returning.

When Voriconazole Richter treatment is stopped by the doctor the patient should not experience any effects.

**Possible side effects**

Like all medicines, Voriconazole Richter can cause side effects, although not everybody experiences them.

If any side effects occur, most of them are likely to be minor and temporary. However, some may be serious and need medical attention.

*Serious side effects* – taking Voriconazole Richter should be stopped and visit a doctor immediately, if any of the following occurs:
- rash,
- jaundice,
- changes in blood tests of liver function,
- pancreatitis.

*Other side effects*

Very common side effects (may affect more than 1 in 10 people) are:
- visual disturbances (change in vision),
- fever,
- nausea, vomiting, diarrhoea,
- headache,
- swelling of the extremities,
- stomach pains,
- breathing difficulties.

Common side effects (may affect up to 1 in 10 people) are:
- flu-like symptoms, irritation and inflammation of the gastrointestinal tract, inflammation of the sinuses, inflammation of the gums, chills, weakness,
- low numbers of some types of red or white blood cells, low numbers of cells called platelets that help the blood to clot,
- allergic reaction or exaggerated immune response,
- low blood sugar, low blood potassium, low sodium in the blood,
- anxiety, depression, confusion, agitation, inability to sleep, hallucinations,
- seizures, tremors or uncontrolled muscle movements, tingling or abnormal skin sensations, increase in muscle tone, sleepiness, dizziness,
- bleeding in the eye,
- heart rhythm problems including very fast heartbeat, very slow heartbeat, fainting,
- low blood pressure, inflammation of a vein (which may be associated with the formation of a blood clot),
- breathing difficulty, chest pain, swelling of the face, fluid accumulation in the lungs,
- constipation, indigestion, inflammation of the lips,
- jaundice, inflammation of the liver, redness of the skin,
- skin rashes which may lead to severe blistering and peeling of the skin characterized by a flat, red area on the skin that is covered with small confluent bumps,
- itchiness,
- hair loss,
- back pain
- kidney failure, blood in the urine, changes in kidney function tests.

Uncommon side effects (may affect up to 1 in 100 people) are:
- inflammation of the gastrointestinal tract causing antibiotic associated diarrhoea, inflammation of the lymphatic vessels,
- inflammation of the thin tissue that lines the inner wall of the abdomen and covers the abdominal organ,
- enlarged lymph glands (sometimes painful), disorder of blood clotting system, failure of blood marrow, other blood cell changes (increased eosinophil and low white blood cells in blood),
- depressed function of the adrenal gland, underactive thyroid gland,
- abnormal brain function, Parkinson-like symptoms, nerve injury resulting in numbness, pain, tingling or burning in the hands or feet,
- problem with coordination,
- swelling of the brain,
- double vision, serious conditions of the eye including: pain and inflammation of the eyes and eyelids, involuntary movement of the eye, abnormal eye movement, damage to the optic nerve resulting in vision impairment, optic disc swelling,
- decreased sensitivity to touch,
- abnormal sense of taste,
- hearing difficulties, ringing in the ears, vertigo,
- inflammation of certain internal organs - pancreas and duodenum, swelling and inflammation of the tongue,
- enlarged liver, liver failure, gallbladder disease, gallstones,
- joint inflammation, inflammation of the veins under the skin (which may be associated with the formation of a blood clot),
- inflammation of the kidney, proteins in the urine,
- very fast heart rate or skipped heartbeats,
- abnormal electrocardiogram (ECG),
- blood cholesterol increased, blood urea increased,
- allergic skin reactions (sometimes severe), including widespread blistering rash and skin peeling, inflammation of the skin, the rapid swelling (oedema) of the dermis, subcutaneous tissue, mucosa and submucosal tissues, itchy or sore patches of thick, red skin with silvery scales of skin, hives, sunburn or severe skin reaction following exposure to light or sun, skin redness and irritation, red or purple discoloration of the skin which may be caused by low platelet count, eczema
- life-threatening allergic reaction.

Rare side effects (may affect up to 1 in 1,000 people) are:
- overactive thyroid gland,
- deterioration of brain function that is a serious complication of liver disease,
- damage to the optic nerve resulting in vision impairment, clouding of the cornea,
- bullous photosensitivity,
- a disorder in which the body’s immune system attacks part of the peripheral nervous system
- severe heart rhythm problems that may be life–threatening.

Other significant side effects whose frequency is not known, but should be reported to the doctor immediately:
- skin cancer,
- inflammation of the tissue surrounding the bone,
  red, scaly patches or ring-shaped skin lesions that may be a symptom of an autoimmune disease called cutaneous lupus erythematosus.

As Voriconazole Richter has been known to affect the liver and the kidney, the doctor should monitor the function of the liver and kidney by doing blood tests. Patients must inform their doctor if they have any stomach pains or if their stools have a different consistency.

There have been reports of skin cancer in patients treated with voriconazole for long periods of time.

Sunburn or severe skin reaction following exposure to light or sun was experienced more frequently in children. If the patient (adult or a child) develops skin disorders, the doctor may refer him/her to a dermatologist, who after consultation may decide that it is important for the patient to be seen on a regular basis.

**How to store Voriconazole Richter?**

This medicine does not require any special storage conditions but keep it out of the sight and reach of children.
Scientific discussion
during the initial phase

This module reflects the scientific discussion for the approval of Voriconazole Richter 50 mg, 200 mg film-coated tablets. The procedure was finalised at 1 June 2015. 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: Bulgaria, the Czech Republic, Latvia, Lithuania, Poland, Romania and the Slovak Republic) concerned the generic version of voriconazole 50 mg and 200 mg film-coated tablets (Voriconazole Richter tablets).

The application has been submitted according to Article 10(1) of 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 (as amended, e.g. a generic application). Therefore, it contained no new non-clinical and clinical data, other than the bioequivalence study as well as supporting literature where necessary, in accordance with the provisions of the article indicated above.

The applicant has adequately demonstrated bioequivalence between Voriconazole Richter film-coated tablets and the reference products. The latter have been Vfend® 50 mg and 200 mg film-coated tablets marketed by Pfizer Ltd., approved for more than 10 years within the European Economic Area.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisation for Voriconazole Richter 50 mg and 200 mg film-coated tablets from Richter Gedeon Plc.

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

Voriconazole is a broad spectrum, triazole antifungal agent and is indicated in adults and children aged 2 years and above as follows:
- treatment of invasive aspergillosis,
- treatment of candidemia in non-neutropenic patients,
- treatment of fluconazole-resistant serious invasive Candida infections (including C. krusei),
- treatment of serious fungal infections caused by Scedosporium spp. and Fusarium spp.

Voriconazole Richter film-coated tablets should be administered primarily to patients with progressive, possibly life-threatening infections.

They are also indicated for prophylaxis of invasive fungal infections in high risk allogeneic hematopoietic stem cell transplant (HSCT) recipients.

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

II.1 Introduction

This chemical-pharmaceutical assessment report concerns the application of Voriconazole Richter 50 mg and 200 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 products have been Vfend film-coated tablets (containing 50 mg and 200 mg voriconazole as active ingredient), the original products of Pfizer Limited.

II.2 Drug substance

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

INN name: voriconazole
Chemical name: (2R,3S)-2-(2,4-Difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1H-1,2,4-triazol-1-yl)-butan-2-ol
Structure:

The active substance is white or almost white powder, freely soluble in acetone and in methylene chloride and very slightly soluble in water. 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 Ph. Eur. monograph, additional specification has only been set for residual solvents, polymorphic identity, particle size distribution, microbial impurities and some heavy metal content.

The Ph. Eur. specification includes the following tests for voriconazole: appearance, solubility, identification (IR and enantiomeric purity by HPLC), clarity and colour of solution, related substances, water, sulphated ash, heavy metals and assay of voriconazole.
Testing methods not described in details in the Pharmacopoeia 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 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.

A retest period and the packaging material [double polyethylene bag (outer black) in a triple laminated bag (polyethylene/aluminium/polyester) placed in a polyethylene container]] have been mentioned on the CEP.

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

II.3 Medicinal product

The aim was to develop film-coated tablets containing voriconazole as drug substance in 50 mg and 200 mg doses, pharmaceutically equivalent and bioequivalent to the reference medicinal product Vfend 50 mg and 200 mg film-coated tablets, the branded original products of Pfizer.

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 product with the following appearance, composition and packaging was obtained.

Voriconazole Richter 50 mg film-coated tablets are white to off white, round, approximately 7.0 mm in diameter film-coated tablets, debossed with "V50" on one side and plain on the other side.

Voriconazole Richter 200 mg film-coated tablets are white to off white, oval, approximately 15.6 mm in length and 7.8 mm in width film-coated tablets, debossed with 'V200' on one side and plain on the other side.

The excipients used in the finished product are magnesium stearate, povidone K25, croscarmellose sodium, pregelatinised maize starch, lactose monohydrate, titanium dioxide (E171), tri-
acetin and hypromellose E5. 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 International Conference on Harmonisation (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, including the batch used in the bioequivalence study.

The container closure system of the product is PVC//Al blister in box. 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 3 years with no special storage conditions 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 products have been shown to meet the current regulatory requirements with regards to their 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 quality points of view the products are approvable.
III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of voriconazole are well known. As it is a generic application based on bioequivalence studies and voriconazole is a widely used, well-known active substance, no further studies are required and the applicant provides none. The non-clinical overview is therefore based on a review of data available in several scientific databases or published in relation to the active substance, voriconazole.

III.2 Pharmacology

The Voriconazole Richter film-coated tablets contain the active substance voriconazole. It is a broad-spectrum, triazole antifungal agent. Voriconazole is indicated in adults and children aged 2 years and above in treatment of invasive aspergillosis, treatment of candidaemia in non-neutropenic patients, treatment of fluconazole-resistant serious invasive Candida infections (including C. krusei), treatment of serious fungal infections caused by Scedosporium spp. and Fusarium spp.. Voriconazole should be administered primarily to patients with progressive, possibly life-threatening infections. It is also indicated in prophylaxis of invasive fungal infections in high risk allogeneic hematopoietic stem cell transplant (HSCT) recipients.

The active substance is a well-known compound. No further information was provided regarding the experimental pharmacology of voriconazole.

III.3 Pharmacokinetics

No new non-clinical pharmacokinetic studies were conducted by the applicant. Such studies are not needed for this type of application.

III.4 Toxicology

Published information on toxicological studies with voriconazole was the basis for the evaluation.

No new toxicity studies were submitted by the Applicant for the product, which is acceptable for this type of application.

III.5 Ecotoxicology/environmental risk assessment (ERA)

Since Voriconazole Richter 50 mg and 200 mg 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

Abridged applications avoid the need for repetitive tests on animals.

Pharmacodynamics, pharmacokinetics and toxicology of voriconazole are well-known. As Voriconazole Richter film-coated tablets are generic products, there is no need for further excessive non-clinical studies.

The non-clinical part of the application is acceptable.
IV. CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology of voriconazole is well known.

Except for demonstrating bioequivalence, no specific clinical studies have been performed, as the application is submitted in accordance with Article 10(1) of Directive 2001/83/EC as amended.

The application contains an adequate review of published clinical data.

IV.2 Pharmacokinetics

IV.2.1 Literature data

Voriconazole is rapidly and almost completely absorbed following oral administration, with maximum plasma concentrations ($C_{max}$) achieved 1-2 hours after dosing. The absolute bioavailability of voriconazole after oral administration is estimated to be 96%. When multiple doses of voriconazole are administered with high fat meals, $C_{max}$ and $AUC_t$ are reduced by 34% and 24%, respectively. The absorption of voriconazole is not affected by changes in gastric pH.

The volume of distribution at steady state for voriconazole is estimated to be 4.6 l/kg, suggesting extensive distribution into tissues. Plasma protein binding is estimated to be 58%. Cerebrospinal fluid samples from eight patients in a compassionate programme showed detectable voriconazole concentrations in all patients.

In vitro studies showed that voriconazole is metabolised by, the hepatic cytochrome P450 isoenzymes, CYP2C19, CYP2C9 and CYP3A4.

The inter-individual variability of voriconazole pharmacokinetics is high.

In vivo studies indicated that CYP2C19 is significantly involved in the metabolism of voriconazole. This enzyme exhibits genetic polymorphism. For example, 15-20% of Asian populations may be expected to be poor metabolisers. For Caucasians and Blacks the prevalence of poor metabolisers is 3-5%. Studies conducted in Caucasian and Japanese healthy subjects have shown that poor metabolisers have, on average, 4-fold higher voriconazole exposure ($AUC_t$) than their homozygous extensive metaboliser counterparts. Subjects who are heterozygous extensive metabolisers have on average 2-fold higher voriconazole exposure than their homozygous extensive metaboliser counterparts.

The major metabolite of voriconazole is the N-oxide, which accounts for 72% of the circulating radio-labelled metabolites in plasma. This metabolite has minimal antifungal activity and does not contribute to the overall efficacy of voriconazole.
Voriconazole is eliminated via hepatic metabolism with less than 2% of the dose excreted unchanged in the urine.

After administration of a radiolabelled dose of voriconazole, approximately 80% of the radioactivity is recovered in the urine after multiple intravenous dosing and 83% in the urine after multiple oral dosing. The majority (>94%) of the total radioactivity is excreted in the first 96 hours after both oral and intravenous dosing.

The terminal half-life of voriconazole depends on dose and is approximately 6 hours at 200 mg (orally). Because of non-linear pharmacokinetics, the terminal half-life is not useful in the prediction of the accumulation or elimination of voriconazole.

**IV.2.2 Bioequivalence study**

The development studies focused on obtaining a product having similar characteristics to the reference product, i.e. dissolution profile and bioavailability.

Essential similarity was demonstrated by means of a pivotal bioequivalence study between the test product and reference product. The study has demonstrated that a single oral dose of the applicant’s voriconazole 200 mg film-coated tablets is bioequivalent to a single oral dose of Vfend 200 mg film-coated tablets.

Similarities of in-vitro dissolution profiles were also justified. Dissolution study was performed for the 2 strengths.

**Biowaiver**

The applicant claimed biowaiver for the 50 mg dose strength on the basis of general biowaiver requirements (CPMP/EWP/QWP/1401/98 Rev 1 Corr**):

a) both strengths (50 and 200 mg) of proposed pharmaceutical products are manufactured by the same manufacturer and using the same manufacturing process;

b) the qualitative composition of Voriconazole Richter 50 mg film-coated tablets is the same as that of Voriconazole Richter 200 mg film-coated tablets;

c) the composition of both strengths are quantitatively proportional, i.e. the ratio between the amounts of each excipient to the amount of active substance is the same for both strengths;

d) the in vitro dissolution profiles are similar under identical conditions for the additional strengths, i.e. 50 mg and the strength of the batch used in the bioequivalence study, i.e. 200 mg;

e) Voriconazole exhibits non-linear pharmacokinetics by a more than proportional increase in AUC.

The biowaiver claim for the 50 mg dose-strengths is justified as general requirements for biowaiver are completely fulfilled.

*The study*
The pivotal bioequivalence study was performed at the strength of 200 mg in line with the requirement of bioequivalence guideline in force (CPMP/EWP/QWP/1401/98 Rev 1 Corr**).

Its main objective was to compare the rate and extent of absorption of voriconazole from the applicant’s 200 mg film-coated tablet (Test) versus Vfend 200 mg film-coated tablet (Reference) administered under fasting conditions.

The bioequivalence study was designed as an open label, balanced, randomised, two-treatment, two-period, two-sequence, single dose, crossover, comparative oral bioequivalence study of two formulations of voriconazole 200 mg tablets in normal, healthy, adult human subjects under fasting conditions.

The voriconazole was determined using a validated method in plasma samples.

Incurred sample reanalysis (ISR) was performed according to the guideline on bioanalytical method validation (EMA/CHMP/EWP/192217/2009, 21 July 2011). Results of the ISR met the acceptance criteria.

All statistical tests were evaluated at the 95% significance level (α=0.05).

All continuous variables were summarized by the usual descriptive statistics: mean, median, minimum, maximum, standard deviation (SD), range.

Demographic parameters were summarized descriptively.

The bioequivalence study was undertaken according to GCP guidelines. No issues regarding GLP or GCP aspects have been identified during the review of this dossier.

Bioequivalence was to be concluded if the 90% geometric confidence intervals of the ratio (T/R) of least-squares means for ln-transformed AUC\(_{0-t}\), AUC\(_{0-\infty}\) and \(C_{\text{max}}\) were within the acceptable range of 80.00% to 125.00%. The results are presented in the Table below.

### Summary of the study results

<table>
<thead>
<tr>
<th>Pharmacokinetic parameters</th>
<th>Ln-transformed Geometric Least Squares Mean Ratio (T/R) %</th>
<th>90% Confidence Intervals (Parametric)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(C_{\text{max}})</td>
<td>90.7</td>
<td>82.32 - 99.89</td>
</tr>
<tr>
<td>AUC(_{0-t})</td>
<td>95.9</td>
<td>91.72 - 100.17</td>
</tr>
<tr>
<td>AUC(_{0-\infty})</td>
<td>95.5</td>
<td>91.67 - 99.50</td>
</tr>
</tbody>
</table>
Conclusion on bioequivalence studies

Results derived from the analysis of log-transformed primary target parameters, $C_{\text{max}}$ and $\text{AUC}_{0-72}$ parameters for voriconazole, the T/R ratios of group means and their 90% confidence intervals were also included within the acceptance range of 80% - 125%. Thus, results support the bioequivalence between the test and reference products.

Based on the clinical laboratory assessments, it can be concluded that both study medications were relatively well tolerated by subjects involved in the study.

Based on the submitted bioequivalence study Voriconazole Richter 200 mg film-coated tablets (Richter Gedeon Plc.) is considered bioequivalent with Vfend 200 mg film-coated tablets (Pfizer Ltd.).

The results of study with 200 mg film-coated tablets formulation can be extrapolated to the other strength 50 mg according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*

IV.3 Pharmacodynamics

No clinical pharmacology studies to evaluate the pharmacodynamics of Voriconazole Richter 50 mg and 200 mg film-coated tablets were performed.

IV.4 Clinical efficacy

No new efficacy data have been submitted and none are required. The applicant has provided an adequate review of clinical trials published in the literature, describing the efficacy and safety profile of voriconazole.

IV.5 Clinical safety

With the exception of the data generated during the bioequivalence studies, no new safety data were submitted and none were required for this application.

No serious or severe adverse events were reported in the bioequivalence study. Thus, the formulations were well tolerated, with no major side effects. No relevant differences in safety profiles were observed between the preparations, particularly with respect to the number of adverse events.

IV.6 Pharmacovigilance

IV.6.1 Summary of the Pharmacovigilance System
The applicant has submitted a signed Summary of the Applicant's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation 520/2012 and as detailed in the relevant GVP module, the Summary is considered acceptable.

**IV.6.2 Risk Management Plan**

<table>
<thead>
<tr>
<th>Summary of safety concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Important identified risks</td>
</tr>
<tr>
<td>Phototoxicity</td>
</tr>
<tr>
<td>Squamous cell carcinoma (SCC)</td>
</tr>
<tr>
<td>Hepatic toxicity</td>
</tr>
<tr>
<td>QTc prolongation</td>
</tr>
<tr>
<td>Visual events</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
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<tr>
<td>Important potential risks</td>
</tr>
<tr>
<td>Skin cancer (non-SCC)</td>
</tr>
<tr>
<td>Suicide-related events</td>
</tr>
<tr>
<td>Missing information</td>
</tr>
<tr>
<td>Effects in pregnancy</td>
</tr>
<tr>
<td>Effects in paediatrics</td>
</tr>
<tr>
<td>Off-label use</td>
</tr>
<tr>
<td>Resistance</td>
</tr>
</tbody>
</table>

*Pharmacovigilance Plan:* routine pharmacovigilance is sufficient to characterise the risks of the product and to monitor the effectiveness of the risk minimisation measures. At the moment no additional pharmacovigilance activity is warranted.

*Risk Minimisation Measures:* the originator products have additional risk minimisation measures (educational materials for healthcare professionals and for patients) relating to the risks of phototoxicity, SCC and hepatic toxicity.

Since in Hungary the originator has distributed these educational materials recently, routine risk minimisation measures (i.e. wording in SmPC, patient information (package) leaflet and classification as a prescription-only medicine) are considered sufficient to manage all of the safety concerns connected to the voriconazole products of Gedeon Richter Plc. No additional activities are requested.

**IV.6.3 Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports (PSURs) for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of the Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Currently, no routine PSUR reporting is required for generic products containing voriconazole.
IV.7 Discussion on the clinical aspects

The application concerns a generic product. Abridged applications avoid the need for repetitive tests on animals and humans. For these application the bioequivalence studies described in section IV.2 are pivotal.

To support the application the Applicant has adequately demonstrated bioequivalence between Voriconazole Richter 50 mg and 200 mg film-coated tablets and the reference product Vfend 50 mg and 200 mg film-coated tablets.

There is no objection against granting the marketing authorization from a clinical point of view.
V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

V.1 Summary

The present application concerns Voriconazole Richter 50 mg and 200 mg film-coated tablets, generic versions of voriconazole succinate. The applicant and the future holder of authorisation is Gedeon Richter Plc.

Voriconazole is a broad spectrum, triazole antifungal agent. The medicinal products are indicated in adults and children aged 2 years and above as follows:
- treatment of invasive aspergillosis.
- treatment of candidemia in non-neutropenic patients.
- treatment of fluconazole-resistant serious invasive Candida infections (including C. krusei).
- treatment of serious fungal infections caused by Scedosporium spp. and Fusarium spp.

Voriconazole Richter film-coated tablets should be administered primarily to patients with progressive, possibly life-threatening infections.

Moreover, their indication is prophylaxis of invasive fungal infections in high risk allogeneic hematopoietic stem cell transplant (HSCT) recipients.

The application was submitted according to Article 10(1) of Directive 2001/83/EC (generic application). The reference medicines have been Vfend® 50 mg and 200 mg film-coated tablets marketed by Pfizer Ltd., approved for more than 10 years within the European Economic Area.

The applicant has adequately demonstrated bioequivalence between Voriconazole Richter film-coated tablets and the reference products.

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 marketing authorisation for Voriconazole Richter 50 mg and 200 mg film-coated tablets.

V.2 Classification

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 Guidelines 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.

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval or non approval</th>
<th>Assessment report attached</th>
</tr>
</thead>
</table>