Summary Public Assessment Report

Generics

Metronidazole VIOSER 500 mg/100 ml solution for infusion
Metronidazole

LT/H/0117/001/DC

Date: 2017-04-06

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Metronidazole VIOSER*

Metronidazole 500 mg/100 ml solution for infusion

* Transfer of Marketing Authorisation Holder from UAB VVB, Lithuania to Parenteral Solution Industry VIOSER SA, Greece has been made during the national phase of procedure. Name of medicinal product was changed from Metronidazole VVB solution for infusion to Metronidazole VIOSER solution for infusion. In this Assessment Report, the name Metronidazole VIOSER is used.

This is a summary of the public assessment report (PAR) for Metronidazole VIOSER. It explains how Metronidazole VIOSER was assessed and its authorisation recommended as well as its conditions of use. It is not intended to provide practical advice on how to use Metronidazole VIOSER.

For practical information about using Metronidazole VIOSER, patients should read the package leaflet or contact their doctor or pharmacist.

What is Metronidazole VIOSER and what is it used for?

Metronidazole VIOSER is a 'generic medicine'. This means that Metronidazole VIOSER is similar to a 'reference medicine' already authorised in the European Union (EU) called Flagyl 500 mg/100 ml solution for infusion.
Metronidazole VIOSER is used in the treatment of infections caused by anaerobic bacteria (e.g., liver abscesses, abdominal abscesses, peritonitis, biliary infections, obstetrics and gynecological infections, etc.) prophylaxis of post-operative infections following gastrointestinal surgery caused by anaerobic bacteria and serious intestinal or hepatic amoebiasis.

How does Metronidazole VIOSER work?

Metronidazole VIOSER is an antibiotic. It works by breaking of the DNA chain and consecutively killing bacteria and parasites that cause serious infections in human body.

How is Metronidazole VIOSER used?

The pharmaceutical form of Metronidazole VIOSER is solution for infusion and the route of administration is intravenous.

Please read section 3 of the PL for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

The medicine can only be obtained with a prescription.

What benefits of Metronidazole VIOSER have been shown in studies?

No additional studies were needed as Metronidazole VIOSER is a generic medicine that is given by intravenous infusion and contains the same active substance as the reference medicine, called Flagyl 500 mg/100 ml solution for infusion.

What are the possible side effects of Metronidazole VIOSER?

Because Metronidazole VIOSER is a generic medicine and is bioequivalent to the reference medicine, its benefits and possible side effects are taken as being the same as the reference medicine.

For the full list of restrictions, see the package leaflet.

Why is Metronidazole VIOSER approved?

It was concluded that, in accordance with EU requirements, Metronidazole VIOSER has been shown to have comparable quality and to be bioequivalent/be comparable to reference medicine. Therefore, the SMCA of Lithuania decided that, as for reference medicine called Flagyl 500 mg/100 ml solution for infusion, the benefits are greater than its risk and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Metronidazole VIOSER?

A risk management plan has been developed to ensure that Metronidazole VIOSER is used as safely as possible. Based on this plan, safety information has been included in the summary of product characteristics and the package leaflet for Metronidazole VIOSER, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously as well.

Other information about Metronidazole VIOSER

The marketing authorisation for Metronidazole VIOSER was granted on 2017-04-06.

The full PAR for Metronidazole VIOSER can be found on the website http://mri.cts-mrp.eu/Human/. For more information about treatment with Metronidazole VIOSER, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in April-2017.

Public Assessment Report

Scientific discussion

Metronidazole VIOSER* 500 mg/100 ml solution for infusion
Metronidazole

LT/H/0117/001/DC

Date: 2017-04-06

This module reflects the scientific discussion for the approval of Metronidazole VVB* solution for infusion. The procedure was finalised at 2017-01-04. For information on changes after this date please refer to the module 'Update'.
*** Transfer of Marketing Authorisation Holder from UAB VVB, Lithuania to Parenteral Solution Industry VIOSER SA, Greece has been made during the national phase of procedure. Name of medicinal product was changed from Metronidazole VVB solution for infusion to Metronidazole VIOSER solution for infusion.**

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have agreed that he application for Metronidazole VVB 500 mg/100 ml solution for infusion is approvable.
Transfer of Marketing Authorisation Holder from UAB VVB, Lithuania to Parenteral Solution Industry VIOSER SA, Greece has been made during the national phase of procedure.
The Member States have granted a marketing authorisation for Metronidazole VIOSER 500 mg/100 ml solution for infusion, from Parenteral Solution Industry VIOSER SA, Greece.
In this Assessment Report, the name Metronidazole VIOSER is used.
The product is indicated for*: the treatment of infections caused by anaerobic bacteria (e.g., liver abscesses, abdominal abscesses, peritonitis, biliary infections, obstetrics and gynecological infections, etc.) prophylaxis of post-operative infections following gastrointestinal surgery caused by anaerobic bacteria and serious intestinal or hepatic amoebiasis.*
A comprehensive description of the indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.
With Lithuania as the Reference Member State in this Decentralized Procedure, Parenteral Solution Industry VIOSER SA, Greece is applying for the Marketing Authorisations for Metronidazole VIOSER 500 mg/100 ml solution for infusion in CMS: AT, CY, FI, RO.

II. QUALITY ASPECTS

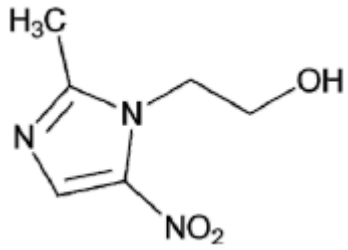
II.1 Introduction

Pharmaceutical form: solution for infusion.
Formulation (excipients): sodium chloride, disodium phosphate dodecahydrate (pH for adjustment) and citric acid monohydrate (pH for adjustment).
Container system: the container is made from low-density polyethylene (LDPE) without additives. The container is formed, filled and sealed in one continuous integrated working cycle, applying the blow-fill-seal technology. On the outer side of the container head a rubber disk is fixed by a polyethylene cap. The cap is designed as a two port cap, including one port for the addition of drugs and one port for the infusion line.
One carton contains 1 or 10 containers. Not all pack sizes may be marketed.

II.2 2.2Drug Substance

The active substance contained in the proposed drug product is metronidazole. This is a well-established active substance, which is subject to a monograph in the European Pharmacopoeia. The CEP procedure is followed for metronidazole.

Nomenclature
INN: metronidazole
Commercial name: metronidazole
Chemical name:
2-Methyl-5-nitroimidazole-1-ethanol
CAS No.: 443-48-1
Structure



Molecular Formula: $C_6H_9N_3O_3$
Molecular Weight: 171.2

General properties
Metronidazole is white to pale yellow crystalline powder slightly soluble in water, acetone, alcohol, methylene chloride.
pH: 5.5-7.5 (1% water).
UV absorption max: 200 nm relative max.
278 nm abs. Maximum.
$E^{(1\%)}_{1cm} = 386$
Melting point: 159-163 °C
pKa: 14.44 ± 0.10 most acidic temp. 25 °C
pKa: 2.58 ± 0.34 most basic temp. 25 °C

Chirality
The molecule of metronidazole does not contain any asymmetric carbon atom, and therefore chirality is not applicable to this substance.
Polymorphism
No different polymorphic forms have been observed in metronidazole, and no information have been found in the literature relevant to this issue.

The specification provided by the applicant is in accordance with the monograph on metronidazole in the current Ph. Eur. and with the CEP. The analytical results indicate that the active substance batches are tested in line with the proposed specification requirements.

II.3 Medicinal Product

The drug product is a sterile solution for infusion containing 100 mg metronidazole per 500 ml. The excipients are sodium chloride, disodium phosphate dodecahydrate, citric acid monohydrate and water for injection. Citric acid monohydrate and disodium phosphate dodecahydrate are used for pH adjustment. The excipients are usual for this type of dosage form.
The development of the product has been described. The choice of excipients is justified and their functions explained. The compatibility with different infusion solutions has not been investigated.
The pharmaceutical development of the product has been adequately performed.
The choice of sterilizing method is considered sufficiently justified. The manufacture of the drug product is straight-forward: preparation of the bulk solution, sterile filtration, filling into containers, sterilization of containers and packaging. The process validation data for pilot batches have been provided.
The excipients comply with Ph.Eur. These specifications are acceptable.
The selected test parameters and acceptance criteria for the release and stability testing of the drug product are considered as appropriate to control the drug product. All critical parameters for this dosage form (extractable volume, pH, visible and sub visible particles, sterility and bacterial endotoxins) are tested.
Results of long term conditions at 25 °C ± 2°C/40 % RH ± 5 % and of accelerated stability studies at 40°C ± 2°C/ not more than 25 % RH of the final dosage form are provided. The conditions used in the stability studies are according to the ICH stability guideline. All results meet their specifications at long term conditions of 25ºC/40% RH and accelerated conditions 40ºC/<25% RH after 6 months.

Photostability studies have been performed in compliance with ICH topic Q1B (CPMP/ICH/279/95). According to the presented data the drug product is not sensitive to UV light
The proposed shelf life of 3 years and the storage condition "This medicinal product does not require any special storage conditions" are accepted.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of metronidazole are well known. As metronidazole is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Metronidazole VIOSER is 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.2 Discussion on the non-clinical aspects

Generic application refers to information that is contained in the pharmacological-toxicological part of the dossier of the authorization of the reference product.
The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate. Metronidazole VIOSER is approvable from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction

No new clinical studies were undertaken in support of this application. The applicant has provided the justification in support of a biowaiver.
No additional studies were needed as Metronidazole VIOSER 500 mg/100 ml solution for infusion is a generic medicine that is given by intravenous infusion and contains the same active substance as the reference medicine Flagyl 500 mg/100 ml solution for infusion.

IV.2 Pharmacokinetics

Biowaiver
According CHMP Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr, 20 Jan 2010), bioequivalence studies are generally not required if the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product.
Metronidazole VIOSER 500 mg/100 ml solution for infusion satisfies the main criteria for a waiver of the need to provide equivalence data for parenteral solutions laid down in the CHMP Guideline on the Investigation of Bioequivalence. Metronidazole VIOSER 500 mg/100 ml solution for infusion is an aqueous parenteral solution and contains the same concentration of the same active substance and the same excipients as those of the reference product, Flagyl 500 mg/100 ml solution for infusion licensed to Sanofi-Aventis Cyprus Ltd. 100 ml of solution contains 500 mg of metronidazole. The other ingredients include sodium chloride, disodium phosphate dodecahydrate, citric acid monohydrate, and water for injections.
Based on the above, a bioequivalence study is not necessary to support this application for Metronidzole VVB 500 mg/100 ml solution for infusion.

IV.3 Pharmacodynamics

No new data have been submitted. No data are required for this generic application.

IV.4 Clinical efficacy

No new data have been submitted. No data are required for this generic application.

IV.5 Clinical safety

Safety information was updated and additional safety information which was approved in the DE/H/1018/001/MR DE/H/1018/001/MR (CMS: AT, BE, CY, EE, LT, LV, PL, SK; Renewal 2014-01-07) for similar medicinal product Metronidazole B. Braun 5 mg/ml solution for infusion was included.

IV.6 Risk Management Plan

The MAH has submitted a risk management plan (RMP-VVB-MET-v02), in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Metronidazole VIOSER 500 mg/100 ml solution for infusion.

- Summary table of safety concerns as approved in RMP

Summary of safety concerns	
Important identified risks	• Serious hypersensitivity reactions • Neurotoxicity • Hepatotoxicity • Alcohol intolerance and disulfiram toxicity • Myelosuppression
Important potential risks	• Increased risk of bleeding due to interactions with oral anticoagulants • Decreased efficacy due to using phenobarbital and phenytoin • Interference with laboratory tests • Reactions in breastfed children • Carcinogenicity
Missing information	• Use during pregnancy

- Summary of Safety Concerns and Planned Risk Minimisation Activities as approved in RMP

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risk		
Serious hypersensitivity reactions	The risk is addressed and communicated in proposed SPC sections 4.3, 4.8 and 6.1	None proposed
Neurotoxicity	The risk is addressed and communicated in proposed SPC sections 4.4 and 4.8.	None proposed
Hepatotoxicity	The risk is addressed and communicated in proposed SPC section 4.4.	None proposed
Alcohol intolerance and disulfiram toxicity	The risk is addressed and communicated in proposed SPC sections 4.5 and 4.7.	None proposed
Myelosuppression	The risk is addressed and communicated in proposed SPC sections 4.4 and 4.8.	None proposed
Important potential risk		
Increased risk of bleeding due to interactions with oral anticoagulants	The risk is addressed and communicated in proposed SPC section 4.5.	None proposed
Decreased efficacy due to using phenobarbital and phenytoin	The risk is addressed and communicated in proposed SPC section 4.5.	None proposed
Interference with laboratory tests	The risk is addressed and communicated in proposed SPC section 4.5 and PIL.	None proposed
Reactions in breastfed children	The risk is addressed and communicated in proposed SPC section 4.6.	None proposed
Carcinogenicity	The risk is addressed and communicated in proposed SPC section 5.3.	None proposed
Missing information		
Use during pregnancy	The risk is addressed and communicated in proposed SPC sections 4.6.	None proposed

Routine pharmacovigilance and risk minimisation activities are planned for all safety concerns.

IV.7 Discussion on the clinical aspects

The submitted documentation is of sufficient quality and is consistent with the current EU regulatory requirements. Satisfactory clinical overview have been submitted.
Generic application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorization of the reference product. The applicant has provided the correct justification in support of a biowaiver.

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

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The use of metronidazole is well established. It has recognised efficacy and acceptable safety.
Generic application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorization of the reference product.
There is no objection raised regarding the quality of the product.
Metronidazole VIOSER is approvable from a non-clinical point of view.
There are no objections to approval Metronidazole VIOSER from a clinical point of view.

Transfer of Marketing Authorisation Holder from UAB VVB, Lithuania to Parenteral Solution Industry VIOSER SA, Greece has been made during the national phase of procedure.

Viešojo vertinimo protokolo apžvalga

Metronidazole VIOSER* 500 mg/100 ml infuzinis tirpalas
Metronidazolas

* Vaistinio preparato pavadinimas nacionalinės fazės metu pakeistas iš Metronidazole VVB 500 mg/100 ml infuzinis tirpalas į Metronidazole VIOSER 500 mg/100 ml infuzinis tirpalas. Toliau apžvalgoje naudojamas vaistinio preparato pavadinimas Metronidazole VIOSER.

Trumpa kokybinės dalies apžvalga

Vaistinio preparato veiklioji medžiaga metronidazolas aprašytas Europos farmakopėjoje.
Veikliosios medžiagos gamintojas turi metronidazolo kokybės atitikties Europos farmakopėjai sertifikatą. Galutinio produkto gamintojo veikliosios medžiagos metronidazolo specifikacija yra tinkamos kokybės, paruota pagal Europos farmakopėjos reikalavimus. Metronidazolo specifikacijoje reglamentuojamų parametrų nustatymui naudojamos analizės procedūros yra tokios pačios, kaip ir reglamentuoja Europos farmakopėja straipsnyje metronidazolo kokybei.
Galutinio produkto sudėtyje esančios pagalbinės medžiagos (natrio chloridas, dinatrio edetatas, dinatrio fosfatas dodekahidratas, citrinų rūgštis monohidratas ir injekcinis vanduo) yra saugios ir plačiai naudojamos farmacinių preparatų kūrimui. Dinatrio fosfatas dodekahidratas ir citrinų rūgštis monohidratas naudojamos infuzinio tirpalo pH sureguliavimui. Pagalbinių medžiagų kokybė atitinka Europos farmakopėjos reikalavimus.
Galutinio produkto specifikacijos kokybė yra tinkama ir atitinka pripažintų standartų reikalavimus. Visi kritiniai šios farmacinės formos kokybės parametrai (ištraukiamasis tūris, pH, endotoksinų likutis, sterilumas ir k.t.) yra kontroliuojami galutinio produkto specifikacijoje. Galutinio produkto kokybei kontroliuoti analizės procedūros yra parinktos tinkamai, šiuolaikinės ir validuotos.
Reglamentuojamos vaistinio preparato tinkamumo laikas ir laikymo sąlygos yra patvirtintos stabilumo tyrimo duomenimis. Stabilumo tyrimų duomenimis siūlomas vaistinio preparato tinkamumo laikas yra 3 metai. Šiam vaistiniam preparatui specialų laikymo sąlygų nėra.
Visus klausimus dėl vaistinio preparato kokybės registruotojas išsprendė todėl esminių prieštaravimų dėl vaistinio preparato kokybės nėra.

Trumpa ikiklinikinės ir klinikinės dalies apžvalga

Metronidazole VIOSER 500 mg/100 ml infuzinis tirpalas yra receptinis vaistinis preparatas, skirtas vartoti suaugusiems ir vyresniems kaip 10 metų pacientams nurodytoms indikacijoms.
Terapinės indikacijos
Metronidazolas yra skirtas toliau išvardytos infekcinėms ligoms, kurių sukėlėjai yra metronidazolui jautrūs mikroorganizmai, gydyti.

- *Anaerobinių bakterijų sukeltoms infekcinėms ligoms (pvz., kepenų abscesui, pilvo abscesui, peritonitui, tulžies pūslės ir latakų infekcinėms ligoms, akušerinėms ir ginekologinėms infekcinėms ligoms ir kt.) gydyti.*
- *Anaerobinių bakterijų sukeltų infekcinių ligų profilaktikai atliekant virškinimo trakto operacijas.*
- *Sergant sunkia žarnyno ir kepenų amebiaze.*

Kai infekcinių ligų sukėlėjai yra ir aerobiniai, ir anaerobiniai mikroorganizmai, kartu su antibiotikais aerobinių mikroorganizmų sukeltoms infekcijoms gydyti skiriamas Metronidazole VIOSER 500 mg/100 ml infuzinis tirpalas.
Reikia atsižvelgti į oficialias tinkamo antibakterinių vaistinių preparatų vartojimo rekomendacijas.

Paraiška registruoti vaistinį preparatą pateikta pagal direktyvos 2001/83/EB 10 str. 1d. („generinis“). Pareiškėjas įrodė, kad vaistinis preparatas Metronidazole VIOSER 500 mg/100 ml infuzinis tirpalas yra iš esmės panašus į referencinį vaistinį preparatą Flagyl 500 mg/100 ml infuzinis tirpalas (Sanofi-Aventis Cyprus Ltd).

Metronidazolas – antibakterinis vaistinis preparatas, imidazolo darinys. Metronidazolas yra stabilus junginys, galintis prasiskverbti į mikroorganizmus. Anaerobinėmis sąlygomis veikiant mikroorganizmo piruvato-ferodoksino-oksireduktazei ir vykstant ferodoksino ir flavodoksino oksidacijai, susidaro nitro-radikalai, veikiantys DNR. Nitro-radikalai sudaro junginius su bazinėmis DNR poromis, todėl suyra DNR grandinė ir ląstelė žūva.

Metronidazolo farmakodinaminės, farmakokinetinės ir toksikologinės savybės yra gerai žinomos.
Kadangi pateikta generinė paraiška, yra referuojama į referencinio vaistinio preparato tyrimų duomenis, todėl naujų ikiklinikinių tyrimų duomenų pareiškėjas nepateikė.
Metronidazole VIOSER 500 mg/100 ml infuzinis tirpalas yra parenteraliai vartojamas vandeninis tirpalas, jo kiekybinė ir kokybinė sudėtis bei farmacinė forma tokios pat kaip referencinio vaistinio preparato Flagyl 500 mg/100 ml infuzinis tirpalas, todėl klinikinių tyrimų, įrodančių šių vaistų biologinį ekvivalentiškumą pateikti nebūtina. Referencinė ir pripažįstanti valstybės narės sutarė, kad Metronidazole VIOSER 500 mg/100 ml infuzinis tirpalas yra panašus į Flagyl 500 mg/100 ml infuzinį tirpalą, todėl Flagyl veiksmingumo ir saugumo duomenys taikomi vaistiniam preparatui Metronidazole VIOSER.

Remiantis pateiktais kokybės, saugumo ir veiksmingumo duomenimis, decentralizuotoje procedūroje dalyvaujančios referencinė valstybė narė (Lietuva) ir pripažįstančios valstybės narės (Austrija, Kipras, Suomija, Rumunija) nutarė, kad vaistinį preparatą Metronidazole VVB* 500 mg/100 ml infuzinis tirpalas registruoti galima ir europinė fazė buvo sėkmingai baigta (210 dieną) 2017-01-04.

* Nacionalinės fazės metu registruotojo teisę UAB VVB, Lietuva perdavė Parenteral Solution Industry VIOSER SA, Graikija. Vaistinio preparato pavadinimas nacionalinės fazės metu pakeistas iš Metronidazole VVB 500 mg/100 ml infuzinis tirpalas į Metronidazole VIOSER 500 mg/100 ml infuzinis tirpalas.

Po nacionalinės fazės Lietuvoje vaistinis preparatas registruotas 2017-04-06.