Summary Public Assessment Report

Generics

Morysa

10 mg, 20 mg, film-coated tablets

(memantine hydrochloride)

PT/H/1056/001-002/DC

infarmed
Autoridade Nacional do Medicamento
e Produtos de Saúde I.P.

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Generics

Morysa
Memantine hydrochloride, 10 mg, 20 mg, film-coated tablets.

This is a summary of the public assessment report (PAR) for Morysa. It explains how Morysa 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 Morysa.

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

What is Morysa and what is it used for?

Morysa is a 'generic medicine'. This means that Morysa is similar to a 'reference medicine' already authorised in the European Union (EU) called Ebixa.
Morysa contains memantine and belongs to a group of medicines known as anti-dementia medicines. Memory loss in Alzheimer's disease is due to a disturbance of message signals in the brain. The brain contains so-called N-methyl-D-aspartate (NMDA)-receptors that are involved in transmitting nerve signals important in learning and memory.

How does Morysa work?

Morysa belongs to a group of medicines called NMDA-receptor antagonists. Morysa acts on these NMDA-receptors improving the transmission of nerve signals and the memory.

How is Morysa used?

The pharmaceutical form of Morysa is film coated tablets and oral solution and the route of administration is oral.

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 Morysa have been shown in studies?

Because Morysa is a generic medicine, studies in patients have been limited to tests to determine that it is bioequivalent to the reference medicine, Ebixa. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Morysa?

Because Morysa 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 Morysa approved?

It was concluded that, in accordance with EU requirements, Morysa has been shown to have comparable quality and to be bioequivalent to Ebixa. Therefore, the Infarmed decided that, as for Ebixa, the benefits are greater than its risk and recommended that it can be approved for use.

Other information about Morysa

The marketing authorisation for Morysa was granted on 09-06-2015.

The full PAR for Morysa can be found on the website www.infarmed.pt/infomed . For more information about treatment with Morysa, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in

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Public Assessment Report

Scientific discussion

Morysa

10 mg, 20 mg, film-coated tablets

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This module reflects the scientific discussion for the approval of Morysa. The procedure was finalised at 09-07-2014. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Farmax Slovakia a.s. has applied for a marketing authorisation for Morysa 10 mg film-coated tablets, 20 mg film-coated tablets containing memantine hydrochloride as the active substance for the treatment of patients with moderate to severe Alzheimer's disease in *CZ, HU, PL, SK.*

This application concerns a generic application claiming essential similarity with the reference product Ebixa, registered since 2002-05-17 by H. Lundbeck A/S SE.

The marketing authorization was granted nationally on 09-06-2015 based on Directive 2001/83/EC article 10.1 (a) (iii) first paragraph.

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. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorized medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. This generic product can be used instead of its reference product.

II. QUALITY ASPECTS

II.1 Introduction

The 10 mg film-coated tablets are white to off-white, caplet shaped, biconvex, film-coated tablet with breaking line on both sides with dimensions 12 mm x 5.4 mm. The tablet can be divided into equal halves. The 20 mg film-coated tablets are brown, oblong shaped, biconvex, film-coated tablets with breaking line on both sides with dimensions 15.25 mm x 8.25 mm. The tablet can be divided into equal halves.

Morysa is available in PVC-PVDC / Alu blister pack sizes of 28, 42, 56, 98 tablets.
Morysa is available in HDPE bottle with white polypropylene cap, white to off-white pulp board/Alu/PVDC induction seal and printed white pillow pack of silica gel in the bottle in pack sizes of 30, 100 and 500 tablets.

The excipients are

Tablet cores for 10 & 20 mg film-coated tablets:

Cellulose microcrystalline
Silica, colloidal anhydrous
Croscarmellose sodium

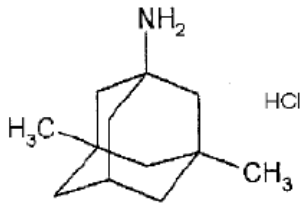
Hypromellose 2910
Purified Talc
Magnesium stearate

Tablet coat for 10 & 20 mg Film-coated Tablets:

Additional for 10 mg film-coated tablets:
Coating
Instacoat Universal White (A05R00013)
(Hypromellose 2910
Macrogol 400
Titanium dioxide (E171))

Additional for 20 mg film-coated tablets:
Coating
Instacoat Universal Brown (A05R00608)
(Hypromellose 2910
Macrogol 400
Titanium dioxide (E171)
Iron oxide yellow (E172)
Iron oxide red (E172)

II.2 Drug Substance



Memantine hydrochloride

The active substance memantine hydrochloride, is in line with requirements of current edition of European Pharmacopoeia.

II.3 Medicinal Product

The documentation provided complies with relevant EU guidelines and directives. Manufacture is performed in accordance with cGMP and consistency in quality and homogeneity is demonstrated.

The finished product specification is based on relevant development and stability studies. The development of the product has been described, the choice of excipients is justified and their functions explained.

Appropriate validation data have been provided for the analytical methods. Batch analyses data support the proposed finished product specification.

Stability studies were performed in line with the ICH guidance.
The proposed shelf-life of 36 months, with no special storage conditions needed, for the drug product is considered acceptable. Once opened, the contents of the bottle should be used within 3 months.

III. NON-CLINICAL ASPECTS

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

Environmental Risk Assessment (ERA)

Despite this medicinal product is intended for generic substitution, the applicant submitted a report evaluating the ERA on basis of log P determination. An environmental impact is not expected for this medicine.

IV. CLINICAL ASPECTS

To support the application, the Applicant has submitted the report of one *single dose bioequivalence study on the 20 mg strength under fasting conditions: "An open-label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, crossover bioequivalence study of Memantine Hydrochloride Tablets 20 mg and EBIXA® (Memantine Hydrochloride) Tablets 20 mg of H. Lundbeck, in healthy, adult, human subjects under fasting conditions".* A biowaiver is adequately addressed and justified. Therefore, waiving a bioequivalence study for the 10 mg strength of the film-coated tablets is acceptable.

Pharmacovigilance system
The applicant certifies that has at disposal the services of a QPPV and necessary means for the collection and notification o any adverse reaction occurring either in the Community or in a third country. We have registered the company and QPPV by EMA, we are in pilot phase in CR, we are or applied for testing phase in other relating EU countries and we are registered in EVMPD.The location where the Pharmacovigilance Systtem Master File is kept is SVUS Pharma a.s., Smetanovo nábřeží 1238/20a, 5600 02 Hradec Králové, Czech Republic.
This is acceptable.

Risk Management Plan

The Risk Management Plan for Memantine Hydrochloride has been created complaining to Guideline on good pharmacovigilance practices (GVP), Module V – Risk management system adopted by EMA and Publisher June 25, 2012.

Important potential risks

The following interactions may occur due to the pharmacological effects and the mechanism of action of memantine:

1. The effects of L-dopa, dopaminergic agonists, and anticholinergics may be enhanced by concomitant treatment with NMDA-antagonists such as memantine. The effects of barbiturates and neuroleptics may be reduced.
2. Concomitant administration of memantine with the antispasmodic agents, dantrolene or baclofen, can modify their effects and a dosage adjustment may be necessary.
3. Concurrent use of memantine and amantadine should be avoided, owing to the risk of pharmacotoxic psychosis. Both compounds are chemically related NMDA-antagonists. The same may be true for ketamine and dextromethorphan.
4. There is one published case report on a possible risk also for the combination of memantine and phenytoin. However, epilepsy is often understood to be an issue of imbalance of the excitatory and inhibitory neural systems leading to the pathological synchronization of neural activities. Memantine is in principle an excitatory inhibitor and can disturb the balance. Therefore, caution is recommended in patients with epilepsy, history of convulsions or patients with predisposing factors for epilepsy.
5. Medication such as such as: cimetidine, ranitidine, procainamide, quinidine, quinine and nicotine use the same renal cationic transport system as amantadine may also possibly interact with memantine leading to a potential risk of increased plasma levels.
6. Possible reduced serum level of hydrochlorothiazide (HCT) when memantine is coadministered with HCT or any combination with HCT.
7. Isolated cases with international normalized ratio (INR) increases have been reported in patients concomitantly treated with warfarin. Although no causal relationship has been established, close monitoring of prothrombin time or INR is advisable for patients concomitantly treated with oral anticoagulants.
The most of above mentioned interactions or needed cautions can appear due to diseases occurring often in the same age as Alzheimer disease appears. On the other hand all are also mentioned in the SmPC. Physicians should be aware of any combination of diseases (and their treatments) if using memantine.
Memantine is, in general, well tolerated (Areosa Sastre A, Sherriff F, McShane R. Memantine for dementia. The Cochrane Database of Systematic Reviews 2005). Therefore, basic routine minimization measures i.e. texts of the SmPC and PI and primary and secondary packaging texts should be sufficient to cover the safety measures.

User testing
The readability of the package leaflet was successfully demonstrated

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The application for *Morysa* contains adequate quality, non clinical and clinical data and the bioequivalence has been shown. A benefit/risk ratio comparable to the reference product can therefore be concluded.