Publikus értékelő jelentés

Termék neve:
Canesten Uno 500 mg lágy hüvelykapszula

(klotrimazol)

Törzskönyvi szám:
OGYI-T-8110

A forgalomba hozatali engedély jogosultja:
Bayer Hungária Kft.

Kelt: 2013. március 5.

TARTALOM

NEM EGÉSZSÉGÜGYI SZAKEMBEREKNEK SZÓLÓ ÖSSZEFOGLALÓ

A Gyógyszerészeti és Egészségügyi Minőség- és Szervezetfejlesztési Intézet (GYEMSZI) Országos Gyógyszerészeti Intézet Főigazgatósága értékelte a Canesten Uno 500 mg lágy hüvelykapszulára vonatkozó kérelmet minőségi, valamint nem-klinikai és klinikai biztonságosság és hatásosság szempontjából, azt megfelelőnek találta, majd az Intézet kiadta a gyógyszer forgalomba hozatali engedélyét.

A készítmény hatóanyaga a klotrimazol széles spektrumú gomba ellenes hatással rendelkezik.

Egy Canesten Uno 500 mg lágy hüvelykapszula 500 mg mikronizált klotrimazolt tartalmaz.

Egyéb összetevők: fehér vazelin, folyékony paraffin, zselatin, glicerin, titán-dioxid (E171), kinolinsárga (E104), sunset yellow (E110). Nyomokban lecitint és közepes szénláncú triglicerideket tartalmazhat.

Külleme: homogén szuszpenziót tartalmazó, csepp alakú, sárga, átlátszatlan lágy hüvelykapszula.

Csomagolása: egy darab lágy hüvelykapszula átlátszó, laminált PVC/PVdC/PVC//Al buborékcsomagolásban és 1 db fehér PE/PP applikátor, dobozban.

Milyen típusú gyógyszer a Canesten Uno 500 mg lágy hüvelykapszula és milyen betegségek esetén alkalmazható?

A Canesten Uno 500 mg lágy hüvelykapszula a nemi szervek gombás fertőzéseinek és az ehhez kapcsolódó gyulladások kezelésére alkalmas. A gyulladásos fertőzés tünetei: a külső nemi szervek vörösek és duzzadtak lehetnek, viszketnek és érzékennyé válnak. Hüvelyi váladékozás alakul ki, a hüvely falát túrós lepedék borítja.

Ezeket a fertőzéseket általában Candida fajok okozzák.

Tudnivalók a Canesten Uno 500 mg lágy hüvelykapszula alkalmazása előtt

Ne alkalmazza a Canesten Uno 500 mg lágy hüvelykapszulát
- ha allergiás (túlérzékeny) a klotrimazolra vagy a gyógyszer egyéb összetevőjére,
- menstruáció ideje alatt. A hüvelyi kezelést a menstruáció kezdete előtt be kell fejezni.

Figyelmeztetések és óvintézkedések

Az alábbi esetekben a készítmény csak a kezelőorvossal történt megbeszélés alapján alkalmazható:
- ha először fordul elő gombás fertőzés,
- ha az elmúlt 6 hónapban több mint 2 alkalommal fordult elő Önnél gombás fertőzés,
- ha Ön vagy partnere nemi úton terjedő betegségben szenved, vagy szenvedett korábban,

- terhesség, vagy annak gyanúja esetén,
- alhasi fájdalom vagy fájdalmas vizelés esetén,
- kellemetlen szagú hüvelyi váladékozás esetén,
- véres hüvelyi váladékozás esetén,
- rendellenes vagy rendszertelen hüvelyi váladékozás esetén,
- amennyiben a szeméremtesten vagy a hüvely területén sebek, fekélyek vagy hólyagok jelennek meg,
- láz vagy hidegrázás esetén,
- amennyiben a kezelés során kipirosodás, irritáció vagy duzzanat fordul elő.

A hüvelykapszula alkalmazásának ideje alatt a latex anyagú fogamzásgátló eszközök (gumióvszer, pesszárium) biztonságossága csökken. Ez a hatás átmeneti és csak a kezelés időtartamára korlátozódik.

A szexuális aktus kerülendő a kezelés alatt, mivel a partner is megfertőződhet.

A Canesten Uno 500 mg lágy hüvelykapszulát nem szabad lenyelni!

A kezelés alatt nem szabad tampont, hüvelyzuhanyt, spermicid készítményt vagy egyéb hüvelyi készítményt alkalmazni.

Gyermekek és serdülők: a Canesten Uno 500 mg lágy hüvelykapszula biztonságosságát és hatásosságát 18 év alatti gyermekek esetében nem igazolták. Ezért 18 éves kor alatti gyermekeknél és serdülőknél nem alkalmazható.

Egyéb gyógyszerek és a Canesten Uno 500 mg lágy hüvelykapszula: feltétlenül tájékoztassa kezelőorvosát vagy gyógyszerészét a jelenleg vagy nemrégiben szedett egyéb gyógyszereiről.

Takrolimusz (immunszupresszáns gyógyszerek hatóanyaga) szedése alatti klotrimazol alkalmazás megemelkedett takrolimusz-szintet eredményezhet, így ha Ön takrolimusz tartalmú gyógyszert szed, konzultáljon orvosával, mielőtt a Canesten Uno 500 mg lágy hüvelykapszulát alkalmazza.

Ha Ön *terhes vagy szoptat*, illetve ha fennáll Önnél a terhesség lehetősége vagy gyermeket szeretne, a gyógyszer szedése előtt beszéljen kezelő orvosával vagy gyógyszerészével. Terhesség első három hónapjában és szoptatás ideje alatt a hüvelykapszula csak a kezelőorvos javaslatára alkalmazható. Terhesség alatt a hüvelykapszulát applikátor nélkül kell használni!

A terhesség utolsó 4-6 hetében a szülőutak fertőtlenítésére is alkalmas.

Hüvelyi alkalmazás során a klotrimazol felszívódása igen alacsony, így szoptatás alatti alkalmazása nem jelent kockázatot a csecsemőre.

A készítmény nem befolyásolja a *gépjárművezetéshez és gépek kezeléséhez* szükséges képességeket.

Hogyan kell alkalmazni a Canesten Uno 500 mg lágy hüvelykapszulát?

A készítmény szokásos adagolása: a hüvelykapszulát egyszeri alkalommal este kell a hüvelybe vezetni Amennyiben a tünetek nem múlnak el az egyszeri kezelés után, a kezelőorvossal történt megbeszélés alapján a kezelés megismételhető.

A Canesten Uno 500 mg lágy hüvelykapszula 18 éves kor alatt nem alkalmazható a biztonságosságra és a hatásosságra vonatkozó adatok hiánya miatt.

Az alkalmazás módja: a hüvelykapszulát este kell az applikátorral mélyen a hüvelybe vezetni. Ez a leghatásosabban háton fekve, kissé felhúzott lábakkal érhető el. Terhesség alatt a hüvelytablettát applikátor nélkül kell használni. Az applikátor használata és a hüvelykapszula alkalmazása applikátor nélkül részletesen a betegtájékoztatóban szerepel.

A hüvelykapszula lágy bevonata hüvely-, és vulvagyulladás esetén is biztosítja a könnyű felhelyezést. A hüvelykapszula percek alatt felolvad, és emulziót képezve bevonja a hüvelynyálkahártya felületét.

Lehetséges mellékhatások

Mint minden gyógyszer, így ez a készítmény is okozhat mellékhatásokat, amelyek azonban nem mindenkinél jelentkeznek.

A forgalomba hozatalt követően az alábbi mellékhatásokat jelentették: allergiás reakciók (ájulás, alacsony vérnyomás, légzési nehézségek, csalánkiütések), hámlás a nemi szervek területén, viszketés, bőrkiütés, ödéma, kellemetlen, égő érzet, irritáció, kismedencei fájdalom, hasi fájdalom.

Hogyan kell a Canesten Uno 500 mg lágy hüvelykapszulát tárolni?

Ez a gyógyszer nem igényel különleges tárolást, de a nedvességtől való védelem érdekében az eredeti csomagolásban tárolandó és gyermekektől elzárva tartandó!

Tudományos összefoglaló

Ez a modul a Canesten Uno 500 mg lágy hüvelykapszula forgalomba hozatali engedélyezési eljárása során végzett tudományos értékelését tartalmazza.
Az eljárás 2012. március 12-én fejeződött be.
Az eljárás lezárása utáni lényeges változtatásokat ld. a "Módosítások" modulban.

I. INTRODUCTION

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

Bayer Hungária Kft. has submitted an application for the marketing authorization of Canesten Uno 500 mg lágy hüvelykapszula containing clotrimazole as an active substance under a national procedure as a line extension.

The existing medicines in the product line are Canesten G 200 mg hüvelytabletta (vaginal tablets, OGYI-T-8110/03) and Canesten Kombi hüvelytabletta és krém (vaginal tablets and crème, OGYI-T-8110/02).

The new formulation is based on a concept of a suspension fill formulation encapsulated by a soft wrap which dissolves shortly after vaginal insertion and is easy to apply even under conditions of vaginal and vulval soreness. The documentation contains references to the originator dossier including clinical trials performed by the applicant where clotrimazole vaginal tablets or cream were tested. The new pharmaceutical form vaginal capsule was studied in a double blind trial according to good clinical practice (GCP) showing the non-inferiority versus clotrimazole 500 mg vaginal tablets in the treatment of vulvovaginal mycoses. The application for marketing authorization was submitted as a hybrid application.

The currently marketed and referenced Canesten G 200 mg vaginal tablet and the Canesten Kombi product contain 3 x 200 mg vaginal tablets that have to be administered on three consecutive days. By contrast, the presently submitted products contain 1 x 500 mg vaginal capsule that has to be applied only once.

There are marketing authorization applications submitted for the same products in UK, ES, SE as EEA countries and in Australia.

Clotrimazole, the prototype of the azole class of substances (imidazole derivatives), is effective against almost all human pathogenic fungi. The substance has already been known and well studied for about 30 years.

The antimycotic effect of clotrimazole is based on the inhibition of ergosterol biosynthesis. *In vitro* and *in vivo* clotrimazole has a broad spectrum of antimycotic activity, being effective against dermatophytes, *Blastomyces*, moulds and dimorphic fungi. The primary mode of action of clotrimazole is fungistatic.

Therapeutic indications: for the treatment of clotrimazole sensitive yeast (generally *Candida albicans*) infections of the genital area (vaginitis, vulvitis).

II. CHEMICAL ASPECTS

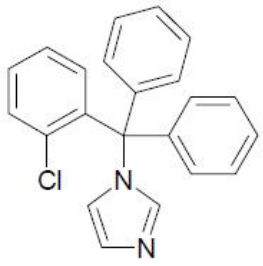
II.1 Introduction

This chemical-pharmaceutical assessment report concerns the application of Canesten Uno 500 mg soft vaginal capsule submitted *via* national procedure, line extension.

II.2 Drug Substance

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

INN name: clotrimazole
Chemical name: 1-(2-chloro-α,α-diphenyl-benzyl)imidazole
Structure:



$C_{22}H_{17}ClN_2$

The active substance is a white or pale yellow, crystalline powder and practically insoluble in water, soluble in ethanol (96 per cent) and in methylene chloride. It shows polymorphism, the manufacturer consistently produces 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 residual solvents, microbiological purity and particle size distribution.

The Ph. Eur. specification includes the following tests for clotrimazole: identification, assay, related substances, loss on drying and sulphated ash.

The presented specification is in accordance with the Ph. Eur. general monograph on *Substances for Pharmaceutical Use* and the ICH Q6A guideline. The specifications reflect all relevant quality attributes of the active substance and were found to be adequate to control the quality of the drug substance. The limits set are properly justified.

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

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

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

Stability studies have been performed with the drug substance. According to the presented stability data a re-test period of 5 years is acceptable with no special storage condition.

GMP compliance of the API manufacture has been demonstrated by the applicant.

II.3 Medicinal Product

The aim was to develop soft vaginal capsule containing clotrimazole as drug substance in 500 mg dose.

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

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 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.

Canesten Uno 500 mg soft vaginal capsules are teardrop yellow opaque capsules containing a homogenous suspension. Its active substance is clotrimazole, micronized, 500 mg.

The excipients used in the finished product are, white soft paraffin, liquid paraffin, gelatin, glycerol, titanium dioxide (E171), Quinoline yellow (E104), Sunset yellow (E110), lecithin, medium chain triglycerides (i.e. fractionated coconut oil) and purified water. All excipients (except Quinoline yellow and Sunset yellow) used comply with their respective Ph. Eur. monographs. Compliance of the product with the general monograph of the European Pharmacopoeia *on the Products with the risk of TSE* has been demonstrated by the applicant.

The finished product specification is satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as specified 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 PVC/PVdC/PVC//Al blister. Specifications and quality certificates for all packaging components are enclosed.

The 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 temperature storage conditions in the original package (in order to protect from moisture) is approved.

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

II.4 Discussion on chemical, pharmaceutical and biological aspects

The product has been 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.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of clotrimazole are well known.

No preclinical studies are available for the clotrimazole soft vaginal formulation being subject of this application. In the oral toxicity studies, the particular pharmaceutical form is of no major relevance, while in local tolerance studies the pharmaceutical form of a locally applied medicinal product (soft vaginal capsule versus vaginal tablet or vaginal cream) may have an influence. To fill this gap and to substantiate the new pharmaceutical form the applicant has conducted a double blind clinical study showing the non-inferiority of the Clotrimazole soft vaginal capsule formulation (500 mg) versus the approved Clotrimazole vaginal tablet (500 mg) in the treatment of candidal vaginitis. An overview based on literature review is, thus, appropriate.

The non-clinical overview refers to publications up to year 2009.

III.2 Pharmacology

The therapeutic effects of clotrimazole are mainly based on its inhibition of the ergosterol biosynthesis, the main sterol in fungal cells and a prerequisite for cell proliferation. In addition, effects on liposomal model membrane, on the mitochondrial and peroxisomal electron transport system, and anti-inflammatory activity may play a role in the therapy.

No new animal experiments have been conducted, the suitability of the new formulation as line extension has been demonstrated in the clinical part.

III.3 Pharmacokinetics

Dermal absorption of clotrimazole from both intact and sore skin is minimal (3-10%). The absorbed clotrimazole undergoes rapid metabolisation in the liver resulting inactive metabolites. Thus, systematic toxic action after administration is not expected.

No new animal experiments have been conducted, the suitability of the new formulation as line extension has been demonstrated in the clinical part.

III.4 Toxicology

Vaginal exposure of clotrimazole in various animals was well tolerated. No specific toxicity or genotoxicity was observed.

No new animal experiments have been conducted, the suitability of the new formulation as line extension has been demonstrated in the clinical part.

III.5 Ecotoxicity/environmental risk assessment

Granting this additional marketing authorisation for Canesten Uno 500 mg soft vaginal capsules as a line-extension is not expected to result in a significant increase of the use of the clotrimazole based formulations. Thus, no increase in the environmental concentration of clotrimazole is assumed. Therefore, no detailed environmental risk assessment is required for the new formulation according to the EMEA guideline CPMP/SWP/4447/00.

III.6 Discussion on the non-clinical aspects

This kind of abridged application avoids the need for repetitive tests on animals. The literature references are acceptable.

IV. CLINICAL ASPECTS

IV.1 Introduction

The clinical overview is considered adequate. It refers to publications up to year 2009.

Clotrimazole is established for medicinal use in the therapy of fungal infection of the genital region since several decades (the first worldwide approval happened in 1972) and is generally acknowledged as being safe and effective. Various clotrimazole-containing medicinal products for local application are marketed in numerous European and non-European countries, often under non-prescription conditions.

The documentation contains references to the reference (authorized earlier in the product line) dossier including clinical trials performed by the applicant where clotrimazole vaginal tablets or cream were tested. The new pharmaceutical form vaginal capsule was studied in a double blind trial according to good clinical practice (GCP) showing the non-inferiority versus clotrimazole 500 mg vaginal tablet in the treatment of vulvovaginal mycoses. The capsule formulation used in the clinical study is identical with the formulation in the present application.

It should be pointed out that all studies were performed in adults. No information is available for the vaginal and external therapy of the vulva with clotrimazole in adolescents and children.

IV.2 Pharmacokinetics

Dermal absorption of clotrimazole from both intact and sore skin is minimal (3-10%). The absorbed clotrimazole undergoes rapid metabolisation in the liver resulting inactive metabolites. Former experiments prove that local application of a 500 mg dose of clotrimazole results in plasma peak concentrations less than 10 ng/ml which is negligible.

No new pharmacokinetic studies were performed.

IV.3 Pharmacodynamics

The therapeutic effects of clotrimazole are mainly based on its inhibition of the ergosterol biosynthesis, the main sterol in fungal cells and a prerequisite for cell proliferation. In addition, effects on liposomal model membrane, on the mitochondrial and peroxisomal electron transport system, and anti-inflammatory activity may play a role in human therapy.

Candida albicans is the most common yeast causing vulvovaginal candidosis (90% to 95%), although non-albicans species such as *C. glabrata* and *C. krusei* also cause infection (about 5% to 10% of cases). *Candida glabrata* is more often detected in recurrent candidosis and up to 47% of recurrent infections may be due to non-albicans species.

Candida albicans, Candida tropicalis, and *Candida parapsilosis* are reported to be susceptible to all azoles, while other non-albicans species have higher minimum inhibitory concentration (MIC) values. Vaginal *Candida glabrata* is about 10-100-fold less susceptible to all azoles than *Candida albicans in vitro.*

Based on clinical investigations, the concentrations of clotrimazole in vaginal secretions after vaginal application exceeded the MIC of relevant yeasts and concentrations remained above the MIC for at least up to 48 hours after treatment. No change in the overall median susceptibility of Candida isolates was observed between isolates obtained before 1972 and between 1992 and 1994. Clotrimazole retained its high activity against relevant fungi causing vulvovaginal mycosis also in the few more recent studies and resistance is only very rarely observed in vaginal isolates.

IV.4 Clinical efficacy

The mycological cure rates achieved with clotrimazole in women with vulvovaginal mycosis exceed 80% in the majority of studies, controlled or non-controlled, independent of the formulation tested.

The different clotrimazole formulations and regimes intended for single-dose treatment or 3- or 6-day courses were generally equally effective in the treatment of vaginal mycoses and are regarded as interchangeable as assessed by experts.

The combination therapy including treatment of vagina and vulva is well documented and justified since both regions are almost always concomitantly affected. Patient acceptance is high and side-effects are rare and similar in all studies.

The new Clotrimazole 500 mg soft vaginal capsules have been developed to provide an alternative compared to the already approved clotrimazole vaginal products. The new formulation is based on a concept of a suspension fill formulation encapsulated by a soft wrap which dissolves shortly after vaginal insertion and is easy to apply even under conditions of vaginal and vulval soreness. Clotrimazole 500 mg soft vaginal capsules are a solid formulation with intermediate mechanical characteristics between a tablet and a cream.

The applicant has conducted a double blind, two-arm, multicentre, randomized clinical trial according to GCP to compare the safety and efficacy of clotrimazole 500 mg soft vaginal capsules with its own clotrimazole 500 mg vaginal tablets as reference preparation after a single dose in 348 women with microbiologically confirmed vulvovaginal mycosis. The clinical symptoms (itching, burning, irritation, discharge, and dysuria) and signs (vaginal and vulval edema, erythema, and excoriation) were assessed and mycological tests (KOH and yeast culture preparation) were performed at baseline and the follow-up visits. The differences between treatments were neither statistically nor clinically significant for any of the efficacy outcomes.

IV.5 Clinical safety

The systemic exposure to clotrimazole after vaginal application is comparatively low, thus, no systemic pharmacological effects are expected. Such have not been reported so far.

The tolerability of vaginal clotrimazole was confirmed for the newly developed soft vaginal capsule formulation in comparison with the vaginal tablet formulation by the clinical trial submitted by the applicant. The (local) tolerance of the new formulation under review can be judged as good from the observations made in the pivotal clinical trial. The local tolerance of clotrimazole and the inactive ingredients is well-established and has been extensively investigated. All excipients are well characterized.

IV.6 Discussion on the clinical aspects

The application contains an adequate review of published clinical data and a non-inferiority comparative clinical trial in respect of the existing vaginal tablets. There is nothing against the granting of the marketing authorisation from clinical point of view.

V. FINAL CONCLUSION, ASSESSMENT OF THE THERAPEUTIC BENEFIT/RISK AND RECOMMENDATION

The present line-extension application concerns clotrimazole 500 mg soft gelatine capsules. The applicant and the future holder of the marketing authorisation is Bayer Hungária Kft.

Therapeutic indications: for the treatment of clotrimazole sensitive yeast (generally *Candida albicans*) infections of the genital area (vaginitis, vulvitis).

The antimycotic effect of clotrimazole is well-known. It is based on the inhibition of ergosterol biosynthesis. *In vitro* and *in vivo* clotrimazole has a broad spectrum of antimycotic activity, being effective against dermatophytes, *Blastomyces*, moulds and dimorphic fungi. The primary mode of action of clotrimazole is fungistatic.

The new formulation is based on a concept of a suspension fill formulation encapsulated by a soft wrap which dissolves shortly after vaginal insertion and is easy to apply even under conditions of vaginal and vulval soreness.

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.

V.1 Conditions for the marketing authorisation

Requirements for specific post-marketing obligations

Not needed.

Pharmacovigilance system

The applicant/marketing authorisation holder submitted detailed description of the Pharmacovigilance System intended to be used, which fulfils the requirements and provides adequate evidence that the marketing authorisation holder has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management Plan

No Risk Management Plan, as per the provisions of the EMEA/CHMP/96268/2005 guideline needs not to be submitted with the present application.

Periodic Safety Update Report (PSUR)

The marketing authorisation holder has already approved vaginal products of the same active ingredient on the market. According to Volume 9A of the Notice to Applicants it is recommended that all formulations of the same active ingredient are included in the same PSUR. Therefore, a PSUR cycle of three years including the new formulation will have the data lock point what is the same as is already in place for other formulation.

Legal status

Non-prescription medicine.

V. 2 Summary of Product Characteristics (SmPC)

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

V.3 Package Leaflet and user testing

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

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

VI. Módosítások: az eredeti eljárás lezárása után tett lépések, amelyek érintik a Nyilvános értékelő jelentés szövegét

Ez a modul az eredeti eljárás befejezése után tett lépésekre vonatkozó információkat tartalmazza.

Tárgy	**Iktatószám**	**A termékinformációt érinti:**	**Az eljárás megkezdésének kelte**	**Az eljárás befejezésének kelte**	**Engedélyezve vagy elutasítva**	**Értékelő jelentés csatolva:**