Publikus értékelő jelentés

Termék neve:
Panadol Rapid 500 mg filmtabletta

(paracetamol)

Törzskönyvi szám:
OGYI-T-22330

A forgalomba hozatali engedély jogosultja:
GlaxoSmithKline Consumer Healthcare
GlaxoSmithKline Export Ltd., Brentford, Nagy-Britannia

Dátum: 2013. január 11.

TARTALOM

NEM EGÉSZSÉGÜGYI SZAKEMBEREKNEK SZÓLÓ ÖSSZEFOGLALÓ

A GYEMSZI Országos Gyógyszerészeti Intézet Főigazgatóság a benyújtott dokumentumok gondos értékelése alapján forgalomba hozatalra engedélyezte a Panadol Rapid 500 mg filmtabletta gyógyszerkészítményt.

Milyen típusú gyógyszer a Panadol Rapid 500 mg filmtabletta és milyen betegségek esetén alkalmazható

A Panadol Rapid 500 mg filmtabletta hatóanyagként tablettánként 500 mg paracetamolt tartalmaz, amely fájdalom és lázcsillapító gyógyszer. Gyorsan és hatékonyan enyhíti:
- a fejfájást és migrént,
- a hátfájdalmakat, idegfájdalmat, fogfájást, reumatikus- és izomfájdalmakat, valamint a menstruációs görccsel járó fájdalmat,
- a megfázással, influenzával és torokfájással együtt járó kellemetlen érzést és csökkenti a fellépő lázat.

Egyéb összetevői:
- *tablettamag*: hidegen duzzadó keményítő, kalcium karbonát, alginsav, „A” típusú kroszpovidon, povidon (K-25), magnézium sztearát, vízmentes kolloid szilícium dioxid, parahidroxibenzoátok (metil-parahidroxibenzoát-nátrium (E219), etil-parahidroxibenzoát-nátrium (E215), propil-parahidroxibenzoát-nátrium (E217.)
- *bevonat*: Opadry white (YS-1-7003), karnauba viasz, tisztított víz.

Fehér színű, kapszula alakú, konvex filmbevonatú tabletta, egyik oldalán egy körben „P” bevéséssel, másik oldalán bemetszéssel ellátva. A tabletta egyenlő adagokra osztható.

A Panadol Rapid 500 mg filmtabletta a szétesést segítő rendszerének (Optizorb formula) köszönhetően, gyorsabban szívódik fel, mint a hagyományos paracetamol tabletták.

Tudnivalók a Panadol Rapid 500 mg filmtabletta szedése előtt

Ne szedje a Panadol Rapid 500 mg filmtablettát
- ha allergiás (túlérzékeny) a paracetamolra vagy a Panadol Rapid 500 mg filmtabletta egyéb összetevőjére,
- más paracetamol tartalmú készítményekkel egyidejűleg,
- máj- és vesekárosodás esetén (ekkor csak orvosi konzultációt követően szedheti),
- glükóz-6-foszfát-dehidrogenáz enzim hiánya esetén.

További figyelmeztetések és óvintézkedések
- Alkoholos eredetű májkárosodás esetén fokozott a túladagolás veszélye.
- Amennyiben Ön máj- vagy vesekárosodásban szenved, csak orvosi konzultációt követően szedheti a készítményt.
- Ha tünetei 3 napon belül nem enyhülnek, forduljon orvosához.

Egyéb gyógyszerek és a Panadol Rapid 500 mg filmtabletta

Tájékoztassa kezelőorvosát vagy gyógyszerészét a jelenleg vagy a közelmúltban szedett egyéb gyógyszereiről, beleértve a vény nélkül kapható készítményeket is.

A készítmény szedése előtt feltétlenül konzultáljon orvosával, amennyiben:
- metoklopramidot vagy domperidont (ezek a szerek hányinger/hányás ellen használatosak), vagy
- magas koleszterinszint kezelésére szolgáló kolesztiramint szed,
- véralvadásgátlókat (pl. warfarint) szed és hosszú időn keresztül, naponta van szüksége fájdalomcsillapítóra, mert ekkor paracetamolt csak alkalmanként vehet be.

A Panadol Rapid 500 mg filmtabletta alkalmazása alkohollal növeli a paracetamol májkárosító hatását.

Amennyiben Ön *terhes vagy szoptat*, kérje ki orvosa tanácsát a Panadol Rapid 500 mg filmtabletta szedése előtt.

A Panadol Rapid 500 mg filmtabletta nincs hatással a *gépjárművezetéshez és gépek kezeléséhez szükséges képességekre.*

Fontos információk a Panadol Rapid 500 mg filmtabletta egyes összetevőiről: parahidroxi-benzoátokat tartalmaz (E215, E217, E219) tartalmaz, amelyek későbbiekben jelentkező allergiás reakciókat okozhatnak.

Hogyan kell szedni a Panadol Rapid 500 mg filmtablettát

Felnőtteknek, időskorúaknak és 12 éves és annál idősebb gyermekeknek:
- egyszeri adagja 1-2 tabletta, amely szükség esetén 4-6 óránként ismételhető.
- az újabb adag bevételéig legalább 4 órának el kell telnie.
- 24 órán belül ne vegyen be 8-nál több tablettát.

Gyermekeknek 6-11 év között:
- egyszeri adagja 1/2-1 tabletta, amely szükség esetén 4-6 óránként ismételhető.
- az újabb adag bevételéig legalább 4 órának el kell telnie.
- 24 órán belül ne vegyen be 4 tablettánál többet.

6 éven aluli gyermekeknek nem adható.

Gyermekeknek orvosi felügyelet nélkül legfeljebb 3 napig adható.

Kizárólag szájon át történő alkalmazásra! A tablettákat vízzel nyelje le. Ne lépje túl az előírt adagot! Más paracetamol tartalmú készítményekkel együtt nem szedhető.

*Ha az előírtnál több Panadol Rapid 500 mg filmtablettát vett be***:** a paracetamol túladagolása májkárosodást okozhat. Amennyiben az előírt adagnál többet vett be, forduljon azonnal orvoshoz, még akkor is, ha nem érzi rosszul magát!

Lehetséges mellékhatások

Mint minden gyógyszer, így a Panadol Rapid 500 mg filmtabletta is okozhat mellékhatásokat, amelyek azonban nem mindenkinél jelentkeznek.

Nagyon ritka mellékhatások (10000-ből kevesebb mint egy embert érint):
- vérlemezkék számának csökkenése a vérben (trombocitopénia),
- májműködési zavar.

Ha az alábbi tünetek bármelyikét észleli, hagyja abba a gyógyszer szedését és azonnal forduljon orvoshoz:
- mellkasi szorító érzés, kapkodó légzés, kiütés és ájulásos rosszullét (anafilaxiás reakció - az egész szervezetre kiterjedő súlyos, azonnali túlérzékenységi reakció),
- a bőr túlérzékenységi reakciói: bőrkiütés; gyorsan fellépő duzzadása a bőrnek, nyálkahártyáknak, és a nyálkahártya alatti szöveteknek (angiödéma); túlérzékenységi reakció, elsősorban a száj, kötőhártya, nemiszervek bőrén, illetve nyálkahártyáján, szimmetrikus, vöröses kiütések, láz kíséretében (Stevens-Johnson szindróma),
- hörgőgörcs acetilszalicilsavra, vagy egyéb nem szteroid gyulladáscsökkentő gyógyszerre érzékenyeknél.

Hogyan kell a Panadol Rapid 500 mg filmtablettát tárolni

A gyógyszer legfeljebb 30°C-on tárolandó, gyermekektől elzárva tartandó!

Tudományos összefoglaló

Ez a jelentés a Panadol Rapid 500 mg filmtabletta forgalomba hozatali engedélyezési eljárása során végzett tudományos értékelését tartalmazza.
Az eljárás 2011. július 27-én fejeződött be.
Az eljárás lezárása utáni lényeges változtatásokat lásd 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.

Having the submitted quality, relative safety and efficacy data assessed, the National Institute of Pharmacy Directorate of the GYEMSZI issued the marketing authorisation of the Panadol Rapid 500 mg film-coated tablets. The holder of the marketing authorisation is GlaxoSmithKline Consumer Healthcare, GlaxoSmithKline Export Ltd., Brentford, Great Britain.

The active substance is paracetamol. It has been widely used as an analgesic and antipyretic for relief of symptoms of mild to moderate pain and reduction of fever. The analgesic effect of paracetamol is indicated for relief of symptoms of sore throat, headache, muscle pain, migraine, dysmenorrhoea, dental pain and the pain of osteoarthritis. Paracetamol is also indicated as an antipyretic agent for the reduction of fever.

The Summary of Product Characteristics contains the detailed description of the indications and dosage.

This application concerns a national procedure, a line extension to an existing marketing authorisation.

The legal base of the application was the Commission Regulation (EC) No 1234/2008 of 24 November 2008 *concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products*: line extension, according to Annex 1, 2 (b): *change of pharmacokinetics, e.g. rate of release.* Panadol Rapid 500 mg film-coated tablets represent a new formulation, a fast-dissolving paracetamol tablets which has been formulated to have an improved dissolution rate compared to standard paracetamol tablets. The original medicine in the product line of the marketing authorisation holder that wax extended with the present application was the Panadol 500 mg film-coated tablets (OGYI-T-01711), authorised for marketing in 1992 in Hungary.

II. QUALITY ASPECTS

II.1 Introduction

This assessment report relates the national application for marketing authorisation of the Panadol Rapid 500 mg film-coated tablets what is the line extension of the Panadol film-coated tablets authorised earlier.

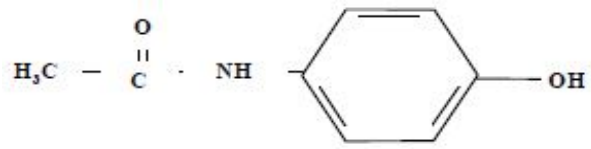
The active principle of the Panadol Rapid 500 mg film-coated tablets is paracetamol what has analgetic and antipyretic effects.

II.2 Active substance

The active substance paracetamol is described in the European Pharmacopoeia (Ph. Eur.).

The Applicant has submitted a Ph. Eur. Certificate of Suitability (CEP) for the drug substance paracetamol. The CEP indicates that the Ph. Eur. monograph is suitable to control the purity of the substance.

Nomenclature:
International non-proprietary name (INN): paracetamol
Chemical name: *N*-(4-hydroxyphenil)acetamide
Structure:



General properties: the active substance is a white or almost white crystalline powder. It is freely soluble in alcohol, sparingly soluble in water and very slightly soluble in methylene chloride. It has not chirality centre.

The substance is specified according to the requirements of the current Ph. Eur. monograph. It includes the following tests for paracetamol: identification, related substances (HPLC), heavy metals, loss on drying (the last solvent is water), sulphated ash and assay. The 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 its quality.

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

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

The reference materials used for the control of the substance are adequately characterized

The re-test period mentioned in the CEP is five years with no special storage conditions.

GMP compliance of the active substance manufacture is demonstrated by the applicant.

II.3 Medicinal Product

The aim of the formulation development was to produce a tablet capable of providing improved paracetamol dissolution compared to standard (already marketed) paracetamol tablets. Changes have been made to the excipients in the formulation to improve the dissolution and absorption characteristics.

As a result of development studies a product with the following composition was obtained. Excipients: pregelatinised starch, calcium carbonate, alginic acid, crospovidone, povidone, magnesium stearate, colloidal silicon dioxid, blend of sodium parabens, Opadry white, carnauba wax and purified water.

All excipients comply with their respective Ph. Eur. monographs, with the exception of blend of sodium parabens and Opadry white that comply with a satisfactory in-house monograph. The final formulation is included in the documentation. Compliance of the product with the general monograph of the Ph. Eur. on *Products with the risk of TSE* has been demonstrated by the applicant.

Data on satisfactory package on development pharmaceutics has been presented. Panadol Rapid 500 mg film-coated tablets are white to off-white film-coated tablets. They are capsule-shaped with convex edges and are debossed with a “P” within a circle on one face and a break line on the other.

A description and flow chart of the manufacturing method has been provided. Appropriate in-process controls are included. Satisfactory batch formulae were also presented. GMP compliance of the manufacturing site has been demonstrated

The finished product specification is adequate. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form monograph of the Ph. Eur. and the ICH Q6A guideline. Appropriate control strategy was selected and presented. The test methods have been described and have been adequately validated. Batch data have been provided and complied with the specification. Certificates of analysis were also provided for the working standard used.

The container closure system of the product is as follows: PVC/Al foil blisters, HDPE bottles closed with screw PP cap or paper/polyethylene sachets.

All plastic materials in contact with the product comply with the current Ph. Eur. monograph.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on their results, a shelf-life of 3 years with storage conditions of "this medicinal product does not require any special storage conditions" is approved.

The pharmaceutical data in the SPC, PIL and label are acceptable.

II.4 Discussion of the chemical, pharmaceutical and biological aspects

The product has been shown to meet consistently the current regulatory requirements with respect to qualitative and quantitative content of the active substance and pharmaceutical form until the end of the approved shelf-life. The manufacture and the quality standards applied adequately support the safe use and efficacy of the product.

III. NON-CLINICAL ASPECTS

No new data are presented in Module 4 (Non-clinical). Therefore, in accordance with Notice to Applicants Volume 2B "Presentation and format of the dossier; CTD", CTD-format Overviews and Summaries are not provided. A Non-Clinical Overview is provided in Module 2 and the content of this is unchanged from the currently approved Expert Report for Panadol 500 mg film-coated tablets, with the exception of the information on excipients.

IV. CLINICAL ASPECTS

IV.1 Introduction

Panadol Rapid 500mg film-coated tablets represent a new formulation, a fast-dissolving paracetamol tablet which has been developed to have an improved tablet dissolution rate compared to standard paracetamol tablets.

IV.2 Pharmacokinetics

IV.2.1 Summary

Results from two pivotal studies (A1900260 and A1900265) comparing the pharmacokinetics of Paracetamol Rapid 500 mg film-coated tablets with standard paracetamol tablets after single dose and replicate dose administration were presented in the submission dossier. The data from the above studies have demonstrated that:

1. Early exposure (rate of absorption) to paracetamol is significantly greater from Panadol Rapid film-coated tablets compared to standard paracetamol tablets. *Panadol Rapid's p*aracetamol can generally be detected in plasma by 10 minutes.
2. Early exposure (rate of absorption) to paracetamol is significantly more consistent for Panadol Rapid film-coated tablets compared to standard paracetamol tablets.
3. Panadol Rapid film-coated tablets are is bioequivalent to standard paracetamol tablets.

Additional results from a human scintigraphy study (A1900279) evaluated the rates of disintegration/dissolution and gastric emptying of Panadol Rapid film-coated tablets versus standard paracetamol tablets after a single dose of radio-labelled study medications. The data showed that the onset of disintegration/dissolution of Panadol Rapid was significantly faster compared to standard paracetamol tablets. The new formulation started to disintegrate within 5 minutes post dose (75% of subjects) in contrast to the standard tablets which showed no instances of onset of disintegration/dissolution within 5 minutes.

IV.2.2 Studies

Pharmacokinetic Study A1900260 was an open, randomized, two-way cross-over study conducted in 40 healthy volunteers. The volunteers received a single 1 g dose of Panadol Rapid 500 mg film-coated tablets and of standard paracetamol tablets after an overnight fast. The primary objective of the study was to compare bioequivalence (AUC0-t, AUC0-∞ and C_{max}) between the two products.

Table 2: Median difference and 95% CI for $AUC_{0\text{-}30\ mins}$ and T_{max} Study A1900260 (n=40)	
	Panadol Tablets(new formula) versus Standard paracetamol tablets
$AUC_{0\text{-}30\ mins}$	
Median difference	1.52
95% CI	0.18, 2.91 (p=0.0318)
$AUC_{0\text{-}60\ mins}$	
Median difference	1.73
95% CI	0.09, 3.88 (p=0.0466)
T_{max} (hr)	
Median difference	-0.25
95% CI	-0.46, -0.08 (p=0.0061)

Table 1: Point estimate and 90% CI for AUC and C_{max}, Study A1900260 (n=40)	
	Panadol Tablets (new formula) versus Standard paracetamol tablets
$AUC_{0\text{-}t}$	
Point estimate	1.02
90% CI	0.98, 1.05
$AUC_{0\text{-}\infty}$	
Point estimate	1.02
90% CI	0.98, 1.05
C_{max}	
Point estimate	1.12
90% CI	0.99, 1.28

The results proved that median $AUC_{0\text{-}30\ minutes}$ and $AUC_{0\text{-}60\ minutes}$ were significantly greater and median T_{max} was significantly faster for Panadol Rapid tablets compared to standard paracetamol tablets. 77% of subjects treated with Panadol Rapid tablets reached the first detectable level of paracetamol in plasma within 10 minutes, compared to 58% of subjects treated with standard paracetamol tablets.

Table 3: Cumulative Frequency Distribution for Time to First Detectable Level (>0.25mcg/ml) of paracetamol in plasma (TLag)

Study A1900260 (n=40)

TLag (min)	Panadol Tablets(new formula) Cumulative freq	%	Standard Paracetamol Tablets Cumulative freq	%
10	30	77	22	58
> 10	39	97.5	39	97.5

Pharmacokinetic Study A1900265 was an open, randomized, replicate dose (eight-way) cross-over study in 76 healthy volunteers. The volunteers received a single 1 g dose on 4 separate days of either Panadol Rapid tablets or standard paracetamol tablets two hours after standard meal. For each treatment, blood samples were taken to 10 hours post-dose after the initial dose and to 4 hours post-dose after the subsequent three doses.

Pharmacokinetic variables were compared after the initial dose of treatment and after replicate dosing. The primary objectives of the study were to compare treatments for

- i) early exposure (rate of absorption - AUC0-30 mins) after both initial and replicate dosing
- ii) inter (between)-subject variability in absorption (after the initial dose) and
- iii) intra (within)-subject variability in absorption (after replicate dosing).

Table 4:
Median difference and 95% CI for early exposure pharmacokinetic variables after initial dosing, Study A1900265 (n=76)

	Panadol Tablets(new formula) versus Standard paracetamol tablets
$AUC_{0\text{-}30\ mins}$	
Median difference	0.77
95% CI	0.53, 1.01 (p<0.0001)
$AUC_{0\text{-}60\ mins}$	
Median difference	2.57
95% CI	1.79, 3.42 (p<0.0001)
C_{pharma} at 30 mins (mcg/ml)	
Median difference	4.15
95% CI	2.76, 5.39 (p<0.0001)
$PDA_{30\ mins}$ (%)	
Median difference	25.28
95% CI	18.28, 33.69 (p<0.0001)
$PDA_{60\ mins}$ (%)	
Median difference	18.63
95% CI	11.16, 26.67 (p<0.0001)
T_{max} (hr)	
Median difference	-0.38
95% CI	-0.59, -0.17 (p=0.0004)

The results proved that $AUC_{0\text{-}30\ mins}$, the median value for Panadol Rapid tablets was very significantly higher versus standard paracetamol tablets after both initial and replicate dosing.

All other early exposure (rate of absorption) pharmacokinetic variables after initial and replicate dosing were also very significantly superior versus standard paracetamol tablets.

In conclusion, both inter (between)-subject and intra (within)-subject variability in early exposure (rate of absorption) were significantly lower for Panadol Rapid tablets compared to standard paracetamol tablets.

Panadol Rapid tablets and standard paracetamol tablets were bioequivalent (AUC and C_{max}).

Table 5: Cumulative Frequency Distribution for Time to First Detectable Level (>0.25mcg/ml) of Paracetamol in Plasma (TLag)
Part a(single dose)
Study A1900265 (n=76)

TLag (min)	Panadol (new formula)		Standard Paracetamol Tablets	
	Cumulative freq	%	Cumulative freq	%
10	62	82	23	30
> 10	76	100	76	100

Table 6:
Median difference and 95% CI for early exposure pharmacokinetic variables after replicate dosing, Study A1900265 (n=75)

	Panadol Tablets versus Standard paracetamol tablets
$AUC_{0\text{-}30\ mins}$	
Median difference	0.99
95% CI	0.81, 1.19 (p<0.0001)
$AUC_{0\text{-}60\ mins}$	
Median difference	2.66
95% CI	2.18, 3.20 (p<0.0001)
C_{plasma} at 30 mins (mcg/ml)	
Median difference	3.88
95% CI	3.09, 4.69 (p<0.0001)
T_{max} (hr)	
Median difference	-0.31
95% CI	-0.43, -0.19 (p<0.0001)

Table 7: Cumulative Frequency Distribution for Time to First Detectable Level (>0.25mcg/ml) of Paracetamol in Plasma (TLag)

Part b(Replicate dose)
Study A1900265 (n=76)

TLag (min)	Panadol Tablets(new formula)		Standard Paracetamol Tablets	
	Cumulative freq	%	Cumulative freq	%
10	67	89	33	43
> 10	76	100	76	100

Table 10: Tmax (hr) difference between Standard Paracetamol Tablets and Panadol (new formula)				
Study	**Median(hr) Standard Paracetamol Tablets**	**Median(hr) Panadol (new formula)**	**Difference (hr)**	**%**
A1900260	0.67	0.5	0.17	25
A1900265 Part a	1.5	1.0	0.5	33
A1900265 Part b	1.5	1.0	0.5	33

Scintigraphy Study A1900279 was an open, randomised two-way cross-over study in *24 healthy male volunteer*s, where single doses of (total 1 g of paracetamol) radio-labelled treatments (^{111}Indium-DTPA) standard paracetamol tablets and Panadol Rapid were administered two hours after a standard radio-labelled breakfast. The primary objective of the study was to assess the time of complete disintegration/dissolution of the tablets. Time to onset of disintegration/dissolution of the tablets and gastric emptying time (onset, t_{50} and t_{90}) were also examined.

The results showed that Panadol Rapid tablets achieved onset of disintegration/dissolution in 75% of subjects within the first 5 minutes, in contrast to the standard Panadol tablets which showed no instances of onset of disintegration/dissolution within 5 minutes.

IV.3 Pharmacodinamics

No new data were submitted corresponding to the type of the application.

IV.4 Clinical efficacy

Paracetamol is widely used as an analgesic for relief of symptoms of mild to moderate pain and reduction of fever. The analgesic effect of paracetamol is indicated for relief of symptoms of sore throat, headache, muscle pain, migraine, dysmenorrhoea, dental pain and the pain of osteoarthritis. Paracetamol is also indicated as an antipyretic agent for the reduction of fever. The applicant provided a detailed review from the published literature of the well established efficacy of paracetamol in alleviating these symptoms.

IV.5 Clinical safety

The overall safety profile of products containing paracetamol is well established with extensive safety monitoring conducted on all currently marketed formulations. The applicant presented a critical analysis of paracetamol safety data, as well as its Post Marketing Experience with regards to the GSK Safety Database.

In addition, the applicant provided clinical safety data from Panadol Rapid 500 mg film-coated tablets pharmacokinetic and scintigraphy Studies (see V.2.2).

IV.6 Discussion of the clinical aspects

Both the literature summaries and the pharmacokinetic studies submitted are adequate. There is no objection against granting the marketing authorization from clinical point of view.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Panadol Rapid 500mg film-coated tablets represent a new formulation, a fast-dissolving paracetamol tablet which has been developed to have an improved tablet dissolution rate compared to standard paracetamol tablets.

The application meets the administrative and scientific requirements. The fast-dissolving character (in comparison with common paracetamol tablets) has been demonstrated by the applicant.

The analgesic and antipyretic efficacy of paracetamol has been clearly demonstrated in well controlled clinical trials. The published literature and post marketing experience with paracetamol indicates that it is a safe drug when taken in therapeutic doses.

There is no objection against granting the marketing authorization.

V.1 Conditions for the marketing authorisation

V.1.1 Requirements for specific post-marketing obligations

Not needed.

V.1.2 Pharmacovigilance system

The pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant 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.

V.1.3 Risk Management Plan

No Risk Management Plan has been appended to the application according to the guideline EMEA/CHMP/96268/2005. There is no need for any other special pharmacological study or risk minimisation activity.

V.1.4. Periodic Safety Update Report (PSUR)

The one year PSUR cycle with the harmonised birthday and Data Lock Point recommended by the applicant has been accepted.

V.1.5 Legal status

Non-prescription medicine.

V. 2 Summary of Product Characteristics (SmPC)

The SmPC is 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. UPDATE: STEPS TAKEN AFTER THE INITIAL PROCEDURE WITH AN INFLUENCE ON THE PUBLIC ASSESSMENT REPORT

This module reflects the procedural steps and scientific information after the finalisation of the initial procedure.

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval or non approval	Assessment report attached
Type II variation, C.I.z for updating the information in Section 5.1 of the SmPC; update of the Product Information according to the newest QRD-template	OGYI/21544/2012	Yes	14.06.2012	02.08.2012	Approval	No