# Publikus értékelő jelentés

**Termék neve:**

**Dalnessa 4 mg/5 mg, 4 mg/10 mg, 8 mg/5 mg és 8 mg/10 mg tabletta**

**perindopril/amlodipin**

**Törzskönyvi szám:**

**OGYI-T-21727**

**A forgalomba hozatali engedély jogosultja:**

**Pharma-Regist Kft. Budapest**

**Kelt: 2013. április 18.**

# TARTALOM

# NEM EGÉSZSÉGÜGYI SZAKEMBEREKNEK SZÓLÓ ÖSSZEFOGLALÓ

A Gyógyszerészeti és Egészségügyi Minőség- és Szervezetfejlesztési Intézet (GYEMSZI) Országos Gyógyszerészeti Intézet főigazgatósága értékelte a Dalnessa 4 mg/10 mg, 4 mg/8 mg, 8 mg/5 mg és 8 mg/10 mg tablettákra 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 hatóanyagai: perindopril-erbumin/amlodipin-bezilát.

Egyéb összetevők: nátrium-hidrogén-karbonát mikrokristályos cellulóz (E460), hidegen duzzadó keményítő, karboximetilkeményítő-nátrium, vízmentes kolloid szilícium-dioxid, magnézium-sztearát (E572).

Külső:
- *Dalnessa 4 mg 5mg*: fehér vagy csaknem fehér, kerek, mindkét oldalán enyhén domború felületű metszett élű tabletta.
- *Dalnessa 4 mg 10mg tabletta:* fehér, vagy csaknem fehér kapszula alakú tabletta mindkét oldalán domború felületű, egyik oldalán törővonallal. A törővonal csak a széttörés elősegítésére és a lenyelés megkönnyítésére szolgál, nem arra, hogy a készítményt egyenlő adagokra ossza.
- *Dalnessa 8 mg 5mg tabletta:* fehér, vagy csaknem fehér, kerek mindkét oldalán domború felületű metszett élű tabletta.
- *Dalnessa 8 mg 10mg tabletta: f*ehér, vagy csaknem fehér, kerek mindkét oldalán domború felületű metszett élű tabletta egyik oldalán törővonallal. A tabletta egyenlő adagokra osztható.

A tabletták OPA/Al/PVC//Al buborékcsomagolásban és dobozban kerülnek forgalomba.

## Milyen típusú gyógyszer a Dalnessa és milyen betegségek esetén alkalmazható

A Dalnessa a magas vérnyomás betegség (hipertónia) kezelésére és/vagy az egyensúlyban lévő szívkoszorúér-betegség (az az állapot, amikor a szív vérellátása csökkent vagy megszűnt) kezelésére szolgál. Azok a betegek, akik már szednek perindoprilt és amlodipint külön-külön tabletták formájában, kaphatják a Dalnessát, amely mindkét hatóanyagot tartalmazza.

Az Dalnessa két hatóanyag kombinációjából áll, a perindoprilból és az amlodipinből. A perindopril egy ACE (angiotenzin konvertáló enzim) gátló. Az amlodipin egy kalcium-antagonista (amely az úgynevezett „dihidropyridinek” gyógyszer-osztályhoz tartozik). Együttes hatásuk nyomán a vérerek kitágulnak és ellazulnak, azért, hogy a vér könnyebben tudjon áramlani rajtuk keresztül, és ezáltal a szívnek könnyebb legyen fenntartani a megfelelő véráramlást.

**Tudnivalók a Dalnessa szedése előtt**

*Ne szedje az Dalnessát*
- ha allergiás (túlérzékeny) a perindoprilra vagy bármely más ACE-gátlóra, illetve az amlodipin-bezilátra vagy bármely más dihidropiridinre vagy a Dalnessa egyéb összetevőjére,
- ha Ön szoptat (lásd „Terhesség és szoptatás”),
- ha több mint 3 hónapos terhes (a terhesség korai szakaszában is jobb kerülni a Dalnessa szedését, lásd „Terhesség és szoptatás”),
- ha Ön korábban ACE-gátló kezelés kapcsán az alábbi tüneteket tapasztalta: nehézlégzés, arc- vagy nyelvduzzanat, intenzív viszketés vagy súlyos bőrkiütések – illetve ha Ön vagy a családjából bárki hasonló tüneteket észlelt bármely más körülmények között (angioödémának nevezett állapot),
- ha Ön sokkban van (eszméletvesztéshez vezető súlyos vérnyomásesés), ideértve a szívproblémák okozta sokkot is,
- ha Önnek nagyon alacsony a vérnyomása (súlyos hipotenziója van),
- ha szívelégtelenségben szenved (amikor a szív nem képes elegendő vért pumpálni és ez nehézlégzést vagy a végtagok, pl a láb, a boka és a lábfej duzzadását okozza) heveny szívroham után,
- ha Önnek a szívből kivezető fő vérerében a szűkület van, ami miatt a szív baloldán nehezebb a vér kipumpálása (pl . aorta sztenózis).

*A Dalnessa fokozott elővigyázatossággal alkalmazható*
- ha Önnek hipertrófiás kardiomiopátiája (szívizom betegség) vagy veseartéria sztenózisa (a vesét vérrel ellátó verőér szűkülete) van,
- ha bármely más szívbetegségben szenved,
- ha májkárosodása van,
- ha vesebe problémai vannak, illetve ha Ön művese kezelésben részesül,
- ha kollagén érbetegsége (kötőszövet betegsége) van, mint például szisztémás lupusz eritematózusz vagy szkleroderma,
- ha cukorbeteg,
- ha Ön korlátozott sóbevitelű diétán van vagy kálium tartalmú sópótlásban részesül (a vér kálium tartalmának a megfelelő egyensúlya alapvető jelentőségű).

Feltétlenül beszéljen orvosával, ha úgy gondolja, hogy teherbe esett vagy teherbe eshet. A Dalnessa tabletta alkalmazása korai terhességben nem javasolt, a 3. hónap után pedig tilos szedni, mert ebben az időszakban súlyosan károsíthatja a babát (lásd „Terhesség és szoptatás”).

Ha Ön Dalnessát szed, ugyancsak tájékoztassa orvosát vagy az egészségügyi személyzetet, ha
- általános anesztéziában végzendő és/vagy nagyobb műtéti beavatkozás előtt áll,
- nemrég hasmenésben vagy hányással járó betegségben szenvedett, vagy jelenleg szenved,
- LDL aferezis (a koleszterin géppel történő eltávolítása a véréből) előtt áll,
- deszenzibilizációs kezelés előtt áll annak érdekében, hogy méh- vagy darázscsípés allergiáját mérsékeljék.

A Dalnessa adása nem javasolt gyermekeknek és serdülőkorúaknak.

*A kezelés ideje alatt szedett egyéb gyógyszerek*: feltétlenül tájékoztassa kezelőorvosát vagy gyógyszerészét a jelenleg vagy nemrégiben szedett egyéb gyógyszereiről, beleértve a vény nélkül kapható készítményeket is.

*Kerülendő a Dalnessa egyidejű szedése* az alábbi gyógyszerekkel:
- lítium (mánia vagy depresszió kezelésére használják),
- esztramusztin (daganatos megbetegedések kezelésére használják),
- káliummegtakarító vízhajtók (spironolakton, triamteren), kálium-pótló szerek, káliumot tartalmazó sópótló szerek.

A Dalnessa-kezelést egyéb gyógyszerek befolyásolhatják. Feltétlenül tájékoztassa kezelőorvosát, amennyiben az alábbi gyógyszerek valamelyikét szedi, mert ez különleges elővigyázatosságot igényelhet:
- egyéb, magas vérnyomás kezelésére szolgáló gyógyszerek, ideértve a vízhajtókat (olyan gyógyszerek, amelyek fokozzák a vesék által termelt vizelet mennyiségét) is,
- fájdalomcsillapításra szedett nem-szteroid gyulladásgátló szerek (pl. ibuprofén) vagy nagy dózisú aszpirin,
- cukorbetegség kezelésére szolgáló gyógyszerek (mint pl. inzulin),
- bizonyos mentális betegségek, mint depresszió, szorongás, vagy skizofrénia kezelésére használatos gyógyszerek (pl. triciklusos antidepresszánsok, antipszichotikumok, imipramin-szerű antidepresszánsok, neuroleptikumok),
- autoimmun betegségekben és transzplantáció után használt immunszupresszánsok (olyan gyógyszerek, amelyek mérséklik a szervezet védekező mechanizmusának a működését) – pl. ciklosporin,
- allopurinol (köszvény kezelésére szolgál),
- prokainamid (szabálytalan szívverés kezelésére szolgál),
- vazodilatátorok, ideértve a nitrátokat is (olyan készítményeket, amelyek tágítják a vérereket),
- heparin (vérhígításra használt gyógyszerek),
- efedrin, noradrenalin vagy adrenalin (alacsony vérnyomás, sokk vagy asztma kezelésére használt gyógyszerek),
- baklofén (izommerevség kezelésére használják olyan betegségekben, mint pl. a szklerózis multiplex),
- bizonyos antibiotikumok, mint pl. rifampicin,
- epilepszia kezelésére szolgáló gyógyszerek, mint pl. karbamazepin, fenobarbitál, fenitoin, foszfenitoin, primidon,
- itrakonazol, ketokonazol (gombás fertőzések kezelésére szolgáló gyógyszerek),
- a megnagyobbodott prosztata kezelésére szolgáló alfa-blokkolók, mint pl. prazozin, alfuzozin, doxazozin, tamzulozin, terazozin,
- amifosztin (daganatos megbetegedéseknél alkalmazott gyógyszeres, illetve sugárterápia mellékhatásainak megelőzésére, illetve mérséklésére szolgál),
- kortikoszteroidok (különféle betegségek kezelésére – ideértve a súlyos asztmát és a reumatoid artritiszt – használatosak),
- arany-sók, különösen intravénásan adagolva (reumatoid artritisz tüneti kezelésére szolgál).

A Dalnessát étkezés előtt kell bevenni.

*Terhesség és szoptatás*

*Terhesség:* ha úgy gondolja, hogy terhes (vagy teherbe eshet), közölje ezt kezelőorvosával. Az orvosa valószínűleg azt fogja javasolni, hogy hagyja abba a Dalnessa szedését a teherbe esést megelőzően, vagy amint kiderül, hogy terhes, és azt fogja javasolni, hogy váltson más gyógyszerre a Dalnessa helyett. A Dalnessa alkalmazása a terhesség első három hónapja alatt nem javasolt, a terhesség negyedik hónapjától kezdve pedig kifejezetten tilos, mivel a terhesség 3. hónapja után szedve súlyosan károsíthatja a magzatot.

*Szoptatás*: tájékoztassa orvosát, ha szoptat, vagy a közeljövőben szoptatni fog. A Dalnessa szoptató anyák számára nem ajánlott, és orvosa valószínűleg más kezelésre fog áttérni, amikor Ön szoptatni szeretne, különösen, ha a baba újszülött, vagy koraszülött.

*A készítmény hatásai a gépjárművezetéshez és gépek kezeléséhez szükséges képességekre*

A Dalnessa nem befolyásolja az éberséget, ám szédülés vagy gyengeség jelentkezhet az alacsony vérnyomás miatt, és ez befolyásolhatja a gépjárművezetéshez és gépek kezeléséhez szükséges képességet. Ezért ne vessen ne vezessen gépjárművet és ne kezeljen gépeket amíg nem tudja biztosan, hogy ez a gyógyszer milyen hatással van Önre.

## Hogyan kell szedni a Dalnessát

Gyógyszerét egy pohár vízzel, lehetőleg mindennap ugyanabban az időpontban, reggel étkezés előtt vegye be. Kezelőorvosa dönt az Önnek megfelelő dózis felől. Ez rendszerint naponta egy tabletta lesz. A Dalnessát általában olyan betegeknek rendelik, akik már szedik a perindoprilt és az amlodipint külön-külön tabletta formájában.

*Ha az előírtnál több Dalnessát vett be*: lépjen kapcsolatba a legközelebbi kórházzal vagy azonnal tájékoztassa kezelőorvosát. Túladagolás esetén a legvalószínűbb következmény az alacsony vérnyomás, amely szédülést vagy ájulást okozhat. Amennyiben ez előfordul, a fekvő testhelyzet felemelt lábakkal segíthet.

*Ha elfelejtette bevenni a Dalnessát*

Fontos, hogy gyógyszerét mindennap bevegye, mert a rendszeres kezelés hatékonyabb. Mindazonáltal, ha elfelejtett bevenni egy adag Dalnessát, a következő dózist a szokott időben vegye be. Ne vegyen be kétszeres adagot a kihagyott adag pótlására.

*Ha idő előtt abbahagyja az Dalnessa szedését*

Tekintettel arra, hogy az Dalnessával folytatott kezelés általában egész életen át tart, beszéljen kezelőorvosával, mielőtt abbahagyja a tabletta szedését.

**Lehetséges mellékhatások**

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

Ha az alábbi tünetek bármelyikét észleli, azonnal hagyja abba a készítmény szedését, és haladéktalanul értesítse kezelőorvosát
– az arc, az ajkak, a száj, a nyelv vagy a torok duzzanata, légzési nehezítettség,
– súlyos szédülés vagy ájulás,
– szokatlanul gyors vagy szabálytalan szívverés.

Egyéb mellékhatások*:*
- *gyakori* (100 beteg közül 1-10 beteget érint):
  - fejfájás, megszédülés, forgó jellegű szédülés, tűszúrás szerű fájdalom, álmosság,
  - látászavarok, fülzúgás (hangok érzékelése a fülekben),
  - nagyon gyors szívverés (palpitáció), forróság vagy melegség érzése az arcon, szédülékenység az alacsony vérnyomás miatt,
  - köhögés, légszomj,
  - émelygés (hányinger), hányás, hasi fájdalom, ízérzés zavarok, diszpepszia vagy emésztési zavar, hasmenés, székrekedés,
  - allergiás reakciók (mint pl. bőrkiütések, viszketés),
  - izomgörcsök, fáradtság, ödéma (lábszár- vagy boka-duzzanat);
- *nem gyakori* (1000 beteg közül 1-10 beteget érint):
  - hangulatváltozások, alvászavarok, remegés, átmeneti eszméletvesztés, fájdalomérzés kiesése, orrdugulás vagy orrfolyás, székelési szokások megváltozása,
  - hajhullás, vörös vagy elszíneződött foltok a bőrön,
  - hát-, izom- vagy ízületi fájdalom, mellkasi fájdalom,
  - fokozott vizelési inger, különösen az éjszaka folyamán,
  - rossz közérzet, mellkasi szorítás, zihálás, légszomj, szájszárazság, angioödéma (tünetei: fulladás, arc- vagy nyelvduzzanat),
  - veseproblémák, impotencia, fokozott verejtékezés, férfiaknál emlőduzzanat,
  - súlygyarapodás vagy súlycsökkenés;
- *nagyon ritka* (10 000 beteg közül kevesebb, mint 1 beteget érint):
  - zavartság, kardiovaszkuláris rendellenességek (szabálytalan szívverés, anginás roham, szívinfarktus, szélütés),
  - eozinofil tüdőgyulladás (a tüdőgyulladás egy ritka formája),
  - eritéma multiforme (egy olyan bőrkiütés, amely gyakran kezdődik az arcon, karokon, lábakon vörös, viszkető foltokkal),
  - vérkép-, hasnyálmirigy-, gyomor- vagy máj-rendellenességek,
  - perifériás neuropátia (olyan betegség, amikor az érzékelés, fájdalomérzés és az izmok működtetésének a képesssége csökken), izomtónus kóros fokozódása, a bőr vérereinek gyulladása, ínyduzzanat, magas vércukor.

**Hogyan kell a Dalnessát tárolni**

A fénytől és a nedvességtől való védelem érdekében az eredeti csomagolásban tárolandó. A gyógyszer gyermekektől elzárva tartandó!

# Tudományos összefoglaló

**Ez a modul a Dalnessa 4/5 mg, 4/10 mg, 8/5 mg és 8/10 mg tabletta forgalomba hozatali engedélyezési eljárása során végzett tudományos értékelését tartalmazza.**
**Az eljárás 2012. június 1-én fejeződött be.**
**Az eljárás lezárása utáni lényeges változtatásokat ld. a "Módosítások" modulban.**

# I. INTRODUCTION

After careful assessment of its quality and therapeutic benefit/risk ration the National Institute of Pharmacy Directorate of GYEMSZI issued marketing authorisation for Dalnessa 4 mg/5 mg, 4 mg/10 mg, 8 mg/5 mg and 8 mg/10 mg tablets. The holder of the marketing authorisation is Pharma-Regist Kft. (Budapest).

The active principles are perindopril and amlodipine.

The application was filed according to Article 7(11) of the Decree No 52/2005 (18 November 2005) EüM of the Minister of Health on *marketing authorisation of medicines for human use* (national procedure, fixed combination). Literature data were presented as the non-clinical justification for the combination of perindopril and amlodipine, based on their synergistic effects on several pathophysiological mechanisms while, as clinical proof, the applicant performed one bioequivalence trial establishing the essential similarity of Dalnessa tablets with two established monocomponent preparations (Prexanil, perindopril, Servier and Istin, amlodipine, H. Mach). Moreover, inn order to further support the evidence of well established use of the free combination the applicant provided supporting evidence from 5 EU markets.

The indication of the Dalnessa tablets is substitution therapy for patients suffering from hypertension or chronic stable angina already adequately controlled with perindopril and amlodipine monocomponent tablets given concurrently in the same doses.

Detailed description of the indication and dosage is in the Summary of Product Characteristics.

# II. QUALITY ASPECTS

## II.1 Introduction

This fixed combination (4 mg/5 mg, 4 mg/10 mg, 8 mg/5 mg, 8 mg/10 mg) of the ACE inhibitor perindopril erbumine and the calcium antagonist amlodipine besylate is indicated as substitution therapy for treatment of hypertension and/or stable coronary artery disease, in patients already controlled with perindopril and amlodipine given concurrently at the same dose level.

Perindopril arginine/amlodipine besylate containing tablets Armixxam and Covercard/Servier were authorised for marketing in 2008 in Hungary. They have also been marketed since then, but in different dosage strengths.

To support the present application a bioequivalence study has been performed with co-administered products Prexanil 8 mg (Servier) and Istin 10 mg (Heinrich Mack Nachf. GmbH & Co. KG).

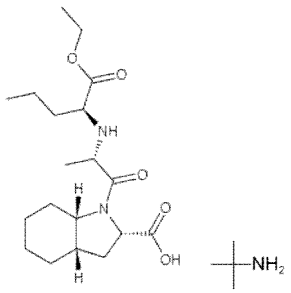
The Dalnessa tablets will be marketed in dosage strengths 4 mg/5 mg, 4 mg/10 mg, 8 mg/5 mg or 8 mg/10 mg of the active substances of perindopril erbumine/amlodipine besylate, respectively, in dose proportional or semi dose proportional formulations, packaged in OPA/Al/PVC//Al blisters and box.

## II.2 Drug Substances

### *II.2.1 Perindopril erbumine*

The applicant indicated to follow a European Drug Master File (EDMF) procedure for polymorph form α of perindopril erbumine. Letter of access for the EDMF has been submitted. Perindopril erbumine is described in the European Pharmacopoeia (Ph. Eur.)

INN name: perindopril erbumine
Chemical name: 2-Methylpropan-2-amine(2S,3aS,7aS)-1-((S)-2-((S) -1- ethoxy- 1 -oxo-pentan-2 ylamino)propanoyl)octahydro-1H-indole-2-carboxylate
Structure:



The active substance is a white or almost white, slightly hygroscopic crystalline powder and is freely soluble in water and in ethanol. It shows polymorphism. Perindopril erbumine exists in hydrate forms and in anhydrous polymorphic forms demonstrated as α, β and γ modifications.

The molecule has five asymmetric centres, thus, theoretically 32 stereo isomers can exist. Stereo chemical purity is routinely controlled according to the Ph. Eur. method.

The proposed manufacturing process has been adequately described; critical steps and corresponding in-process controls have been defined to ensure quality of the final substance.

In-process controls performed during the synthesis are suitable to control the reaction progress. Appropriate specifications for starting materials, solvents and reagents have been established.

Evidence of the structure has been confirmed by elementary analysis, mass spectra, and NMR spectra and by FT-IR spectra. Polymorphism is controlled by X-ray powder diffraction test which is routinely performed as an in-process control to demonstrate the consistency of the manufacturing process.

Potential impurities originating from starting materials, intermediates, by-products, and degradation products have been discussed in respect of their origin and potential carry-over into the final drug substance.

The substance is specified according to the requirements of the current Ph. Eur. monograph, additional specification have been set for heavy metals and residual solvents used in the last step of the synthesis (routinely controlled by a GC method).

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

The Ph. Eur. specification includes the following tests for perindopril erbumine: appearance, solubility, identification (specific optical rotation, IR, TLC), impurity A (TLC), stereo chemical purity (HPLC), related substances (HPLC), water content, sulphated ash, assay (titration). The specification is in accordance also with the Ph. Eur. general monograph on *Substances for pharmaceutical use* and the ICH Q6A guideline.

Testing methods not described in details in the Pharmacopoeia are adequately drawn up and sufficiently validated. Reference materials used for the control of the substance are adequately characterised.

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.

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

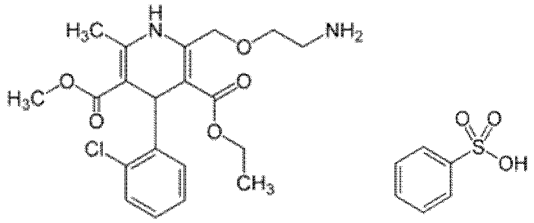
During the stability studies no significant changes in any parameters were observed. The proposed retest period of 2 years is supported by the submitted stability data with the storage condition: "*Do not store above 25°C. Store in the original packaging, in order to protect from moisture*".

GMP compliance of the API manufacturer has been demonstrated.

### *II.2.2 Amlodipine besylate*

The Applicant has submitted a Ph. Eur. *Certificate of Suitability* (CEP) for drug substance amlodipine besylate. The CEP indicates that the Ph. Eur. monograph is suitable to control the purity of the substance, provided that it is supplemented with a test for residual solvents by GC.

INN name: amlodipine besylate
Chemical name: 3-ethyl-5-methyl-2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate benzenesulphonate
Structure:




The active substance is a white to almost white powder slightly soluble in water, freely soluble in methanol, sparingly soluble in ethanol, slightly soluble in 2-propanol.

The substance is specified according to the requirements of the current Ph. Eur. monograph; additional specification has only been set for residual solvents.

The Ph. Eur. specification includes the following tests for amlodipine besylate: appearance, solubility, identification (IR), optical rotation, related substances (HPLC), water content, and sulphated ash, assay (HPLC). Residual solvents (GC) are also controlled. 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 the quality of the drug substance.

Residual solvent method not described in the Pharmacopoeia is adequately drawn up and sufficiently validated.

Reference materials used for the control of the substance are adequately characterized

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

The re-test period mentioned in the CEP is five years.

GMP compliance of the API manufacturer has been demonstrated by the Applicant.

## II.3 Medicinal Product

The medicinal products are immediate release tablets containing a fixed combination of perindopril erbumine form α and amlodipine besylate.

The aim of the formulation development was to develop a single fix combination formulation containing perindopril erbumine and amlodipine besylate in different dosage strengths. Combinations of perindopril and amlodipine are already approved, the manufacturer is Servier, but they are marketed in different dosage strengths.

This formulation study was based on the development of the single entities of perindopril erbumine tablets and amlodipine tablets, in terms of both formulation and process. The formulation development was performed on Perindopril erbumine/Amlodipine 8 mg/10 mg tablets.

All four products have the same qualitative composition, two strengths of tablets (4 mg/5 mg and present developed 8 mg/10 mg) are dose-proportional, while the two other strengths of the tablets are semi dose-proportional (4mg/10 mg and 8 mg/5mg). They are manufactured according to the same manufacturing directions.

Satisfactory package of data on development pharmaceutics has been presented. Brief discussion on reasons for inclusion and quantity of excipients has been provided. The compositions and the pharmaceutical tests evaluated during development of the final formulation are included in the documentation.

The excipients used in the finished product are microcrystalline cellulose, starch pregelatinised, sodium starch glycolate, sodium hydrogen carbonate, colloidal anhydrous silica and magnesium stearate. All excipients used comply with their respective Ph. Eur. monographs. Compliance of the product with the general monograph of the Ph. Eur. regarding the *risk of TSE* has been demonstrated by the applicant. The function related characteristics of the excipients has been discussed.

As regards dissolution and impurity profile the product is shown to be similar to the reference monocomponent products.

Dalnessa 4 mg/5 mg tablets are presented as white to almost white, round, slightly biconvex tablets with bevel edges.

Dalnessa 4 mg/10 mg tablets are presented as white to almost white, capsule shaped, biconvex, one-side scored tablets.

Dalnessa 8 mg/5 mg tablets are presented as white to almost white, round, biconvex tablets with bevel edges.

Dalnessa 8 mg/10 mg tablets are presented as white to almost white, round, biconvex, one-side scored tablets with bevel edges. The tablet can be divided into equal halves.

Description and flow chart of the manufacturing method have been provided. Appropriate in-process controls are included in the manufacturing process. Satisfactory batch formulae were also presented. Validation data on three industrial scale batches are presented. GMP compliance of the manufacturing sites 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 European pharmacopoeia and the ICH Q6A guideline. Appropriate control strategy was selected. Certificates of analysis for the batches involved in the bioequivalence study are presented.

Standard pharmacopoeial test methods are used in respect of disintegration, uniformity of dosage units by content uniformity, microbiological purity. Validated analytical methods have been presented for assay, test for impurities and degradation products, as well as dissolution test (HPLC method).

According to dissolution characteristics of the products, batch and stability data the proposed specification limit is justified and therefore acceptable.

Batch data have been provided and complied with the specification set by the manufacturer. Certificates of analysis were also provided for the working standard used.
The tablets are packed into OPA/Al/PVC//Al blisters. IR spectra and certificates of analysis justifying the conformity to the Ph. Eur. monograph No 3.1.11. as well as compliance with European requirements (78/142/EEC and 1935/2004/ EC) are provided.

Finished product stability studies have been conducted in accordance with the current guidelines.
Based on the presented results, a shelf-life of 24 months when "*stored in the original packaging in order to protect from moisture and light"* is approved.

The Summary of Product Characteristics, package 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 respect to qualitative and quantitative content of the active substance and pharmaceutical form 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 products. From chemical-pharmaceutical point of view the products are approvable.

# III. NON-CLINICAL ASPECTS

## III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of both perindopril and amlodipine are well known. The non-clinical dossier is based on a review of published literature; some study reports from studies conducted by the applicant with amlodipine maleate and amlodipine besylate are also included.

As perindopril/amlodipine combination is indicated for substitution therapy only for hypertension and chronic stable angina and the scientific knowledge and clinical experience is vast, no further non-clinical studies are required. Overview based mostly on literature review is, thus, appropriate.

## III.2 Pharmacology

### *III.2.1 Perindopril*

Perindopril is a prodrug; it exerts its angiotensin converting enzyme (ACE)-inhibitory effect by the main metabolite perindoprilate. By inhibiting ACE it reduces the production of angiotensin II, a potent vasopressor thus dilates blood vessels. Angiotensin II also stimulates aldosterone release consequently increasing plasma volume and excreting potassium. Therefore the lower plasma level of angiotensin II leads to decreased aldosterone secretion as well. Furthermore, as ACE is involved in the metabolism of bradykinin the higher level of bradykinin may also contribute to the vasodilatory effect of perindopril.

*In vivo* studies show, under various experimental conditions in normotensive, renovascular hypertensive, spontaneously hypertensive animals and experimental models of heart failure, that perindopril inhibits the pressor response to angiotensin II and induces the predicted modifications in the plasma levels of the components of the renin-angiotensin-aldosterone system (RAS): raised plasma renin activity, raised angiotensin I and decreased angiotensin II and aldosterone.

ACE inhibitors may display antidepressant-like properties in rats.

### *III.2.2 Amlodipine*

Amlodipine belongs to the dihydropyridine $Ca^{++}$-channel blockers. It inhibits the calcium influx through the L-type (slow) $Ca^{++}$-channels. As calcium is an essential mediator of smooth muscle contraction amlodipine relaxes smooth muscles especially the blood vessels. Amlodipine also inhibits calcium influx through cardiac muscle but this effect is less pronounced than the relaxation of the peripheral arterioles. It mainly produces peripheral vasodilation and subsequent reduction in systemic vascular resistance, which leads to reduction in blood pressure.

*In vivo* pharmacodynamic studies in several animal models of hypertension, after single or repeated administration, demonstrated effective antihypertensive action following oral or intravenous administration. In addition to its antihypertensive action, amlodipine was demonstrated to have antiatherosclerotic effects, beneficial effects on renal function as well as cardioprotective effects.

### *III.2.3 Perindopril/amlodipine combination*

Perindopril or amlodipine alone or the combination of low doses of each agent was administered orally to stroke-prone spontaneously hypertensive rats (SHRSP) for 4 weeks to compare the hypotensive or cardiovascular effects. Perindopril (2 mg/kg) or amlodipine (3 mg/kg) alone caused comparable hypotensive effects in SHRSP. The combination of perindopril and amlodipine was more effective in the treatment of cardiac and vascular diseases than the monotherapy with each agent.

Anti-remodelling properties of amlodipine and perindopril in pulmonary hypertensive rats were investigated in hypoxic pulmonary hypertensive rats. Medial thickening of pulmonary arteries (30–500 μm o.d.) was attenuated by amlodipine whereas it was totally prevented by the combination treatment (amlodipine (10 mg/kg/day, p.o.) + perindopril (30 mg/kg/day, p.o.); neomuscularisation of small alveolar arteries (assessed from critical closing pressure in isolated perfused lungs) was not affected.

Pulmonary vascular resistance (isolated perfused lungs) was reduced by both treatment regimes but only combination treatment reduced right ventricular hypertrophy.

## III.3 Pharmacokinetics

### *III.3.1 Perindopril*

Perindopril is a prodrug and is rapidly absorbed after oral administration. It is extensively metabolised in the liver to the active metabolite perindoprilat and other, inactive, metabolites including glucuronides. Peak plasma concentrations are achieved 3 to 4 hours after an oral dose of perindopril. Perindoprilat is about 10–20 % bound to plasma proteins in humans. The binding of perindopril and percentage of bound drug or metabolite is below that which would be expected to cause drug interactions.

Perindopril crosses the blood-brain barrier and inhibited brain ACE at high doses. Milk of lactating rats contained radioactivity following administration $^{14}$C-perindopril. It is not known whether perindopril is secreted in human milk.
Perindopril is excreted predominantly in urine in humans, but the main excretory route in laboratory species was via the faeces.

### *III.3.2 Amlodipine*

Amlodipine is almost completely absorbed after oral administration, peak plasma concentrations are achieved slowly (2-7 hours post-dose). The drug substance is widely distributed and extensively bound to plasma proteins (94 % in rats, 97 % in dogs and 97% in man).

Metabolism studies indicated extensive biotransformation of the drug in laboratory animal species and humans. The major metabolic pathways are initial oxidation of the dihydropyridine ring to the pyridine analogue, side chain oxidation and hydrolysis of one or both side chain ester groups.

Only small amounts of unchanged drug (up to 4 % dose) were determined in the urine of rats, dogs and man. Amlodipine metabolites are excreted via kidney and gastrointestinal tract. No difference between besylate and maleate salts of amlodipine was found.

## III.4 Toxicology

### *III.4.1 Single dose toxicology*

*Perindopril*

The $LD_{50}$ values in mice and rats are higher than 2000 mg/kg and in dogs higher than 1000 mg/kg after oral administration indicating low toxicity of perindopril.

*Amlodipine*

Single dose administration of amlodipine besylate in rats resulted in a moderate toxicity after oral dosing. The $LD_{50}$ values were between 250 and 700 mg/kg. Mice seemed to be more sensitive to the toxic action of orally administered amlodipine than rats. In single-dose toxicity studies with amlodipine besylate performed in mice, $LD_{50}$ values were in the range between 30 and 45 mg/kg.

### *III.4.2 Repeated dose toxicity*

*Perindopril*

The minimum oral lethal dose of perindopril was greater than 100 mg/kg and about 1024 mg/kg in rat and monkey, respectively. The maximum tolerated oral dose was about 30 mg/kg about 64 mg/kg in rats and monkey, respectively. Perindopril (1 mg/kg/day) (about 3 times the maximum recommended human doses (16 mg) assuming a 50 kg adult) was well tolerated in rats in 3- and 6-months oral study. Toxic effects were more pronounced at the 30 mg/kg/day of perindopril in 3 months study. Generally, male rats were more sensitive than female rats to the toxic effects of perindopril. Doses of 3 and 12 mg/kg altered renal function to cause osmotic nephrosis in 6-months study in rats. This was reversible after 6 weeks of no treatment.

Monkeys well tolerated perindopril at oral doses up to 10 mg/kg and up to 16 mg/kg/day for 13 weeks and 52 weeks, respectively. Monkeys also well tolerated perindopril at very high dosages up to and including the 200 mg/kg/day in repeated administration (4-9 weeks). From 250 mg/kg/day on up to 450 mg/kg/day, depending on animal individual sensitivities, behavioural alterations as well as body weight loose could appear and a significant rise of blood urea and creatinine was seen. Stoppage of the treatment led to a very rapid reduction of clinical symptoms and to a return to normal, within less than one week.

In general, perindopril and perindoprilat were well tolerated in long-term animal (rat, dog, monkeys) studies at the lower dosages. The applied doses were sometimes higher than were the maximum recommended human doses (16 mg) assuming a 50 kg adult. Toxic effects were pronounced in kidneys at higher doses and were reversible after stopping the treatment.

*Amlodipine*

Results of repeat-dose toxicity studies revealed evidence that body weight gain was altered when either maleate or besylate salt of amlodipine were administered orally in rats at doses between 15 and ≥30 mg/kg/day. Higher doses needed shorter time of dosing to suppress weight gain that did lower ones. Similarly, mortality was registered at doses higher than 20 mg/kg/day when the drug substance was administered for 1 month or more, and no differences were noted among two amlodipine salts. Diuretic effect of amlodipine was registered already at 10 mg/kg/day dose, and changes of some clinical biochemistry parameters indicated altered renal (8 and 16 mg/kg/day for 1 month) and liver (30 mg/kg/day for 2 week, 15 mg/kg for 3 months) function without significant histopathological findings. The most prominent drug-related finding in rats was enlargement of the zona granulosa of the adrenal gland. This toxic effect was noted in animals administered the drug substance at doses 5 to 25 mg/kg/day for 2 months to 1 year regardless of amlodipine salt used.

The NOEL for amlodipine maleate in rats, determined in repeat-dose toxicity studies was between 3 and 10 mg/kg/day, while NOEL for amlodipine besylate was between 2 and 3 mg/kg/day. In general NOEL was reversely proportional to the treatment duration. Dogs seemed to be more sensitive to the toxic action of amlodipine than rats. Repeated administration of the drug substance (studies were performed only with maleate salt) caused lesions of the right atria. These lesions occurred only when treatment duration exceeded 6 months and administered doses increased to up to 7-times maximal human daily dosage.

### *III.4.3 Genotoxicity and carcinogenicity*

No genotoxic potential was detected for amlodipine (maleate or besylate) or perindopril in various *in vitro* and *in vivo* investigations.
No evidence of carcinogenic effects of either perindopril or amlodipine has been observed.

### *III.4.4 Reproductive and developmental toxicity*

*Perindopril*

No teratogenic effects of perindopril were seen in studies of pregnant rats, mice, rabbits and cynomolgus monkeys.

ACE inhibitors can cause foetal and neonatal morbidity and death when administered to pregnant women. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible. This guidance is in line with Pharmacovigilance Working Party recommendation on the use of ACE inhibitors in pregnancy, and the appropriate text is used in the proposed SmPC.

*Amlodipine*

GLP-complaint reproductive and developmental toxicity studies with both amlodipine salts were performed according to ICH guidance.
Fertility studies in male and female rats indicated no adverse effects on reproductive function, although recently a published paper indicated that amlodipine besylate could alter male reproductive function if administered to young rats. Both amlodipine maleate and besylate were not embryotoxic, foetotoxic or teratogenic in rats and rabbits and did not influence postnatal development of offspring. Amlodipine prolonged the length of gestation and cause difficulties in littering in rats at doses 50 times the maximum recommended human dose.

## III.5 Ecotoxicity/environmental risk assessment

The combination product is indicated for a substitution indication and as such will replace the use of the co-administered single products. Thus the exposure of the environment to perindopril and amlodipine will not increase by use of this product and an environmental risk assessment was not required. A suitable justification for the absence of an environmental risk assessment was provided by the applicant.

## III.6 Discussion on the non-clinical aspects

The Application is based on Article 10b of Directive 2001/83/EC, fixed dose combination. Pharmacodynamics, pharmacokinetics and toxicology of both perindopril and amlodipine are well-known. As the combination is only for substitution therapy 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 justification for a combination of perindopril and amlodipine is based on their synergistic effects on several pathophysiological mechanisms. The combination is intended for use as a substitution in patients suffering from hypertension or chronic stable angina. In this case no specific clinical pharmacological study is needed in agreement with the requirements stated in the documents CHMP/EWP/240/95 Rev. 1 "Guideline on Clinical Development of Fixed Combination Medicinal Products" and CHMP/EWP/191583/2005 "Questions and answers on the clinical development of fixed combinations of drugs belonging to different therapeutic classes in the field of cardiovascular treatment and prevention".

The applicant adequately summarized the clinical experience with perindopril and amlodipine and presents the synergistic effects between the ACE inhibitors and calcium-channel blockers. The justification of the missing specific pharmacokinetic interaction studies between perindopril and amlodipine is acceptable. To support the application the Applicant submitted one bioequivalence study conducted in accordance with the Guideline on Bioequivalence (CHMP/EWP/QWP/1401/98/Rev.1).

## IV.2 Pharmacokinetics

### *IV.2.1 Literature data*

*Perindopril*

Perindopril is rapidly absorbed following oral administration, with peak plasma concentrations occurring at 1 hour after administration. The absolute oral bioavailability is approximately 75%. Literature data on perindopril erbumine showed that it exhibits a dose linear behaviour within the therapeutic dose range. Perindopril undergoes extensive metabolism after oral administration, resulting in formation of perindoprilat. Following absorption, approximately 30 to 50% of systemically available perindopril is hydrolyzed to its active metabolite, perindoprilat. The formation of perindoprilat is slow. Mean $t_{max}$ for perindoprilat is generally within 3 to 7 hours, and was at the lower end of this range after repeated administration for 4 weeks.

Perindopril is approximately 60% perindoprilat is about 10-20% bound to plasma proteins. Values for volume of distribution for perindopril and free perindoprilat are 0.22 and 0.16 L/kg, respectively, after single oral dose of perindopril 8 mg.

Food did not affect the bioavailability of perindopril. It alters the conversion of perindopril to its active metabolite perindoprilat after single-dose administration of perindopril 4 mg. Concomitant administration of perindopril and food is unlikely to be clinically significant during long-term administration.

Conversion of perindopril to perindoprilat is thought to take place primarily in the liver, although some hydrolysis may also occur in the plasma, and the intestinal wall. After absorption perindopril also undergoes first-pass metabolism to form perindopril glucuronide, which is subsequently hydrolyzed to perindoprilat glucuronide. This metabolite in comparison to perindoprilat has a weak affinity for ACE. Formation of perindoprilat, the active ACE inhibitor, is gradual with peak plasma concentrations occurring between 3 and 7 hours. The subsequent decline in plasma concentration shows an apparent mean half-life of 3 to 10 hours for the majority of the elimination, with a prolonged terminal elimination half-life of 30 to 120 hours resulting from slow dissociation of perindoprilat from plasma/tissue ACE binding sites. The clearance of perindoprilat and its metabolites is almost exclusively renal.

*Amlodipine*

Amlodipine is slowly but almost completely absorbed from the human gastrointestinal tract. Oral bioavailability of amlodipine ranges from 52 to 88%, with the mean of 64%. After oral doses of 2.5, 5, and 10 mg, linear and age-independent relationships were observed between the dose and both AUC and $C_{max}$. Time to $C_{max}$ ($t_{max}$) after oral administration was ranging from 6 to 12 h. Absorption of amlodipine is unaffected by food, peak concentration, time to peak concentration, plasma half life and area under the plasma concentration curve (AUC) were not significantly different between fed and fasting state.

The mean volume of distribution ($V_d$) after a single dose intravenous application of amlodipine was 21 l/kg indicating that a large proportion of the body load of drug is in the tissues rather than in the blood. Amlodipine is highly protein bound with more than 95 %.

Amlodipine is slowly but extensively (about 90%) metabolised in the liver with possible involvement of CYP3A activity, therefore caution is advised when amlodipine is administered concomitantly with CYP3A inducers or inhibitors. Only 4-5% of unchanged drug recovered in the urine. Elimination from the plasma is biphasic with a terminal elimination half-life of about 30–50 hours. Steady-state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing. Amlodipine has no active metabolites.

*Perindopril/amlodipine combination*

According to the literature data and the results of several pharmacokinetic studies performed by the Applicant, although they were not designed specifically to study kinetic interactions, the two compounds do not interact in the pharmacokinetic processes.

### *IV.2.2 Bioequivalence study*

In order to demonstrate pharmacokinetics of the fixed dose combination and to establish bioequivalence (BE) with the free combination of the monocomponents, the applicant conducted one BE study. The study utilised the highest dose forms (8 mg perindopril erbumine and 10 mg amlodipine besylate). The conduct of the study was satisfactory and the results complied with the acceptance criteria for bioequivalence as detailed in the CHMP guideline.

*Design*

It was a comparative, randomised, single-dose, 2-way crossover bioavailability study of perindopril erbumine / amlodipine besylate 8 mg / 10 mg combination tablet and co-administration of perindopril erbumine 8 mg and amlodipine besylate 10 mg as separate tablets in healthy adult male volunteers under fasting conditions. Blood samples for perindopril and amlodipine were collected before dosing and at appropriate intervals taking the literature data into account.

*Bioanalytics*

Plasma concentrations of perindopril, perindoprilat and amlodipine were determined by a validated LC-MS-MS method. The upper and lower quantification limits were determined and presented.

*Statistics*

Analyses of variance (ANOVA) were performed on the ln-transformed $AUC_{0-t}$, $AUC_{inf}$, and $C_{max}$ for perindopril, on the ln-transformed $AUC_{0-72}$ and $C_{max}$ for perindoprilat and amlodipine, and on the ln-transformed $AUC_{0-t}$ for perindoprilat. The ANOVA model included sequence, formulation, and period as fixed effects, and subject nested within sequence as a random effect. Sequence was tested using subject nested within sequence as the error term at a 10% level of significance. Each ANOVA included calculation of least squares means (LSM), the difference between formulation LSM, and the standard error associated with this difference. The above statistical analyses were done using the SAS® GLM procedure.
Predefined bioequivalence criteria were the following:

- For perindopril: The 90% confidence interval of the ratios of least-squares means of $AUC_{0-t}$, $AUC_{inf}$ and $C_{max}$ of the test to reference formulation were to be within 0.80 to 1.25.
- For amlodipine and perindoprilat: The 90% confidence interval of the ratios of least-squares means of $AUC_{0-72}$ and $C_{max}$ of the test to reference formulation were to be within 0.80 to 1.25.

*Results*

**Perindopril PK parameters (Arithmetic Mean ± SD)**

| | $AUC_t$ (ng*h/ml) | $AUC_{inf}$ (ng•h/ml) | $C_{max}$ (ng/ml) | $T_{max}$ |
|---|---|---|---|---|
| Test (A) | 84.82± 19.77 | 85.76 ±19.85 | 73.19 ± 19.57 | 0.63 ± 0.28 |
| REF (B) | 82.48± 19.71 | 83.32± 19.74 | 71.52 ± 18.63 | 0.68 ± 0.24 |
| | | | | |

**90% CI and point estimates for perindopril**

| Perindopril in Plasma<br>Test Formulation vs. Reference Formulation | | | |
|---|---|---|---|
| **Parameter** | **Ratio of LSM (A/B)** | **90% Confidence Intervals** | **CV (%)** |
| AUC 0-t | 103.00% | 99.84 – 106.27% | 8.1% |
| AUCinf | 103.08% | 99.95 – 106.31% | 8.0% |
| Cmax | 101.92% | 94.19 – 110.27% | 20.5% |

**Perindoprilat PK parameters (Arithmetic Mean ± SD)**

| | $AUC_t$ (ng*h/ml) | $AUC_{72}$ (ng•h/ml) | $C_{max}$(ng/ml) | $T_{max}$ |
|---|---|---|---|---|
| Test (A) | 159.72±45.94 | 161.81± 47.68 | 11.30±5.53 | 4.81 ± 1.46 |
| REF (B) | 153.46±40.25 | 155,07± 40.99 | 11.23±5.18 | 4.55 ± 1.15 |

**90% CI and point estimates for perindoprilat**

| Perindoprilat in Plasma<br>Test Formulation vs. Reference Formulation | | | |
|---|---|---|---|
| **Parameter** | **Ratio of LSM (A/B)** | **90% Confidence Intervals** | **CV (%)** |
| AUC 0-72 | 102.45% | 98.23 – 106.86% | 9.9% |
| AUC 0-t | 103.80% | 99.82 – 107.93% | 10.1% |
| Cmax | 99.12% | 92.00 – 106.80% | 19.4% |

**Amlodipine PK parameters (Arithmetic Mean ± SD)**

| | $AUC_{72}$ (pg•h/ml) | $C_{max}$ (pg/ml) | $T_{max}$ (h) |
|---|---|---|---|
| Test (A) | 231735.8 ± 66538.1 | 5884.74± 1400.19 | 7.11 ± 2.59 |
| REF (B) | 221839.1± 59113.9 | 5760.79 ± 1284.84 | 7.26 ± 2.53 |
| | | | |

**90% CI and point estimates for Amlodipine**

| Amlodipine in Plasma<br>Test Formulation vs. Reference Formulation | | | |
|---|---|---|---|
| **Parameter** | **Ratio of LSM (A/B)** | **90% Confidence Intervals** | **CV (%)** |
| AUC 0-72 | 104.07% | 101.07 – 107.17% | 7.6% |
| Cmax | 101.76% | 98.87 – 104.73% | 7.4% |

*Conclusion*

The results of the bioequivalence study comply with the requirements of the CPMP/EWP/QWP/1401/98 Rev. 1. Note for Guidance on the Investigation of Bioavailability and Bioequivalence except that according to the Guideline the pharmacokinetic parameters of the active metabolite is not necessary to measure. Therefore the essential similarity of the applicant's product perindopril 8 mg / amlodipine 10 mg combination and the originator monocomponent tablets administered concomitantly is established.

*Biowaiver*

For the other perindopril erbumine/amlodipine strengths which are also applied for in this marketing authorization application (perindopril erbumine/amlodipine 8 mg/5 mg, perindopril erbumine/amlodipine 4 mg/10 mg, and perindopril erbumine/amlodipine 4 mg/5 mg fixed combination tablets) additional dissolution studies were performed to confirm the adequacy of waiver of additional bioequivalence studies. Accordingly, dissolution was investigated at different pH values (0.01 M hydrochloric acid, acetate buffer solution pH 4.5 and phosphate buffer solution pH 6.8). Similarity of dissolution was demonstrated at all conditions within the applied product series, i.e. between additional strengths and the strength used for the BE testing. As pharmacokinetics of perindopril and amlodipine are linear and all the stipulated biowaiver criteria are fulfilled (CPMP/EWP/QWP/1401/98 Rev. 1) additional in vivo studies for the bioequivalence assessment of 8 mg/5 mg, 4 mg/10 mg and 4 mg/5 mg product series may be waived.

## IV.3 Pharmacodynamics

### *IV.3.1 Perindopril*

The pharmacodynamics of perindopril is well established.

Perindopril is a prodrug, its main and active metabolite perindoprilat is responsible for the inhibition of ACE, the key enzyme in the production of a potent vasopressor, angiotensin II. By inhibiting ACE the reduced level of angiotensin II will result in vasodilatorion as well as decreased secretion of aldosterone. Furthermore, ACE inhibitors also inhibit the degradation of bradykinin and this way they may further

reduce vascular tension. The higher level of bradykinin may be responsible for dry cough, the common adverse effect of the ACE inhibitors.

Perindopril significantly reduces systolic blood pressure (SBP) and diastolic blood pressure (DBP) from baseline levels in patients with hypertension, with a dose-response effect for doses of ≤8 mg, and maintains these reductions during the 24 hours dosing interval (conformed with ambulatory intra-arterial BP monitoring). Most of its antihypertensive effect appears to persist over the 24 to 48 hours after dosing.

Perindopril most likely inhibits pathological remodelling of both the vasculature and the cardiac muscles. Long-term treatment with perindopril significantly reduced systemic vascular resistance and produced a marked increase in arterial compliance, mainly due to increased dispensability, in the large arteries. In patients with hypertension perindopril reduces left ventricular (LV) hypertrophy (LVH), a powerful predictor of cardiovascular risk. The reduction of hypertrophy induced by perindopril appears to be partly independent of BP decrease and therefore partly related to a direct action of perindopril on the myocardium (decrease in septal wall thickness and posterior wall thickness).

### *IV.3.2 Amlodipine*

The pharmacodynamics of amlodipine is well established.

Amlodipine belongs to the dihydropyridine $Ca^{++}$-channel blockers. It inhibits the calcium influx through the L-type (slow) $Ca^{++}$-channels. As calcium is an essential mediator of smooth muscle contraction amlodipine relaxes smooth muscles especially the blood vessels. By this vasodilatoring effect amlodipine reduces the peripheral vascular resistance this way it reduces blood pressure and the afterload for the heart as well. By decreasing afterload it reduces the oxygen demand of the heart. Furthermore, dilation of coronary arteries improves the cardiac oxygen supply. These two latter mechanisms may result in preventing angina attacks in chronic stable angina as well as in Prinzmetal's angina (coronary spasm). Despite its marked vasodilatorory effect it does not cause strong reflex tachycardia. The negative inotropic effect of amlodipine on the heart is weak provided by its good vasoselectivity over the cardiac L-type channels.

In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24-hour interval. Due to the slow onset of action, acute hypotension is not a feature of its administration.

In patients with angina, by once daily administration it increases total exercise time, time to angina onset, and time to significant ST segment depression, and decreases both angina attack frequency and glyceryl trinitrate tablet consumption.

It has not been associated with any adverse metabolic effects: it had no effect on the level of plasma lipids, blood glucose and serum uric acid and it was suitable for use in patients with asthma.

### *IV.3.3 Perindopril/amlodipine combination*

Combinations of an ACE inhibitor and a calcium channel blocker have been shown to be significantly more effective at lowering blood pressure than monotherapy with either agent alone.

## IV.4 Clinical efficacy

The efficacy of perindopril and amlodipine has already been demonstrated during the clinical development of both substances.

As for perindopril/amlodipine combinations, clinical trials have demonstrated that the use of antihypertensive agents with complementary or synergistic modes of action combined in a single pill offers advantages of simplicity, tolerability, and convenience and therefore lead to better patient compliance and the potential for more patients to achieve their blood pressure targets.

- The applicant has discussed data on the efficacy of perindopril and amlodipine combination through the results of relevant clinical studies in addition to the trials of the individual agents

In order to further support the evidence of well established use of the free combination the applicant provided supporting evidence from IMS MIDAS database from 5 EU markets.

## IV.5 Clinical safety

The clinical safety of the individual components has been well established. The IMS MIDAS dataset establishes increased use of the combination and absence of any safety related regulatory action. The bioequivalence study did not raise any safety concerns.

## IV.6 Discussion on the clinical aspects

The application concerns a new fixed combination of perindopril erbumine and amlodipine. The claimed indication is substitution therapy for patients suffering from hypertension or chronic stable angina already adequately controlled with monocomponent containing tablets given concurrently.

To support the application the applicant has adequately demonstrated bioequivalence between the combination and the monocomponent originators given at the same time. For further justification the Applicant has provided co-prescription data from 5 EU markets. Although the indication does not require further justification the applicant has detailed the results of relevant clinical studies that indicates worldwide usage of both substances together.

The discussion of the lack of pharmacokinetic interactions between perindopril and amlodipine is sufficient and therefore acceptable.

There is no objection against granting the marketing authorization from a clinical point of view.

# V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The present line-extension application concerns perindopril/amlodipine 4 mg/5 mg, 4 mg/10 mg, 8 mg/5 mg and 8 mg/10 mg fixed combination tablets. The applicant and the future holder of the marketing authorisation is Pharma-Regist Kft. Budapest.

The indication of the Dalnessa tablets is substitution therapy for patients suffering from hypertension or chronic stable angina already adequately controlled with perindopril and amlodipine monocomponent tablets given concurrently in the same doses.

The application is based on literature review, a bioequivalence study of the fixed combination tablets with two existing perindopril and amlodipine monocomponent preparations and co-prescription data proving the rationality and wide use of the combinations.

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)*

A three-year PSUR cycle was requested that corresponds to that of similar medicinal products.

*Legal status*

Prescription-only 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 and the harmonised Hungarian piece of law, Article 3(4) of the Decree No. 30/2005 (12 August 2005) EüM of the Minister of Health on *the labelling and patient information leaflet of medicines for human use*. 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* and above the Hungarian Decree.

# 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: |
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