CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Vagrecor 40/80/160/320 mg film-coated tablets
Laboratorios Liconsa S.A., Spain

valsartan

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/1590/001- 004/DC
Registration number in the Netherlands: RVG 103974-7

14 July 2011

Pharmacotherapeutic group:	angiotensin II antagonists, plain
ATC code:	C09CA03
Route of administration:	oral
Therapeutic indication:	essential hypertension
Prescription status:	prescription only
Date of authorisation in NL:	18 January 2011
Concerned Member States:	Decentralised procedure with DE, ES, FR, IT, PT, and UK
Application type/legal basis:	Directive 2001/83/EC, Article 10(1) or 10(3), depending on availability of innovator strengths in RMS and CMSs.

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Vagrecor 40 mg, 80 mg, 160 mg, and 320 mg film-coated tablets, from Laboratorios Liconsa S.A.. The date of authorisation was on 18 January 2011 in the Netherlands. The product is indicated for:

40 mg
Recent myocardial infarction
Treatment of clinically stable patients with symptomatic heart failure or asymptomatic left ventricular systolic dysfunction after a recent (12 hours-10 days) myocardial infarction.

Heart failure
Treatment of symptomatic heart failure when Angiotensin Converting Enzyme (ACE) inhibitors cannot be used, or as add-on therapy to ACE inhibitors when beta blockers cannot be used.

80 mg and 160 mg
Hypertension
Treatment of essential hypertension.

Recent myocardial infarction
Treatment of clinically stable patients with symptomatic heart failure or asymptomatic left ventricular systolic dysfunction after a recent (12 hours-10 days) myocardial infarction.

Heart failure
Treatment of symptomatic heart failure when Angiotensin Converting Enzyme (ACE) inhibitors cannot be used, or as add-on therapy to ACE inhibitors when beta blockers cannot be used.

320 mg
Treatment of essential hypertension.

A comprehensive description of the indications and posology is given in the SPC.

Valsartan is an orally active, potent, and specific angiotensin II (Ang II) receptor antagonist. It acts selectively on the AT1 receptor subtype, which is responsible for the known actions of angiotensin II. The increased plasma levels of Ang II following AT1 receptor blockade with valsartan may stimulate the unblocked AT2 receptor, which appears to counterbalance the effect of the AT1 receptor. Valsartan does not exhibit any partial agonist activity at the AT1 receptor and has much (about 20,000 fold) greater affinity for the AT1 receptor than for the AT2 receptor. Valsartan is not known to bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Diovan 40 mg, 80 mg, 160 mg and 320 mg film-coated tablets (NL license RVG 32137, 26939, 26940, 34472, and 34472) which have been registered in the Netherlands by Novartis B.V. since 2005, 2001, 2001, and 2007 respectively (original product). The data-protection period is determined by the reference product Diovan 80 mg, authorised since 1996 in Germany. In addition, reference is made to Diovan authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC. The application for the 160 mg strength in the UK, and the 320 mg strength in France are based on article 10(3) of Directive 2001/83/EC, because for these strenghts the innovator is not registered in these countries. Therefore, In the UK, for the 160 mg tablets reference is made the Diovan 40 mg authorization. Similarly, in France, for the 320 mg tablets reference is made to the 80 mg authorization.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal

product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Diovan 160 mg film-coated tablets, registered in Spain. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products, and no paediatric development programme has been submitted, as this is not required for generic medicinal products.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is valsartan, an established active substance described in the USP*. Valsartan is a white to off-white powder, which is soluble in methanol and ethanol, and slightly soluble in water. It has various polymorphic forms. The form used in this drug product is sufficiently described and is derived from all three different manufacturing routes. The proposed particle size distribution of valsartan has been adequately justified in view of the biobatch.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMEA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacture
Valsartan is manufactured through three different routes of synthesis (route A, B, and C respectively). After crude valsartan is formed a purification process follows that is the same for all routes. The manufacturing process has been sufficiently described.

Quality control of drug substance
The drug substance specification of valsartan is in line with the USP monograph. Impurities and residual solvents have been adequately limited. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full-scale batches of three different production routes. It was also demonstrated that no difference in quality was observed between the various production routes.

Stability of drug substance
Stability data on valsartan have been provided for seven full-scale batches (three of route B, one of route A and three of route C). The batches were stored at accelerated condition for 6 months and at long-term condition for 24 months from route B, 18 months from route A and C. The batches were adequately stored. Based on the stability data a retest period of 24 months can be granted. No special storage conditions are deemed necessary.

* *USP is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the USA.*

Medicinal Product

Composition

Vagrecor 40 mg - are cylindrical, coated, yellow film-coated tablets, scored on one side.
Vagrecor 80 mg - are cylindrical, coated, pink, film-coated tablet which are scored on one side.
Vagrecor 160 mg - are cylindrical, coated, ochre film-coated tablets which are scored on one side.
Vagrecor 320 mg - are oblong, coated, greyish-violet film-coated tablets, which are scored on one side.
The tablets are packaged in PVC/PE/PVDC/aluminium blisters.

The 40 mg, 80 mg, 160 mg, and 320 mg tablets are dose proportional.

The excipients are:
Tablet core – microcrystalline cellulose (E 460), colloidal anhydrous silica (E 551), sorbitol (E-420), magnesium carbonate (E 504), pregelatinised maize starch, povidone K-25 (E 1201), sodium stearylfumarate, sodium lauryl sulphate, crospovidone Type A (E 1202).
Tablet coating - lactose monohydrate, hypromellose (E 464), titanium dioxide (E 171), macrogol.
Only 40 mg – yellow iron oxide (E 172)
Only 80 mg – red iron oxide (E 172)
Only 160 mg – yellow iron oxide (E 172), brown iron oxide (E 172)
Only 320 mg – yellow iron oxide (E 172), brown iron oxide (E 172), and indigo carmine aluminium lake (E 132).

The excipients and packaging are usual for this type of dosage form. The different strenghts are fully dose proportional.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. Formulation development was based on the pharmaceutical characteristics and dissolution profile of the innovator Diovan. The pharmaceutical development of the product has been adequately performed. Equivalence of the reference products with the reference product marketed in the Netherlands is inferred as the innovator was registered via a MRP procedure with the applicable countries as concerned member states. The 160 mg strength tablet has been used in the bioequivalence study. This has been adequately justified in line with the *NfG on the investigation of bioavailability and bioequivalence*. Essential similarity and bioequivalence with the innovator product has been demonstrated. The container closure system and microbiological attributes have been described adequately.

Container closure system
The packaging materials were based on the innovator and consist of triplex PVC-PE-PVDC foil laminated to Alu foil . The triplex was chosen for better resistance to water steam permeability and oxygen.

Manufacturing process
Wet granulation is chosen for the manufacturing process. The granulate is compressed into tablets, coated and packed.

The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for pilot-scale batches of all strengths and for both manufacturing sites. The product is manufactured using conventional manufacturing techniques. For the intended full-scale batch sizes of the 160 mg and 320 mg strengths an additional mixing step is needed at on of the sites. As this has not been performed yet, the proposed batch sizes for the 160 mg strength and the 320 mg strength can be accepted for this site. For the other site the proposed batch sizes for the 160 mg strength and the 320 mg strength can also be accepted.
The MAH has committed to provide the validation protocols and results of process validation on the first three full production scale batches of all strengths.

Excipients
The excipients sorbitol, pregelatinised starch, povidone, sodium lauryl sulphate, crospovidone, colloidal anhydrous silica, sodium stearyl fumarate comply with their respective Ph.Eur monographs. For the colouring agents, quantitative compositions, where applicable, specifications and analytical procedures have been provided. The specifications are acceptable. Only lactose monohydrate is of animal origin. No novel excipients are present in the formulation.

Quality control of drug product
The finished product specification includes tests for appearance, identification (HPLC, UV and colouring matter), uniformity of dosage units, loss on drying, dissolution, assay, related substances and microbiology. The shelf-life specification includes appearance, loss on drying, dissolution, assay, related substances and microbiology. The analytical methods have been adequately described. The methods have been adequately validated for all strengths. Batch analytical data from the proposed production site have been provided on 11 pilot-scale batches, demonstrating compliance with the release specification. For batches manufactured by one specific manufacturer, batch analysis data of the 80mg and 320mg strength will be provided when available.

Microbiological Attributes
Microbiological tests were performed as per Ph.Eur.

Stability tests on the finished product
Stability data on the product has been provided on three pilot-scale batches of each of the 40 mg, 80 mg and 160 mg drug products stored at 25°C/60%RH (24 months), 30°C/65%RH (12 months) and 40°C/75% RH (6 months) and two pilot-scale batches of the 320 mg strength stored at 25°C/60%RH (12 months), 30°C/65%RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVC-PE-PVDC/Al blisters.
After 24 months of long-term stability testing, no clear trends could be observed for the 40 mg tablets and a slight decrease in assay is observed for the 80 mg and 160 mg tablets. After 12 months of intermediate stability testing a slight decrease in assay is observed. All results remain well within limits. A significant decrease in dissolution is observed after 6 months of accelerated stability testing with values as low as 32.1% (40mg), 28.6% (80mg) and 49.9% (160mg) of valsartan dissolved in 30 minutes. The extreme decrease in dissolution was seen for the innovator product as well. Due to these out of specification results, no extrapolation of the stability data is allowed and a shelf-life of 24 months can be granted. The claimed storage condition '*do not store above 30°C, store in the original package in order to protect from moisture* ' is justified. For the 320mg strength a shelf-life of 12 months can be granted. The photostability study demonstrated that the drug product is photostable.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Only lactose monohydrate is of animal origin. TSE statements have been provided for all excipients and for lactose monohydrate a statement has been provided that the material is obtained from milk sourced from healthy animals in the same conditions as milk collected for human consumption and that no other ruminant materials are used in the preparation.

II.2 Non clinical aspects

This product is a generic formulation of Diovan, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of valsartan released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Valsartan is a well-known active substance with established efficacy and tolerability.

For this generic application, the MAH has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Vagrecor 160 mg film-coated tablets (Laboratorios Liconsa S.A., Spain) is compared with the pharmacokinetic profile of the reference product Diovan 160 mg film-coated tablets (Novartis Farmaceutica, Spain).

The choice of the reference product
The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products (if applicable) in different member states.

Study design
A single-dose, crossover bioequivalence study was carried out under fasted conditions in 44 healthy (21 male/21 female) subjects, aged 19-54 years. Each subject received a single dose (160 mg) of one of the 2 valsartan formulations. The tablet was orally administered with 200 ml water after an overnight fast of 10 hours. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 5, 6, 8, 10, 12, 14, 24, 34 and 48 hours after administration of the products.
The analytical method is adequately validated and considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Food decreases exposure to valsartan by about 40% and peak plasma concentration (Cmax) by about 50%, although from about 8 h post dosing plasma valsartan concentrations are similar for the fed and fasted groups. This reduction in AUC is not, however, accompanied by a clinically significant reduction in the therapeutic effect, and valsartan can therefore be given either with or without food.

Results
During the study 12 adverse events were notified (feeling of discomfort, hypotension, headache and tachycardia), 5 of which were potentially associated with the study medication. With regard to the severity of the adverse events, all were classified as mild to moderate, and disappeared spontaneously. No serious or unexpected adverse event was detected during the study.
All subjects completed both treatments and were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of valsartan under fasted conditions.

Treatment N=44	**AUC_{0-t}** µg.h/ml	**$AUC_{0-\infty}$** µg.h/ml	**C_{max}** µg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	27.9 ± 12.3	29.4 ± 12.4	4.82 ± 2.13	2.67 (1.3 – 5.0)	5.7 ± 2.7
Reference	27.8 ± 10.9	29.5 ± 11.1	4.86 ± 2.10	2.8 (1.3 - 5.0)	7.2 ± 12.9
***Ratio (90% CI)**	0.97 (0.91 – 1.10)	0.96 (0.90 – 1.09)	0.98 (0.90 – 1.09)	---	---
CV (%)	35	37	31	---	---

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of valsartan under fasted conditions, it can be concluded that Vagrecor 160 mg film-coated tablets and Diovan 160 mg film-coated tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Extrapolation of results

According to the CPMP guideline "Note for guidance on the investigation of bioavailability and bioequivalence" (CPMP/EWP/QWP/1401/98), a bioequivalence study investigating only one tablet strength may be acceptable if all of the following conditions are fulfilled:

- the pharmaceutical products are manufactured by the same manufacturer and process
- the pharmacokinetics has been shown to be linear over the therapeutic range
- the qualitative composition of the different strengths is the same
- the ratio between amounts of active substance and excipients is the same
- the dissolution profile should be similar under identical conditions for the additional strengths and the strength of the biobatch.

All these conditions apply to Vagrecor tablets as manufactured by the MAH. The results of the bioequivalence study performed with the 160 mg tablets therefore apply to the 40 mg, 80 mg, and 320 mg tablets.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Risk management plan

Valsartan was first approved in 1996, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of valsartan can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC
The SPC is in accordance with the recently finalised art 30 Referral text of Diovan (Commission Decision in February 2009) and is accepted.

Readability test
The package leaflet of the 160 mg strength 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 test consisted of a pilot test with 2 participants, followed by two rounds with 10 participants each.
The test persons were men and women aged 18 to 66 years with a mean of 37.7 years, 50% males and 50 % females. Inclusion and exclusion criteria were specified in the protocol. The test was performed in Spanish. Educational levels correspond with the inclusion criteria set in the protocol.

The test was performed by face-to-face interviews. Questions were designed to determine whether users can identify key information that is necessary for appropriate use.
There were sufficient questions about the critical sections and the areas traceability, comprehensibility and applicability were sufficiently covered. The test included 16 questions related to the content of the PL. Three questions were related to the structure/appearance of the PL.
Participants were interviewed individually by one experienced and trained interviewer. The interviewer also observed the behaviour of the participant. The responses were written down by hand. Respondents were asked to give their answer in their own words. A satisfactory outcome was achieved when 16 out of 20 participants were able to find information and answer each question correctly and act appropriately.

In round 1 information, on average of 98% of the time the correct section was located to answer the question. Each question was correctly answered 97% of the time. For some questions difficulties were observed in answering the questions.
In the second round 100% of the participants were able to locate the section and 100% were able to answer the questions. Therefore no further changes were considered to be required.
The results of the test were satisfactory. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Vagrecor 40 mg, 80 mg, 160 mg, and 320 mg film-coated tablets have a proven chemical-pharmaceutical quality and are a generic form of Diovan 40 mg, 80 mg, 160 mg, and 320 mg film-coated tablets. Diovan is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is in accordance with the recently finalised art 30 Referral text of Diovan (Commission Decision in February 2009) and is accepted. The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Vagrecor 40 mg, 80 mg, 160 mg, and 320 mg film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 3 December 2009. Vagrecor is authorised in the Netherlands on 18 January 2011.

A European harmonised birth date has been allocated (13 May 1996) and subsequently the first data lock point for valsartan is May 2012. Therefore, the first PSUR will cover the period from first registration in Europe until May 2012, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: January 2013.

The following post-approval commitments have been made during the procedure:

Quality - medicinal product

- The MAH has committed to perform long term, intermediate and accelerated stability studies on the first three production scaled batches.
- The MAH has committed to provide batch analyses data for of the 80 mg and 320 mg the tablets manufactured by one specific manufacturer, when available.
- The MAH has committed to provide the validation protocols and results of process validation on the first three full production scale batches of all strengths.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Change in the manufacturer of a starting material/reagent/intermediate used in the manufacturing process of the active substance or change in the manufacturer (including where relevant quality control sites) of the active substance, where no Ph. Eur. Certificate of Suitability is part of the approved dossier. Introduction of a new manufacturer of the active substance that is supported by an ASMF. New ASMF.	NL/H/1590/ 002-003/II/ 001	II	16-12-2010	6-4-2011	Approval	N
• Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non- sterile medicinal products. • Change to batch release arrangements and quality control testing of the finished product. Replacement or addition of a manufacturer responsible for batch release, including batch control/testing. • Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. Primary packaging site. • Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. Secondary packaging site.	NL/H/1590/ 002-003/IB/ 002/G	IB/G	13-1-2011	12-2-2011	Approval	N
Change of product name in Spain and Italy.	NL/H/1590/ 001-004/IB/ 004	IB	1-6-2011	1-7-2011	Approved	N