PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands

Candesartan cilexetil/HCT Jubilant
16/12.5 mg and 32/25 mg, tablets
Jubilant Pharmaceuticals N.V., the Netherlands

candesartan cilexetil/hydrochlorothiazide

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/2737/001-002/DC
Registration number in the Netherlands: RVG 112656-112657

11 March 2014

Pharmacotherapeutic group: angiotensin II antagonists and diuretics
ATC code: C09DA06
Route of administration: oral
Therapeutic indication: essential hypertension not optimally controlled with candesartan cilexetil or hydrochlorothiazide monotherapy.

Prescription status: prescription only
Date of authorisation in NL: 27 August 2013
Concerned Member States: Decentralised procedure with BG, DK, MT, SE
Application type/legal basis: Directive 2001/83/EC, Article 10(1) and 10(3)

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 Candesartan cilexetil/HCT Jubilant 16/12.5 mg and 32/25 mg, tablets from Jubilant Pharmaceuticals N.V. The date of authorisation was on 27 August 2013 in the Netherlands.

The product is indicated for treatment of essential hypertension in adult patients whose blood pressure is not optimally controlled with candesartan cilexetil or hydrochlorothiazide monotherapy.

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

Angiotensin II is the primary vasoactive hormone of the renin-angiotensin-aldosterone system and plays a role in the pathophysiology of hypertension and other cardiovascular disorders. Furthermore, it is also significant in the pathogenesis of organ hypertrophy and end-organ damage. The most important physiological effects of angiotensin II, e.g. vasoconstriction, aldosterone stimulation, regulation of salt and water homeostasis and stimulation of cell growth, are mediated via the receptor subtype 1 (AT1).

Candesartan cilexetil is a prodrug which is rapidly converted into its active form, candesartan, by ester hydrolysis during absorption from the gastrointestinal tract. Candesartan is an angiotensin-II receptor antagonist with selectivity for the AT1 receptor, with which it has a high binding affinity and from which its dissociation is slow. It has no agonist activity.

Hydrochlorothiazide inhibits active sodium reabsorption mainly in the distal renal tubules and promotes the excretion of sodium, chloride and water. Renal excretion of potassium and magnesium increases dose-dependently, whilst calcium is largely reabsorbed. Hydrochlorothiazide decreases plasma volume and extracellular fluid, reduces cardiac output and lowers the blood pressure. In long-term therapy, reduced peripheral resistance contributes to the reduction in blood pressure.

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Atacand Plus 16 mg/12.5 mg tablets (NL License RVG 24995) which has been registered in the Netherlands by AstraZeneca through MRP SE/H/0162/002 since 23 March 2000. In addition, reference is made to Atacand Plus authorisations in the individual member states (reference product). The 32/25 mg strength concerns a hybrid application (difference in strength). This formulation is in accordance with the maximum daily dose: 32 mg for candesartan cilexetil and 25 mg for hydrochlorothiazide. Atacand Plus forte 32/25 mg tablets is available on the European market, however not in the Netherlands.

The marketing authorisation is granted based on article 10(1) (16/12.5 mg strength) and 10(3) (32/25 mg product) of Directive 2001/83/EC.

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 Atacand Plus forte 32/25 mg tablets, registered in Germany. 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. These generic products can be used instead of their 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 a generic application.

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 – candesartan cilexetil
Candesartan cilexetil is an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The drug substance is a white or almost white powder, which is practically insoluble in water, freely soluble in methylene chloride and slightly soluble in anhydrous ethanol. The drug substance has one chiral center, rendering S- and R-isomers, the active substance is a racemate. The drug substance used is Polymorph C (Form I).

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The Ph. Eur. specifications and an additional CEP requirement are applied. This is acceptable. Batch analysis results for 3 batches have been provided showing results meeting the set specification.

Stability of drug substance
Three batches have been stored for 6 months at 40°C/75% RH and 36 months at 25°C/60% RH in the proposed packaging. All results of the pilot-scale batches were within specification after 6 months accelerated and after 36 months long-term testing. There were no significant changes observed during the stability study. Based on the available long-term stability data, a retest period of 48 months was approved.

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

Active substance – hydrochlorothiazide
Hydrochlorothiazide (HCTZ) is an established active substance described in the (Ph.Eur.*). It is a white to almost white crystalline powder, which is very slightly soluble in water, soluble in acetone, sparingly soluble in ethanol (96%). It dissolves in dilute solutions of alkali hydroxides.

The CEP procedure is used for hydrochlorothiazide. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the new general monograph, or both.
This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

**Manufacturing process**
A CEP has been submitted; therefore no details on the manufacturing process have been included.

**Quality control of drug substance**
The Ph. Eur. specifications and additional CEP requirements are applied. This is acceptable. Batch analysis results for 3 batches have been provided showing results meeting the set specification.

**Stability of drug substance**
The active substance is stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

**Medicinal Product**

**Composition**
Candesartan cilexetil/HCT Jubilant 16/12.5 mg is a pink coloured, oval shaped, biconvex, uncoated tablet of approximately 9.7 mm length, 4.5 mm width and 3.5 mm thickness, scored on both sides and coded with "424" on one side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

Candesartan cilexetil/HCT Jubilant 32/25 mg is a pink coloured, oval shaped, biconvex, uncoated tablet of approximately 11.4 mm length, 6.7 mm width and 4.1 mm thickness, scored on both sides and coded with "426" on one side. The tablet can be divided into equal doses.

The tablets are packed in PVC-PVDC/Al blister packs.

The excipients are: carmellose calcium, lactose anhydrous, maize starch, ferric oxide red (E172), ferric oxide yellow (E172), mono-, di-fatty acid glycerides, hydroxypropyl cellulose, lactose monohydrate, colloidal anhydrous silica, magnesium stearate.

The qualitative and quantitative compositions of both strengths are dose-proportional.

**Pharmaceutical development**
The aim of this development was to generate a formulation of a generic product of Atacand tablets, marketed by AstraZeneca. The qualitative composition of the reference product has been approximated by using identical excipients or excipients having the same functional properties.

In view of the poor flow-ability and the low percentage of drug substance in the product, a wet-granulation manufacturing process was chosen. The choice of packaging material has been adequately justified.

Bioequivalence studies have been performed using a pilot-scale 32/25mg test bio-batch and the DE corresponding reference product Atacand Plus. The reference product is acceptable. Comparative dissolution studies have been performed for the bio-batch and reference bio-batch, showing comparable dissolution profiles. The given arguments to support the claimed bio-waiver (i.e. waiving the 16/12.5 mg strength from a bioequivalence study) is endorsed from chemical-pharmaceutical point of view.

The development of the dissolution method has been adequately described, and the method chosen for release of batches appears to be sufficient discriminative.

For the 32/25 mg tablet satisfactory data on weight uniformity of halved tablets have been provided. The score line on the 16 mg/12.5 mg tablet is only to facilitate breaking for ease of swallowing and not to divide into equal doses. This information is included in the SPC.

The manufacturing process development and scale-up optimization studies have been adequately described.

**Manufacturing process**
The straightforward manufacturing process has been adequately described, and manufacturing steps are given in sufficient detail. The batch formulae are in accordance with the product composition.
adequate compatibility of the intragranular materials with the extragranular materials is controlled by the blend uniformity tests and the uniformity of mass testing during compression.

By applying all routine in-process controls and the additional validation studies the manufacturing process is considered under sufficient and adequate control.

Validation protocols are provided for both strengths, which is acceptable.

Control of excipients
All excipients meet the requirements of the respective Ph. Eur. monograph except ferric oxide red, ferric oxide yellow, and mono- and diglycerides which are in-line with respective US/NF monograph. These specifications are acceptable.

Quality control of drug product
In general adequate specifications are applied for the drug product and include requirements identification of the two drug substances, identification of the colourants, related substances, dissolution, disintegration, uniformity of dosage units, water content and microbiological purity. Adequate limits on water content during release, shelf-life and as in-process control for the final lubricated blend are applied. The analytical methods have been validated. Batch analysis results are provided for 2 batches of each strength showing results meeting the set specification.

Stability of drug product
Eighteen months stability data at 25°C/60% RH and 6 months accelerated data are available for 2 batches of 16/12.5 mg tablets and for 2 batches of 32/25 mg tablets. Test parameters are description, water content, dissolution, assay, related substances and microbiological examination. All accelerated and normal stability results met specification requirements at all testing points. No significant changes or trends were observed. The drug product is not sensitive to light. Based on the provided stability data the claimed shelf-life of 2 years in Alu–PVC/PVdC blisters without specific storage condition can be granted.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
For lactose anhydrous and lactose monohydrate TSE statements (milk from healthy animals) have been provided, and magnesium stearate is from vegetable origin. There are no other substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product.

II.2 Non-clinical aspects
This product is a generic formulation of Atacand Plus, 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 candesartan cilexetil or hydrochlorothiazide 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
Candesartan cilexetil and hydrochlorothiazide are well-known active substances with established efficacy and tolerability.

A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Candesartan cilexetil/HCT Jubilant 32/25 mg (Jubilant Pharmaceuticals N.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Atacand Plus forte 32/25 mg tablets (AstraZeneca GmbH, Germany).
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 in different member states. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 36 healthy male subjects, aged 19-42 years. Each subject received a single dose (32/25 mg) of one of the 2 candesartan/HCTZ formulations. The tablet was orally administered with 240 ml water under fasted conditions. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected at pre-dose and at 0.5, 1.0, 1.5, 1.75, 2.0, 2.33, 2.67, 3.0, 3.25, 3.5, 3.75, 4.0, 4.33, 4.67, 5.0, 5.5, 6.0, 8.0, 10, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable, the washout and sampling period were long enough, the sampling scheme adequate to estimate the pharmacokinetic parameters.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

All 36 subjects completed the study and were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t\text{max} (median, range)) of candesartan cilexetil under fasted conditions.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N=36</th>
<th>AUC\text{0-\infty}</th>
<th>AUC\text{0-t}</th>
<th>C\text{max}</th>
<th>t\text{max}</th>
<th>t\text{1/2}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td></td>
<td>3811 ± 1204</td>
<td>3904 ± 1206</td>
<td>321 ± 110</td>
<td>4.33</td>
<td>--</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(1.75-6.00)</td>
<td></td>
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<tr>
<td>Reference</td>
<td></td>
<td>3825 ± 1123</td>
<td>3908 ± 1118</td>
<td>313 ± 103</td>
<td>4.33</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>(2.33-8.00)</td>
<td></td>
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<tr>
<td>*Ratio (90% CI)</td>
<td></td>
<td>1.00 (0.92-1.08)</td>
<td>1.00 (0.93-1.08)</td>
<td>1.02 (0.93-1.12)</td>
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<tr>
<td>CV (%)</td>
<td></td>
<td>20</td>
<td>19</td>
<td>24</td>
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</tbody>
</table>

\(\text{AUC}_{0-\infty}\) area under the plasma concentration-time curve from time zero to infinity

\(\text{AUC}_{0-t}\) area under the plasma concentration-time curve from time zero to \(t\) hours

\(C_{\text{max}}\) maximum plasma concentration

\(t_{\text{max}}\) time for maximum concentration

\(t_{1/2}\) half-life

*In-transformed values

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t\text{max} (median, range)) of hydrochlorothiazide under fasted conditions.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N=36</th>
<th>AUC\text{0-\infty}</th>
<th>AUC\text{0-t}</th>
<th>C\text{max}</th>
<th>t\text{max}</th>
<th>t\text{1/2}</th>
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<td></td>
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<tr>
<td>Test</td>
<td>1517 ± 606</td>
<td>1566 ± 623</td>
<td>225 ± 77</td>
<td>1.75 (1.00-4.67)</td>
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<tr>
<td>Reference</td>
<td>1502 ± 553</td>
<td>1549 ± 568</td>
<td>219 ± 66</td>
<td>2.00 (1.00-3.25)</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>1.00 (0.96-1.05)</td>
<td>1.00 (0.96-1.05)</td>
<td>1.02 (0.96-1.08)</td>
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<td></td>
</tr>
<tr>
<td>CV (%)</td>
<td>12</td>
<td>11</td>
<td>15</td>
<td>--</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>AUC$_{0-t}$</th>
<th>area under the plasma concentration-time curve from time zero to t hours</th>
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<tbody>
<tr>
<td>AUC$_{0-\infty}$</td>
<td>area under the plasma concentration-time curve from time zero to infinity</td>
</tr>
<tr>
<td>C$_{\text{max}}$</td>
<td>maximum plasma concentration</td>
</tr>
<tr>
<td>t$_{\text{max}}$</td>
<td>time for maximum concentration</td>
</tr>
<tr>
<td>t$_{1/2}$</td>
<td>half-life</td>
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</tbody>
</table>

*ln-transformed values

The 90% confidence intervals calculated for AUC$_{0-t}$, AUC$_{0-\infty}$ and C$_{\text{max}}$ 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 candesartan cilexetil and HCTZ under fasted conditions, it can be concluded that Candesartan cilexetil/HCT Jubilant 32/25 mg and Atacand Plus forte 32/25 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Candesartan and HCTZ may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of candesartan or HCTZ. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

**Safety**
There was only one adverse event (headache) of moderate severity in the study, and was assessed as possibly related to the test study drug. There was no serious adverse event. No clinically significant vital sign changes were observed during the study.

**Biowaiver**
A biowaiver has been granted for the 16/12.5 mg strength, as all the following criteria are fulfilled:

a) the pharmaceutical products are manufactured by the same manufacturing process

b) the qualitative composition of the different strengths is the same

c) the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substances is the same for all strengths: The 16/12.5 mg strength is dose proportional to 32/25 mg strength on which the bioequivalence study has been carried out.

d) Comparative *in vitro* dissolution data were submitted to support waiving for the 16/12.5 mg tablet.

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**
The combination of candesartan and HCTZ has been authorised since 1999, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of candesartan/HCTZ 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. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation.
In line with Risk Management Plans (RMPs) for other fixed-dose combinations containing an ATII-
antagonist and hydrochlorothiazide authorised through MRP or DCP procedures, the following risks are
included in the RMP:

| Important identified risks | Hyperkalaemia          |
|                           | Hypotension            |
| Important potential risks | Elevation of liver function values |
|                           | Renal impairment       |
|                           | Hypersensitivity reactions incl. angioedema |
|                           | Renal impairment       |
|                           | Decrease in haemoglobin and/or hematocrit |

**Product information**

**SPC**
The content of the SPC approved during the decentralised procedure is in accordance with that accepted
for the reference product Atacand Plus.

**Readability test**
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 test consisted of a pilot test, followed by two
rounds with 10 participants each. There were sufficient questions about the critical sections. The
conclusions are clear, concise and clearly presented. Furthermore, the following areas have been
sufficiently covered: traceability, comprehensibility and applicability.
The two rounds of testing showed that, for each question, 100% of participants were able to find the
correct section, and 100% of the participants were able to answer the questions correctly. No changes
were made to the PL. The readability test has been sufficiently performed.
III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Candesartan cilexetil/HCT Jubilant 16/12.5 mg and 32/25 mg, tablets have a proven chemical-pharmaceutical quality and are generic forms of Atacand Plus 16 mg/12.5 mg tablets and Atacand Plus forte 32 mg/25 mg tablets. Atacand Plus 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 consistent with that of the reference product. 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 Candesartan cilexetil/HCT Jubilant 16/12.5 mg and 32/25 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 29 July 2013. Candesartan cilexetil/HCT Jubilant 16/12.5 mg and 32/25 mg, tablets were authorised in the Netherlands on 27 August 2013.

The date for the first renewal will be: 29 July 2018.

There were no post-approval commitments made during the procedure.
### List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ASMF</td>
<td>Active Substance Master File</td>
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<tr>
<td>ATC</td>
<td>Anatomical Therapeutic Chemical classification</td>
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<tr>
<td>AUC</td>
<td>Area Under the Curve</td>
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<tr>
<td>BP</td>
<td>British Pharmacopoeia</td>
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<tr>
<td>CEP</td>
<td>Certificate of Suitability to the monographs of the European Pharmacopoeia</td>
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<tr>
<td>CHMP</td>
<td>Committee for Medicinal Products for Human Use</td>
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<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>C\textsubscript{max}</td>
<td>Maximum plasma concentration</td>
</tr>
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<td>CMD(h)</td>
<td>Coordination group for Mutual recognition and Decentralised procedure for human medicinal products</td>
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<tr>
<td>CV</td>
<td>Coefficient of Variation</td>
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<tr>
<td>EDMF</td>
<td>European Drug Master File</td>
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<td>EDQM</td>
<td>European Directorate for the Quality of Medicines</td>
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<td>EU</td>
<td>European Union</td>
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<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
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<td>GLP</td>
<td>Good Laboratory Practice</td>
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<tr>
<td>GMP</td>
<td>Good Manufacturing Practice</td>
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<tr>
<td>ICH</td>
<td>International Conference of Harmonisation</td>
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<tr>
<td>MAH</td>
<td>Marketing Authorisation Holder</td>
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<tr>
<td>MEB</td>
<td>Medicines Evaluation Board in the Netherlands</td>
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<tr>
<td>OTC</td>
<td>Over The Counter (to be supplied without prescription)</td>
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<tr>
<td>PAR</td>
<td>Public Assessment Report</td>
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<tr>
<td>Ph.Eur.</td>
<td>European Pharmacopoeia</td>
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<tr>
<td>PIL</td>
<td>Package Leaflet</td>
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<tr>
<td>PSUR</td>
<td>Periodic Safety Update Report</td>
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<tr>
<td>SD</td>
<td>Standard Deviation</td>
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<tr>
<td>SPC</td>
<td>Summary of Product Characteristics</td>
</tr>
<tr>
<td>t\textsubscript{1/2}</td>
<td>Half-life</td>
</tr>
<tr>
<td>t\textsubscript{max}</td>
<td>Time for maximum concentration</td>
</tr>
<tr>
<td>TSE</td>
<td>Transmissible Spongiform Encephalopathy</td>
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<tr>
<td>USP</td>
<td>Pharmacopoeia in the United States</td>
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</table>
## STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Type of modification</th>
<th>Date of start of the procedure</th>
<th>Date of end of the procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
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