Public Assessment Report

Decentralised Procedure

IRBESARTAN/HYDROCHLOROTHIAZIDE ARROW 300 MG/12.5 MG FILM-COATED TABLETS

IRBESARTAN/HYDROCHLOROTHIAZIDE ARROW 300 MG/25 MG FILM-COATED TABLETS

(Irbesartan and hydrochlorothiazide)

Procedure No: UK/H/3095/002-3/DC

UK Licence No: PL 33786/0006-7

ARROW APS.
LAY SUMMARY

On 09 July 2012, Czech Republic, Germany, Denmark, Greece, Spain, Finland, France, Ireland, Italy, Malta, the Netherlands, Norway, Sweden and the UK agreed to grant Marketing Authorisations to Arrow ApS for the medicinal products Irbesartan/Hydrochlorothiazide Arrow 300 mg/12.5 mg and 300 mg/25 mg Film-coated Tablets (PL 33786/0006-7; UK/H/3095/002-3/DC). The licences were granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After a subsequent national phase, Marketing Authorisations were granted in the UK on 16 November 2012. These are Prescription-Only Medicines (POM).

Irbesartan/Hydrochlorothiazide Arrow 300 mg/12.5 mg and 300 mg/25 mg Film-coated Tablets contain irbesartan and hydrochlorothiazide as the active ingredients.

Irbesartan belongs to a group of medicines known as angiotensin-II receptor antagonists. Angiotensin-II is a substance produced in the body that binds to receptors in blood vessels causing them to tighten. This results in an increase in blood pressure. Irbesartan prevents the binding of angiotensin-II to these receptors, causing the blood vessels to relax and the blood pressure to lower.

Hydrochlorothiazide is one of a group of medicines (called thiazide diuretics) that causes increased urine output and so causes a lowering of blood pressure.

These two active ingredients work together to lower blood pressure further than if either was given alone.

Irbesartan/Hydrochlorothiazide Arrow 300 mg/12.5 mg and 300 mg/25 mg Film-coated Tablets are used to treat high blood pressure, when treatment with irbesartan or hydrochlorothiazide alone did not provide adequate control of your blood pressure.

No new or unexpected safety concerns arose from these applications and it was judged that the benefits of taking Irbesartan/Hydrochlorothiazide Arrow 300 mg/12.5 mg and 300 mg/25 mg Film-coated Tablets outweigh the risks and therefore Marketing Authorisations were granted.
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</tbody>
</table>
# Module 1

| **Product Name** | Irbesartan/Hydrochlorothiazide Arrow 300 mg/12.5 mg Film-coated Tablets  
|                 | Irbesartan/Hydrochlorothiazide Arrow 300 mg/25 mg Film-coated Tablets |
| **Type of Application** | Generic, Article 10.1 |
| **Active Substances** | Irbesartan and hydrochlorothiazide |
| **Form** | Film-coated tablets |
| **Strength** | 300 mg/12.5 mg and 300 mg/25 mg |
| **MA Holder** | Arrow ApS, Sankt Peders Stræde 2,1, 4000 Roskilde, Denmark |
| **Reference Member State (RMS)** | UK |
| **Concerned Member States (CMS)** | Czech Republic, Germany, Denmark, Greece, Spain, Finland, France, Ireland, Italy, Malta, the Netherlands, Norway, Sweden |
| **Procedure Number** | UK/H/3095/002-3/DC |
| **Timetable** | Day 210–09 July 2012. |
Module 2
Summary of Product Characteristics

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.
Module 3
Patient Information Leaflet

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.
Module 4
Labelling

Carton:

Blister:
PAR Irbesartan/Hydrochlorothiazide Arrow 300 mg/12.5 mg and 300 mg/25 mg Film-coated Tablets

Carton:

Irbesartan/Hydrochlorothiazide 300mg/25mg film-coated tablets
28 film-coated tablets

Irbesartan / Hydrochlorothiazide 300mg/25mg film-coated tablets
Irelcsetan / hydrochlorothiazide
28 film-coated tablets

Keep this medicine out of the reach and sight of children.
Marketing Authorisation Holder:
Arrow ApS, Sankt Peders Stræde 2, 1, 4000 Roskilde, Denmark PL 33796/0007

Blister:

Irbesartan / Hydrochlorothiazide 300mg/25mg film-coated tablets
Irbesartan / hydrochlorothiazide
Arrow ApS
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Member States considered that the applications for Irbesartan/Hydrochlorothiazide Arrow 300 mg/12.5 mg and 300 mg/25 mg Film-coated Tablets (PL 33786/0006-7; UK/H/3095/002-3/DC) could be approved. These applications were submitted via the decentralised procedure, with the UK as Reference Member State (RMS) and Czech Republic, Germany, Denmark, Greece, Spain, Finland, France, Ireland, Italy, Malta, the Netherlands, Norway and Sweden as Concerned Member States (CMS). These products are prescription-only medicines (POM).

Irbesartan/Hydrochlorothiazide Arrow 300 mg/12.5 mg and 300 mg/25 mg Film-coated Tablets are indicated for treatment of essential hypertension.

This fixed dose combination is indicated in adult patients whose blood pressure is not adequately controlled on irbesartan or hydrochlorothiazide alone.

These are abridged applications submitted under Article 10(1) of Directive 2001/83/EC as amended, cross-referring to CoAprovel 300 mg/12.5 mg and 300 mg/25 mg film-coated tablets (Sanofi Pharma Bristol-Myers Squibb SNC), which were first authorised in October 1998 by the Centralised Procedure.

Irbesartan is an Angiotensin II receptor antagonist. Angiotensin II receptor antagonists, also known as angiotensin receptor blockers (ARBs), AT1-receptor antagonists or sartans, are a group of pharmaceuticals which modulate the renin-angiotensin-aldosterone system. AT1-receptor antagonists block the activation of angiotensin II AT1-receptors. Blockade of AT1-receptors directly causes vasodilatation, reduces secretion of vasopressin, reduces production and secretion of aldosterone, amongst other actions – the combined effect of which is reduction of blood pressure.

Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts.

No new non-clinical studies were conducted, which is acceptable given that the products are intended to be generic versions of the originator products that have been licensed for over 10 years.

Two bioequivalence studies (single dose) were submitted to support these applications, comparing the test products Irbesartan/Hydrochlorothiazide Arrow 300 mg/12.5 mg and 300 mg/25 mg Film-coated Tablets (Arrow Aps) with the reference products CoAprovel 300 mg/12.5 mg and 300 mg/25 mg film-coated tablets (Sanofi Pharma Bristol-Myers Squibb SNC, Germany).

With the exception of the bioequivalence studies, no new clinical studies were conducted, which is acceptable given that the applications were for products that are intended to be
generic versions of the originator products that have been licensed for over 10 years. The bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture, assembly and batch release of these products.

The RMS and CMS considered that the applications could be approved with the end of procedure (Day 210) on 09 July 2012. After the subsequent national phase, the licences were granted in the UK on 16 November 2012.
### II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Irbesartan/Hydrochlorothiazide Arrow 300 mg/12.5 mg Film-coated Tablets  
Irbesartan/Hydrochlorothiazide Arrow 300 mg/25 mg Film-coated Tablets |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Irbesartan and hydrochlorothiazide</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Angiotensin-II antagonists and diuretics (C09DA04).</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>300 mg/12.5 mg and 300 mg/25 mg film-coated tablets</td>
</tr>
<tr>
<td>Reference numbers for the Mutual Recognition Procedure</td>
<td>UK/H/3095/002-3/DC</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Concerned Member State</td>
<td>Czech Republic, Germany, Denmark, Greece, Spain, Finland, France, Ireland, Italy, Malta, the Netherlands, Norway, Sweden</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 33786/0006-7</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Arrow ApS, Sankt Peders Stræde 2,1, 4000 Roskilde, Denmark</td>
</tr>
</tbody>
</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substances

(1) Hydrochlorothiazide

INN: Hydrochlorothiazide
Chemical names: 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide
OR
2H-1, 2, 4-benzothiadiazine-7-sulfonamide, 6-chloro-3, 4-dihydro-1, 1-dioxide

Structure:

```
\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{O} \\
\text{S} & \quad \text{O} \\
\text{Cl} & \quad \text{N} \\
\text{H} & \quad \text{H}
\end{align*}
\]
```

Molecular formula: \( C_7H_8ClN_3O_4S_2 \)
Molecular mass: 297.7
Appearance: Hydrochlorothiazide is a white or almost white, crystalline powder.
Solubility: Hydrochlorothiazide is very slightly soluble in water, soluble in acetone, sparingly soluble in ethanol (96%) and it dissolves in dilute solutions of alkali hydroxides.

Hydrochlorothiazide is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance hydrochlorothiazide are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

(2) Irbesartan

INN: Irbesartan
Chemical names: 2-Butyl-3-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-1,3-diazaspiro[4.4]non-1-en-4-one
OR
2-Butyl-3-[P-(o-1H-tetrazol-5-ylphenyl) benzyl]-l, 3- diazasiropo [4.4] non-1-en-4-one
OR
2-n-butyl-4-spirocyclopentane-l-[(2'- (tetrazol-5-yl)biphenyl-4-yl)methyl]-2-imidazolin-5-one
OR
1,3-Diazaspiro [4.4] non-1-en-4-one, 2-butyl-3-[(2'-(1H-tetrazol-5-yl)] [1,1'-biphenyl]-4-yl] methyl]
Structure:

![Structure](image)

Molecular formula: \(C_{25}H_{28}N_6O\)
Molecular mass: 428.5
Appearance: Irbesartan is a white or almost white, crystalline powder.
Solubility: Irbesartan is practically insoluble in water, sparingly soluble in methanol and slightly soluble in methylene chloride.

Irbesartan is the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised. Satisfactory Certificates of Analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated to support a suitable retest period when stored in the proposed packaging.

P. Medicinal Product

Other Ingredients

Other ingredients consist of the pharmaceutical excipients microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, povidone, poloxamer, pregelatinised maize starch, colloidal anhydrous silica and magnesium stearate. In addition:

The 300 mg/12.5 mg strength also contains:
- Opadry II 85F64712 pink [consisting of, polyvinyl alcohol-part hydrolysed, titanium dioxide (E171), macrogol 3350, talc, iron oxide red (E172), iron oxide yellow (E172) and iron oxide black (E172)].

The 300 mg/25 mg strength also contains:
Opadry II 85F66815 brown [consisting of, polyvinyl alcohol- part hydrolysed, macrogol 3350, talc, titanium dioxide (E171), iron oxide red (E172), allura red (E129), iron oxide yellow (E172) and iron oxide black (E172)].

All excipients comply with their respective European Pharmacopoeia monographs with the exception of Opadry II 85F64712 pink, and Opadry II 85F66815 brown which are controlled to suitable in-house specifications. Satisfactory certificates of analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

With the exception of lactose monohydrate, none of the excipients contain materials of animal or human origin. The supplier of lactose monohydrate has confirmed that the lactose is sourced from healthy animals under the same conditions as milk for human consumption.

None of the excipients contain materials of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development
The objective of the development programme was to formulate stable, robust, film-coated tablets containing 300 mg/12.5 mg and 300 mg/25 mg irbesartan and hydrochlorothiazide, which could be considered generic medicinal products of CoAprovel 300 mg/12.5 mg and 300 mg/25 mg film-coated tablets (Sanofi Pharma Bristol-Myers Squibb SNC, Germany).

A satisfactory account of the pharmaceutical development has been provided.

Comparative in vitro dissolution and impurity profiles have been provided for the proposed and originator products.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at pilot scale and has shown satisfactory results.

Finished Product Specification
The proposed finished product specifications are acceptable. Test methods have been described and have been adequately validated. Batch data have been provided, which comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Container-Closure System
All strengths of the finished product are packaged in polyvinylchloride (PVC)-polyvinylidene chloride (PVdC)/aluminium foil blister strips in pack sizes of 14, 28, 30, 56, 84, 90 and 98 film-coated tablets.

It has been stated that not all pack sizes may be marketed. However, the Marketing Authorisation Holder has committed to submitting the mock-ups for any pack size to the relevant regulatory authorities for approval before marketing.
Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

**Stability of the product**
Stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years with the storage conditions ‘Store below 25°C. Store in the original package in order to protect from light and moisture.’

**Bioequivalence/bioavailability**
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels**
The SmPCs, PIL and labels are acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

**Marketing Authorisation Application (MAA) form**
The MAA forms are satisfactory.

**Quality Overall Summary**
The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

**Conclusion**
There are no objections to the approval of these products from a pharmaceutical viewpoint.

**III.2 NON-CLINICAL ASPECTS**
As the pharmacodynamic, pharmacokinetic and toxicological properties of irbesartan and hydrochlorothiazide are well-known, no new non-clinical studies are required and none have been provided.

The applicant’s non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant pharmacology and toxicology.

Since Irbesartan/Hydrochlorothiazide Arrow 300 mg/12.5 mg and 300 mg/25 mg Film-coated Tablets are intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment (ERA) is therefore not deemed necessary.

There are no objections to the approval of these products from a non-clinical viewpoint.
III.3 CLINICAL ASPECTS
Pharmacokinetics
In support of these applications, the marketing authorisation holder has submitted the following bioequivalence studies:

STUDY 1
An open label, randomised, single-dose, two-period, two-sequence, two treatment, crossover study to compare the pharmacokinetics of the test product Irbesartan/Hydrochlorothiazide Arrow 300 mg/25 mg Film-coated Tablets (Arrow ApS) versus the reference product CoAprovel 300 mg/25 mg film-coated tablets (Sanofi Pharma Bristol-Myers Squibb SNC, Germany) in healthy adult volunteers under fasted conditions.

All volunteers received a single oral dose of either the test or reference product as a 1 x 300 mg/25 mg tablet administered with 240 ml of water after an overnight fast of at least 10 hours. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 48 hours post dose. The washout period between treatment periods was at least 7 days.

The pharmacokinetic results for irbesartan are presented below (log-transformed values; arithmetic and geometric mean and 90% confidence intervals):

<table>
<thead>
<tr>
<th>Parameter</th>
<th>TRT</th>
<th>Arithmetic (mg/mL)</th>
<th>Geometric (mg/mL)</th>
<th>Contrast</th>
<th>Ratio (% lower CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax</td>
<td>A</td>
<td>3740.26</td>
<td>3549.31</td>
<td>A vs. B</td>
<td>101.61</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>3645.53 (36)</td>
<td>3493.06</td>
<td></td>
<td>95.60 - 108.00</td>
</tr>
<tr>
<td>AUCt</td>
<td>A</td>
<td>21188.32 (39)</td>
<td>19864.52</td>
<td>A vs. B</td>
<td>100.29</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>20979.38 (40)</td>
<td>19806.96</td>
<td></td>
<td>96.57 - 104.16</td>
</tr>
<tr>
<td>AUCInf</td>
<td>A</td>
<td>22949.96 (42)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>22524.66 (41)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The pharmacokinetic results for hydrochlorothiazide are presented below (log-transformed values; arithmetic and geometric mean and 90% confidence intervals):

<table>
<thead>
<tr>
<th>Parameter</th>
<th>TRT</th>
<th>Arithmetic (mg/mL)</th>
<th>Geometric (mg/mL)</th>
<th>Contrast</th>
<th>Ratio (% lower CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax</td>
<td>A</td>
<td>186.603</td>
<td>172.405</td>
<td>A vs. B</td>
<td>95.85</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>190.826 (34)</td>
<td>179.861</td>
<td></td>
<td>90.19 - 101.87</td>
</tr>
<tr>
<td>AUCt</td>
<td>A</td>
<td>1167.095 (34)</td>
<td>1084.797</td>
<td>A vs. B</td>
<td>96.34</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>1194.971 (33)</td>
<td>1125.965</td>
<td></td>
<td>91.80 - 101.12</td>
</tr>
<tr>
<td>AUCInf</td>
<td>A</td>
<td>1197.943 (34)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>1227.799 (34)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
STUDY 2
An open label, randomised, single-dose, two-period, two-sequence, two treatment, crossover study to compare the pharmacokinetics of the test product Irbesartan/Hydrochlorothiazide Arrow 300 mg/12.5 mg Film-coated Tablets (Arrow ApS) versus the reference product CoAprovel 300 mg/12.5 mg film-coated tablets (Sanofi Pharma Bristol-Myers Squibb SNC, Germany) in healthy adult volunteers under fasted conditions.

All volunteers received a single oral dose of either the test or reference product as a 1 x 300 mg/12.5 mg tablet administered with 240 ml of water after an overnight fast of at least 10 hours. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 48 hours post dose. The washout period between treatment periods was at least 7 days.

The pharmacokinetic results for irbesartan are presented below (log-transformed values; arithmetic and geometric mean and 90% confidence intervals):

<table>
<thead>
<tr>
<th>Parameter</th>
<th>TRT</th>
<th>Means</th>
<th>90% CI</th>
<th>Intra-Sub CV(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Based on Measured Data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cmax (mg/mL)</td>
<td>A</td>
<td>3503.33</td>
<td>27</td>
<td>3402.04</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>3667.69</td>
<td>33</td>
<td>3523.41</td>
</tr>
<tr>
<td>AUCinf (mg*h/mL)</td>
<td>A</td>
<td>19552.14</td>
<td>33</td>
<td>18736.33</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>19150.69</td>
<td>36</td>
<td>18313.37</td>
</tr>
<tr>
<td>AUCt (mg*h/mL)</td>
<td>A</td>
<td>20587.22</td>
<td>38</td>
<td></td>
</tr>
</tbody>
</table>

AUCt area under the plasma concentration-time curve from time zero to t hours
AUCinf area under the plasma concentration-time curve from time zero to infinity,
Cmax maximum plasma concentration
A = Test product
B = Reference product

The pharmacokinetic results for hydrochlorothiazide are presented below (log-transformed values; arithmetic and geometric mean and 90% confidence intervals):

<table>
<thead>
<tr>
<th>Parameter</th>
<th>TRT</th>
<th>Means</th>
<th>90% CI</th>
<th>Intra-Sub CV(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Based on Measured Data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cmax (mg/mL)</td>
<td>A</td>
<td>85.359</td>
<td>29</td>
<td>81.722</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>81.182</td>
<td>32</td>
<td>77.737</td>
</tr>
<tr>
<td>AUCinf (mg*h/mL)</td>
<td>A</td>
<td>521.305</td>
<td>22</td>
<td>509.190</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>503.386</td>
<td>19</td>
<td>494.548</td>
</tr>
<tr>
<td>AUCt (mg*h/mL)</td>
<td>A</td>
<td>534.767</td>
<td>21</td>
<td></td>
</tr>
</tbody>
</table>

AUCt area under the plasma concentration-time curve from time zero to t hours
AUCinf area under the plasma concentration-time curve from time zero to infinity,
Cmax maximum plasma concentration
A = Test product
B = Reference product

The 90% confidence intervals for AUC and Cmax for test versus reference product for irbesartan and hydrochlorothiazide for both strengths (300 mg/12.5 mg and 300 mg/25 mg) are within predefined acceptance criteria specified in "Guideline on the Investigation
of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev 1/, Corr). Thus, the data support the claim that the test products are bioequivalent to the reference products.

**Pharmacodynamics**
No new pharmacodynamic data were submitted and none were required for these applications.

**Efficacy**
No new efficacy data were submitted and none were required for these applications.

**Safety**
With the exception of the data generated during the bioequivalence studies, no new safety data were submitted and none were required for these applications. No new or unexpected safety issues were highlighted by the bioequivalence data.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels**
The SmPCs, PIL and labels are acceptable. The SmPCs are consistent with that for the originator products. The PIL is consistent with the SmPCs and in line with current guidelines. The labelling is in-line with current guidelines.

**MAA Forms**
The MAA forms are satisfactory.

**Clinical Overview**
The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

**Pharmacovigilance System and Risk Management Plan**
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Suitable justification has been provided for not submitting a Risk Management Plan for these products.

**Conclusion**
There are no objections to the approval of these products from a clinical view-point.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The quality characteristics of Irbesartan/Hydrochlorothiazide Arrow 300 mg/12.5 mg and 300 mg/25 mg Film-coated Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type. The pharmacodynamic, pharmacokinetic and toxicological properties of irbesartan and hydrochlorothiazide are well-known.

EFFICACY
With the exception of the bioequivalence studies, no new data were submitted and none are required for applications of this type.

Bioequivalence has been demonstrated between the applicant’s Irbesartan/Hydrochlorothiazide Arrow 300 mg/12.5 mg and 300 mg/25 mg Film-coated Tablets and the respective reference products CoAprovel 300 mg/12.5 mg and 300 mg/25 mg film-coated tablets (Sanofi Pharma Bristol-Myers Squibb SNC, Germany).

SAFETY
With the exception of the bioequivalence studies, no new data were submitted and none are required for applications of this type. As the safety profile of irbesartan and hydrochlorothiazide is well-known, no additional data were required. No new or unexpected safety concerns arose from the safety data from the bioequivalence study.

PRODUCT LITERATURE
The SmPCs, PIL and labelling are satisfactory and consistent with that for the reference products, and in line with current guidelines.

BENEFIT-RISK ASSESSMENT
The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence studies support the claim that the applicant’s products and the originator products are interchangeable. Extensive clinical experience with irbesartan and hydrochlorothiazide is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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<th>Date submitted</th>
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