European Medicines Agency
Evaluation of Medicines for Human Use

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CHMP ASSESSMENT REPORT

FOR

Irbesartan krka

International Nonproprietary Name: **irbesartan**

Procedure No. EMEA/H/C/000962

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Krka, d.d., Novo mesto submitted on 06 December 2007 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Irbesartan Krka, in accordance with the centralised procedure falling within the scope of the Annex to Regulation (EC) 726/2004 under Article 3 (3) – 'Generic of a Centrally authorised product'.

The legal basis for this application refers to Article 10(1).

The chosen reference product is:

■ Reference medicinal product which is or has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: **Aprovel 75mg, 150mg, 300mg tablets and 75mg, 150mg, 300mg film-coated tablets**
- Marketing authorisation holder: **Sanofi Pharma Bristol Myers Squib SNC**
- Member State (EEA)/Community: **Community**
- First authorisation: Date **27-08-1997**

■ Reference medicinal product authorised in the Community/Member State where the application is made:

- Product name, strength, pharmaceutical form: Aprovel 75mg, 150mg, 300mg tablets
- Marketing authorisation holder: Sanofi pharma Bristol Myers Squib SNC
- Marketing authorisation number(s): **EU/1/97/046/004-006**

■ Medicinal Product used for bioequivalence study (where applicable)

- Product name, strength, pharmaceutical form: Aprovel 300 mg film coated tablets
- Marketing authorisation holder: Sanofi Pharma Bristol Myers Squib SNC
- Member State of source: **Germany**

- Bioavailability study number(s):
  Study No IBA-P7-064

The Rapporteur appointed by the CHMP was: Concepción Prieto Yerro

Scientific Advice:

The applicant did not seek scientific advice at the CHMP.

Licensing status:
The product was not licensed in any country at the time of submission of the application.

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 6 December 2007.
- The procedure started on 26 December 2007.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 17 March 2008.
- During the meeting 21-23 April 2008 the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 28 April 2008.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 22 May 2008.

- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 8 July 2008.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 22 August 2008.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 2 September 2008.
- During the meeting on 22-25 September 2008, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Irbesartan Krka on 25 September 2008.
- The CHMP opinions were forwarded in all official languages of the European Union, to the European Commission, which adopted the corresponding Decision on 1 December 2008.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

Irbesartan Krka 75 mg, 150 mg or 300 mg film-coated tablet is a generic medicinal product containing irbesartan as irbesartan hydrochloride as active substance.

Irbesartan is a potent, orally active, selective angiotensin-II receptor (type AT1) antagonist. It is expected to block all actions of angiotensin-II mediated by the AT1 receptor, regardless of the source or route of synthesis of angiotensin-II. The selective antagonism of the angiotensin-II (AT1) receptors results in increases in plasma renin levels and angiotensin-II levels, and a decrease in plasma aldosterone concentration. Serum potassium levels are not significantly affected by irbesartan alone at the recommended doses. Irbesartan does not inhibit ACE (kininase-II), an enzyme which generates angiotensin-II and also degrades bradykinin into inactive metabolites. Irbesartan does not require metabolic activation for its activity.

The efficacy and safety of irbesartan has been demonstrated in several randomised, double-blind placebo controlled studies, and controlled studies with active comparators in patients with hypertension. Irbesartan was also studied in two large studies in kidney disease in patients with type 2 diabetes. A summary of these studies can be found in the EPAR of Aprovel.

The indication proposed for irbesartan is the same as authorised for the reference medicinal product Aprovel.

2.2 Quality aspects

Introduction

Irbesartan Krka is presented in the form of film coated tablets.

The film coated tablets contain 75 mg, or 150 mg or 300 mg of irbesartan as active substance. Other ingredients are defined in the SPC section 6.1.

It is packaged into blisters made of PVC/PE/PVDC/Al.

Active Substance

The chemical name of irbesartan hydrochloride is 3-((2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl)methyl)-2-butyl-1,3-diazaspiro[4.4]non-1-en-4-one hydrochloride or,
2-Butyl-3-(*p*-(*o*-1*H*-tetrazol-5-ylphenyl)benzyl)-1,3-diazaspiro(4.4)non-1-en-4-one hydrochloride.
Corresponding to the molecular formula C25H28N6O*HCl and relative molecular mass 465.0

It appears as a crystalohydrate salt in an average ratio to water content of 1: 3/2. It is a white to almost white powder, sparingly soluble in ethanol, practically insoluble in chloroform and water. It does not show polymorphism. Irbesartan hydrochloride is not described in Ph Eur.

- Manufacture

Irbesartan HCl is manufactured by a two step chemical synthesis. The first step (path A) includes preparation of the intermediate product. The quality profile of the active substance obtained by path A is considered sufficiently described and adequately supported by data. Therefore path A is approvable and can be used for the synthesis of the active substance to be used for the manufacture of the finished product.
In the second step the final synthesis and purification of irbesartan HCl takes place. The material can be re-processed if necessary.
In summary, sufficient information has been provided to demonstrate that the active substance manufactured by path A is meets all relevant specifications.

- Specification

The drug substance specification as tested by the finished product manufacturer includes tests for appearance (visual), identification (IR and in-house), solubility (PhEur), water (PhEur), heavy metals (PhEur), sulphated ash (Ph.Eur), related substances (HPLC), assay (titration), residual solvents (GC).
The specifications reflect all relevant quality attributes of the active substance and were found to be adequate to control the quality of the active substance.
A total of three batches manufactured by the synthetic route path A. The results are within the specifications and consistent from batch to batch.

- Stability

Three production scale batches were put on long-term (25±2°C/60±5%RH) and accelerated (40±2°C/75±5%RH) stability testing conditions respectively.
6 months stability testing results of the active substance at controlled room temperature 25±2°C/60±5%RH, accelerated conditions 40±2°C/75±5%RH and intermediate condition 30±2°C/65±5% RH are currently available. The stability study is ongoing.
Appearance, water content, content of irbesartan hydrochloride and related substances are being monitored using the same analytical methods used in the stability program as for release.
No significant changes have been observed at accelerated and long term stability conditions.
The photostability test performed according to the ICH Q1B, on one batch revealed no significant changes in the sample after 23 h.
The proposed re-test period is justified based on the stability results when the active substance is stored in the original packing material.

Medicinal Product

- Pharmaceutical Development

Different compositions of irbesartan HCl were tested, initially prepared by direct compression. During the tabletting process some technological problems appeared. Using a combination of two polyol diluents and different lubricant brought no significant improvement.
Subsequently a wet granulation process was employed using ethanol as granulating agent. During the drying step the wet granulate is put in combination with the mannitol as the main diluent, which is known to be easily dried. Using this process previously observed problems were overcome.
The formulation was further optimised using different excipients and studying their influence on tablet hardness and disintegration times. A relatively simple composition with well defined excipients was selected in order to prepare a stable and bioequivalent formulation.
Film coating was applied in order to protect the core with the active substance against light and humidity.

Extensive experimental work has been done by the applicant in order to develop a discriminatory dissolution test method which reflects in vivo bioequivalence as required by the guideline on Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98). This work has led to the establishment of an appropriate dissolution test method for QC purposes. Comparative dissolution studies between the reference and generic product for all strengths have shown the dissolution profiles can be considered similar as defined by the same guideline.
The excipients selected are commonly used for the manufacture of pharmaceutical preparations. These are Mannitol, Hydroxypropylcellulose, Talc, Macrogol 6000, Low-substituted hydroxypropylcellulose, Hydrogenated Castor Oil; the coating is Opadry White (Polyvinyl alcohol, Titanium dioxide, Macrogol 3000 and Talc). None of the excipients used for the manufacture of the drug product contain materials that are of animal or human origin.
Comparative results of impurities profile of these batches (see above) and innovator batches are provided. All detected impurities are present in concentrations below reporting level.

Bioequivalence study was performed for the 300 mg strength under fasting conditions in healthy volunteers. Plasma concentrations of irbesartan were determined using a validated LC/MS method.
The impurity profile of the biobatch is very similar to the reference biobatch. Satisfactory certificates of analysis for the reference biobatch and test biobatch were provided.

- Adventitious Agents

The applicant has declared that starting materials and excipients used for the manufacture irbesartan film-coated tablets do not contain materials that are of animal or human origin and are not in contact with materials of animal or human origin, during their manufacture.

- Manufacture of the Product

The manufacturing process is a standard wet granulation method where the active substance is granulated with ethanol and part of the excipients. After drying, the granulate is mixed with the remainder of the excipients and compressed into tablets. The process comprises the following stages: Mixing, Granulation, Drying/Sieving, Mixing, Compression/tabletting and Film coating.

- Product Specification

The product specifications include tests by validated methods for Appearance (visual), Identification (irbesartan: HPLC, UV, Titanium dioxide: TLC), Uniformity of dosage units-mass variation (PhEur), Dissolution (PhEur), Assay (HPLC), Degradation products (HPLC), Microbial contamination (PhEur), water (PhEur) and hardness (PhEur).
Batch information for six batches of drug product (2 batches for each dose) is provided. All batches comply with the proposed specification. The batch analysis data presented indicate that the film-coated tablets can be manufactured reproducibly according to the finished product specification.
There are no unqualified impurities present.

- Stability of the Product

Three pilot scale batches of Irbesartan film-coated tablets 300 mg were put on long-term (25±2°C/60±5%RH) up to six months, intermediate(30±2°C/65±5%RH) up to six months and accelerated (40±2°C/75±5%RH) stability testing conditions up to three months.
Two pilot scale batches of Irbesartan film-coated tablets 75 mg and two pilot scale batches of 150 mg tablets were put on long-term (25±2°C/60±5%RH) up to six months, intermediate (30±2°C/65±5%RH) up to six months and accelerated (40±2°C/75±5%RH) stability testing conditions up to three months.
The stability testing is performed according to the Reduced stability testing protocol (matrixing) following currently valid Note for guidance on bracketing and matrixing for stability testing of drug substances and drug product, CPMP/ICH/4104/00, according to which for conventional dosage forms and when active substances are know to be stable, stability data on at least two pilot batches are

acceptable. Stability studies include testing of those attributes of the drug product that are susceptible to change during storage.
All tested attributes remained within the limits of specifications for all tested batches at all testing conditions.
The results of dissolution of Irbesartan Krka film-coated tablets at accelerated conditions after 6 months were below the limit of specification for all tested batches due to this reason the stability testing is being continued at intermediate stability testing condition.
Photostability test was performed according to the ICH Guidelines (Q1B), on one batch for each strength. No significant differences in irbesartan assay and degradation products content were observed. In conclusion, Irbesartan Krka film-coated tablets (75 mg, 150 mg and 300 mg strengths) are not sensitive to light.
Based on the stability studies results the shelf life and storage conditions as defined in the SPC are supported.

Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the drug substance and drug product has been presented in a satisfactory manner. The quality of the active substance obtained by path A is considered sufficiently described and adequately supported by data. Therefore only active substance manufactured by path A is considered acceptable. The applicant should manufacture the finished product using only active substance obtained by path A. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.3 Non-clinical aspects

This is a generic application containing a different salt of the active substance. The safety of Krka's irbesartan hydrochloride as alternative salt was demonstrated with acute toxicity study (T-2614), 90-day toxicity study (T-2615) and Ames test (A-22/06). The results of these studies were in accordance with the available data in published literature and confirmed the safety of Krka's generic product.

Irbesartan Krka film-coated tablets are similar to the reference medicinal product with respect to the impurity profile. Since Irbesartan Krka is essentially similar product and its safety was proven, no additional toxicology/impurities studies were considered necessary.

No ERA has been submitted and the Applicant has presented a justification. It is accepted that the introduction of Irbesartan Krka is unlikely to result in any significant increase in the combined sales volumes for all irbesartan containing products. The risk of an environmental impact from the use of irbesartan is of no concern.

2.4 Clinical aspects

Introduction

The CHMP assessment addressed pharmacokinetic data in respect of a bioequivalence study.

GCP

The bioequivalence study is stated to have been performed in accordance with GCP and the ethical requirements of Directive 2001/20. The clinical part of the study and the pharmacokinetic and statistical analyses were performed by a CRO, Canada. The bioanalysis was carried out in a CRO, Canada.

The Applicant has clarified that the clinical centre has been inspected regularly by Regulatory Agencies, including FDA (USA) in April 2007, MHRA (UK) in October 2007 and AGES (Austria) in

February 2008. This is considered sufficient demonstration of the reliability of the study taking into account that no concern on this respect has been observed during the study assessment.

Clinical study

To support the application, the applicant has submitted a single-dose, fasted-state bioequivalence study.

Pharmacokinetics

- Methods

STUDY DESIGN

In study IBA-P7-064, the pharmacokinetics of irbesartan was investigated after a 300 mg single dose under fasting conditions in 24 healthy male healthy volunteers. Irbesartan was administered with 240 mL of water at ambient temperature. Blood samples were collected prior to and after drug administration. There was a 1-week washout between treatments.

The clinical part of the study, pharmacokinetic and statistical analyses, and bioanalysis were performed by CROs.

The Protocol was approved on the 03/05/2007. It was subsequently approved by the Ethics Committee on the 04/05/2007. Amendment 01 dated 05/06/2007 was approved on the 06/06/2007.
The clinical phase was performed in two groups. Subjects of group I were tested on the 13/06/2007 and 20/06/2007. Subjects of group II were dosed on the 04/07/2007 and 11/07/2007.
The analysis of the samples was conducted in the period from 20/07/2007 to 03/08/2007.

TEST AND REFERENCE PRODUCTS

Irbesartan 300 mg film coated tablets by KRKA, Slovenia has been compared to Aprovel 300 mg film coated tablets, (Sanofi Pharma Bristol-Myers Squibb), purchased in Germany.

Biowaiver

According to the Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98 a bioequivalence study investigating only one strength may be acceptable if a new application concerns several strengths of the active substance. In such a case the choice of the strength used should be justified on analytical, pharmacokinetic and safety grounds. Furthermore all the following conditions must be fulfilled:

- the pharmaceutical products are manufactured by the same manufacturer and process,
- the drug input has been shown to be linear over the therapeutic range (if this is not the case the strengths where the sensitivity is largest to identify differences in the two products should be used),
- the qualitative compositions of the different strengths is the same,
- the ratio between amounts of active substance and excipients is the same, or, in the case of preparations containing a low concentration of the active substance (less than 5%), the ratio between the amounts of excipients is similar,
- the dissolution profile should be similar under identical conditions for the additional strength and strength of the batch used in bioequivalence study.

All the above points were met; however, the *in vitro* dissolution profiles submitted were inconclusive.
The dissolution profiles should be carried out with a sampling time at 15 minutes. This time point is essential to decide whether the calculation of f2 similarity factor is necessary. Without a sampling time at 15 minutes, it is not possible to calculate the similarity factor (f2) because there are not three time points with only one of them above 85%. This point was considered a major objection.

Therefore, the applicant was asked to submit comparative *in vitro* dissolution profiles in 0.1 M HCl media for the three different strengths of Irbesartan Krka (75, 150 and 300 mg) with sampling times at 10, 15 and 20 minutes at least, in order to investigate with the adequate methodology the similarity of the dissolution profiles so that it is possible to justify a biowaiver for the 75 and 150 strengths.

The assessment of the applicant's responses showed that Irbesartan Krka only shows high solubility in the physiological pH range at very acid pH (1.2). In dissolution media with this pH value the dissolution profiles have shown to be similar now with the correct methodology. Dissolution profiles have shown to have the necessary low variability to employ the f2 similarity factor and the differences in the amount dissolved in the first 3 times points is lower than 10%. Therefore, the dissolution profiles are considered similar, and the biowaiver for the 75 and 150 strengths granted.

POPULATION(S) STUDIED

Twenty-seven healthy male volunteers were included in the study, 26 completed the cross-over design. One subject withdrew his consent after period 2 for personal reasons. Twenty-four subjects were analysed and included in the statistical analysis. One subject was enrolled but was not included in the study. He did not receive any medication. Two alternate subjects were not used; therefore, their samples were not assayed.

ANALYTICAL METHODS

Irbesartan was analysed in plasma by HPLC with MS/MS detection.
The validation of the analytical method is satisfactory

PHARMACOKINETIC VARIABLES

Standard pharmacokinetic variables were determined through non-compartmental analysis by the linear trapezoidal rule. The pharmacokinetic analysis was performed with the program Kinetic 8.0.

STATISTICAL METHODS

The statistical analyses were performed with SAS 9.1. Descriptive statistics were calculated by treatment for the estimated pharmacokinetic parameters. Analysis of Variance (ANOVA) was also carried out on the natural log-transformed AUC_t, AUC_{inf}, C_{max}, and untransformed K_{el} and $t_{1/2}$ data. Values for the T_{max} parameter were analyzed by a nonparametric approach in accordance with the NfG on the investigation of bioavailability and bioequivalence and its Questions and Answer document. Based on the log-transformed parameters, the following criteria were used to evaluate the bioequivalence between the test and reference products:
• The 90% confidence intervals of the relative mean AUC_t, AUC_{inf} and C_{max} of the test to reference products should be between 80% and 125%.

- Results

Irbesartan

PARAMETER	TEST		REFERENCE		F (treatment)	p *
	MEAN	C.V. (%)	MEAN	C.V. (%)		
C_{max} (ng/mL)	3945.00	36.2	3703.53	25.1	0.87	N.S.
ln (C_{max})	8.2264	3.9	8.1865	3.1	0.48	N.S.
T_{max} (hours) §	1.38	60.3	1.50	57.7	165.5	N.S.
AUC_T (ng·h/mL)	20011.34	27.5	19367.33	28.2	0.50	N.S.
ln (AUC_T)	9.8657	2.9	9.8305	3.0	0.48	N.S.
AUC_∞ (ng·h/mL)	20840.53	26.6	19476.16	25.3	1.52	N.S.
ln (AUC_∞)	9.9079	2.9	9.8430	2.8	1.43	N.S.
$AUC_{T/\infty}$ (%)	96.27	3.7	97.41	1.4	1.63	N.S.
K_{el} ($hour^{-1}$)	0.0734	42.0	0.0771	41.8	0.36	N.S.
$T_{½el}$ (hours)	11.19	51.3	10.42	39.3	0.30	N.S.

* N.S.= Not Significant. Significant whenever p-value < 0.05.
§ For T_{max}, the median is presented and the statistical analysis is based on a non-parametric approach.

Table 1: Main pharmacokinetic parameters of the individual formulations (without log-transformation)

PARAMETER	INTRA-SUBJECT CV (%)	GEOMETRIC LSMEANS *		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		TEST	REFERENCE		LOWER	UPPER
C_{max}	20.2	3738.28	3592.18	104.07	94.22	114.95
AUC_T	17.8	19258.12	18591.81	103.58	94.90	113.07
AUC_∞	16.4	19446.58	18253.50	106.54	97.15	116.82

* units are ng/mL for C_{max} and ng·h/mL for AUC_T and AUC_∞

Table 2: 90% Confidence intervals for the ratio of the PK parameters (after log-transformation)

All pre-dose samples were found to be below the LLOQ.
Data of 24 subjects were taken into account for C_{max} and AUC_{0-t}. AUC_{inf} was not calculated in four subjects for the reference because the terminal phase of elimination could not be adequately estimated for these subjects.
The ratios of $AUC_0.t/AUC_{inf}$ were all above 80% in all cases where the AUC_{inf} could be estimated.
No statistically significant period effect or sequence effect was detected in the ANOVA table of the primary PK metrics AUC_t and C_{max}. The ANOVA table took into consideration the existence of two groups of subjects.

Based on the pharmacokinetic parameters of Irbesartan, the reference and test are considered bioequivalent with respect to the extent and rate of absorption / exposure. The 90% confidence intervals calculated for $AUC_{(0-t)}$, $AUC_{(0-inf)}$ and C_{max} of irbesartan were inside the normal range of acceptability (0.80 – 1.25).
The absence of quantifiable levels in pre-dose samples of period 2 indicates the lack of carryover effect. Therefore, an unequal carry-over effect can be excluded and the cross-over design represents validly the relative bioavailability between test and reference products. This is also confirmed in the absence of period and sequence effects in the ANOVA table

The AUC estimated is considered representative enough of the extent of absorption / exposure since the extrapolation is minor. It is acceptable the absence of adequate data on the elimination rate constant in 4 subjects.
The C_{max} was not observed in the first sampling time, therefore, the C_{max} is considered to have been estimated correctly due to the adequate frequency of the sampling around T_{max}.

Protocol deviations:

Fifty-nine deviations in the blood sampling were reported. If the deviation was equal or greater than 2 minutes it was taken into account for PK calculations. The other time deviations were considered to have a negligible impact on the study outcome. These deviations were due to technical problems, late arrival of subjects or administrative errors.

There were 2 deviations with regards to xantine consumption, 1 with regards to vital signs measurements, 14 in sample processing, storage and shipping and 1 subject who withdrew the consent was substituted according to the protocol.

These deviations are considered normal and acceptable since they do not alter the validity of the study conclusion.

Safety data:

The safety analysis includes the 27 subjects who entered the study and received at least one of the treatments. Fourteen adverse events were reported in subjects receiving the test and also 14 adverse events were reported in those receiving the reference product.

The safety profile of both products seems to be comparable although the design was not powered to compare the safety profile. No difference in the safety profile is anticipated.

- Conclusions

Based on the presented bioequivalence study Irbesartan Krka is considered bioequivalent with Aprovel.

The results of study IBA-P7-064 with 300 mg formulation can be extrapolated to the other strengths (75 mg and 150 mg) submitted for the marketing authorisation, according to conditions in Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98, section 5.4.

Pharmacodynamics

No studies were submitted.

Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

No description of Risk Management Plan has been provided by the applicant. Since the application concerns a generic with a reference medicinal product for which no safety concerns requiring additional risk minimisation activities have been identified this approach is considered acceptable.

PSUR

The PSUR submission schedule for Irbesartan Krka should follow PSURs submission schedule for the reference medicinal product.

User consultation

The Package leaflet with a few minor exceptions has been harmonised with the originator PL.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Overall conclusion and Benefit/risk assessment

The application contains adequate quality, non clinical and clinical information and the bioequivalence has been shown. A benefit/Risk ratio comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

Recommendation

Based on the CHMP review of available data, the CHMP considered by consensus that the risk-benefit balance of Irbesartan Krka in the "Treatment of essential hypertension. Treatment of renal disease in patients with hypertension and type 2 diabetes mellitus as part of an antihypertensive drug regimen", was favourable and therefore recommended the granting of the marketing authorisation.