European Medicines Agency
Evaluation of Medicines for Human Use

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CHMP ASSESSMENT REPORT FOR Repaglinide Teva

International Nonproprietary Name:
Repaglinide

Procedure No. EMEA/H/C/001067

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

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 85 45
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Teva Pharma B.V. submitted on 03 September 2008 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Repaglinide Teva, 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) of Directive 2001/83/EC.

The application concerns a generic medicinal product as defined in Article 10(1) of Directive 2001/83/EC and refers to a reference product for which a Marketing Authorisation is or has been granted in the Community on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC, as amended.

The chosen reference product is:

■ *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(s), pharmaceutical form(s): **NovoNorm 0.5 mg, 1 mg and 2 mg, Tablets**
- Marketing authorisation holder: **NovoNordisk A/S**
- Date of authorisation : **1998-08-17**
- Marketing authorisation granted by: **EU registration**
- Marketing authorisation number(s): **EU/1/98/076/004-7, EU/1/98/076/011-14, EU/1/98/076/018-24**

■ Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength(s), pharmaceutical form(s): **NovoNorm, 2 mg, Tablet**
- Marketing authorisation holder[4]: **Novo Nordisk A/S**
- Date of authorisation: **1998-08-17**
- Marketing authorisation(s) granted by: **EU registration**
- Marketing authorisation number(s): **EU/1/98/076/018-22**
- Member State of source: **Germany**
- Bioavailability study(ies) reference number(s)/EudraCT number(s): **2007-1438**

The Rapporteur appointed by the CHMP and the evaluation team was: Prof. Dr. János Borvendég

Scientific Advise:

The Applicant did not seek Scientific Advice at the CHMP.

Licensing status:

Repaglinide Armstrong has been given a Marketing Authorisation in Argentina on April 2000.

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 03 September 2008.
- The procedure started on 24 September 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 11 December 2008 (Annex 1).
- During the meeting on 19-22 January 2009, 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 22 January 2009 (Annex 2).
- The applicant submitted the responses to the CHMP consolidated List of Questions on 19 February 2009.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 31 March 2009 (Annex 3).
- The applicant submitted additional minor clarifications on 06 April 2009.
- The Rapporteur circulated a revised Assessment Report to all CHMP members on 15 April 2009 (Annex 4).
- During the meeting on 20-23 April 2009 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 Repaglinide Teva on 23 April 2009.

2. SCIENTIFIC DISCUSSION

2.1 Introduction

Repaglinide Teva 0.5 mg, 1 mg and 2 mg tablets is a generic medicinal product containing repaglinide as the active substance.

Repaglinide is a meglitinide antidiabetic used for the treatment of type 2 diabetes (Non Insulin-Dependent Diabetes Mellitus (NIDDM)). Repaglinide lowers blood glucose levels by stimulation of insulin production from the pancreas. It has a chemical structure which is different from the sulfonylureas, but has a similar mode of action.

The efficacy and safety of repaglinide has been demonstrated in several well-controlled studies, with sulphonylureas as comparators. In one study the effect of adding repaglinide to metformin was investigated. A summary of these studies can be found in the EPAR of the reference product NovoNorm.

The indication proposed for Repaglinide Teva is the same as the authorised indication for the reference medicinal product.

2.2 Quality aspects

Introduction

Composition

Repaglinide Teva is presented as capsule-shaped immediate release tablets, containing 0.5, 1.0 and 2.0 mg of repaglinide as the active substance.

Other ingredients include anhydrous calcium hydrogen phosphate, microcrystalline cellulose, pre-gelatinised starch, povidone, colloidal anhydrous silica, magnesium stearate, poloxamer 188, meglumine, polacrilin potassium and ferric oxide colorants..

The tablets are packaged in Alu-Alu blister packs.

Active Substance

The active substance is repaglinide a well known active substance described in Ph. Eur (monograph n° 2135). Its chemical name is (+)-2-Ethoxy-a-[[(S)-α-isobutyl-o-piperidinobenzyl]carbamoyl]-p-toluic acid. It is a white or almost white powder, practically insoluble in water, but freely soluble in organic solvents like methanol and methylene chloride. Repaglinide has one chiral centre and is dextrorotatory. The chemical structure repaglinide has been confirmed with IR, UV, 1H NMR and mass spectroscopic studies.

- Specification

The active substance is analysed according to the Pharm. Eur. monograph.

Batch analysis data from 3 batches used in the manufacturing of the biobatch and other pilot batches have been provided. The results demonstrated compliance to the Pharm. Eur. monograph and the additional specifications.

- Stability

The active substance has a retest period of 2 years when the active substance is stored in a triple low-density polyethylene bag placed inside a high-density polyethylene container.
No additional stability data have been presented.

Medicinal Product

- Pharmaceutical Development

The aim of the pharmaceutical development was to obtain immediate-release tablets containing qualitatively and quantitatively the same active substance and exhibiting the same bioavailability as the already marketed reference product NovoNorm® tablets marketed by Novo Nordisk, in order to comply with the regulations pertaining to abridged applications in the European Union.

The qualitative composition for Repaglinide Teva and the EU reference product is similar

A common manufacturing process was developed for all strengths.

The bioequivalence study was performed using Repaglinide 2 mg tablets, (pilot) versus NovoNorm® 2mg tablets,. Given that:

- The pharmaceutical products are manufactured by the same manufacturer and process
- The drug input has been shown to be linear over the therapeutic dose range (from 0.125 to 20mg).
- The qualitative composition of the strengths is the same and the quantitative formula is also essentially similar.
- The ratio between amounts of active substance and excipients is similar.
- The dissolution profile for the 0.5, 1.0 and 2.0 mg strengths is similar under identical conditions.

It is acceptable to rely on the 2 mg bioequivalence study for the 0.5 mg and 1 mg strengths.

- Manufacture of the Product

The manufacturing process is a standard process and consists of the following steps: mixing, final mixing, compression and packaging.
All critical process parameters have been identified and controlled by appropriate in process controls. The validation report from 3 production scale batches demonstrates that the process is reproducible and provides a product that complies with the in-process and finished product specifications.

- Product Specification

The finished product specification includes tests for description, appearance, identification, assay (HPLC), dissolution, content uniformity (Ph. Eur.), friability (Ph. Eur.), thickness, resistance to crushing (Ph. Eur.), impurities and degradation products (HPLC), microbial count, water content and colour identification.

Batch analysis data from 3 production scale batches for each strength have been presented. All batches met the test limits as defined in the release specification and test methodology valid at the time of batch release. The batch analyses data together with the results obtained from the stability testing confirm consistency and uniformity of the product and indicate the reproducibility of the manufacturing process.

- Stability of the Product

Data from stability studies on three production scale batches for each strength have been provided. Samples were stored for up to 24 months at long term conditions (25°C/60% RH) and for 6 months at accelerated conditions (40°C/75% RH) in accordance with ICH requirements. All batches have been tested for physical and technological (appearance, colour, dissolution), chemical (assay, degradation products) and microbiological parameters using stability indicating methods. In all cases the parameters tested remained within the proposed specifications and no significant trends were observed.

The results of photostability studies show that the finished product is sensitive to light and that the aluminium blister packaging provides adequate protection against the light influence. For this reason a warning to keep the product in the original packaging in order to protect from light has been added in the carton, PIL and SmPC.

As a conclusion the proposed shelf-life of 2 years (store in the original packaging in order to protect from light) has been sufficiently supported by the stability studies performed.

Discussion on chemical, pharmaceutical and biological aspects.

The quality of Repaglinide Teva is adequately established. In general, satisfactory chemical and pharmaceutical documentation has been submitted for marketing authorization. There are no major deviations from EU and ICH requirements.

The active substance is well known and has is described in a Ph. Eur. monograph. The quality of the active substance is regarded to be suitable for the intended use and appropriately controlled by the applicant. The excipients are commonly used in these types of formulations and comply with Ph. Eur. requirements. The packaging material is commonly used and well documented. Stability tests indicate that the product under ICH guidelines conditions is chemically stable for the proposed shelf life.
In comparison with the EU reference product Repaglinide Teva has been shown to have the same qualitative and quantitative composition in terms of the active substance. The excipients used are mostly the same. Both the EU reference product and Repaglinide Teva exhibit similar dissolution profiles.

2.3 Non-Clinical aspects

No further studies are required and the applicant has justified why no such data was provided.

No ERA has been submitted and the applicant has presented a justification. The introduction of Repaglinide Teva is unlikely to result in any significant increase in the combined sales volumes for all repaglinide containing products. The risk of an environmental impact from the use of Repaglinide Teva is of no concern.

2.4 Clinical Aspects

Introduction

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

GCP

The submitted bioequivalence study complied with GCP as claimed by the applicant.

The clinical and bioanalytical parts of the study have been conducted by CROs in Canada..

The applicant has clarified that the clinical investigational site has been inspected by Regulatory Agencies, the sponsor fulfilled its quality control obligations to oversee the bioequivalence trial.

Clinical studies

To support the application, the applicant has submitted one bioequivalence study, study 2007-1438.

Pharmacokinetics

- Methods

STUDY DESIGN

Study 2007-1438 is an open-label, single-dose, randomized, two-period, two-sequence, two-treatment, crossover study, designed to evaluate the comparative bioavailability of two formulations of repaglinide 2 mg tablets administered to healthy male and female subjects under fasting conditions.
Subjects were randomly assigned to one of the two dosing sequences AB or BA under fasting conditions. Concentrations of repaglinide were measured from samples collected over a 12-hour interval after dosing in each period.

During each study period, blood samples were collected prior to drug administration and at the times specified in the protocol following drug administration

TEST AND REFERENCE PRODUCTS

Repaglinide 2mg Tablets by Teva Pharmaceutical Industries Ltd has been compared to NovoNorm® 2mg (sourced from DE)

The reference product can be accepted as European reference product. The batch size of the test product is in line with requirements of the CHMP Note for Guidance on Bioequivalence.

POPULATION(S) STUDIED

Diagnosis and main criteria for inclusion:
The study population included non-smoking, male and female volunteers between 18-55 years of age (inclusive) with a BMI between 19 and 30 (inclusive), who were judged to be healthy based on a medical examination.

Number of subjects (planned and analysed):

- Seventy (70) subjects were dosed in Period 1.
- Sixty-six (66) subjects completed the study and are included in the analysis.

ANALYTICAL METHODS

The analytical validation and the analytical report were missing in the initial application and the Applicant was requested to submit these data. The full Analytical Report for the Bioequivalence study was provided in the applicant`s response to the Day120 CHMP LOQ.

The submitted analytical report describes an HPLC-MS-MS method for the determination of repaglinide in human plasma. The method was validated by the bioanalytical division of the CRO which is a well-known investigational site. The CRO validated the method according to FDA bioanalytical method validation guideline which is currently the industry standard guideline. Long-term stability of the clinical samples has been demonstrated for more than 100 days which greatly exceeds the actual storage period of the clinical samples (57 days).

PHARMACOKINETIC VARIABLES

Pharmacokinetic parameters: AUC_t, AUC_{inf}, C_{max}, T_{max}, K_{el} and $T_{1/2}$ were estimated based on plasma repaglinide levels.
The calculation of the original pharmacokinetic parameters was conducted with AS. In order to verify the values obtained, the calculation of the same pharmacokinetic parameters was repeated using Excel and WinNonLin software. The results of the second approach confirmed the original values.

Criteria for Evaluation:
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 plasma repaglinide AUC_t, AUC_{inf} and Cmax of the test to reference products should be between 80% and 125%.

STATISTICAL METHODS

Descriptive statistics were calculated by treatments for the estimated pharmacokinetic parameters. Analysis of Variance (ANOVA) was also carried out on the natural log-transformed AUC_t, AUC_{inf}, C_{max}, T_{max}, K_{el} and $T_{1/2}$ data. Values for the T_{max} parameter were analyzed by a non-parametric approach. The following results are included:
Geometric and arithmetic means of AUCs and C_{max} for the test product and reference product.

- Ratios of geometric means of the test product versus the reference product for AUCs and C_{max}.

- 90% confidence intervals of the above ratios.

The statistics described were adequate and the methods acceptable.

- Results

Pharmacokinetics:

The pharmacokinetic results are presented in table 1 and Figure 1and 2 below:

Table 1. PK results for analyte: repaglinide (N=66)

Parameter	Geometric Means Arithmetic Means (CV%)		Ratio of Geometric Means (%)	90% Confidence Interval (%)	Intra-Subject (CV%)
	Treatment A	Treatment B			
AUCt (pg*h/mL)	49563.14 53732.48 (44)	49063.81 52697.94 (38)	101.02	97.12 - 105.07	14
AUCinf (pg*h/mL)	49955.84 52725.27 (36)	49897.67 53953.45 (38)	100.12	96.25 - 104.14	13
Cmax (pg/mL)	18422.79 20290.94 (51)	18451.44 20256.15 (50)	99.84	92.64 - 107.61	26
Tmax[a] (h)	1.07 (65)	1.24 (94)	-	-	-
Kel[a] (1/h)	0.3769 (30)	0.3833 (37)	-	-	-
Thalf[a] (h)	2.06 (42)	2.13 (49)	-	-	-

[a]Presented as arithmetic mean (CV%) only.

Based on the pharmacokinetic parameters of repaglinide, the reference and test are considered bioequivalent with respect to the extent and rate of absorption for the 2 mg tablet. The 90% confidence intervals calculated for AUC(0-t), AUC(0-inf) and Cmax of repaglinide are within the range of acceptability 0.8-1.25.

The Applicant submitted comparative dissolution curves of the different strengths at pH 6.8.

The formula of the 0.5 and 1 mg tablets fulfils the conditions for exemption of a biostudy. In accordance with the Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98, section 5.1 an exemption for the lower strengths was agreed because:

- the kinetic is dose-proportional
- dissolution is very fast at 3 substantially different pH values (more than 85% of each strength dissolve in less than 15 minutes at pH 2, 5 and 6.8 respectively)
- the composition of tablets of different strengths is essentially the same
- there is one single manufacturer

Therefore the Applicant's request for biowaver is justified according to the Note for Guidance on the Investigation of Bioavailability and Bioequivalence MP/EWP/QWP/1401/98, and separate bioequivalence studies for the 0,5 and 1 mg strengths are not needed.

Safety

No serious AEs were reported during the conduct of this study.

None of the AEs had a significant impact on the safety of the subjects or on the integrity of the study results.

- Conclusions

Based on the presented bioequivalence study Repaglinide Teva is considered bioequivalent with NovoNorm.
The results of study 2007-1438 with the 2 mg formulation can be extrapolated to other strengths 0.5mg and 1mg, according to conditions in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98.

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

- **PSUR**

The PSUR submission schedule for Repaglinide Teva should follow the PSUR submission schedule for the reference medicinal product.

- **Description of the Pharmacovigilance system**

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements. The company must ensure that this system is in place and functioning before the product is placed on the market.

- **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 management activities have been identified this approach is considered acceptable.

2.6 Overall conclusions, benefit/risk 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 that the benefit/risk ratio of Repaglinide Teva in the treatment of:

> -"Patients with type 2 diabetes (Non Insulin-Dependent Diabetes Mellitus (NIDDM)) whose hyperglycaemia can no longer be controlled satisfactorily by diet, weight reduction and exercise. Repaglinide is also indicated in combination with metformin in type 2 diabetes patients who are not satisfactorily controlled on metformin alone. Treatment should be initiated as an adjunct to diet and exercise to lower the blood glucose in relation to meals"."

was favourable and therefore recommended the granting of the marketing authorisation.