European Medicines Agency
Evaluation of Medicines for Human Use

ASSESSMENT REPORT

FOR

Enyglid

International Non-proprietary Name: repaglinide

Procedure No. EMEA/H/C/001065

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 03 September 2008 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Enyglid, 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 application legal basis 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, pharmaceutical form: NovoNorm 0.5 mg, 1 mg, 2 mg Tablets
- Marketing authorisation holder: Novo Nordisk A/S
- Date of authorisation: 17 August 1998
- Marketing authorisation granted by: EU registration
- (Community) Marketing authorisation number: EU/1/98/076/004-007, 011-014, 018-024

■ 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, pharmaceutical form: NovoNorm 2 mg Tablets
- Marketing authorisation holder: Novo Nordisk A/S
- Date of authorisation: 17 August 1998
- Marketing authorisation granted by: EU registration
- (Community) Marketing authorisation number(s): EU/1/98/076/018-022
- Member State of source: Germany
- Bioavailability study number(s): 08-205

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur :	Robert James Hemmings
Pharmacovigilance Rapporteur :	Pieter de Graeff

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 03 September 2008.
- The procedure started on 24 September 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 12 December 2008.
- 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.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 26 March 2009.
- The Rapporteur circulated the Day 150 Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 08 May 2009.
- During the CHMP meeting on 26-29 May 2009, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP list of outstanding issues on 19 June 2009.
- During the meeting on 20-23 July 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 Enyglid on 23 July 2009. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 7 July 2009.

2. SCIENTIFIC DISCUSSION

2.1 Introduction

Enyglid 0.5 mg, 1 mg and 2 mg tablets is a generic medicinal products containing repaglinide as the active substance. The reference product NovoNorm 0.5 mg, 1 mg and 2 mg tablets was centrally authorised on 17 August 1998.

Repaglinide is a carbamoylmethyl benzoic acid derivative. It is a short-acting oral antidiabetic of the meglitinide class, which lowers the blood glucose levels acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning β-cells in the pancreatic islets. Repaglinide closes ATP-dependent potassium channels in the β-cell membrane via a target protein different from other secretagogues. This depolarises the β-cell and leads to an opening of the calcium channels. The resulting increased calcium influx induces insulin secretion from the β-cell.

The efficacy and safety of Enyglid 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 may be found in the EPAR of the reference product NovoNorm.

The indication proposed for Enyglid is the same as for the authorised Reference medicinal product NovoNorm.

NovoNorm is indicated in 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.

2.2 Quality aspects

Introduction

Enyglid is presented as tablets containing 0.5 mg, 1 mg and 2 mg of repaglinide as active substance. The other ingredients are calcium hydrogen phosphate anhydrous, cellulose microcrystalline, croscarmellose sodium, meglumine, poloxamer, glycerol, povidone K25 and magnesium stearate.
1 mg tablets contain iron oxide yellow as a colorant and 2 mg tablets contain Iron oxide red as colorant.
The tablets are marketed in OPA/Al/PVC foil in combination with aluminium foil (OPA/Al/PVC-Al). The blisters are packed in cartons.

Active substance

The active substance, repaglinide is a single S enantiomer of (+)-2-ethoxy-4-(2-((3-methyl-1-(2-(1-piperidinyl)phenyl)-butyl)amino)-2-oxoethyl) benzoic acid.
It appears as white or almost white powder, practically insoluble in water, freely soluble in methanol and in dichloromethane. The structure is sufficiently elucidated by infrared absorption spectroscopy, ^{1}H-NMR spectroscopy, ^{13}C-NMR spectroscopy, X-ray powder diffraction and mass spectroscopy and elemental analysis. Repaglinide shows polymorphism. However, it was confirmed that the same polymorphic form is always obtained when using the synthetic route, which was described by the applicant.

- **Manufacture**

Repaglinide is synthesised in ten reactions steps by the manufacturing process which has been adequately described. Critical parameters have been identified and adequate in-process controls included. Specifications for starting materials, reagents, and solvents have been provided. Adequate control of critical steps and intermediates has been presented. The active substance is purified by recrystallisation. The purified active substance packed in carton drums containing primary transparent LDPE bag in secondary black LDPE bag.

- **Specification**

The active substance specifications include tests for appearance (white almost white powder), solubility, identification (optical rotation & IR), enantiomeric purity (HPLC), impurities (HPLC), loss on drying (Ph.Eur.), sulphated ash (Ph.Eur.), assay and residual solvents (GC). All specifications reflect the relevant quality attributes of the active substance. The analytical methods, which were used in the routine controls, were well described and their validations are in accordance with the relevant ICH guidelines. Based on the data provided it was concluded that Repaglinide is controlled in accordance with the European pharmacopeia monograph.
Impurities were described, classified as process related impurities (starting materials and by-products) and possible degradation products, and specified. It was noted that no metal catalysts have been used during manufacturing procedure. Residual solvents were satisfactorily controlled in the active substance according to the relevant ICH requirements. Certificates of analyses for the active substances were provided and all batch analysis results comply with the specifications and show a good uniformity from batch to batch.

- **Stability**

Three production batches of the active substance were put on long-tern condition (25±2°C/60±5%RH), on intermediate condition (30±2°C/65±5%RH) and accelerated condition (40±2°C/75±5%RH). All stability studies were completed according to ICH guidelines demonstrated adequate stability of the active substance. The following parameters were monitored during the stability studies: appearance, loss on drying, specific optical rotation, assay, enantiomeric purity and related substances. The same analytical methods have been used in the stability program as for release. It was noted that the results of the photostability study, which was performed in accordance with the note for guidance on photostability testing of new active substances and medicinal products (CPMP/ICH/279/95), are within specifications and no significant changes were observed. Based on the stability results it was concluded that the proposed re-test period is justified when the active substance is stored in the original packing material.

Medicinal Product

- **Pharmaceutical Development**

All information regarding the choice of the active substance and the excipients are sufficiently justified.
The main aim of the applicant not only was to develop a medicinal product bioequivalent to the reference product (NovoNorm) but also to develop a stable dosage form, which could be produced through a simple production process. All the excipients used are well known and commonly used in the pharmaceutical industry.

It was noted that a range of different compositions and manufacturing techniques were studied. Based on the dissolution studies the wet granulation was selected.
The selected formulation was used to manufacture batches for bioequivalence and stability. This formulation corresponds to that proposed for commercial manufacturing. It was confirmed a satisfactory bioequivalence against the reference product NovoNorm 2mg. For the lower dosage

strengths (0.5 mg and 1 mg) a biowaiver has been applied successfully, since all the conditions for a biowaiver have been fulfilled.
Comparative dissolution profiles for the three strengths have been provided and it was verified that no significant differences has been observed. It is important to underline that comparative impurity profiles against the reference product for all three strengths have shown no significant differences between these two products.

- **Manufacture of the Product**

The proposed commercial manufacturing process involves standard technology using standard manufacturing processes such as mixing, dissolving, blending, wet granulation, sieving and compressing.
Furthermore, the equipment used is commonly available in the pharmaceutical industry. The proposed in-process control limits were considered acceptable.
It was noticed that the manufacturing process has been adequately validated on production scale batches and the results of the manufacturing validation reports were considered satisfactory.

- **Product Specification**

The finished product specifications were established according the ICH guidelines and include the following tests: appearance, uniformity of dosage units (Ph.Eur), identification (HPLC & TLC), impurities (HPLC), assay, dissolution and microbial limits (Ph.Eur).
It was verified that no new impurities have been arising compared to the active substance. Furthermore, it was noted that the degradation products, which are presented in the finished product in concentrations below the reporting threshold and not significantly increase during stability testing.
All analytical procedures that were used for testing the drug product were properly described. Moreover, all relevant methods were satisfactorily validated in accordance with the relevant ICH guidelines.
The batch analysis data confirm that the tablets can be manufactured reproducibly according to the agreed finished product specification, which is suitable for control of the finished product.

- **Stability of the Product**

The stability studies were conducted according to the relevant ICH guidelines. Pilot and production scale batches of each strength have been stored at long term, intermediate and accelerated conditions. It was verified that the following parameters were controlled: appearance, water content, hardness, friability, disintegration, dissolution, assay, impurities and microbial purity.
One batch of each strength was stored for photostability at ICH conditions and results obtained comply with the prescribed specifications. Based on the available stability data, the proposed shelf life and storage conditions as stated in the SPC are acceptable.

Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture, control of the active substance and the finished product have been presented in a satisfactory manner and justified in accordance with relevant CHMP and ICH guidelines. The results of tests carried out indicate satisfactory consistency and uniformity of the finished product. Therefore, this medicinal product should have a satisfactory and uniform performance in the clinic. Dissolution studies results indicate comparability with the reference product (NovoNorm) and this is confirmed by in-vivo bioequivalence results (see the clinical part of the report). At the time of the CHMP opinion, there was one minor unresolved quality issue, which will not have an impact on the benefit/risk ratio of the medicinal product. Therefore, it can be concluded that the quality characteristics of the finished product are adequate and should have a satisfactory and uniform performance in the clinic.

2.3 Non-Clinical aspects

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

No environmental risk assessment has been submitted and the applicant has presented a justification. The introduction of Enyglid 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 Enyglid is of no concern.

2.4 Clinical Aspects

Introduction

The rapporteur assessment addressed pharmacokinetic data in respect of a bioequivalence study, and literature references submitted.

GCP

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

The applicant has clarified that study facilities have been inspected by Regulatory Agencies, including EMEA inspection of the site used for bio-analysis (USA) in 2005, and EMEA inspection of the site used for bio-analysis and clinical work (Canada) in 2007.

Exemption

One bioequivalence study was performed on Enyglid (repaglinide) 2 mg tablets. A biowaiver has been requested for lower dosage strengths of Enyglid tablets (0.5 mg and 1 mg).
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 provided that the choice of the strength used is justified on analytical, pharmacokinetic and safety grounds and the following conditions are fulfilled:

1. The pharmaceutical products are manufactured by the same manufacturer and process.
2. The drug input has been shown to be linear over the therapeutic range. (If this is not the case, the strength for which the sensitivity is largest to identify differences in the two products should be used).
3. The qualitative composition of the strengths is the same.
4. The ratio between amounts of active substance and excipient is the same, or in the case of preparations containing a low concentration of the active substance (less than 50%) the ratio between the amounts of excipients is similar.
5. The dissolution profile should be similar under identical conditions for the additional strengths and the strength of the batch used in the bioequivalence study.

All the above points were met. The manufacturer submitted data to support points 1, 3 and 4.
Repaglinide tablets contain less than 5% active ingredient. The qualitative composition of the different strengths is the same (except for colorants in the 1 and 2 mg tablets).
Literature references have been provided showing the dose linear behaviour up to 2mg. The results of in vitro dissolution tests with repaglinide were provided, covering at least three time points, attained at three different buffers in pH range 1-8 (pH 1, pH 4.5 and pH 6.8). Percent of the drug dissolved was followed up to 30 minutes; concentrations of dissolved repaglinide were measured with HPLC.
The results showed profiles where more than 85% of repaglinide is released in 15 minutes from all tablet formulations.

In conclusion the request for biowaiver has been adequately justified and separate bioequivalence studies for the 0.5 mg and 1 mg strengths are not needed.

Clinical studies

To support the application, the applicant has submitted one bioequivalence study AA44393 (KRKA study code 08-205): a comparative, randomised, single Dose, 2-way crossover bioavailability Study of 2 mg Repaglinide tablets in Healthy Adult Volunteers under Fasting Conditions.

The clinical part of the study as well as pharmacokinetic, statistical analyses and clinical laboratory tests has been conducted by Clinical Research Organisation in Canada.

The analytical part (sample analyses for repaglinide) was carried out by Clinical Research Organisation in the USA.

Pharmacokinetics

- Methods

STUDY DESIGN

This was an open-label, randomised, single-dose, 2-way crossover, 2-sequence, comparative bioavailability study of KRKA, d.d. 2 mg repaglinide tablets and Novo Nordisk A/S (NovoNorm®) 2 mg repaglinide tablets, under fasting conditions. Subjects were divided into two groups for dosing: Group 1 (Subject Nos. 1 - 34) and Group 2 (Subject Nos. 35 – 68).

Subjects were randomised to receive the test and reference products according to the randomisation scheme. In the evening prior to each dosing, subjects were screened for cocaine, cannabinoids, cotinine and alcohol, and a serum pregnancy test was performed for all female subjects. Subjects received a dinner at approximately 20:00 hours and then observed a 10-hour overnight fast.
On the mornings of Day 1 in each period (Group 1: 26/Feb/2008, 04/Mar/2008; Group 2: 29/Feb/2008, 07/Mar/2008), subjects received a single oral 2 mg repaglinide dose of their assigned formulation, with 240 mL of water at room temperature, under fasting conditions. Food was restricted from at least 10 hours before dosing and for at least 4 hours thereafter. Water was not permitted from 1 hour before until 1 hour after dosing, but was allowed at all other times. Meal and water restrictions did not apply to the administration of sugar-containing beverages. Blood samples (1 x 3 mL) were collected in blood collection tubes containing EDTA before dosing and at the following times thereafter: 0.167, 0.333, 0.5, 0.667, 0.833, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8 and 9 hours. Doses were separated by a 7-day washout period. In each period, subjects were housed in the clinic from at least 10 hours before dosing until after the 12-hour post-dose events recording.

Study design, sampling scheme, sampling period and washout are adequate to estimate PK parameters (Tmax 1 hour, and the plasma elimination half-life is approximately one hour). Repaglinide is given preprandially. Food has no effect on repaglinide PK (NovoNorm SPC). A fasting study is acceptable. The clinical phase occurred after Institutional review approval had been granted. The protocol and randomisation scheme have been provided. The analysis of the parent repaglinide compound is appropriate; no metabolites with clinically relevant hypoglycaemic effect have been identified.

TEST AND REFERENCE PRODUCTS

Enyglid 2 mg by KRKA, d.d. (batch No. 1227 03 P028 0108, retest date: 06.2008) has been compared to NovoNorm® 2 mg tablets (Batch No: SM70056, exp. date 10/2010).

Test and reference products

Test Product: **A.** Repaglinide 2 mg tablets
Manufacturer: KRKA, d.d., Novo mesto Slovenia
Lot No.: 1227 03 P028 0108
Manufactured date: 01.2008
Retest date: 06.2008

Reference Product: **B**. NovoNorm® 2 mg tablets (repaglinide)
Manufacturer: Novo Nordisk A/S Denmark
Ch.-B.: SM70056
Expiration date: 10/2010

The batch size of the test product is in line with requirements of the CHMP Note for Guidance on Bioequivalence.

POPULATION(S) STUDIED

Subjects were healthy adult male or female volunteers, 18-55 years of age, and continuous non-smokers for at least 3 months prior to the first dose. No subject was to take medication (including over-the-counter products) or herbal products for the 7 days prior to the first dose. A sample size of 64 subjects was calculated. Four additional subjects were added to account for possible dropouts; thus leading to a total sample size of 68 subjects. A total of 68 healthy non-smoking adult subjects (39 males and 29 females) satisfying inclusion and exclusion criteria were enrolled in the study and 64 subjects (36 males and 28 females) completed the clinical phase of the study, with a mean age of 37 years (range: 24 – 55 years), mean height of 171 cm (range: 150 – 189 cm) and mean weight of 71.3 kg (range: 52.2 – 97.1 kg).
There were 4 subjects who were withdrawn / discontinued from the study due to the following reasons: positive urine cocaine, positive urine cotinine, personal reasons.

The population studied is appropriate.

ANALYTICAL METHODS

Blood samples were collected, cooled in an ice bath and centrifuged under refrigeration as soon as possible. Plasma samples were divided into 2 aliquots and stored in suitably labelled tubes at -20±10°C, pending assay. The samples were shipped in two separate shipments to Analytical Laboratories (USA) for analysis. Repaglinide in plasma was analysed using a validated LC/MS/MS method. The analytical range for repaglinide in plasma was 0.300 – 75.0 ng/mL.

Sample analysis was conducted between 14-Mar-2008 and 03-Apr-2008.
After initial analysis, upon which no value was obtained, study samples that were identified for re-assay due to analytical reasons were re-assayed only if sufficient sample volume remained. Twelve (12) samples were re-assayed. The analytical laboratory analysts did not have access to the randomisation scheme.

The method has been adequately validated (See Quality part).

PHARMACOKINETIC VARIABLES

The following PK variable were calculated according to non compartmental methods

AUC 0-t: The area under the plasma concentration versus time curve, from time 0 to the last measurable concentration, as calculated by the linear trapezoidal method.

AUCinf: The area under the plasma concentration versus time curve from time 0 to infinity. AUCinf was calculated as the sum of AUC 0-t plus the ratio of the last measurable plasma concentration to the elimination rate constant.
AUC/AUCinf: The ratio of AUC 0-t to AUCinf.
Cmax: Maximum measured plasma concentration over the time span specified.
tmax: Time of the maximum measured plasma concentration. If the maximum value occurred at more than one time point, tmax was defined as the first time point with this value.
kel: Apparent first-order terminal elimination rate constant calculated from a semi-log plot of the plasma concentration versus time curve. This parameter was calculated by linear least-squares regression analysis using the maximum number of points in the terminal loglinear phase (e.g. three or more non-zero plasma concentrations).
t½: Apparent first-order terminal elimination half-life was calculated as 0.693/kel.

The choice of PK variables is acceptable. AUC 0-t, AUCinf and Cmax were pre-specified as primary PK variable for the determination of bioequivalence.

STATISTICAL METHODS

ANOVA were performed on the ln-transformed PK parameters AUC 0-t, AUCinf, and Cmax. The ANOVA model included group, sequence, period nested within group, formulation, and formulation*group interaction as fixed effects, and subject nested within group*sequence as a random effect. Each ANOVA included calculations of LSM, the difference between formulation LSM, and the standard error associated with this difference. The above statistical analyses were performed using the SAS® GLM procedure.

90% confidence intervals for the ratios were derived by exponentiation of the confidence intervals obtained for the difference between formulation LSM resulting from the analyses on the ln-transformed AUC 0-t, AUCinf and Cmax. Non-parametric analysis of tmax was performed for repaglinide BLQ values were set to zero for PK and statistical analyses, unless they were flanked by measurable concentrations. Acceptance criteria were pre-specified as: The 90% confidence interval of the ratios of least square means of AUC0-t, AUCinf and Cmax of the test to reference formulation lying within 0.80-1.25

The statistical handling is appropriate; the pre-specified acceptance limits are acceptable.

- Results

Pharmacokinetics:

Protocol or SOP deviations were described in the dossier; none were major or would significantly impact on study results. They related to final 9 hour blood draw, urine samples, sugar beverages, small amount of alcohol in one subject at -46 hours pre dose. Where actual sampling times exceeded the deviation windows outlined, the times were adjusted accordingly.

The PK parameters AUCinf, AUC 0-t/AUCinf, t½ and kel could not be calculated for some subjects (Reference 9 subjects, test 8 subjects) because the terminal elimination phase in their repaglinide plasma concentration versus time profiles could not be characterized.

There were no instances of non-zero pre-dose concentrations reported in this study. Tmax was not recorded in the first sample in either test or reference. Where evaluable, the size of the extrapolated areas was less than 20% in all cases.
There were no period or sequence effects.

Cmax was measured outside of the validated range for test and reference; Test -2 subjects (nos. 34 and 43 with Cmax= 119 and 87ng/ml) and 1 subject for reference 43; Cmax=106ng/ml). However the dilution of the samples was validated up to 400ng/ml.

The pharmacokinetic results are presented in table 1 below.

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

Treatment	**AUC_{0-t}** ng/ml/h	**$AUC_{0-\infty}$** ng/ml/h	**C_{max}** ng/ml	**t_{max}** h	**$T_{1/2}$** h
Test	43.63(24.727)	45.89(26.328)	33.325 (19.43461)	0.667 (0.333-1.500)	1.7811 (0.71670)
Reference	41.86 (23.322)	43.62(24.951)	30.7158 (16.564)	0.667 (0.333-1.769	1.7227 (0.54085)
***Ratio (90% CI)**	1.04(0.99-1.09)	1.05(0.99-1.11)	1.09 (0.97-1.22)		
CV (%)	17.4%	18.1%	39.7%		

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

**ln-transformed values*

Review of individual plasma concentration time curves did not raise concerns. The lower number of subjects evaluable for AUCinf is not considered an issue as results for AUC 0-t are consistent, and both test and reference were balanced in this regard.

The 90% confidence intervals of the ratios of LSM (least square means) derived from the analyses on the ln-transformed PK parameters AUC 0-t, AUCinf and Cmax for repaglinide in plasma were within the 0.80-1.25 acceptance range.

Safety

Overall, 27 subjects (40.9% of the study population receiving Treatment A) experienced at least 1 adverse event that was possibly, probably, or definitely related to Treatment A, and 24 subjects (36.4% of the study population receiving Treatment B) experienced at least 1 adverse event that was possibly, probably, or definitely related to Treatment B.

Review of the study report did not highlight safety concerns with the test product.

- Conclusions

Based on the presented bioequivalence study Enyglid 2mg tablet is considered bioequivalent with NovoNorm® 2 mg tablets.

The results of study *AA44393* // Krka study code: 08-205 with KRKA, d.d repaglinide 2mg formulation can be extrapolated to other strengths 0.5mg and 1mg, 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. This medicinal product has not been marketed in any country.

2.5 Pharmacovigilance

- **Description of the Pharmacovigilance system**

The CHMP considered that the Pharmacovigilance system as described by the applicant (DescPhSys000001/17 - 29 January 2009) fulfils the legislative requirements. The company must ensure that this system is in place and functioning before the product is placed on the market. The company should ensure that the pharmacovigilance activities are in line with the current safety measures applied to the reference medicinal product.

- **Risk Management Plan**

A Risk Management Plan was not submitted. Since the application concerns a generic of a reference medicinal product for which no safety concerns requiring additional risk minimisation activities have been identified, a Risk Management Plan was not required.

- **PSUR**

The PSUR submission schedule for Enyglid tablets should follow the PSUR schedule for the reference medicinal product (NovoNorm).

- **User consultation**

The results of user consultation provided indicate that the Package leaflet is well structured and organised, easy to understand and written in a comprehensible manner. The test shows that the leaflet is readable and patients /users are able to act upon the information that it contains.

2.6 Overall conclusions, benefit/risk assessment and recommendation

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. At the time of the CHMP opinion, there were one minor unresolved quality issues, which do not have any impact on the benefit/risk ratio of the medicinal product. This will be addressed as part of the follow-up measures to be addressed post-authorisation.

The application contains adequate non clinical and clinical data and the bioequivalence has been shown. A benefit/risk ratio comparable to the originator 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 majority that the benefit/risk ratio of Enyglid 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.