EMA/316506/2010

WITHDRAWAL ASSESSMENT REPORT

FOR

REPAGLINIDE SUN 0.5 mg, 1 mg and 2 mg tablets

International Nonproprietary Name:

Repaglinide

Procedure No. EMEA/H/C/001145

Day 180 Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

This should be read in conjunction with the "Question and Answer" document on the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application.

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I. RECOMMENDATION

Based on the CHMP review of the data provided by the Applicant on quality, safety and efficacy, the CHMP considers that the application for REPAGLINIDE SUN 0.5 mg, 1 mg and 2 mg tablets (repaglinide) indicated for type 2 diabetes 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.

is not approvable since "major objections" have been identified, which preclude a recommendation for the granting of the marketing authorisation at the present time.

These "major objections" are made with regard to quality and clinical aspects:

- on the impact on safety of a degradation product;
- on the bioequivalence (BE) of the generic drug products to the reference counterparts.

Inspection issues

Considering that the BE study is pivotal for this application and that the Clinical Research Organization (CRO) performing the study is unknown from the EMA, an inspection of this study has been performed.

The inspection of the BE study has been carried out by the European Medicines Agency (EMA) inspectors team. No major or critical deviation from Good Clinical Practice (GCP) and Good Laboratory Practice (GLP) was identified during the inspection. Therefore, data regarding clinical and analytical aspect could be considered as reliable.

Nevertheless, the inspection outcome brought confirmation of concerns regarding the validity of the analytical results of the bioequivalence trial outlined by the CHMP.
Indeed, one observation was found to be of a major importance during the inspection of the clinical part of the trial and four observations were considered as major in the context of the conduct of the bioanalytical part of the trial.
The observations are liable to call into question the acceptability of the trial data, since accuracy of the bioanalytical method cannot be established with certainty in the absence of demonstration that the variation of internal standard response had no impact on the concentration of Repaglinide.

II. EXECUTIVE SUMMARY

This application of Repaglinide Sun 0.5 mg, 1 mg and 2 mg tablets has been submitted in accordance with Article 3(3) of Regulation (EC) No 726/2004 for centralised procedure of generic medicinal products.

The reference medicinal product is Novonorm tablets, authorised by the European Medicines Agency (EMA) via the Centralised Procedure (European marketing authorisation EU/1/98/076) since 17 August 1998. Novonorm's Marketing Authorisation Holder is NovoNordisk A/S Denmark, .

Repaglinide is a meglitinide oral antidiabetic and is proposed for the treatment of type 2 diabetes mellitus. Diabetes mellitus is one of the most common endocrine disorders of the world. Type 2 diabetes mellitus (non-insulin dependent diabetes mellitus) covers approximately 90% of the patients with diabetes. The prevalence of type 2 diabetes mellitus increases with age and obesity. Type 2 diabetes mellitus is a complex and heterogeneous disorder with multiple mechanisms that contribute to hyperglycaemia.

II.1 Quality

Based on the review of the data on quality, **a major objection** regarding the impact on safety of a degradation product with an alerting structure found in the drug product during stability studies has been identified.

A summary of the drug substance and the drug product sections is provided below.

Drug substance

The drug substance Repaglinide is described in the Ph. Eur. The Applicant has provided full details of manufacture into the ASMF application.

Repaglinide is manufactured in four steps. The complete manufacturing process has been described in detail in the restricted part of Active Substance Master File (ASMF).

Repaglinide is routinely controlled by Ph. Eur. monograph completed by additional tests. Specifications comply with Ph. Eur. monograph and with Note for guidance on impurities testing: Impurities in new drug substance, CPMP/ICH/2737/99.

In-house methods have been sufficiently described and validated.

Repaglinide is sensitive to oxidation. Stability studies according to the relevant EU/ICH stability guidelines have been submitted with pilot scale batches and industrial scale batch. No trend of degradation is observed under accelerated and long term conditions. Based on stability results submitted, a retest period of 12 months could be granted.

The specifications, limits and test procedures, apply by the drug product manufacturing site are the same as those from the active substance manufacturing site.

Drug product

The medicinal products Repaglinide Sun 0.5mg, 1mg and 2mg consist in circular, biconvex, uncoated tablets which differ from each other in colour (0.5mg: white, 1mg: yellow, 2mg: pink) and debossing on one side (0.5mg: '744', 1mg: '745', 2mg: '747').

They contain respectively 0.5mg, 1mg and 2mg of Repaglinide as drug substance. The three strengths have the same weight, and the amount of the main diluent is changed to account for the change in amount of active substance which represents less than 5% of the tablet weight.

The formulation comprises standard excipients only.

Tablets are packaged in push through aluminium foil with heat seal lacquer and with OPA/ Aluminium/ PVC cold form laminate film in blisters.

The pharmaceutical development of the formulation and the manufacturing process is satisfactorily documented. One bioequivalence study was performed on the test product Repaglinide Sun 2mg tablet *versus* the reference product Novonorm® 2mg tablet sourced from the danish market. Additionally, comparative *in vitro* dissolution profiles of the test product and the reference product are provided to support the essential similar character.

The manufacturing process is described. Critical steps are identified. Manufacturing flow-chart is provided with suitable in-process controls.

One commercial batch size is proposed for each of the three strengths. The manufacturing process is adequately validated at the declared manufacturing site.

The excipients used in the manufacture of Repaglinide Sun tablets comply with the corresponding Ph. Eur. or with NF monographs. The colouring agents comply with the European requirements for colours for use in foodstuffs.

The drug product specifications cover appropriate parameters for this dosage form.
Analytical methods are well described and validated in agreement with ICH guidelines.
Batch analysis results are presented on the validation batches. Results show that the finished products meet the specifications proposed.

The quality of the packaging materials is considered as suitable according to data obtained in stability testing.
The conditions used in the stability studies comply with the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up.
Based on the submitted stability data the proposed shelf life could have been approved.

II.2 Non-Clinical

No non-clinical data are provided in support of this application. The applicant's non-clinical overview provides an acceptable summary of the pharmacology, pharmacokinetics and toxicology of repaglinide.

Environmental risk assessment
The Applicant did not provide any environmental risk assessment (ERA) (CHMP guideline on the environmental risk assessment of medicinal products for human use CHMP/SWP/4447/00).

II.3 Clinical

The efficacy, safety and clinical pharmacology of the active ingredient repaglinide are already well established and documented for the original medicinal product NovoNorm.

Pharmacokinetics

Based on the review of the data on pharmacokinetics, **two major objections** were identified.
Indeed, the bioequivalence of the generic drug product to the reference counterparts could not be considered demonstrated. The performances of the analytical technique are insufficient for a suitable investigation of the bioavailability of repaglinide by oral route.

Bioequivalence study
One bioequivalence study was performed on Repaglinide Sun (repaglinide) 2 mg tablets and the clinical study report submitted- A comparative, randomised, single dose, 2-way crossover bioavailability study of 2 mg repaglinide tablets in healthy adult volunteers under fasting conditions.

Test and reference products

Test: Repaglinide 2 mg tablets manufactured by the applicant.

Reference: NovoNorm 2 mg tablets manufactured by Novo Nordisk,A/S Novo Alle, DK-2880, Bagsvaerd, Denemarken (Denmark). The tablets used in the study originate from batch n°TM70476; Exp. Date: 09/2011.

The bio-batch is clearly described and could be considered representative of the full scale production of the generic product under review.

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

Nevertheless, **at Day 120 the bioequivalence of the generic drug product to NovoNorm was not considered demonstrated as the validity of the analytical used in the study was questionable**. The performances of this technique did not allow a proper investigation of the plasma concentration versus time profile:
- The LLOQ (2 ng/ml) is too high to allow a proper investigation of the plasma concentration versus time profile of repaglinide. For instance the Lower Limit of Quantification (LLOQ) is about 10 times less than the actual Cmax observed in the study (approximately 18 ng/ml). As a consequence, the AUCt are not accurately estimated as well as the elimination half-life and the extrapolated AUC.
- The robustness of the study is questionable as 20 runs out of 74 were rejected and re-analysed.
- Also a total of 75 samples were re-analysed due to" unacceptable internal standard response". The decision of re-analysis based on this criterion may be discretionary as no definition of this criteria is found by the CHMP. Additionally, despite the re-analysis leads in numerous cases to a huge discrepancy between the initial estimation and the re-assay, this latter estimation was reported with no further verification.

Based on the review of the data and the Applicant's response to the CHMP List of Questions, the bioequivalence of the generic drug products to the reference counterparts could not be considered demonstrated**.** The performances of the analytical technique are insufficient for a suitable investigation of the bioavailability of repaglinide by oral route.

It is widely admitted for analytical techniques used for BE investigation that the LLOQ should allow detection of 5 % of Cmax (in order to exclude any carry-over effect). In general, LLOQ should be 1/20 of the Cmax or lower, in order to investigate the elimination phase and subsequently the extrapolated AUC. In the study under review, the analytical technique does not meet such criteria. For instance, the actual LLOQ, observed in the pivotal study is approximately 9.4 % and 9% of Cmax observed in the Test and Reference group respectively.

Thus, the Lower Limit Of Quantification (LLOQ) is not low enough to allow a proper investigation of the bioavailabilty of repaglinide.

Considering that the BE study is pivotal for this application and that the CRO performing the study is unknown from the EMA, an inspection of this study was performed.

The sample re-assays were reviewed during the inspection and raised one major deviation.
A large proportion of subject samples were reanalysed due to an unacceptable internal response and the comparison between the initial concentrations and the re-assays showed significant differences without any investigation. This observation casts a doubt about the accuracy of the bioanalytical method used in order to determine the concentration of Repaglinide. This observation may be also considered in relation with the significant differences also observed regarding the re-assays without any investigation.
An investigation of the difference of results between initial and repeat analysis was performed in response to the inspection report for subject samples reanalysed due to an unacceptable internal response. No specific reason was given for significant difference between initial and repeat analysis for 20 samples out of 74 repeated samples. Moreover, this variation of the internal standard response was also observed for other runs which were not reanalysed in accordance with the SOP applicable at the time of the trial. Consequently, the explanation given in response to the inspection report didn't permit to dispel doubts about the accuracy of the bioanalytical method used to determine the concentration of Repaglinide.

Thus, apart from the unusually high rate of runs rejection and reanalysis, a total of 75 samples were re-analyzed due to "unacceptable internal standard response". Despite the re-analysis leads in numerous cases to a huge discrepancy between the initial estimation and the re-assay, this latter estimation was reported. The validity of the reanalyzed samples could not be endorsed.

A biowaiver is requested for lower dosage strengths of Repaglinide Sun tablets (0.5 mg and 1 mg), on the basis of the claim that all the requirements for biowaiver as per Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98) are fulfilled. The criteria are considered satisfied.

II.4 Pharmacovigilance system

In his original submission the applicant has provided documents that set out a detailed description of the system of pharmacovigilance (DDPS). A statement signed by the applicant and the qualified person for pharmacovigilance (QPPV), indicating that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country has been provided.

Nevertheless, it was asked to the Applicant's pharmacovigilance system, i) to describe the interaction between local offices and the QPPV ii) to indicate the period of retention of pharmacovigilance documentation.

In the response to Day 120 LoQ the applicant described the interaction between local offices and the QPPV which consists of open direct communication lines by phone and e-mail. The collection, collation and reporting to European Authorities is done centrally through the EU QPPV Office at the European headquarter.

Regarding the period of retention of pharmacovigilance documentation, Pharmacovigilance documentation is archived in accordance with SOP PV-012 for a period of at least 15 years.

15 years is not acceptable as a general rule (and not for product-specific reasons).
As a matter of fact, Volume 9 A of the Rules Governing Medicinal Products in the European Union does not specify any period of retention but some national legislations have legal requirements.
For example, in France, Marketing Authorisation Holders are usually asked for legal reasons to keep pharmacovigilance data for 30 years at least. In UK, Good Pharmacovigilance Practice Guide indicates that pharmacovigilance data must be stored for an indefinite period.

Thus, as Competent Authorities may request pharmacovigilance data at any time, the Applicant is asked to justify the short period of retention of pharmacovigilance documentation.

Risk Management Plan

The company provided a justification for not submitting a Risk Management Plan (RMP) for this generic medicinal product which is acceptable.

Comments on compliance with GLP, GMP, GCP

GCP

The CHMP has requested a GCP inspection of the clinical study PKD_08_059: A RANDOMIZED, OPEN LABEL, TWO TREATMENT, TWO PERIOD, TWO SEQUENCE, SINGLE DOSE, CROSSOVER, BIOEQUIVALENCE STUDY OF REPAGLINIDE 2MG TABLETS AND NOVONORM(r) 2 MG (REPAGLINIDE) TABLETS OF NOVO NORDISK, A/S NOVO ALLE, DK-2880 BAGSVAERD, DENMARK, IN 74 HEALTHY HUMAN ADULT SUBJECTS UNDER FASTING CONDITIONS.

Considering that the BE study is pivotal for this application and that the CRO performing the study is unknown from the EMA, an inspection of this study has been performed.

Conclusion of the report:

No major or critical deviation from GCP and GLP was identified during the inspection. Therefore, data regarding clinical and analytical aspect could be considered as reliable.

Nevertheless, the inspection outcome brought confirmation of concerns regarding the validity of the analytical results of the bioequivalence trial outlined by the CHMP.
Indeed, one observation was found to be of a major importance during the inspection of the clinical part of the trial and four observations were considered as major in the context of the conduct of the bioanalytical part of the trial.
The observations are liable to call into question the acceptability of the trial data, since accuracy of the bioanalytical method cannot be established with certainty in the absence of demonstration that the variation of internal standard response had no impact on the concentration of Repaglinide.

GMP

An inspection request for the manufacturing facility of the finished product: has been endorsed by CHMP. This inspection was then cancelled when this site received a manufacturing authorisation for another product with the same pharmaceutical form.