ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORM, STRENGTHS OF THE MEDICINAL PRODUCTS, ROUTE OF ADMINISTRATION, APPLICANTS IN THE MEMBER STATES

Member State EU/EEA	**Applicant**	**(Invented) Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Germany	Olinka (UK) Limited 38/40 Chamberlayne Road London, United Kingdom NW10 3JE	Pantoprazole 20 mg Volkspharma Gastro-resistant tablets	20 mg	Gastro-resistant tablet	Oral use
Germany	Olinka (UK) Limited 38/40 Chamberlayne Road London, United Kingdom NW10 3JE	Pantoprazole 40 mg Volkspharma Gastro-resistant tablets	40 mg	Gastro-resistant tablet	Oral use
Poland	Olinka (UK) Limited 38/40 Chamberlayne Road London, United Kingdom NW10 3JE	Pantoprazole Phargem	20 mg	Gastro-resistant tablet	Oral use
Poland	Olinka (UK) Limited 38/40 Chamberlayne Road London, United Kingdom NW10 3JE	Pantoprazole Phargem	40 mg	Gastro-resistant tablet	Oral use
United Kingdom	Olinka (UK) Limited 38/40 Chamberlayne Road London, United Kingdom NW10 3JE	Pantoprazole 20 mg Gastro-resistant tablets	20 mg	Gastro-resistant tablet	Oral use
United Kingdom	Olinka (UK) Limited 38/40 Chamberlayne Road London, United Kingdom NW10 3JE	Pantoprazole 40 mg Gastro-resistant tablets	40 mg	Gastro-resistant tablet	Oral use

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR POSITIVE OPINION

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF PANTOPRAZOLE OLINKA AND ASSOCIATED NAMES (SEE ANNEX I)

Pantoprazole is a proton pump inhibitor (PPI), indicated for the treatment of gastrointestinal diseases associated with acid hypersecretion as gastric and duodenal ulcer, reflux oesophagitis (treatment and prevention of relapse) treatment of non-erosive gastroesophageal reflux disease (GERD), prevention non steroid anti-inflammatory drugs (NSAIDs) related ulcers, Zollinger-Ellison-Syndrome and eradication of H. pylori.

The Reference Member State (RMS) for the decentralised procedure for Pantoprazole Olinka application was UK and the Concerned Member States (CMS) were: Germany and Poland. The originator medicinal product used in the bioequivalence studies was Pantecta 40 mg developed by Altana Pharma AG, Spain. During the DCP a CMS raised major objections concerning the bioequivalence with the originator under fed conditions. The following Potential Serious Risk to Public Health (PSRPH) concern was therefore referred to the CHMP: the Study PAN 2006/006 (fed bioequivalence) did not adequately evaluate the properties of the test formulation in relation to the intake of a meal and the possibility of a formulation difference between the test and the reference product has therefore not been sufficiently excluded. The design of this study was considered inappropriate with respect to the following:
- sampling times (should have been at least 24 h)
- protocol specifications regarding outliers, and the subsequent exclusion of the outliers.
The CHMP addressed a List of Questions and a further List of Outstanding Issues to the Applicant on issues related the bioequivalence with the originator under fed conditions.

The CHMP, in the adopted List of Questions, requested the Applicant to discuss the design and results of the fed bioequivalence study, in the following key aspects:
(i) The justification for the design of the study, particularly the 15 h sampling schedule and the rationale for pre-defining outliers based on the well-characterised and anticipated delayed absorption of pantoprazole with food in a small proportion of subjects – this should be discussed with reference to the current guidelines and in terms of the ability of the evaluable data to exclude a formulation difference under fed conditions.
(ii) The results of the analyses of the data from the study and why the applicant considers they exclude a formulation difference under fed conditions.
(iii) The results of additional dissolution testing, designed to mimic the gastric environment under fed conditions, and the further support provided by these data together with the discussion of the possible clinical relevance/applicability.

The Applicant, given the degree of overlap between the first two parts of the question [(i) and (ii)] combined its response to these. The response to the third part (iii) has been provided separately. Within the response, the Applicant submitted also the results of the confirmatory bioequivalence study (2009-2106) with sampling period up to 30 hours.

The basis of Pantoprazole Olinka application is the establishment of bioequivalence between the proposed generic formulation and the originator (Pantecta 40 mg by Altana Pharma AG, Spain). Olinka submitted two bioequivalence studies which compared the proposed 40 mg formulation to the reference product, Pantecta 40 mg gastro-resistant tablets; one study was conducted under fasting conditions [PAN-2006/007] and the other study under the fed condition [PAN-2006/006].
The Applicant considered that the design of both of these bioequivalence studies took into account the requirements of the current bioequivalence guidelines (CPMP/EWP/QWP/1401/98), the known pharmacokinetic characteristics of pantoprazole, and the stated administration instructions as detailed in the SmPC ("*swallow whole with water before a meal*"). The findings from the food interaction study together with the demonstration of bioequivalence in the fasting state (the recommended method of dosing), and with the extensive in vitro dissolution data (designed to mimic the gastric "milieu" after food) were considered to

adequately exclude a formulation difference in terms of the integrity of the enteric coating and the risk of dose dumping.

Initial Bioequivalence Studies

The Applicant presented the results of two bioequivalence studies at a single oral dose of 40 mg, in healthy volunteers: **PAN-2006/007** (fast study), **PAN-2006/006** (fed study). These studies were: cross-over, open-label, randomised treatment sequence bioequivalence studies carried out in healthy volunteers; they took into account the current guidelines and the pharmacological characteristics of pantoprazole, the prolonged T-max, the increased variability (especially Cmax), and the unaltered half-life under fed conditions.

In the food-interaction study, the protocol set-out criteria for outliers based on pilot data that defined possible exclusions based on the following:

- The rate of outlying cases from the test formulation must be no greater than the reference + 20 % (rounded to the nearest integer value).
- A case will be considered to be an outlier if at least one of the following conditions apply:

- There is complete or almost complete lack of absorption of the drug (AUClast is less than 10 % of the mean values of the corresponding formulation)
- If T-max is >12 h

The Applicant showed that the 'predefinition' of outliers was consistent with the current guidance on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 and in EMEA/CHMP/EWP/40326/2006).
It was anticipated that outliers would occur with both study groups (test and originator groups) in the fed study.
The CHMP noted that the results were coherent with the available published information on food interaction of pantoprazole formulations, which describe a potential delayed absorption and an increase in variability.

Analytical Methods and Pharmacokinetic Variables

The Applicant submitted analytical reports for the studies. Standard criteria for bioequivalence were used i.e**.** the 90 % CI for the AUC and Cmax ratios must lie within the accepted range of 80.00-125.00.
The Applicant presented several literature references to justify the PK variability of pantoprazole.
According with *Coupe A.J. et al. (1991)* food may delay gastric emptying up to 10-11 hours and thus can influence the timing of the absorption of orally administered drugs. Pantoprazole is also known to exhibit delayed absorption and increased pharmacokinetic variability when taken with food in some individuals, though the extent of absorption [AUC] is generally considered not to be affected *(Radhofer-Welte, 1999, and Fitton and Wiseman and 1996 Andersson).* Furthermore, an increase in T-max from 1-4 hours under fasting conditions to between 5 and 12 hours (attributed to delayed absorption with food) was published by the FDA in their Summary of Approval of the originator, Protonix 20 mg and Protonix 40 mg. *[US FDA Summary of Approval Protonix 20 mg and Protonix 40 mg]*.
It was demonstrated that the effect of such delays on the absorption of pantoprazole in terms of the drug efficacy, in individual patients is relevant for AUC, but not for the Cmax as AUC correlates with the degree of acid suppression *[Hatlebakk, 1996; Thompson, 1997]*.
This kinetic alteration appears frequently with pantoprazole and is the basis as to why the Summary of Product Characteristics for Pantoprazole products in the EU state: *'Swallow whole with water before a meal'.*

Sampling Schedule

The European Guidelines lay down the criteria for the design of bioavailability and bioequivalence studies (CPMP/EWP/QWP/1401/98). As such, the planned sampling schedule should provide an adequate estimation of the Cmax and should cover the plasma concentration time curve sufficiently to provide a reliable estimate of the extent of absorption.

This, in general, is achieved if the AUC derived from measurements is at least 80 % of the AUC extrapolated to infinity. If a reliable estimate of terminal half-life is necessary this should be obtained by collecting at least three to four samples during the terminal log linear phase.
Based on a terminal elimination half-life of approximately 1 hour, three times the half-life was considered sufficient to cover the elimination of 83 % of the drug, and five times the half-life was considered to allow for almost complete elimination. A period of 15 hours was consequently deemed to be suitable for quantification of at least 80 % of the total AUC, as recommended in the guidelines.

The Applicant determined the sampling schedule in the study undertaken taking into account the general information from the available published references which in general supported a gastric emptying time range of less than 1 hour to approximately 5 hours where varying intakes of food were involved.
Given the main analysis results, the probability for bioinequivalency was evaluated by the Applicant and it resulted to be less than 1 % for Cmax and 0.02 % for AUClast.
The CHMP concluded, based on the study results, that a difference in PK mechanism for the test and the originator is extremely unlikely given the clear demonstration of bioequivalence in the main analysis and in the secondary (whole analysis with measurable values).

Confirmatory Pharmacokinetic Study (study code: 2009-2106)

The Applicant presented the results of a further confirmatory fed study, with a final sampling point of 30 hours. The aim of this study was to test the effect of food on the kinetics of the two pantoprazole formulations and their stability/degradation, the absence of dose dumping, and to exclude formulation differences.
The study was conducted in fed conditions and a high fat, high calorie breakfast was served 30 minutes prior to drug administration. The samples were immediately stored at -25°C and transferred to the analytical facility. The wash-out phase was 7 days.

The CHMP considered that the drug intake after breakfast (30 minutes) was sufficiently short. The sampling times were extended at the end of the observation period, which seemed to be considering the weaknesses of the previous study. The observation period of 30 hours exceeded the minimal requirement for studies with pantoprazole, which is considered to be 24 hours. The wash-out phase was sufficiently long considering the short half-life of the compound.
The CHMP concluded that the overall study design was acceptable.

Because different batches were used in the previous bioequivalence studies and in the confirmatory one, the Applicant presented comparative dissolution studies at pH 6 and 6.8 for these different batches. For these two pH values similar dissolutions were proven.

Population studied

The Applicant presented the population recruited for the confirmatory study. Usual in- and exclusion criteria for studies in healthy volunteers were applied in order to exclude subjects with relevant illness.
The CHMP acknowledged that in and exclusion criteria, as well as subjects included, number and type of protocol deviations were considered acceptable.

Analytical methods -fasted and fed studies

The documentation of the analytical methods comprised an Analytical Report and a Re-validation report.
The CHMP considered that the overall analytical documentation was satisfactory, however retrieved the issue of long-term stability as a major objection and requested the Applicant to submit long-term stability data in the answer to the adopted LoOI.

Pharmacokinetic Variables

The primary analysis was conducted on AUClast and Cmax, using the log-transformed ratios and 90 % Confidence Intervals (CIs). Standard criteria for bioequivalence were used i.e. the 90 % CI for the AUC and Cmax ratios must lie within the accepted range of 0.80-1.25.
The mean ratio "test over reference" was calculated as 85.6 with 90 % confidence intervals of 77.6-95.6 %.
The Applicant pointed out that in defined situations, as for pantoprazole, wider interval (75-133 %) for Cmax may be acceptable *"if justified, addressing in particular any safety or efficacy concerns for patients switched between formulations".* The wider acceptance interval (75-133 %) for bioequivalence is considered justified, since pantoprazole is found to be highly variable under fed conditions.
The Applicant justified the **highly variable pharmacokinetics** of pantoprazole, after food administration, referring to the biopharmaceutical classification system (BCS). According to this, pantoprazole is classified as a provisional BCS class III, i.e. a high solubility-low permeability drug. *Fleisher et al, 1996 and de Campos et al. 2007,* described that BCS class III drugs present a highly variable pharmacokinetic disposition when taken with a meal due to a reduction of the absorption by simple physical barriers. In individual patients it was demonstrated that AUC, but not Cmax, correlates with the degree of acid suppression, which is known to correlate with the cure of acid-related diseases, and that there is no temporal association between the peak plasma concentration and the maximum acid suppression caused by the proton pump inhibitors *[Hatlebakk, 1996]*.

The CHMP noted that the expansion of the stated confidence interval for Cmax was not prospectively defined in the study protocol. The parameters determined, methods used for analysis, and success criteria appear to be standard and are considered acceptable; however the CHMP asked the Applicant to clarify the failed demonstration of bioequivalence regarding the parameter Cmax in the study report.

The Applicant answered that a less strict requirement may apply for pantoprazole and submitted a report on the expected clinical relevance of the delayed absorption of pantoprazole observed in the study 2009-2106. In its first part the expert report displays the basic facts on pantoprazole PK and PD: the previously known properties of pantoprazole of a 77% bioavailability, an only modest delay of absorption, increased variability, but unaltered rate and extent of absorption when given with food. Then the expert referred to two newer studies (De Campos DR et al: Drug Res 2007; Filipe A et al. Drug Res 2008; and Mendes Drug Res 2008) which revealed that administration of pantoprazole with food can provoke decreases in Cmax and AUC and markedly delay the absorption.
The expert referred to the results of study 2009-2106 and concluded that there was no dose dumping effect, that a delayed start of the antisecretory effect was observed corresponding to the first dose, and subsequent doses had a minor effect on acid suppression.
The CHMP noted that the difference in the Cmax between the test and the originator has no clinical significance. The CHMP concluded that both formulations are equivalent and are therapeutically equivalent and that there is no risk to the clinical management of the patients.

Safety results

During the course of the study, 80 adverse events were reported. All of them were of mild severity, some adverse events were eventually related to the study medication. There were laboratory abnormalities in the post-study laboratory evaluations for altogether 11 subjects. All but one of them had either been classified as being clinically not significant or been resolved after the follow-up conducted by the Applicant. There were no deaths, and no serious or other significant adverse events in the course of the study.
The CHMP concluded that no safety concerns can be derived from the submitted data.

Absence of a Formulation Difference

Introduction to the Study - PAN-2006-006, Food Interaction
The Applicant presented the main analysis of the plasma samples excluding outliers in study PAN-2006/006 and also the analysis of the whole sample including all cases. Furthermore, the *in vitro* gastro-resistance and *in vitro* dissolution data presented and discussed in this response support bioequivalence conclusion.

Main Analysis
The statistical analysis carried out according to the predefined criteria established in the protocol was presented as the main analysis. To carry out the main analysis, the data of those volunteers that were identified as outliers was excluded from the set of data included in the analysis. No extrapolation or imputation has been used in the statistical analysis.

Secondary Analysis
The statistical analysis carried out with all the evaluable data for all volunteers was presented as the secondary analysis. All the available data were included without any imputation or extrapolation.
The CHMP acknowledged the analysis of the whole sample including all cases and concluded that both of the formulations studied can be considered as bioequivalent.

Confirmatory Food Interaction Study -2009-2106
In this study, the AUC met the required acceptance interval for bioequivalence (80-125). For Cmax the confidence interval is 77.6-95.6% which is slightly below the acceptance interval (80-125) but the intra-individual variability (2 period 2 sequence design) is higher than 30% (36%), similar to the data reported in the literature for pantoprazole.
The CHMP, considering the data reported, concluded that there was no formulation difference of any clinical significance.

The CHMP adopted also a LoOIs asking the Applicant to further clarify the pending issues.

Major concern- LoOI - Q1: The Applicant was requested to submit the documentation of long-term stability of frozen plasma in order to fully document the accuracy of laboratory evaluations.

The Applicant submitted an additional validation study. It included the requested data about long-term stability of human plasma samples along with long-term stability data of stock solutions (749 days at -25°C) and auto-sampler stability (122.5 hours at 5°C).
All tests achieved satisfactory results with only small deviations. For long-term stability a reduction was seen in pantoprazole content of between 6-8% of the nominal content, which was considered acceptable.
The detailed results of the long-term stability data of human samples were given.

The CHMP considered that the Applicant has complied with the requested response and submitted the data, along with additional data regarding stability of pantoprazole under different conditions. All tests revealed acceptable results. The CHMP considered this issue resolved.

Other concerns LoOI–Q1: The Applicant was requested to clarify the origin and name of the reference product used in the new bioequivalence study.

The Applicant stated that the reference product in all bioequivalence studies conducted was Pantecta, marketed in Spain. The manufacturer was Altana for studies Pan 2006/006 and Pan 2006/007, and Nycomed for study 2009-2106. The change of name was caused by company takeover. The reference product patients' leaflet was also provided.
The CHMP considered the Applicant's response acceptable. The information on the originator product has been clarified to a satisfactory extent.

LoOI–Q2: The Applicant was requested to state the batch size of the batch used for the new bioequivalence study for the test product.

The Applicant reassured in its answer on the above. Furthermore a complete analytical certificate (of test and reference product) was provided with all results being compliant with specifications.
The CHMP considered this issue resolved.

LoOI - Q3: The Applicant was requested to submit additional PK evaluations for test and reference product for the new bioequivalence study as the Lag-times and the % extrapolated AUC.

The Applicant provided the evaluation of lag-times and % extrapolated AUC. In addition, data on the PK parameters from study 2009-2106 were provided. The Applicant showed that the number of patients with an increased % of extrapolated AUC was very low and the variability in both parameters of interest was very high.

The CHMP concluded that the evaluation of the percentage of the extrapolated AUC showed completely appropriate sampling period/sampling times. The evaluation of the lag-time showed clinically negligible differences regarding the delay of absorption of pantoprazole from the two preparations.
In conclusion, both results were considered to be fully acceptable.

GROUNDS FOR POSITIVE OPINION

Whereas,

The CHMP found satisfactory justifications regarding the study design in respect to:

-the sampling schedule,
-the pre-definition of outliers,
-the results of the confirmatory study, the dissolution testing, and the result of long term stability of the frozen plasma.

The CHMP considers that bioequivalence between the test and the originator has been demonstrated also under fed conditions;

the CHMP has recommended the granting of the Marketing Authorisations subject to the conditions, as set out in Annex IV. The valid Summary of Product Characteristics, labelling and package leaflet are the final versions achieved during the Coordination group procedure as mentioned in Annex III for Pantoprazole Olinka and associated names (see Annex I).

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

The valid Summary of Product Characteristics, labelling and package leaflet are the final versions achieved during the Coordination group procedure.

ANNEX IV

CONDITIONS OF THE MARKETING AUTHORISATION

CONDITIONS WITH REGARDS THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

The Applicant committed to update the Summary of Product Characteristics and Package Leaflet in accordance to the outcome of the ongoing SPC harmonisation procedure under Article 30 of Directive 2001/83/EC with the reference product Protium and associated names.