ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORM(S), STRENGTH(S) OF THE MEDICINAL PRODUCT(S), ROUTE(S) OF ADMINISTRATION, APPLICANT(S) / MARKETING AUTHORISATION HOLDER(S) IN THE MEMBER STATES

Member State EU/EEA	**Marketing Authorisation Holder**	**Applicant**	**(Invented) Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Czech Republic	PRO.MED.CS Praha a.s. Telčská 1 Prague 4		Prokanazol	100 mg	Hard capsules	Oral use
Latvia		PRO.MED.CS Praha a.s. Telčská 1 Prague 4	Prokanaz 100 mg cietās kapsulas	100 mg	Hard capsules	Oral use
Lithuania		PRO.MED.CS Praha a.s. Telčská 1 Prague 4	Prokanaz	100 mg	Hard capsules	Oral use
Poland		PRO.MED.CS Praha a.s. Telčská 1 Prague 4	Prokanazol	100 mg	Hard capsules	Oral use
Slovak Republic		PRO.MED.CS Praha a.s. Telčská 1 Prague 4	Prokanazol	100 mg	Hard capsules	Oral use
Slovenia		PRO.MED.CS Praha a.s. Telčská 1 Prague 4	Prokanazol 100 mg trde kapsule	100 mg	Hard capsules	Oral use

ANNEX II

SCIENTIFIC CONCLUSIONS

SCIENTIFIC CONCLUSIONS

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

Itraconazole is an antimycoticum active against infections caused by dermatophytes, yeasts, Aspergillus spp, Histoplasma spp., Paracoccidioides brasiliensis, Sporothrix schenckii, Fonsecaea spp., Cladosporium spp., Blastomyces dermatitidis, and various other yeasts and fungi. The oral bioavailability of itraconazole is maximal when the capsules are taken immediately after a full meal. Peak plasma levels are reached within 3 to 4 hours following an oral dose. One of the metabolites is hydroxy-itraconazole, which has *in vitro* antifungal activity comparable to itraconazole.

The product was authorised in the reference member state under Article 10.1 of Directive 2001/83/EC and the application was submitted in the concerned member states under the Mutual recognition procedure. Disagreement remained between the concerned member states regarding the bioequivalence of Prokanazol to the originator, as no agreement could be reached with regards to the limits of quantification (LOQ) of itraconazole, the validation of calculation method of Cx/λz ratio (Cx being the last evaluable concentration and λz being the last exponential elimination constant) or the justification of values of AUC residual above 20% of AUC total. The procedure was therefore referred to the CHMP and a List of Questions was adopted:

The applicant is asked to justify the results of the presented bioequivalence study, mainly the calculation of the AUC_{inf} and λ_z (last exponential elimination constant) as well as to provide all AUC_t data. The calculation of AUC_{inf} and λ_z could be affected by the fact that the elimination phase was not achieved in some volunteers, mainly due to the arbitrary acceptance of the limit of quantification (LOQ). Moreover, in certain volunteers (based on the submitted data) the terminal phase was derived from C_{max}.

The Applicant stated that because the method to calculate the area under the curve is not described in the European guide (EMA), the method described in the FDA guide (page 9, paragraph III.A.8c) was used, applying the software WinNonlin which uses the module NCA ("Non compartmental Analysis"). The algorithm used to calculate the "*last exponential elimination constant"* in the NCA module is based on least squares regression and adjustment by the determination coefficient (square R) as a function of the number of points employed in the calculations. The Applicant also provided all the different pharmacokinetic parameters, among others the area under the curve until the last quantified concentration (AUCt).

Regarding the statement that elimination phase was not achieved in some volunteers, the Applicant considered that the assessment of whether a volunteer has achieved elimination phase needs to take into account the experimental sample points and the concentrations values obtained. Likewise it will be important to take into account the last quantified concentration in comparison with the value of the lower limit of quantification (LLOQ). As it was stated in the protocol of the trial, the elimination half-life of the drug is about 26 hours. In the Applicant study, mean results of this pharmacokinetic parameter were 19.3 and 19.0 hours for the reference and the test compounds, respectively. Therefore, selecting the last sample point as being at +96 hours corresponds to more than 3 half-lives (based on the theoretical a priori information) and more than 5 half-lives (based on the experimental value obtained in the study). In nearly all cases (65/70), the obtained values were not higher than 3 times the LLOQ and in no cases was the last quantified sample higher than 4 times the LLOQ. The Applicant included data on Clast, providing the last quantified concentration for each volunteer and formulation and the individual semi-logarithm pharmacokinetic figures.

Regarding the arbitrary acceptance of the lower limit of quantification (LLOQ), the Applicant considered that the LLOQ is complying with the requirements recommended by the FDA in relation to "response compared to blank response" and "precision and accuracy". The Applicant argued that the fulfilment of both conditions is confirmed and that accuracy can be estimated. The Applicant provided both values (precision and accuracy) for both products (hidroxi-itraconazol and itraconazol) from the 6 chromatograms obtained.

With regards to the terminal phase being derived from Cmax in certain volunteers, this could be a matter of concern if the pharmacokinetic analysis applied had been compartmental, as it would suggest that a fast disposition phase did not exist in those cases compared with the remaining ones. The pharmacokinetic analysis applied, following the recommendations from the regulatory agencies, was non-compartmental amodelistic. Using this approach, the regression with the best adjustment is retained from the experimental data in order to provide a reliable estimation of the elimination constant and thereby of the pharmacokinetic parameters derived from it.

The CHMP considered that the applied methods for calculating the AUCt and AUCinf and the 'last exponential elimination constant' are standard and general accepted methods and noted that the requested data were provided, with at least 3 data points being used for estimation of the elimination phase. Furthermore, the elimination half-life of itraconazole is about 26 hours and blood samples were obtained over at least 3-times the elimination half-life. Itraconazole shows a rather long tmax (about 6 h) as a result of the long elimination half-life, however estimation of AUC was at least 4 times the tmax, indicating that in these subjects the drug has been absorbed from the gastrointestinal-tract, and that the drug in the body is not dependent on differences between the 2 formulations.

However, the CHMP noted that the Applicant did not properly determine the LOQ limits and did not provide detailed information on the choice of points for the calculation of the terminal phase, nor on the points chosen for the individual profile and segments. It is therefore unknown how the terminal phase and the residual area were calculated. The problem is thus not only the five subjects of the original dossier but also the absence of pharmacokinetic calculations. The CHMP expressed doubts on the quality of LOQ, noting the lack of summary specifications and concluded that similar problems of residual areas are likely to affect further subjects beyond the five already identified. Values for the pharmacokinetic parameters were presented, but without any documentation of their calculation, preventing verification. The sampling schedule should cover the plasma concentration time curve long enough to provide a reliable estimate of the extent of exposure which is achieved if AUC_t is at least 80% of the AUC_∞. No valid arguments were provided to justify the lack of credible pharmacokinetic calculations, as the LOQ value used in analytical method was not determined by a validation process, but arbitrarily accepted as 5 ng/ml (the lowest calibrator). If the actual LOQ of the method is much lower than that assumed, this may result in a greater error factor, in particular for the determination of terminal phase of extrapolated line and residual area. The confidence interval range for total and residual areas does not explain nor improve the credibility of the calculations, especially as no estimator points were provided. The correctness of the estimator point calculations could not be assessed and there is no summary of the specification calculations for the analysis of variance and intra- and inter-variability, individual ratios and differences for pharmacokinetic parameters. The CHMP considers that the lack of assessment of the estimators of kinetic parameters analysis hampers the proper assessment of the data.

In conclusion, the Applicant did not provide sufficient information on the sample size, the power test or the coefficients of inter- and intra-variability. Some variability coefficients and data on the variability of the main pharmacokinetic parameters of the parent drug were provided but its origin could not be determined. Due to these outstanding concerns and the lack of documentation, the CHMP was unable to consider Prokanazol as being bioequivalent to the reference product and considered that more data was needed before an opinion could be provided. The CHMP therefore adopted a List of Outstanding Issues:

1. *Please produce calculations of the following after removal of volunteers with values below the LOQ: a. AUCinf; b. AUCt; c. Cmax*

2. *Please provide the raw data of all volunteers used for calculations.*

The Applicant submitted Cmax, AUCt and AUCinf values for all the volunteers and stated that the design of the study included sampling times in the absorption and late elimination phases in order to use results not exceeding the limit of quantification. As a consequence, all or almost all the volunteers had one or several points with values below the limit of quantification (BLQ). Volunteer number 24 showed a decreased

absorption with 52% of the sampling points BLQ, and only one sampling point with quantifiable values from his maximum concentration. As a result, WinNonlin cannot calculate the portion of area until infinite and the AUCinf therefore appears to be missing. The analytical centre gives only numerical results when the concentration is not BLQ, so is not possible to perform any calculations with these results. A more detailed analysis of the quantifiable determinations indicated that in the case of the reference formulation, 4 of 9 concentrations did not reach values above 4xLOQ and none reached these levels for the test formulation. It is thus impossible to calculate any AUC with a minimum robustness. Inter-patient variability in serum concentrations following oral administration of itraconazole has been described in the literature, and is most notable with the capsule formulation (up to 15-fold differences). Therefore, pharmacokinetic and bioequivalence results were analysed with all the data available obtained from 35 of the 36 volunteers included in the study, after removing volunteer 24 who presented a clearly atypical absorption pattern that prevented evaluating the area under the curve. The confidence intervals and the value of relative bioavailability for the 3 parameters (Cmax, AUCt and AUCinf) were provided. The Applicant also provided the raw data for all volunteers as requested by the CHMP.

The CHMP noted that no values were used below the estimated LOQ of 5 ng/ml and that the last value above the LOQ was used for the estimation of AUCinf. No volunteers had to be removed by misinterpretation or an incorrect use of values below the LOQ and furthermore, the Applicant provided the calculated 90% confidence intervals for all 36 subjects and by exclusion of subject 24. The CHMP recalculated the 90% confidence intervals and obtained comparable results to those provided by the Applicant. Therefore, bioequivalence can be considered to be proven for the 35 subjects who were included in the analysis. However, excluding subject 24 because of low itraconazole plasma concentrations is not acceptable. In accordance with the Questions & Answers document of the CHMP EWP subgroup on pharmacokinetics on the bioavailability and bioequivalence guideline, exclusion of data is not justified and cannot be accepted on the basis of statistical analysis or for pharmacokinetic reasons alone, because it is impossible to distinguish between formulation effects and pharmacokinetic effects. Acceptable explanations to exclude pharmacokinetic data or to exclude a subject would be protocol violations, which are not observed in this study. When including the data for subject 24, bioequivalence cannot be proven, as the 90% confidence intervals for AUC and Cmax then fall outside the normal acceptance criteria of 80 – 125%. Therefore the potential serious potential risk to public health due to the lack of bioequivalence remains unresolved. Based on the totality of the data from all 36 subjects, bioequivalence has not been proven and as such the benefit risk ratio for this generic product is considered negative.

GROUNDS FOR NEGATIVE OPINION

The CHMP considered that the bioequivalence between the test and reference product has not been sufficiently proven, and that as such the product is not considered approvable for the sought indications.

Whereas

- of the CHMP considered that bioequivalence could not be shown,

- the exclusion of an outlier subject is not accepted, as the data must be interpreted in its totality,

- the benefit risk of the generic product Prokanazol is considered to be negative,

the CHMP has recommended the refusal of the granting of the Marketing Authorisations in the Concerned Member States and the suspension of the Marketing Authorisation in the Reference Member State, where the product is currently authorised, for Prokanazol and associated names (see Annex I).

ANNEX III

CONDITIONS FOR THE LIFTING OF THE MARKETING AUTHORISATION SUSPENSION

The National Competent Authorities, coordinated by the Reference Member State, shall ensure that the following conditions are fulfilled by the Marketing Authorisation Holders:

The Marketing Authorisation Holder should submit the result of a properly conducted bioequivalence study, in compliance with the Questions & Answers document of the CHMP EWP subgroup on pharmacokinetics on the Bioavailability and Bioequivalence Guideline.