PUBLIC CONTRACTS REVIEW BOARD

Case No. 434

GHPST/725/11
Tender for the Supply of Cyclosporin 25mg capsules

This call for tenders was published in the Government Gazette on the 5th August 2011. The closing date for this call with an estimated budget of € 99,543.84 was the 5thSeptember 2011.

Two (2) tenderers submitted their offers.

Messrs Cherubino Ltd filed an objection on the 14th May 2012 against the decision of the Ministry for Health, the Elderly and Community Care to disqualify its tender and to recommend the award of tender in favour VJ Salomone Pharma Ltd.

The Public Contracts Review Board composed of Mr Alfred Triganza as Chairman, Mr. Joseph Croker and Mr Paul Mifsud as members convened a public hearing on Monday 23rd July, 2012 to discuss this objection.

Present for the hearing were:

Cherubino Ltd

Dr Adrian Delia	Legal Representative
Dr Francis Cherubino	Representative

VJ Salomone Pharma Ltd

Dr Roderick Zammit Pace	Legal Representative
Mr Adrian Salomone	Representative
Ms Jacqueline Scerri	Representative
Mr Michael Sultana	Representative
Ms Alessandra Camilleri	Representative

Central Procurement and Supplies Unit (CPSU) – Ministry for Health, the Elderly and Community Care (MHEC)

Ms Connie Miceli	Representative

Evaluation Board

Ms Miriam Dowling	Chairperson
Mr David Baldacchino	Member
Ms Sonia Bonnici	Member
Ms Audrey Sciberras	Secretary

The Chairman Public Contracts Review Board informed those present at the hearing that two other objections had already been lodged with the said Board with regard to two separate cases on, more or less, the same grounds and that the state of affairs with regard to these two objections was as follows:-

a. GHPST/410/11 (Case No. 407) - Tender for the Supply of Cyclosporin 25mg capsules – hearing was held on 11th May 2011 and it was agreed that the Public Contracts Review Board should seek independent technical advice on the bioequivalence clause that featured in the tender specification. After strenous efforts, the Public Contracts Review Board has succeeded to commission a foreign expert to tender this advice and he was expected to submit his advice by the 10th August 2012;

and

b. GHPST/928/11 (Case No. 408) – this call for tenders excluded the bioequivalence clause and the Public Contracts Review Board had ruled the issue of this call for tenders as null and void on 28th May 2012 since it was published on the 28th October 2011 when the tender procedure Ref. No. GHPST/410/11 was still taking its course.

Dr Adrian Delia, legal representative of Messrs Cherubino Ltd, the appellant company, made the following submissions:

i. by letter dated 8th May 2012 the contracting authority had informed his client that his tender submission was not successful since it could not *"be confirmed whether product offered is compliant with published specifications regarding bioavailability since section 4.2 of SPC submitted states that:-*

> *patients should not be transferred to or from other oral formulations of cicloporin without appropriate close monitoring ...* ' and
> '*that substitution of Deximune capsules for other formulations may lead to alterations in cicloporin blood levels'"*

ii. the case under reference and the previous ones were quite similar, with the main difference being that, this time, the contracting authority also stated in its letter of rejection that:

> *"Following recommendations by Clinical Section, DPA have reviewed specifications. Item is not according to the new updated specifications (due to the nature of product, in the updated specifications, the bioequivalence clause has been removed and the originator 'Neoral' is requested)*"

iii. it, therefore, followed that this call for tenders was issued with the bioequivalence clause which read as follows:-

> *"Cyclosporin 25mg soft gelatine capsules in a micromulsified formulation (Neoral (R), Novartis). The capsules should be presented in blister packs.*

Pertinent storage conditions are to be clearly indicated on the label of the outer pack.

Evidence of Bioequivalence with the Originator product is to be submitted in those cases where product being offered is a Generic one. The supplier must ensure that the evidence is based on the best scientific state of the art technique."

iv. since the above-mentioned clause allowed bidders to offer generic products then his client's offer was compliant and should not have been disqualified;

and

v. if anything, the contracting authority might have cancelled the tender - as was the case with GHPST/410/11 - and not recommend award to the bidder who offered the originator product and excluded his client for offering a generic product as requested in the tender document.

Mr David Baldacchino, a member of the adjudicating board, explained that:-

a. the preferred bidder offered the originator product and, as a result, the offer was compliant with or without the bioequivalence clause;

b. when the adjudicating board was evaluating the tender submissions it noted that the offers submitted referred to both the originator product and to a generic product and, as a consequence, it referred the matter to the Clinical Section which, in turn, declared that the generic product was not acceptable and recommended a revision of the specifications to remove the bioequivalence clause;

and

c. this call for tenders did include the bioequivalence clause but future calls for tenders for the same product would be issued without that clause thereby requesting only the originator 'Neoral (R) Novartis'.

Dr Delia intervened to remark that, given this scenario, one had to question the purpose for a contracting authority to issue a call for tenders when only the originator product would be requested. He reiterated that both this tender and tender Ref. No. with GHPST/410/11 had been issued with the bioequivalence clause with the difference being that the contracting authority had recommended the cancellation of the latter whereas the same contracting authority was recommending this tender for award to VJ Salomone Pharma Ltd.

Dr Roderick Zammit Pace, legal representative of the recommended tenderer, remarked that:-

i. the technical specifications at page 30 of the tender document were, in a way, rather contradictory in the sense that, whereas the second paragraph allowed bidders to offer a generic product, the previous (first) paragraph, clearly and

specifically, requested *Cyclosporin 25mg soft gelatine capsules in a micromulsified formulation (Neoral (R), Novartis)* and no alternatives were mentioned;

and

ii. although his client was the only distributor in Malta of Neoral (R) Novartis, still, this tender was published EU-wide and, as a result, distributors of this particular product in other EU states could have submitted a bid.

Dr Delia declared that:-

a. the technical specifications at page 30 allowed bidders to offer generic products and, accordingly, his client offered a generic product together with the required bioequivalence evidence and the contracting authority did not rule out his client's product for not being bioequivalent but it stated that it *was not successful since it cannot be confirmed whether the product offered was compliant with published specifications regarding bioavailability*.. namely the same reason quoted with regard to the previous tender procedure (GHPST/410/11);

and

b. at the hearing held in connection with calls for tenders' reference numbers GHPST/410/11 and GHPST/928/11, it had been agreed that one had to establish whether his client's product was bioequivalent or not.

The Chairman Public Contracts Review Board informed those present that given the specific nature of the product under reference and the limited local market, it was difficult to find a local source that could give professional and independent advice to this Board. Yet, he continued, following strenuous efforts, a competent source has been identified from overseas and the Public Contracts Review Board should receive that advice by the 10th August 2012. He added that the outcome with regard to case GHPST/411/11 would probably be applicable to the case in hand.

The Chairman Public Contracts Review Board also remarked that, in his view, the wording of the technical specifications at page 30 of the tender document was quite clear in so far as it did allow bidders to offer generic products. He added that the contracting authority could have been more explicit by requesting the originator and the generic products but, on the other hand, if the bidder had any doubts as to what the contracting authority was actually requesting then the bidder could have asked for a clarification at the opportune time.

Dr Delia shared the Public Contracts Review Board's view that one should await the independent technical advice sought by the Public Contracts Review Board and if it would result that his client's product was bioequivalent then his offer should be reinstated even in the case of this tendering procedure and if it would result that his client's product was not bioequivalent then his disqualification ought to be confirmed in both cases.

At this point the hearing was brought to a close.

This Board,

- having noted that the appellants, in terms of their 'reasoned letter of objection' filed on the 14th May 2012 and also through their verbal submissions presented during the hearing held on the 23rd July, 2012, had objected to the decision taken by the pertinent authorities;

- having noted all of the appellant company's representatives' claims and observations, particularly, the references made to the fact that (a) by letter dated 8th May 2012 the contracting authority had informed the appellant company that its tender submission was not successful since it could not *"be confirmed whether product offered is compliant with published specifications regarding bioavailability since section 4.2 of SPC submitted states that patients should not be transferred to or from other oral formulations of cicloporin without appropriate close monitoring ...* ' and '*that substitution of Deximune capsules for other formulations may lead to alterations in cicloporin blood levels'*", (b) the case under reference and the previous ones were quite similar, with the main difference being that, this time, the contracting authority also stated in its letter of rejection that *"Following recommendations by Clinical Section, DPA have reviewed specifications. Item is not according to the new updated specifications (due to the nature of product, in the updated specifications, the bioequivalence clause has been removed and the originator 'Neoral' is requested*)", (c) it, therefore, followed that this call for tenders was issued with the bioequivalence clause, (d) since the tender specifications allowed bidders to offer generic products then the appellant company's offer was compliant and should not have been disqualified, (e) if anything, the contracting authority might have cancelled the tender - as was the case with GHPST/410/11 - and not recommend award to the bidder who offered the originator product and excluded the appellant company for offering a generic product as requested in the tender document, (f) given this scenario, one had to question the purpose for a contracting authority to issue a call for tenders when only the originator product would be requested, (g) both this tender and tender Ref. No. with GHPST/410/11 had been issued with the bioequivalence clause with the difference being that the contracting authority had recommended the cancellation of the latter whereas the same contracting authority was recommending this tender for award to VJ Salomone Pharma Ltd, (h) the technical specifications at page 30 allowed bidders to offer generic products and, accordingly, the appellant company offered a generic product together with the required bioequivalence evidence and the contracting authority did not rule out the appellant company's product for not being bioequivalent but it stated that it *was not successful since it cannot be confirmed whether the product offered was compliant with published specifications regarding bioavailability*.. namely the same reason quoted with regard to the previous tender procedure (GHPST/410/11), (i) at the hearing held in connection with calls for tenders' reference numbers GHPST/410/11 and GHPST/928/11, it had been agreed that one had to establish whether the appellant company's product was bioequivalent or not and (j) one had to share the Public Contracts Review Board's view that one should await the independent technical advice sought by the Public Contracts Review Board and if it would result that the appellant company's product was

bioequivalent then its offer should be reinstated even in the case of this tendering procedure and if it would result that the appellant company's product was not bioequivalent then its disqualification ought to be confirmed in both cases;

- having considered the contracting authority's representatives' reference to the fact that (a) the preferred bidder offered the originator product and, as a result, the offer was compliant with or without the bioequivalence clause, (b) when the adjudicating board was evaluating the tender submissions it noted that the offers submitted referred to both the originator product and to a generic product and, as a consequence, it referred the matter to the Clinical Section which, in turn, declared that the generic product was not acceptable and recommended a revision of the specifications to remove the bioequivalence clause and (c) this call for tenders did include the bioequivalence clause but future calls for tenders for the same product would be issued without that clause thereby requesting only the originator 'Neoral (R) Novartis';

- having considered the recommended tenderer's representatives' reference to the fact that (a) the technical specifications at page 30 of the tender document were, in a way, rather contradictory in the sense that, whereas the second paragraph allowed bidders to offer a generic product, the previous (first) paragraph, clearly and specifically, requested *Cyclosporin 25mg soft gelatine capsules in a micromulsified formulation (Neoral (R), Novartis)* and no alternatives were mentioned and (b) although the recommended tenderer was the only distributor in Malta of Neoral (R) Novartis, still, this tender was published EU-wide and, as a result, distributors of this particular product in other EU states could have submitted a bid;

- having gone through the following administrative 'iter' to enable the Board to obtain an independent, international professional advice, namely:

  - Contacted a pharmacological expert based in Aberdeen Scotland – 14.05.2012

  - Expert placed this Board in touch with Dr Rachel Knott from the Robert Gordon University – 15.5.2012 – who showed interest and requested further information

  - Received confirmation from Dr Knott that Dr Yash Kumarasamy, a Clinical Pharmacology Senior Lecturer, at the Robert Gordon University was interested – 22.06.2012

  - Contract finalised for signature 20.07.2012

  - Prof Anne Humphrey from the Robert Gordon University informed the Board on the 23.07.2012 that Dr Yash Kumarasamy passed away

  - Prof Cherry Wainwright, Robert Gordon University, informed the Board that it was not possible to assign anyone else from the University – 26.07.2012

- Prof Susan Klein, Robert Gordon University, proposed Dr Peter Mullen who had been confirmed by Ms Hazel O'Mullen that he is a member of the British Pharmacology Society – 07.08.2012

- Negotiations started with Peter W. Mullen, PhD, FCSFS, Consultant Pharmacologist/Toxicologist, Kemic Bioresearch Laboratories Limited, Kentville, Nova Scotia, Canada and were concluded on the 15.09.2012

- A report was submitted by Dr Peter Mullen on 3rd November 2012

- having gone through Dr Mullen's detailed report a copy of which is reproduced hereunder:

A Review of the Bioequivalence of the Cyclosporin Formulations Deximune (Generic Product) and Neoral (Reference Product)

by

Peter W. Mullen, PhD

31 October, 2012

Kemic Bioresearch Laboratories Limited

Kentville, Nova Scotia, Canada

B4N 4H8

A Review of the Bioequivalence of the Cyclosporin Formulations Deximune (Generic Product) and Neoral (Reference Product)

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A Review of the Bioequivalence of the Cyclosporin Formulations Deximune (Generic Product) and Neoral (Reference Product)

Introduction

The review contained herein was undertaken at the request of the Public Contracts Review Board, Ministry of Finance, the Economy and Investment of the Government of Malta.

The review was initiated by the Public Contracts Review Board subsequent to the cancellation of a tender by the Government Health Procurement Services division of the Malta Ministry for Health, the Elderly and Community Care (the Contracting Authority) for the supply of "Cyclosporin 100 mg Capsules". The tender cancellation occurred due to doubt on the part of the Contracting Authority that the product offered by the supplier is "...compliant with specifications vis-à-vis bioavailability..." Essentially the focus of this matter is whether the generic cyclosporin[†] product, "Deximune", manufactured by Dexcel is "bioequivalent" to the innovator (reference) cyclosporin product, "Neoral", manufactured by Novartis.

Towards resolving the "bioequivalence dispute" I agreed to review documentation submitted by the generic manufacturer, Dexcel Pharma Limited, in support of its claim that the Deximune formulation is bioequivalent to the Neoral formulation, and to provide an independent opinion in this matter.

[†]Herein, the drug under consideration will be referred to as "cyclosporin" consistent with the spelling used in the original tender document. In the international literature, this drug is also known as "ciclosporin" (the International Nonproprietary Name), "cyclosporine" and "cyclosporine A".

The documentation provided for my review consisted of:

i) Tender Technical Specifications (one page from volume 3) re. "Cyclosporin 100 mg capsules";

ii) Letter from Miriam Dowling, Chairperson, Contracts Committee, Government Health Procurement Services to Messrs Cherubino Ltd notifying cancellation of the tender contract;

iii) A "To whom it may concern" letter from Mr. Terry Grigg, Managing Director, Dexcel Pharma Limited, Daventry, UK, Re. "Bioavailability of Deximune® (ciclosporin) vs Neoral";

iv) Summary of Product Characteristics (for both Deximune and Neoral from their respective manufacturers);

v) Letters (x5) from physicians at various Israeli medical centres briefly stating their clinical experience with Deximune;

vi) Two published papers, namely those by Avramoff *et al*[1] and Berger *et al*[2] listed under **References** at the end of this report.

Bioavailability and Bioequivalence: A Brief Introduction

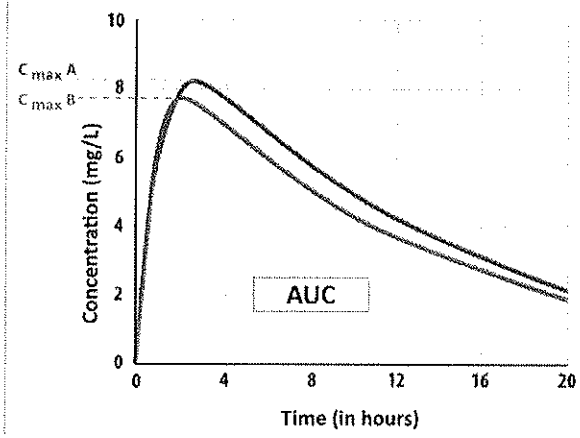
Bioavailability refers to the rate at which and extent to which a drug chemical is absorbed from a drug product into the systemic circulation (blood) subsequent to its administration into the body.

For drugs which can be readily determined in body fluids, blood drug concentrations measured after (oral) administration provide a valid means of assessing bioavailability. By conducting a **pharmacokinetics** study in which blood samples are drawn at intervals subsequent to administration, a plot of measured blood drug concentrations against time reflects the overall processes leading to the drug's appearance in blood, namely its release from the product formulation into, and its

absorption from, the gastrointestinal tract, as well as the processes of drug distribution within, and elimination from, the body.

Two basic pharmacokinetic "metrics" are used to quantitatively assess bioavailability: the area under the blood drug concentration-time curve (**AUC**) which directly reflects the extent of drug absorption, and the peak concentration value (**Cmax**), an indirect indication of the rate of drug absorption. (See Figure 1.) (**Tmax**, the time at which Cmax occurs, is also noted but is given relatively little weight in bioequivalence assessments.)

Figure 1. Hypothetical blood drug concentration–time curves for Products A and B



Bioequivalence refers to the sameness of two drug formulations (products) in respect to **rate** and **extent** of absorption when studied under essentially identical experimental conditions.

While there are many facets of bioequivalence, depending on the type of drug and its intended route of administration in the body, a summary of those most relevant to cyclosporin are here reviewed.

For orally administered drugs having systemic effects, determining whether a generic drug product is "bioequivalent" to the originator (innovator, reference) product is a matter of conforming with procedures and criteria established by various government regulatory (and some supranational) agencies (e.g. the European Medicines Agency, the US Food and Drug Administration, Health Canada, the World Health

Organization). Regulatory criteria pertaining to "average bioequivalence", which currently are fairly similar internationally, are compiled and published in national guidelines (guidances). For drugs which can be readily measured in body fluids, these guidelines require the conduct of a "comparative bioavailability" pharmacokinetics study, typically in healthy volunteer subjects, the data from which are subjected to specified statistical analyses. As would seem obvious, the drug products to be comparatively studied must also be "pharmaceutically equivalent" {i.e. they have the same active ingredient, the same dosage form, the same intended route of administration and the same strength (quantity per unit dosage form)}.

A typical comparative bioavailability study is characterized by a randomized, two-way crossover (2-sequence) design (i.e. subjects act as their own controls since they receive both the Test and Reference products on different occasions with an appropriate "washout" period between dosing phases). For "uncomplicated drugs", the study is normally conducted under fasting conditions and involves 12 to 36 healthy volunteer subjects.

From the results of such a study, bioequivalence is established by comparing the key metrics AUC and Cmax obtained for the generic (Test) and originator (Reference) products. {With respect to area under the concentration-time curve, both "AUCt, the area to the last blood sampling time (t) and AUCinf, the area extrapolated to "infinity", are typically examined.} The mean values of these metrics obtained for each product are compared relatively by examining their ratios. For immediate release drug products, most regulatory authorities require that the mean Test to mean Reference ratio value and its **90% confidence interval (C.I.),** statistically calculated by a "two, one-sided t-test", must be within 80 to 125 %. (Another requirement is that the original Cmax and AUC values for each drug product in each subject must be converted to their natural logarithm values; thus the Test to Reference ratios for Cmax and AUC are actually calculated as the "antilogarithm" of the difference in geometric means.)

Bioequivalence of "Narrow Therapeutic Index Drugs"

The foregoing basic information concerning bioequivalence applies to uncomplicated, immediate release drug products. Other "bioequivalence categories" exist including

that of **Narrow Therapeutic Index Drugs**, a category also referred to as "Critical Dose Drugs", which has been associated with much controversy in recent years as to whether it is needed and, if so, what criteria should distinguish it from those applicable to other drug products.

Narrow Therapeutic Index Drugs (NTIDs) are those for which a relatively small margin exists between those doses which are ineffective (subtherapeutic) and those which are potentially toxic (life-threatening) and thus require regular therapeutic monitoring of blood (serum, plasma) concentrations. (Some regulatory authorities actually list specific drugs to be considered within this category. Cyclosporin is usually included in the list although in the FDA guidance, this drug is not included in the "examples" cited.)

An examination of the positions of three regulatory authorities concerning this drug category follows.

The European Medicines Agency (EMA) in its current (1 August, 2010) "Guideline on the Investigation of Bioequivalence"[3] does not list specific drugs included in the NTID category but rather merely states (page 16) that: *"In specific cases of products with a narrow therapeutic index, the acceptance interval for AUC should be tightened to 90.00-111.11%. Where Cmax is of particular importance for safety, efficacy or drug level monitoring the 90.00-111.11% acceptance interval should also be applied for this parameter. It is not possible to define a set of criteria to categorise drugs as narrow therapeutic index drugs (NTIDs) and it must be decided case by case if an active substance is an NTID based on clinical considerations."* [3]

However, a 22 July, 2010 EMA document[4] subtitled: "Questions & Answers: Positions on specific questions addressed to the EWP therapeutic subgroup on Pharmacokinetics" explicitly states (page 17): *"As EWP has defined ciclosporine to be a NTID, for which both AUC and Cmax are important for safety and efficacy, a narrowed (90.00-111.11%) acceptance range should be applied for both AUC and Cmax, under fasting as well as under fed conditions, in line with the guideline on bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1.)."* [4]

Apparently, the above cited EMA "Q&A" document is not to be considered legally binding or applicable to existing marketed drug products, based on this statement (page 1): *"The positions in this document are addressing very specific aspects. They should not be quoted as product-specific advice on a particular matter as this may require reflection of specific data available for this product. By no means should these positions be understood as being legally enforceable."* [4]

An interpretation sequentially of the various EMA documents indicates that, providing the 90% C.I. range of 90 – 111.11% was achieved for the ratios of the geometric means for AUC and Cmax, the bioequivalence of a new generic cyclosporin formulation to Neoral could be established solely under fasting conditions prior to 22 July, 2010 but would need to be compared under both fasting and fed conditions thereafter.

The **United States FDA** has avoided setting specific guidelines pertaining to the bioequivalence of Narrow Therapeutic Index Drug products as indicated by the following statement in its 2003 "Guidance for Industry" [5]: *Unless otherwise indicated by a specific guidance, this guidance recommends that the traditional BE limit of 80 to 125 percent for non-narrow therapeutic range drugs remain unchanged for the bioavailability measures (AUC and Cmax) of narrow therapeutic range drugs.* [5]

However, at FDA Advisory Committee Meetings held in April 2010 and July 2011, [6] substantial changes to the FDA's current position on NTI drugs were discussed. These included a novel scaling approach to determine the 90 % C.I. for each study based on the results of a replicated crossover design. Thus, participants would receive both products twice so as to access the variability of each. The 90% C.I. for the Test/Reference ratios of Cmax and AUC would then be determined (scaled) based on the variability in these key metrics observed for the reference product. If the reference product showed greater than 10 % variability, the C.I. would widen from a default range of 90 to 111% to a maximum of 80 to 125%. (Aside: Some stakeholders will likely regard the four-way replicated study design as unnecessary, if not excessive. Whether it becomes an actual bioequivalence requirement for NTIDs or rather an

option similar to that which befell the FDA's "individual bioequivalence" approach touted in the early 2000s, remains to be seen.)

Health Canada has had guidelines pertaining to NTIDs ("**Critical Dose Drugs**") in place since 2006. [7] The Canadian position concerning the determination of the bioequivalence of such drugs requires the 90% confidence intervals for the Test/Reference ratios for AUC and Cmax to be within 90 to 112%, and 80 to 125%, respectively, under both fasted and fed conditions. (Note the narrower 90% C.I. only applies to AUC not Cmax in Canada.)

Critical dose drugs are defined by Health Canada *"...as those drugs where comparatively small differences in dose or concentration lead to dose-and concentration-dependent, serious therapeutic failures and/or serious adverse drug reactions which may be persistent, irreversible, slowly reversible, or life threatening, which could result in inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, or death. Adverse reactions that require significant medical intervention to prevent one of these outcomes are also considered to be serious."* [7]

Cyclosporin – A Brief Review[1,2 (+ Deximune & Neoral SPCs)]

Cyclosporin is a highly lipophilic cyclic peptide compound of 11 amino acids which was initially isolated from a fungus found in Norwegian soil samples in 1969. Introduced as a unique immunosuppressant drug in 1978, it was first marketed by Sandoz Pharmaceuticals under the brand name Sandimmune (now a Novartis product) in 1982. Since this formulation is known to have poor and variable bioavailability especially in some patient populations, a new microemulsion formulation of cyclosporin, Neoral, was introduced by Sandoz (but now a Novartis product) in 1994.

Cyclosporin is used to prevent rejection of kidney, heart, liver, pancreas and lung transplants and to treat graft-versus-host reactions in patients receiving transplanted bone marrow. It is also used to treat severe cases of various diseases having an autoimmune component (e.g. psoriasis, rheumatoid arthritis).

Cyclosporin is extensively metabolized and secreted into the bile; less than six percent of a dose is found as metabolites or unchanged drug in the urine. In patients receiving organ transplants, the pharmacokinetics of cyclosporin may differ substantially between and within individual patients. Absorption and exposure appear to vary depending on such factors as the type of organ transplanted, the temporal stage (*de novo* versus later maintenance) following transplantation, concomitant medications, co-morbidities and the particular characteristics of the patient population (e.g. pediatric, diabetic, ethnicity). Underdosing of an immunosuppressive NTID such as cyclosporin could lead to graft rejection while overdosing may cause nephrotoxicity and/or an increased risk of infections and certain types of cancer.

It is assumed, however, that the use of different cyclosporin dosage formulations will lead to similar therapeutic outcomes providing they are pharmaceutically equivalent and bioequivalent. In other words, the disease state and other conditions are expected to similarly affect both generic (test) and originator (reference) products which have been deemed to be bioequivalent. (Where differences between cyclosporin products have been reported the formulations compared were not pharmaceutically equivalent.)

Are Deximune and Neoral Bioequivalent? A Review of Available Findings

In the context of the focus of this report it bears mentioning at the outset that Deximune is already marketed as a generic alternative to Neoral in the United Kingdom, Germany, the Netherlands, Denmark, Bosnia-Herzegovina and Israel indicating that these two products must be considered "bioequivalent" in those countries. (Deximune was officially launched in the UK in December, 2009.)

Pharmacokinetic study findings

To facilitate a review of the information submitted by Dexcel Pharma in respect to this manufacturer's claim that Deximune is bioequivalent to the Neoral product, the summary findings presented in that company's "Summary of Product Characteristics" (SPC) concerning AUCinf and Cmax (in units of ng x hour/ml and ng/ml, respectively) are partially reproduced herein below in Tables 1, 2 and 3. Each of the three studies summarized in these tables involved the oral administration of 200 mg

(as two 100 mg capsules) of both products in healthy male subjects. (Note: Herein the ratios and 90% C.I. intervals in these tables are presented as percentages rather than the ratio fraction values cited in the Dexcel SPC document for Deximune.)

In Table1, the results of a comparative bioavailability pharmacokinetics study conducted under fasting conditions in 24 subjects show that the mean Deximune (Test) to Neoral (Reference) ratios for the key parameters, AUCinf and Cmax, and their 90 % confidence intervals are well within the range of 80 to 125 % as prescribed internationally to establish the bioequivalence of most immediate release drug products. The results obtained also meet the more stringent 90% C.I. requirements for NTIDs set by Health Canada in 2006 (90 – 112 %) and those (90 – 111.11 %) more recently (22 July, 2010) introduced explicitly for cyclosporin by the EMA. Thus, these findings demonstrate that in the fasting state, Deximune is bioequivalent to the Neoral product since the extent of absorption (AUC) and peak blood concentrations (Cmax) are similar for both products.

Table 1 contains the essential bioequivalence findings presented in the 2007 paper by Avramoff *et al*[1] This paper also includes additional pharmacokinetics parameters such as AUCt (where t = 24 hours) which was shown to have mean values of 4,418 and 4,345 ng x hour/ml for Deximune and Neoral, respectively, and a Test/Reference 90% C.I. of 93 – 110 %. Tmax, the time to the peak blood cyclosporin concentration, was essentially the same for both products (mean = approximately 1.65 hours). Avramoff *et al* also noted the similarity in the "C2" values (blood cyclosporin concentration 2 hours after dosing) obtained with both products. (Although not a required measurement from a regulatory standpoint in respect to bioequivalence determination, some clinical investigations believe that C2 may correlate better than other single concentration measurements with the early incidence of rejection and graft outcome in kidney transplant patients.)

Table 1 Mean (n=24) values ± standard deviation for the parameters AUCinf and Cmax plus Test (Deximune) to Reference (Neoral) geometric mean ratios and 90% confidence intervals under fasting conditions.

Parameter	Deximune (Test) 2x100 mg	Neoral (Reference) 2x100 mg	Test / Reference Ratio & 90% CI
AUCinf ± SD (ng·h/ml)	4930 ± 1283	4866 ± 1107	101 % 93 – 109 %
Cmax ± SD (ng/ml)	1184 ± 215	1203 ± 231	99 % 90 – 109 %

The results of a study to determine the effects of food (high fat, high calorie meal) on the bioavailability of the two products in 39 subjects are summarized in Table 2. Although not included in this table, Tmax under fed conditions occurred on average at 1.68 and 1.75 hours for Deximune and Neoral, respectively.

Again the Test to Reference ratios and their 90 % C.I. findings for AUCinf and Cmax are within the 80 – 125% range as set for determining "uncomplicated drug" bioequivalence internationally. However, as seen in Table 2, the 90% C.I. for the mean Cmax ratio of 105 - 122 % extends beyond the 90 - 111.11% range recently established by the EMA. On the other hand, these findings would be in concurrence with the existing guidelines of the US FDA (where, as mentioned above, no special consideration is given to NTIDs) and those of Health Canada (where the wider 80 - 125% 90% C.I. applies to the Cmax ratio for drugs of this type). The results under fed conditions compiled in Table 2 would also have met the European bioequivalence guidelines prior to the changes explicitly stated for cyclosporin in the 2010 EMA "Q & A" position document[4].

Table 2 Mean (n=39) values ± standard deviation for the parameters AUCinf and Cmax plus the Test (Deximune) to Reference (Neoral) geometric mean ratios and 90% confidence intervals under fed conditions.

Parameter	Deximune (Test) 2x100 mg	Neoral (Reference) 2x100 mg	Test / Reference Ratio & 90% CI
AUCinf ± SD (ng·h/ml)	4323 ± 883	4098 ± 934	106 % 103 -110 %
Cmax ± SD (ng/ml)	1076 ± 294	958 ± 311	113 % 105 - 122 %

The results of a study in 16 subjects to determine the effects of food (high fat, high calorie meal) on the Deximune product solely are summarized below in Table 3. Although not shown in the table, Tmax occurred at 1.81 and 1.31 hours for Deximune under fed and fasting conditions, respectively. The results indicate that food ingestion lessens the extent of absorption (AUCinf) of cyclosporin from the Deximune product by approximately 7% and lowers the peak blood concentration (Cmax) by approximately 15%; these food effects were not statistically significant, however. No pharmacokinetic data concerning the effects of food solely on the Neoral product were provided for the present review although the 2010 EMA "Q&A" document[4] on pharmacokinetics indicates that this product may be similarly (or slightly more) affected by food intake. This document states that a high fat meal may decrease the cyclosporin AUC and Cmax values observed after Neoral administration by 15% and 26%, respectively[4].

Table 3 Mean (n=16) values ± standard deviation for the parameters AUCinf and Cmax plus the Fed to Fasting geometric mean ratios and 90% confidence intervals for Deximune only.

Parameter	**Deximune (Fed) 2x100 mg**	**Deximune (Fasting) 2x100 mg**	**Fed / Fasting Ratio & 90% CI**
AUCinf ± SD (ng·h/ml)	4992 ± 1237	5359 ± 1073	93 % 86 – 101 %
Cmax ± SD (ng/ml)	1109 ± 191	1308 ± 299	85 % 76 – 96 %

Clinical findings

Observations made during the clinical use of Deximune, specifically in patients receiving various organ transplants, were presented in the 2008 paper by Berger *et al*[2]. This paper describes findings obtained retrospectively in 174 patients from five hospital transplantation centres in Israel. Eleven patients received only Deximune, four received only Neoral, while 157 patients received both formulations in a dosing regimen in which Neoral was first administered and then later replaced with Deximune. (In the case of two patients, there was uncertainty as to which of the two products was actually administered.) The average dose administered was 110 mg/day.

The average duration of treatment was 31 months for Neoral and 11.5 months for Deximune[2].

Based on computed least square mean values adjusted for type of transplantation, dose and time after transplantation, blood concentrations of cyclosporin obtained with both products were not significantly different when compared on three occasions. The authors also report that the toxicity profiles and incidence of side effects were similar for both Deximune and Neoral[2].

A possible problem in interpreting aspects of this study[2] relates to the complicated analyses necessitated by its retrospective nature including the fact that toxicity profiles for Neoral were apparently sourced from an external database (Micromedex). Nevertheless, the authors concluded that: "*Since they have similar efficacy and toxicity profiles, these two products can be interchanged without the need for dosage adjustment.*"

Five letters in support of the use of Deximune in patients receiving various organ transplants were perused. These letters, four of which were addressed to "To Whom it May Concern", originated from four senior physicians associated with organ transplantation facilities at major Israeli medical centres and were dated November 21, 2006 (3) and July 5, 2009 (1) and July 14, 2009 (1). (One writer, Dr. Reuven Or, wrote two letters, one in 2006 and a more detailed one in 2009.) The writers indicated that in their experience treating hundreds of transplant patients, Deximune was safe and effective. Three writers also mentioned that required blood cyclosporin concentrations were attained when this product was administered under both fasting and fed conditions.

While these anecdotal "letters of support" are of little direct relevance to the quantitative aspects of determining bioequivalence *per se*, they at face value do suggest that Deximune and Neoral may be clinically interchangeable.

Comments and Opinion

Bioequivalence studies summary

Concerning the key issue of the bioequivalence (BE) of Deximune and Neoral, the relevant available findings (i.e. the paper by Avramoff *et al*[1] and the Deximune SPC data) considered in the context of the guidelines from three regulatory agencies are here summarized. Thus, these two products may be deemed bioequivalent on the basis of meeting guideline criteria set by:

i) the **EMA** prior to July 2010 (BE then required under only fasting conditions),
ii) **Health Canada** (current - BE, fasting & fed with 80-125% C.I. for Cmax), and
iii) the US **FDA** (current - BE, fasting & fed with 80-125% C.I. for Cmax & AUC).

The interchangeability of bioequivalent drug products

Regarding the ongoing controversies about whether generic cyclosporin and other NTID products are readily interchangeable with the innovator product in clinical practice, it must be noted that in some instances such misgivings and the associated confusion propagated amongst medical professionals and patients alike are deliberately fuelled by certain stakeholders within the pharmaceutical industry. A related common misunderstanding is that since the basic bioequivalence criteria are based on an 80 to 125 % C.I., then a difference in the bioavailability of the generic product of up to 45 % relative to the brand product may exist. In reality the difference between the products is only approximately 10% and actual investigations conducted by the FDA involving over 2000 bioequivalence studies conducted between 1996 and 2007 revealed a mean difference of approximately only 4% between the key bioavailability characteristics of generic and originator drug products[8, 9].

It should be noted in the clinical context that the pharmacokinetic and therapeutic variability of brand name drug products arising from subtle batch-to-batch differences has seldom been investigated *per se*. It should also be realized that innovator products must likewise undergo bioequivalence assessment (the same as for generic drugs) subsequent to any modifications in the composition of the drug formulation or changes in the manufacturing facility.

In the case of cyclosporin any attempts to reliably distinguish genuine differences between Neoral and a bioequivalent product such as Deximune in a transplant patient population are fraught with difficulty given the many inter- and intra-patient variables, as mentioned above, which bear on the pharmacokinetics and therapeutic efficacy of the drug. It would be wrong, perhaps, even naïve, to assume that the innovator product is likely to be more pharmacokinetically predictable in patients than a bioequivalent generic product. In this regard, a major Canadian study of kidney transplant patients receiving only Neoral showed that the pharmacokinetics of cyclosporin varied wildly especially during the first two weeks post-transplant[10].

The matter of "interchangeability" of bioequivalent drug products leads to consideration of the rather abstract concepts of "prescribability" and "switchability" – terms introduced by Anderson and Hauck in 1990[11]. Prescribability, merely refers to the choice between products for first-time administration of a drug. Bioequivalent drug products certainly have equal prescribability – either could be prescribed successfully initially with expected similar effects and clinical outcomes. Switchability, which is particularly relevant to NTIDs, requires consideration in instances where a patient, "titrated" on one formulation, is to be switched to another formulation of the same drug. Truly interchangeable drug products possess equivalent prescribability and switchability attributes. As discussed herein, unbiased investigations have concluded that bioequivalent drugs should be interchangeable.

Prescribing physicians who maintain doubts about the "equivalence" of a generic product could implement more rigorous clinical assessments of patients for a period following the switch from the innovator to the generic product. Given the importance of achieving appropriate blood cyclosporin concentrations in organ transplant patients, such an "err on the side of caution" approach would obviously include increasing the frequency of blood drug concentration monitoring. Pertinent here is this quote from a recent invited commentary in the Canadian Medical Association Journal: "*Decades of experience and numerous clinical studies suggest that patients and physicians can be confident in the bioequivalence of brand-name and generic drugs approved by Health Canada, the FDA or other similar regulatory authorities. In the rare circumstances where there is concern over interchangeability, such as for*

high-risk patients, it may be reasonable for physicians to take extra precautions, such as additional monitoring, when substitution occurs. In addition... policymakers and physicians should work together to address any remaining questions with well-controlled trials that have clear and clinically relevant end points, rather than by voicing unfounded skepticism or building legislative barriers to substitution." [12]

Considering the bioequivalence testing results (especially) reviewed at length herein, the stated clinical experience of established clinicians involved in organ transplantation and the undisputed fact of its marketed status and apparently unblemished clinical reputation in the UK and elsewhere, it is my considered opinion that there is sufficient evidence, to conclude that **Deximune is bioequivalent to Neoral.**

I trust that my observations and opinion will be genuinely useful in resolving the matter of contention which necessitated this review.

Respectfully submitted,

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Kemic Bioresearch

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this Board concludes that "Deximune is bioequivalent to Neoral" as, according to its appointed arbitrary professional consultant on subject matter, Peter W. Mullen, PhD, FCSFS, Consultant Pharmacologist/Toxicologist, Kemic Bioresearch Laboratories Limited, "Considering the bioequivalence testing results (especially) reviewed at length herein, the stated clinical experience of established clinicians involved in organ transplantation and the undisputed fact of its marketed status and apparently unblemished clinical reputation in the UK and elsewhere" he opines that that there is sufficient evidence to conclude that *Deximune* is bioequivalent to *Neoral*.

As a result, this Board concludes that *Deximune* products can be used interchangeably and, as a result, does not concur with the contracting authority that there was enough reason for the latter to disqualify the appellant company's tender.

In view of the above, this Board finds in favour of the appellant company and, apart from recommending the reintegration of the appellant company's bid in the re-evaluation process, this Board also recommends that the deposit paid by the same company for the appeal to be lodged should be reimbursed

Alfred R Triganza	Joseph Croker	Paul Mifsud
Chairman	Member	Member

14 November 2012