Case No. 7

CT 297/2002 – Supply of Leflunomide 10mg Tablets

The call for offers, with an estimated value of Lm 48,567, covering a period of three years was published in the Government Gazette on the 4th October, 2002 following a request received by the Director of Contracts from the Government Pharmaceutical Services (GSP). .

Two offers were received with the cheapest offer being the one submitted by Messrs. Drugsales Limited for a total average price of Lm 3,604.20. The other offer was the one submitted by Messrs. Charles de Giorgio Ltd.

Following relevant recommendations made by the Adjudication Panel, the Contracts Committee awarded the tender to Messrs. Drugsales Limited.

On the 12th February, 2003, soon after the publication of the award, Messrs. Charles de Giorgio Ltd filed an objection with the Director of Contracts.

The Public Contracts Appeals Board met on 29th October, 2003 to discuss the objection raised by Aventis Pharma (Charles de Giorgio Ltd) against the decision to award the said tender to Drugsales Limited.

Mr. A. Triganza chaired proceedings accompanied by Messrs. A. Pavia and E. Muscat who formed the other Board members.

During the hearing

a. the Health Department was represented by Ms. Miriam Dowling (Chairperson of the adjudication board), Ms. Amanda Camilleri (Pharmacist) and Mr. David Cordina (Senior Pharmacy Technician).

b. Mr. David Stellini and Mr. Vincent Briffa spoke on behalf of Messrs. Charles Degiorgio, exclusive local agents for the *Arava* brand.

c. Mr. Alfred Gera de Petri and Mr. Philip Moran represented Messrs. Drugsales Limited, local agents for *Cipla Limited*.

d. other witnesses included Mr Joseph V. Spiteri (DG Contracts), Ms Anna Debattista (Director GPS) and Profs. Carmel Mallia (Chairman, Drugs and Therapeutic Committee)

Mr Vincent Briffa, initiated proceedings by elaborating on the objections raised in the Company's letter of objection dated 17.02.2003. The Aventis Pharma (Charles de Giorgio Ltd.) representative stated that Leflunomide was a new Disease Modifying Anti-Rheumatic Drug (DMARDs) that could have serious side effects, including liver toxicity, which could have fatal consequences. He said that Aventis Pharma recommended a washout programme to eliminate the active compound quickly. Furthermore he said that Aventis was the originator of this product and that they provided Rheumatologists with guidelines for liver function monitoring. He said that as most cases of side effects occur within the first 6 months of treatment with

leflunomide, patients were tested during this period. He stated that the body took 2 years to eliminate the active compound while the washout procedure would take 2 weeks. Washout procedures had to be performed when serious undesirable effects occur (allergic reactions) and in case of desired or unintended pregnancy.

He said that their medical representatives regularly attended refresher courses at Aventis and participated in international medical conferences to keep up to date with latest developments in rheumatology. Avantis Pharma provided blood sample collection equipment, collection of same blood samples from Saint Luke's Hospital and transportation by courier to a specialised laboratory in the US for immediate analysis. He said that Aventis did not simply provide the product but also took into account the 'after sales service'. They took precautions to ensure that the toxicity is lowered to acceptable levels. He said that other companies did not manufacture the starting (loading dose) of leflunomide, which was taken before the actual treatment. This was required to ensure the maximum benefit from treatment.

He said that GPS accepted the sample of the Indian leflunomide without testing for bio equivalence, which was extremely important because they determined whether the generic version is bio equivalent to the original drug – that is , whether the two drugs had virtually the same effect in humans. Generic drugs could have ingredients that were different from those of the original drug, which sometimes could have a negative effect on patients. These bio equivalence tests were carried out to prove that the generic product was as good as the original drug (in this case Cipla and Arava respectively).

Mr. Briffa stated that their product (Arava) was approved in the USA and all of Europe. In spite of all side effects, if guideline were strictly followed, benefits would outweigh the risks. The climatic zone where the product was manufactured and distributed was significant because the dosage and the shelf life of the product depended thereon. He said that another factor that had to be taken into consideration was the *narrow therapeutic index* because even the slight variation could have devastating effects since dosage should neither be excessive nor below the required level/s.

It was also argued that Aventis would not shoulder responsibility for supplying 100mg dose if the maintenance dose of 10mg were to be supplied by another company. The reason given was that, should the patient show any side effects, it could not be ascertained that this would be due to the starting dose or the maintenance dose.

Mr. Briffa concluded by claiming that, apart from the product, Aventis offered a wash-out programme, updated the Health officials with the latest information and developments and followed them while treating patients so that any problems that might emerge would be referred to the company to solve them. He emphasised that with the product they were offering a service.

Mr Alfred Gera de Petri proceeded by giving his views on the matter. At the beginning of his intervention he produced samples of a Starter Pack of leflunomide 100mg and of 10mg and 20mg maintenance dose to prove that Cipla Ltd, contrary to what was stated by Mr Vincent Briffa, produced all kinds of products. When the latter examined these samples, he accepted the samples produced by Drugsales'

representative. Hence, it was agreed that the statements made at point no 6 in Aventis' motivated letter of objection were unfounded.

Although, specification did not require bio equivalence testing of the product, Mr. Gera de Petri exhibited a report thereon. He said that Government only wanted to purchase 10mg dose and declared that they were compliant with specifications.

With regard to Cipla Ltd, he said that it was a serious Indian Company that employed about 60,000 people and exported its products to many different countries. This parent company was supplying Government with 33 different products and they never had any complaints.

When Mr. Gera de Petri mentioned the price factor, Mr David Stellini said that the difference in price between Aventis and Drugsales was due to the fact that Arava produced the original drug whilst Cipla Ltd produced the generic ones. Mr. Stellini said that leflunomide was a specific product which could be life threatening and so there were people's lives at risk. They had to be extremely cautious about how to use this product. He said that bio equivalence studies were indispensable and that Arava (leflunomide) was centrally registered in the EU while Cipla Ltd's product was not.

Ms Anna Debattista testified that the Director General (Health) had approved the tender for the Leflunomide (10mg tablets) on 6 August 2001. She confirmed that the product offered by Drugsales complied with specifications and also the offer complied with the conditions as per declaration and receipt of certificate submitted by the Qualified Person (QP). This certificate issued by MRU confirmed that the product was up to standard.

She said that before medicine was introduced in hospital a lot of research was carried out (particularly by the Drug and Therapeutic Committee), then specifications were drafted and eventually recommended to the Director General and finally tenders were issued accordingly.

When asked about the washout programme, Ms. Debattista confirmed that they would consider including it in future tender conditions. She stated that the difference in price between the originator and the generic drugs was always substantial. She added that some years ago the Health Department took the stand and decided not to make specific requests for bio equivalence studies. However, she declared that tests were carried out when something prompted them to do so. She said that the specification issued for the supply of leflunomide 10mg tablets, which were approved by the Health Department, were very generic.

During his intervention, Mr. Spiteri (DG Contracts) stated that when specialists required certain medicine products, tenders were issued with trade/brand name. In such instances, contracts were awarded to those who offered the best price. He added that if specialists would notice side effects they stopped the importation of such product.

The last witness to give his evidence was Professor Mallia who is the Chairman of the Drugs and Therapeutic Committee.

He gave detailed information about the procedure used before a new drug was introduced locally. He said that before drugs became available to the public and relative licences issued, these drugs would be passed through various trials over a number of years. However, he added that medicine would immediately be withdrawn if certain side effects that were not recognised in trials emerged when used on a wider scale. Here he emphasised the importance of what was known as the *'post marketing surveillance'*.

He declared that he was not involved in the drawing up of the specifications of this tender. He stated that the leflunomide was a new drug that was still being researched. The Drug and Therapeutic Committee evaluated and recommended the introduction of the leflunomide on the basis of an assessment and the results that were being obtained by the originators product Arava.

Professor Mallia said that, in principle, they found no objection to use generic vice originator product provided that it was as safe and effective as the originator product. The only concern he had, as a user, about this generic drug was that there was a certain "fear of the unknown" because this particular brand of drug was so new, that there was lack of documented detailed information, for example,

- which countries were using it
- the number of patients that were using it,
- the results that were being obtained,
- the side effects emanating therefrom,
- the extent of bio equivalence studies

and so forth.

Therefore, in the absence of such information, the quality of the drug would be known when professional end users would eventually get hands-on experience using this drug. For this reason he was feeling considerably uncomfortable to use this type of medicine.

When the Chairman asked whether there were any further comments, Mr. Gera de Petri intervened by stating that he was prepared to provide Professor Mallia with all the required information about the product. Messrs. Drugsales' representative declared that if Professor Mallia's doubts were not resolved and all questions answered to his satisfaction, he would withdraw his offer. Mr David Stellini objected as he was of the opinion that the matter should be clarified during the public hearing.

After deliberating about the procedure that had to be followed, this Board ruled that, in the prevailing circumstances, it agreed with Mr. Gera De Petri's proposal.

As a consequence, Professor Mallia, in his capacity of Chairman of the Drugs and Therapeutic Committee, agreed to hold a meeting with Mr. Gera de Petri within 15 days so that by the 14 November 2003, he would be in a position to inform the DG Contracts whether, following the said meeting with Mr. Gera de Petri, he still has reservations about the usage of the drug being offered by Cipla.

The hearing was adjourned pending the outcome of the meeting between Professor Mallia and Mr. Gera de Petri.

This Board was subsequently informed that the said meeting took place and as a direct result Professor Mallia and Mr. Gera de Petri wrote the following declaration dated 8th November 2003:

Quote:

"We, the undersigned, met on Friday 7th November, to discuss aspects relating to the drug leflunomide, as suggested by the Public Contracts Appeals Board on Wednesday 29th October. We came to the following conclusions.

As explained by Prof. Mallia during the public hearing, leflunomide is still a new drug and certain aspects of the drug are still under review. In this connection it was noted that on 22nd October, Aventis, the manufacturer of the originator product (Arava), published changes that were being recommended in monitoring patients using this drug. Prof. Mallia felt that clinicians who would be using this drug still had to get a hands-on experience with it. It was imperative that they did not have any doubt that results they would be getting with the drug, both in terms of efficacy and side effects, were due to the drug itself and not due to a particular preparation. This was even more important because the side effect profile of leflunomide included potential harmful effects on the liver – which in some instances, resulted in fatalities. It would be easier to do this if clinicians could compare their results with published studies, which are based on the originator product, Arava. Prof. Mallia made it clear that he did not want to cast any doubts on the Cipla brand of leflunomide: his concern was that since the drug was so new, there was a certain "fear of the unknown". He felt that it was quite possible that in future, with more widespread use of generic forms of leflunomide, including the Cipla brand, these doubts would be resolved and all questions answered satisfactorily.

Mr. Gera de Petri fully understood Prof. Mallia's concerns about using the drug, and under the circumstances he decided to withdraw the Cipla brand of leflunomide from the tender. He stressed, however, that this decision should not be allowed to cast any doubt on the efficacy and safety of Cipla products. Professor Mallia agreed and said that the case of leflunomide was different for the reasons explained above.

Signed	Signed
Prof. C. Mallia Chairperson, Drugs and Therapeutics Committee Department of Health	Mr. A Gera de Petri Managing Director Drugsales Ltd."

Unquote

The Public Contracts Appeals Board, taking full cognisance of the said declaration, has decided to award the tender to Messrs. Charles de Giorgio Ltd. subject to the client being satisfied that their offer meets all the conditions as stipulated in the tender documents.

Alfred R. Triganza	**Anthony Pavia**	**Edwin Muscat**
Chairman	Member	Member

Date: *05.12.2003*