**Title:** ZINC MONOGLYCEROLATE COMPLEX FOR ANTI-REJECTION TREATMENT OF THE HUMAN OR ANIMAL BODY

It is found that Zinc Monoglycerolate when used in combination with Cyclosporine enhances the capacity of lower doses of Cyclosporine to act to alleviate acute rejection reactions in the rat heterotopic heart model. It is proposed to use Zinc Monoglycerolate on its own, or in combination with other anti-rejection drugs or measures, in the prevention of initial rejection and in the maintenance of transplanted organs and tissues in humans and animals.
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ZINC MONOGLYCEROLATE COMPLEX FOR ANTI-REJECTION TREATMENT OF THE HUMAN OR ANIMAL BODY

FIELD OF THE INVENTION

This invention relates to a Zinc Monoglycerolate complex when used for the anti-rejection treatment of the human or animal body.

BACKGROUND OF THE INVENTION

When failure of an organ occurs in an individual, it is desirable to surgically transplant a replacement organ from another individual to act in place of the failed organ.

Difficulties arise when a transplanted organ does not have an identical phenotype to the organ being replaced, and it is recognised by the recipient as foreign, leading to one of several forms of immune rejection. Generally transplant donors are matched as much as possible with the recipient, but unless an identical twin acts as a donor then the immune system of the recipient will mount a rejection response or a graft versus host reaction may result.

The rejection may be almost immediate where the recipient has been sensitized to the donor organ and a hyperacute reaction takes place within a few hours; sometimes the organ does not survive the duration of the transplant operation. Alternatively an acute rejection reaction takes place where an immune response is mounted, which usually takes the form of an antibody response and might take between 5 and 10 days. A third type of rejection is known as chronic rejection and takes the form of a gradual deterioration of the transplanted organ. Chronic rejection is thought to be associated with a humoral immune response, a different response than that of the acute reactions, and is quite uncommon.

To facilitate survival of the transplant, immunosuppressive drugs are administered to minimize the effects of the rejection reaction, initially in high dose to establish the transplant, and then in a much smaller maintenance dose whilst the transplant is resident in the recipient. From time to time during maintenance, an acute rejection reaction might occur and larger doses may be needed to overcome the rejection.
Several drugs are used for immunosuppressive therapy, but they are relatively nonspecific. Their action is not directed at the cause of the disease, and they can therefore inhibit normal immune and inflammatory responses as well. Agents such as Mercaptopurine, Azathioprine, Cyclophosphamide, and Methotrexate are cytotoxins and they interfere with cell replication and metabolism in various ways causing disruption of normal cell function. Interference with replication or rapidly dividing cells results in several undesirable side effects.

Azathioprine was introduced in the early 1960's for maintenance immunosuppression in clinical renal transplantation. Azathioprine interferes with nucleic acid synthesis in all replicating cells. It first affects the most actively dividing cells, which are the lymphocytes, to temporarily prevent rejection of the grant. It also inhibits replication of cells in bone marrow and in the gastrointestinal tract.

Adrenocorticosteroids, such as Prednisone, have anti-inflammatory as well as immunosuppressive actions. Prednisone was used in high does therapy shortly after the introduction of Azathioprine. Prednisone, which promotes lysis of lymphocytes, was then used in lower doses in combination with Azathioprine, as it was found that the combination provided even greater immune suppression. Unfortunately the use of the combination did not prevent the side effects or the increased incidence of secondary infection which results from the use of these agents.

Cyclosporine, or Cyclosporin A as it is commonly known, is a unique immunosuppressant. It is a metabolite of a solid fungus which has proved to be superior to Azathioprine as an immunosuppressant in organ transplantation. It is more selective than Azathioprine because it primarily affects lymphoid cells and does not cause bone-marrow suppression. In addition, it is not directly cytotoxic. A major and very serious problem with Cyclosporine is its nephrotoxicity, and this occurs at almost the same dose as that required to achieve adequate immunosuppression. There is therefore a relatively narrow range of doses in which the medication will both prevent rejection and be tolerated by the recipient. A further disadvantage with Cyclosporine is that it is an expensive medicine.
Immunosuppressive treatments are sometimes used and these include administration of antibodies against T-cells, the monoclonal antibody version of which is extremely effective. However, it is so effective that it compromises the host to an extent that very minor infections can become life threatening.

Radiation therapy of either the transplant, or the lymphatic system to immuno-suppress the individual, or other drugs such as Actinomycin D, (Dactinomycin), and Cyclophosphamide can also be used.

It is an object of this invention to minimize the problems associated with existing treatments for alleviating rejection reactions, or at least to provide the public with a useful choice.

It has been now been found by the applicant that Zinc Monoglycerolate can also play a role in the inhibition of transplant rejection. This is significant because of the non-toxic nature of Zinc Monoglycerolate.

Zinc Monoglycerolate is produced by mixing zinc oxide or zinc hydroxide together with glycerol at elevated temperatures. Zinc monoglycerate is also known as zinc glycerolate, or more correctly zinc(1,2,3-propanetriolato(2-)-O₁,O₂), homopolymer, stereoisomer. Zinc Monoglycerolate is a white lubricous powder, the latter property being imparted but its polymeric two-dimensional structure. The compound has very little taste. The formula for Zinc Monoglycerolate is (C₃H₆O₅Zn)ₓ.

Zinc Monoglycerolate complexes were first described in a paper in the Australian Journal of Chemistry volume 23, 1970, page 1963 and in that paper the method of forming these compounds and some of their physical properties are given.

Zinc Monoglycerolate is described for instance in P.C.T. International Publication WO82/01867 in the names of Taylor and Brock and is mentioned as having a number of prophylactic and therapeutic uses. Thus Zinc Monoglycerolate is mentioned as being effective in the treatment and prevention of ammoniacal dermatitis (nappy rash), in the treatment of pruritis, especially in people confined to bed or immobility, for the alleviation of psoriasis, for the treatment and prevention of fungal or bacteriological decomposition of tissue and the resultant odours arising in such complaints.
as tinea pedis and for the prevention of industrial dermatitis arising from particular environments.

Reference is also made to P.C.T International application WO87/01281 in the name of the present applicant, which refers to the use of the Zinc Monoglycerolate as a per oral treatment for gastric bleeding or ulceration or in a topical application as a depot for the slow release of the compound and refers to diffusion through the skin for the treatment of arthritis and zinc insufficiency and includes psoriasis, and refers also to tests against various organisms including fungi.

Previous work has shown that Zinc Monoglycerolate has a very definite anti-inflammatory action and that this anti-inflammatory action in the rat footpad model is rather similar to that obtained by Cyclosporine (Rainsford et al, Agents and Action 1990; 31:47-58).

SUMMARY OF THE INVENTION
The invention results from the finding that Zinc Monoglycerolate can play a role in the inhibition of transplant rejection.

In one form the invention resides in a method of treatment of a human or animal body comprising the step of administering a pharmaceutically acceptable amount of Zinc Monoglycerolate by oral, parenteral, or topical administration for the prevention of organ or tissue rejection.

Zinc Monoglycerolate may be used either separately or in combination with other anti-rejection measures. Zinc Monoglycerolate is relatively non-toxic, and it is anticipated that the side effects caused by the anti-rejection drugs can be minimised when Zinc Monoglycerolate is used in combination with them, because the dose of the anti-rejection drug can be decreased and the side effects accordingly minimised. This is certainly applicable with the use of Cyclosporine where the narrow choice of ranges of dose is quite limiting.

It is suggested that the activity of Zinc Monoglycerolate by itself may not be potent enough to act to regress acute rejections, however it may be sufficiently active by itself to act as a maintenance program.
For a better understanding of the invention the invention will now be described by reference to a number of examples.

DETAILED DESCRIPTION OF THE INVENTION

EXAMPLE 1

The efficacy of Zinc Monoglycerolate as an anti-rejection agent has been tested in the heterotopic heart model in rats. In this model the heart is transplanted onto the abdominal vessels and begins to beat immediately after revascularisation. The heartbeat can be palpated when the animal recovers from anaesthesia by simply feeling through the abdominal wall. Rejection results in cessation of heartbeat, which is recorded on the day on which it occurs. This simple method does not require the withdrawal of blood or the use of complicated tests and is a most helpful method of evaluating whether a drug does or does not have significant immunosuppressive qualities.

When using the PVG rat as the donor and the Wistar rat as the recipient, the additional advantages are that the strains are extremely well known and background data on the model is easily available from the literature as a comparison. Unprotected hearts in this model should stop in between six and eight days.

The Zinc Monoglycerolate was made up as a 0.02% suspension in water with Tween 20 using sodium chloride 0.15 mole / Litre as the diluent, and injected within 20 minutes of it being suspended. Cyclosporin A was given by gavage.

Materials and Methods

Seven (7) groups were used, consisting of at least six (6) animals in each group. Donor animals were PVG rats of either sex, approximately 250 gm. Recipients were Wistar rats of either sex weighing 300 gm.

Group A - after transplantation the recipient rats did not receive any immunosuppressive drugs.
Group B - the recipient rats received 4 mg/kg body weight of Cyclosporin A by gavage daily.

Group C - rats received 2 mg/kg of Cyclosporin A daily by gavage.

Group D - rats received 1 mg/kg of Cyclosporin A daily by gavage.

Group E - rats received Zinc Monoglycerolate 62.5 mg/kg given by subcutaneous injection once daily.

Group F - rats received 125 mg/kg Zinc Monoglycerolate given by subcutaneous injection once daily.

Group G - rats received Zinc Monoglycerolate 62.5 mg/kg body weight given by subcutaneous injection once daily, plus 2 mg/kg body weight of Cyclosporin A, given by gavage also once daily.

Donor Procedure
All animals undergoing this procedure or the recipient procedure received a subcutaneous injection premedication consisting of Thelaminil (Fentanyl), Droperidol 0.1 to 0.15 ml (contain Fentanyl 0.05 mg/ml and Droperidol 0.25 mg/ml) together with 0.15 mg of Diazepam (5 mg/ml).

Approximately 30 minutes after premedication, gaseous anaesthesia by face mask was given. This consisted of Nitrous Oxide, 500 ml/min flow, Halothane 0.5 - 2.0% and Oxygen 500 ml/min.

After induction, the animal was placed in a supine position. When full, deep anaesthesia had been attained the animal was shaved and the chest swabbed with iodine. Thoraxotomy was performed via a medial sternotomy. In quick succession the superior and inferior vena cava were transected, followed by the Aorta just proximal to the right innominate artery and the pulmonary artery proximal to its bifurcation. The pulmonary veins were then cut and the heart placed in saline slush at 4°C and covered with moist gauze. The procedure took approximately 10 minutes. This is a non-recovery procedure and the animal dies, immediately after removal of the heat, by exsanguination.
Recipient Procedure
Premedication and anaesthesia were carried out as for the donor operation. The anaesthetised animal was placed in the supine position and the abdomen shaved. The midline laparotomy was performed. A retractor was inserted and the viscera deflected to the left and covered with a moist swab. The abdominal aorta and vena cava were dissected from the renal vessels to the bifurcation. Bulldog clips were placed on the proximal and distal ends of the dissected vessels and the ascending aorta of the donor anastomosed end to side to the recipient's abdominal aorta, followed by anastomosis of the donor pulmonary artery, end to side, to the vena cava. 10/0 silk was used. The anastomotic time varied from 20 to 35 minutes. After placing swabs around the anastomosis the bulldog clips were removed and the donor heart began to beat. The abdominal cavity was irrigated with warm saline. This technique required the use of magnifying loops, 1 to 2 ml of saline being given as required into the abdominal vena cava via a 27 gauge needle. The abdomen was sutured with a 5-0 nylon and skin with subcutaneous 4-0 nylon. Injection of 0.5 ml of 0.25% Marcaine into the abdominal incision wound prior to closure was given to ensure excellent post-operative analgesia for up to six hours.

The animal was returned to a single cage and covered with a swab.

Return to full consciousness usually occurred within 60 minutes and ambulation within 3 hours. Food and water was provided and usually taken within 12 hours.

Following the absence of a heartbeat, the animals was sacrificed. Any animals which showed clinical evidence of significant blood loss or evidence of any disturbance to the blood supply to the limbs were also sacrificed.
Results

Table 1. Survival of rats (days) following treatments with Cyclosporin A (CYA) and Zinc Monoglycerolate (ZMG) in varying doses.

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<tr>
<th>Control</th>
<th>CYA 1 mg</th>
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<th>CYA 4 mg</th>
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<tr>
<td>Mean 6.4</td>
<td>8.3</td>
<td>7.3</td>
<td>19.0</td>
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<td>1.0</td>
<td>10.8</td>
<td>2.1</td>
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p rel to Control 0.0011 0.084 0.013 0.15 0.82 0.00091
p rel to CYA 1mg 0.065 0.026 0.018 0.0086
p rel to CYA 2mg 0.065 0.026 0.018 0.0086
p rel to CYA 4mg 0.026 0.018 0.0086 0.0025
r rel to ZMG 62.5mg 0.2 0.0058
p rel to ZMG 125 mg 0.13 0.0013

Results are shown in Table I. Student's t-test was used to make statistical comparisons, and the level of significance is given below the table. It is clear that the control experiments indicate that when transplantation is performed between these two well defined strains of rat, without immunosuppression, the heart arrest occurred at a mean of 6.4 days, with the standard deviation of 0.9. The same narrow deviation is also seen in the groups receiving 1 mg of Cyclosporin A per kg/body weight or 2 mg of Cyclosporin A per kg body weight, or 62.5 mg of Zinc Monoglycerolate per kg body weight, or 125 mg of Zinc Monoglycerolate per kg body weight. Thus these substances given in that dosage have no effect on the rejection rate of this model. It was also clear that when Cyclosporin A is given at 4 mg/kg body weight, a significant prolongation to 19 days with a rather wide standard deviation of 10.8 days was obtained. The combination of two ineffective doses, one of Cyclosporin A at 2 mg/kg body weight together with
Zinc Monoglycerolate at 62.5 mg/kg body weight, gave a modest prolongation time of 12.2 days with a standard deviation of 3.2 days. This is clearly in excess of the controls with a p value of less than 0.001. Thus there is less than 0.1% of this result being due to chance.

Discussion
The results of the experiment are very clear and show that Zinc Monoglycerolate has a definite, albeit moderate, immunosuppressive effect. When given on its own at 62.5 mg/kg body weight it has no immunosuppressive effect. When Cyclosporin A was given at 2mg/kg body weight, it, too, had no statistical effect when compared to the controls or to the Zinc Monoglycerolate. However, when the two substances were combined there was a clear statistical prolongation of the number of days for which the hetetotropic heart was tolerated by the recipient, the values being significant to a p value of less than 0.001. The prolongation in survival of the group which received the combined therapy, that is 2 mg Cyclosporin A and 62.5 mg of Zinc Monoglycerolate per kg body weight, may be by reason of a number of explanations.

It is reasonable to assume that 2 mg of Cyclosporin A per kg body weight was just below the borderline of the immunosuppressive effect of Cyclosporin A. This is indicated by the clear cut prolongation obtained when the dose is increased to 4 mg/kg body weight. 125 mg of Zinc Monoglycerolate per kg body weight is also not adequate to give a direct immunosuppressive effect although a greater dose of Zinc Monoglycerolate might reveal an immunosuppressive effect of Zinc Monoglycerolate. Thus a first explanation for the result is that Zinc Monoglycerolate has an immunosuppressive effect which is additive or even synergistic with the effect of Cyclosporin A.

A second explanation is that Zinc Monoglycerolate is acting by means of its known anti-inflammatory properties. The mode of action derives from the concomitant inflammatory results of an acute rejection episode being diminished by Zinc Monoglycerolate and hence the heart is able to continue beating longer than the control period. A non-specific anti-inflammatory action is used in the treatment of acute rejection episodes, when Methyl Prednisolone is given in high dose by injection.
Alternatively Zinc Monoglycerolate could be altering the kinetics of Cyclosporine absorption, disposition and elimination.

EXAMPLE 2

5 Should the results obtained in rats be emulated in humans, then lower doses of Cyclosporine treatment may be achieved in combination with Zinc Monoglycerolate, for acute rejection reactions, or where Cyclosporine is used in a maintenance schedule.

10 The method of administering treatments for humans will be varied to suit acceptable standards and dose levels, and as is presently the case these doses will be tailored to suit the recipient.

The present example is a postulated procedure for use in humans where an admixture of Cyclosporine and Zinc Monoglycerolate is used, as part of an anti-rejection therapy.

The dose to be used will vary and will depend upon the individual concerned. A clinical appraisal of the patient may change the anti-rejection drug being administered where adverse effects become apparent.

The usual oral dose for human patients of Cyclosporine is 10 to 15mg/kg daily starting a few hours before transplantation and continuing for 1 to 2 weeks; dosage is then gradually reduced to a maintenance level of 5 to 10 mg/kg daily. The effect of the treatment will be monitored as is presently the practice to determine where changes are required.

For oral use, Cyclosporine is dissolved in olive oil based solution, and for intravenous use in a polyoxyethylated castor oil and alcohol solution. For patients unable to tolerate oral medication, Cyclosporine may be given by intravenous infusion over 4 to 12 hours, at approximately one third the oral dose, for example 5mg/kg body weight daily, initially or this may be administered during surgery as a single dose injection.

35 Protocols for the use of Cyclosporine are well known, and several early studies exemplify protocols used. Examples can be found in the following publications; European Multicentre Trial Group, The Lancet October 29, 1983, pp986; The Canadian Multicentre Transplant Study Group, The New

5 It is anticipated that the general range of Cyclosporine that is to be used may be reduced perhaps by as much as half of the values used above where it is used in conjunction with Zinc Monoglycerolate.

10 The dose of Zinc Monoglycerolate to be administered will need to be determined empirically, however an oral dose in the range of 50 to 500mg/kg body weight daily is suggested as an appropriate starting point for dose-ranging studies, where Zinc monoglycerolate is used in conjunction with Cyclosporine for immediate post operative treatment. This dose is understood to decrease where Zinc Monoglycerolate is used as a maintenance dose.

This dose is likely to be dependant on the mode by which it is delivered and it is anticipated where intravenous administration is used then a decrease in the dose given will be possible. Where perhaps better means of solubilizing Zinc monoglycerolate is achieved, lower doses may also be achieved.

Where rejections episode occur pulses of any usually used anti-rejection drug may be administered, which pulse may be an effective dose of Methyl Prednisolone

FURTHER EXAMPLES
It has been shown that Zinc Monoglycerolate has a synergistic effect in combination with Cyclosporine in the rat models described above, however, it is also to be understood that Zinc Monoglycerolate may have a synergistic effect when used together with other immunosuppressive steroid drugs such as Prednisone, Azathioprine and Methyl Prednisolone.

Larger doses of Zinc Monoglycerolate than those used in the investigation above may show an immunosuppressive effect on its own in acute reaction, or perhaps might simply act to reduce the chance of a rejection action
occurring. The activity may be ideally suited to use for the maintenance of a transplant.

It is also to be understood that the activity of Zinc Monoglycerolate may supplement the activity of other anti-rejection treatments such as treatment with anti-immune anti-sera such as the OT3 or Orthoclone anti-sera which is a monoclonal antibody sometimes used during acute rejection.

Zinc Monoglycerolate may also be used in combination with other drugs such as Cyclophosphamide or Actinomycin D as a maintenance treatment in the first instance or as a treatment against chronic rejection in the latter case.

Depending upon its mode of action with rejection Zinc Monoglycerolate may also be used as an immunosuppressant for purposes other than as an anti-rejection role, for example for experimental purposes.

Application of Zinc Monoglycerolate can be topical and can be applied as a dry powder or as a suspension in a suitable liquid medium and can be applied topically by an applicator (e.g. by transdermal delivery patch) where internal mobilisation in the blood is required for transport to other internal remote areas. Alternatively it can be applied by parenteral means such as by injection in a suitable suspension or solution. Oral intake in the form of a tablet, capsule or lozenge may also be suitable for some applications of the invention.
CLAIMS

1. A method of treating a human or animal body comprising the step of administering a pharmaceutically acceptable amount of Zinc Monoglycerolate by oral, parenteral or topical administration for the prevention of organ or tissue rejection.

2. A method as in claim one where the treatment additionally includes the application of a second anti-rejection treatment to the human or animal.

3. A method as in claim 2 wherein the second anti-rejection treatment includes the administration of an immunosuppressive drug.

4. A method as in claim 3 wherein the drug is selected from the group comprising Prednisolone, Azathoprine, Cyclosporine, or Methyl Prednisolone.

5. A method as in claim 4 wherein the drug is Cyclosporine.

6. A method as in claim 5, wherein Cyclosporine is delivered at a dose lower than is effective by itself.

7. A method as in claim 5 wherein Cyclosporine is delivered in a human at a dose of less than about 10mg/kg of body weight of the individual being treated.

8. A method as in claim 2, wherein the second treatment is irradiation therapy of parts of the immune system of the human or animal.

9. A method as in claim 2 wherein the second treatment is the administration of anti-serum active against one part of the immune system of the human or animal.

10. A method as in claim 9 wherein the antiserum is a monoclonal antibody.

11. A method as in claim 1 wherein the application is to prevent initial rejection of the organ or tissue.
12. A method as in claim 1 wherein the application is as a maintenance dose.

13. A method as in claim one wherein the application is to counter an acute rejection reaction.

14. A method as in claim one wherein the application is to prevent rejection during transplant operations.

15. An immunosuppressive composition having anti-rejection properties comprising an effective dose of Zinc Monoglycerolate.

16. The composition of claim 15 including an otherwise ineffective dose of another immunosuppressive drug.

17. The composition as in claim 16 wherein the drug is selected from the group comprising Prednisolone, Azathoprine, Cyclosporine, or Methyl Prednisolone.

18. The composition as in claim 17 wherein the drug is Cyclosporine.
A. CLASSIFICATION OF SUBJECT MATTER  
Int. Cl.5 A61K 031/045  
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED  
Minimum documentation searched (classification system followed by classification symbols) 
IPC5: A61K  
CHEMICAL ABSTRACTS  

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base, and where practicable, search terms used) 
DERWENT FILE WPAT; A61K/1C, ZINC(1)GLYCER:, ZINC(1) MONOGLYCER; CYCLOSPOR; PREDNISOL:  
AZATHOPRIN:  
FILE CASM

C. DOCUMENTS CONSIDERED TO BE RELEVANT  

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<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to Claim No.</th>
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Further documents are listed in the continuation of Box C.  
See patent family annex.

* Special categories of cited documents:  
"A" document defining the general state of the art which is not considered to be of particular relevance  
"E" earlier document but published on or after the international filing date  
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"O" document referring to an oral disclosure, use, exhibition or other means  
"P" document published prior to the international filing date but later than the priority date claimed  
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention  
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone  
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art  
"&" document member of the same patent family

Date of the actual completion of the international search: 23 August 1994 (23.08.94)  
Date of mailing of the international search report: 15 Sept 1994 (15.09.94)  
Name and mailing address of the ISA/AU  
AUSTRALIAN INDUSTRIAL PROPERTY ORGANISATION  
PO BOX 200  
WODEN ACT 2606  
AUSTRALIA  
Facsimile No. 06 2853929  
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<td>A</td>
<td>WO, 82/01867 (TAYLOR et al) 10 June 1982 (10.06.82)</td>
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This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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END OF ANNEX