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66793 U.S. PTO  
04/01/98

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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT  
under 37 C.F.R. §1.53(c).

Atty. Docket: HALLGREN=1

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<input type="checkbox"/> Additional inventors are being named on separately numbered sheets attached hereto.			
TITLE OF THE INVENTION (280 characters max)			
NEW THERAPY IN GLOMERULONEPHRITIS			
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ENCLOSED APPLICATION PARTS (check all that apply)			
<input checked="" type="checkbox"/> Specification Number of Pages <u>13</u> <input type="checkbox"/> Small Entity Statement			
<input type="checkbox"/> Drawing(s) Number of Sheets <u>    </u> <input type="checkbox"/> Other (specify) _____			
METHOD OF PAYMENT (check one)			
<input checked="" type="checkbox"/> A check no. 18338 is enclosed to cover the Provisional filing fee of <input checked="" type="checkbox"/> \$150 large entity <input type="checkbox"/> \$75 small entity			
<input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any deficiency in the filing fees and credit any overpayment to Deposit Account Number 02-4035.			

35 FORM 7-2000

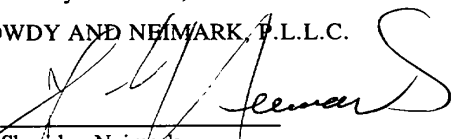
The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

No  Yes, the name of the U.S. Government agency and the Government contract number are:

Date: 01 April 1998

Respectfully submitted,

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Exhibit 1042  
ARGENTUM

## NEW THERAPY IN GLOMERULONEPHRITIS

### *Field of Invention*

The present invention provides a new treatment for glomerulonephritis.

5

### *Background to the Invention*

The functional units of the kidney, such as the glomeruli may suffer from inflammation.

An inflammatory attack in the glomeruli is termed glomerulonephritis and can be classified into subgroups such as membranous glomerulonephritis, focal segmental

10 glomerulosclerosis, mesangial diffuse proliferative glomerulonephritis, endocapillary or extracapillary proliferative glomerulonephritis. Using histopathological techniques these subgroups vary with respect to microscopical or immunohistochemical picture. One cause of inflammation is due to the deposition of immunoglobulin A (IgA) in glomeruli. This condition is termed IgA nephropathy (1-3), which is the most common form of

15 glomerulonephritis in a global perspective.

Assessment of the degree of severity of glomerulonephritis is based on different investigation results. The most important findings are 1) the degree of urinary excretion of protein (proteinuria) and 2) the filtering function of the kidney, which can be assessed by

20 serum creatinine (s-creatinine). Histological examination of material from kidney (renal biopsy) yields information about the type of renal damage as well as the severity of the injury. The outcome of a glomerulonephritis is variable and is dependent upon the histological and the immunohistochemical findings in a renal biopsy. Patients with IgA nephropathy having a constant proteinuria often develop renal failure and uraemia after 5

25 to 20 years of illness (4).

Various treatments for glomerulonephritis are known. For example substances which act on the immune system, e.g. Cyclophosphamide, Azathioprine and Cyclosporine have been used. Glucocorticoids have also been used (mainly prednisone or prednisone

acetate) which may be administered orally or by venous infusion (5, 6). Unfortunately, these treatments cause severe side effects and are not particularly effective. Other suggested treatments include ACE inhibitors (7), polyunsaturated fatty acid preparations (8) and vitamin E (9). The treatment results for these therapies for IgA nephropathy have been quite disappointing and it has been concluded that an effective treatment against progressive IgA nephropathy is basically missing (10). For this reason, a substantial number of patients with IgA nephropathy, 20-30%, will eventually develop renal insufficiency and uraemia (1-4). The available treatment for uraemia today is dialysis or kidney transplantation. Renal transplant patients who have been transplanted because of uraemia due to glomerulonephritis frequently suffer from recurrence of glomerulonephritis in the transplant and subsequently a gradual loss of transplant function (11, 12). This is most common in patients who previously suffered from IgA nephropathy. Today there is no effective treatment against recurrence of glomerulonephritis in a transplant.

The glucocorticoids that have been used in IgA nephropathy and in other types of glomerulonephritis are characterised by a substantial gastrointestinal absorption after oral administration, aiming to exert a direct effect on circulating leukocytes and cells that have infiltrated the kidney or the renal transplant, thus having a systemic effect. Such a systemic effect is also achieved if glucocorticoids are administered as an intravenous infusion. Systemic administration of glucocorticoids may have influenced the outcome of IgA nephropathy in some cases.

It has now surprisingly been found that a glucocorticoid substance which has a minimal systemic effect, but exerts its effect preferably in the intestinal wall of a certain part of the gut (the lower third of the small intestine and the upper fourth of the large intestine), is effective in controlling IgA nephropathy in a native kidney or a kidney transplant. It would not be expected that treatment of an apparently healthy intestine has an effect on an inflamed kidney. This discovery represents a breakthrough in the treatment of

glomerulonephritis since it has the advantage of reduction of severe side effects on the body, including effects on skeleton, metabolism and muscles, caused by systemic glucocorticoids.

5 *Summary of the Invention*

According to the invention there is provided the use of a glucocorticoid substance which has a minimal systemic effect in the manufacture of a medicament for oral or rectal administration for use in the treatment of glomerulonephritis.

10 According to the invention there is further provided a method of treating a patient suffering from glomerulonephritis which comprises administering orally or rectally to the patient a therapeutically effective amount of a glucocorticoid substance which has a minimal systemic effect.

15 According to the invention there is further provided a pharmaceutical composition comprising a glucocorticoid substance which has a minimal systemic effect for oral or rectal administration in association with a pharmaceutically acceptable diluent, adjuvant or carrier, which composition is for use in the treatment of glomerulonephritis.

20 *Detailed Description of the Invention*

The invention is preferably used to treat a patient who suffers from acute or chronic glomerulonephritis. Glomerulonephritis may be divided into subtypes such as membranous glomerulonephritis, focal segmental proliferative glomerulonephritis, diffuse mesangioproliferative glomerulonephritis, endocapillary or extracapillary proliferative  
 25 glomerulonephritis, depending on where the inflammation is located. This invention is preferably used to treat the IgA nephropathy type of glomerulonephritis. The invention is particularly suitable for treating patients who have suffered from glomerulonephritis (particularly IgA nephropathy), had a transplant, and suffered from a recurrence of glomerulonephritis (particularly IgA nephropathy) in the transplanted kidney.

The glucocorticoid substance used in the present invention is preferably one which has a first pass metabolism of at least 90% for the minimisation of the systemic effects. The first pass metabolism of a glucocorticoid substance can be determined using the method disclosed previously (13). More preferably it is budesonide, rofleponide or derivatives thereof, belcomethasone dipropionate, belcomethasone monopropionate, ciclesonide, tipredane, flunisolide, traimcinolone acetonide or fluticasone propionate. Budesonide, which is a 16,17-bytylidenedioxy-11 $\beta$ ,21-dihydroxypregna-1,4-diene-3,20-dione, is particularly preferred.

10

The glucocorticoid substance when administered orally is generally administered in the form of tablets, pills, capsules, syrups, powders or granulates and when it is administered rectally, is in the form of foams, suppositories or enemas.

15 The glucocorticoid substance may be administered on its own or as a pharmaceutical composition in combination with a pharmaceutically acceptable diluent, adjuvant or carrier. particularly preferred are compositions not containing material capable of causing an adverse, e.g. an allergic reaction.

20 The glucocorticoid substance may be admixed with an adjuvant or a carrier, e.g. lactose, saccharose, sorbitol, mannitol, starches such as potato starch, corn starch or amylopectin, cellulose derivatives, a binder such as gelatine or polyvinylpyrrolidone, and a lubricant such as magnesium stearate, calcium stearate, polyethylene glycol, waxes and/or paraffin, and then compressed into tablets. If coated tablets are required, the cores, prepared as  
25 described above, may be coated with a concentrated sugar solution which may contain e.g. gum arabic, gelatine, talcum and/or titanium dioxide. Alternatively, the tablet may be coated with a suitable polymer dissolved in a readily volatile organic solvent. The tablet

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