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(54) Title: USE OF ZOLENDRONATE FOR THE MANUFACTURE OF A MEDICAMENT FOR THE TREATMENT OF BONE METABOLISM DISEASES

(57) Abstract: A method of intravenously administering a bisphosphonate to a patient in need of bisphosphonate treatment comprising intravenously administering 4 mg of 2-(imidazol-1-yl)-1-hydroxyethane-1,1-diphosphonic acid (zoledronic acid) or a pharmaceutically acceptable salt hereof over a period of 15 minutes to a patient in need of said treatment.

Method of Administering a Bisphosphonate

The present invention relates to a method of intravenously administering a bisphosphonate, specifically 2-(imidazol-1-yl)-1-hydroxyethane-1,1-diphosphonic acid (zoledronic acid) to a patient in need of bisphosphonate treatment.

Bisphosphonates are widely used to inhibit osteoclast activity in a variety of both benign and malignant diseases that involve excessive or inappropriate bone resorption. These pyrophosphate analogues not only reduce the occurrence of skeletal related events but they also provide patients with clinical benefit and improved survival. Bisphosphonates are able to prevent bone resorption *in vivo*; the therapeutic efficacy of bisphosphonates has been demonstrated in the treatment of osteoporosis, osteopenia, Paget's disease of bone, tumour-induced hypercalcemia (TIH) and, more recently, bone metastases (BM) and multiple myeloma (MM) (for review see Fleisch H 1997 Bisphosphonates clinical. In Bisphosphonates in Bone Disease, From the Laboratory to the Patient. Eds: The Parthenon Publishing Group, New York/London pp 68-163).

Recently, it has been reported that bisphosphonate (clodronate, etidronate, alendronate and pamidronate) administration has a favourable effect on bone pain in patients with metastatic prostate cancer carcinoma (Silvio Adami, Cancer 1997; **80**: 1674-79). Recently, it has also been reported that bisphosphonates inhibit breast and prostate carcinoma cell adhesion to bone *in vitro* (Boissier et al., Cancer Res; 57: 3890-3894, 1997) and further that pre-treatment of breast and carcinoma cells with bisphosphonates inhibited tumour cell invasion via a direct action on the tumour cells. Yet more recently, it has been reported that *in vitro* treatment of prostate cancer cell lines with zoledronic acid significantly reduced the growth of the cell lines (Brown et al. Effects of Zoledronate on Prostate Cancer Cells, ASBMR 2000; Lee et al., Bisphosphonate Treatment Inhibits the Growth of Prostate Cancer Cells, Cancer Research, 2000/2001); whereas no significant decrease in tumour volume was detected for subcutaneous prostate cancer cell line tumours treated with zoledronic acid (Corey et al., Effects of Zoledronic Acid on Prostate Cancer in Vitro and in Vivo, Amer. Assoc. Cancer Res. Submitted Oct 2000).

Additionally, it has now been shown in a double blind, placebo-controlled clinical study that zoledronic acid (zoledronate) demonstrates a statistically significant efficacy

benefit over placebo in the treatment of bone metastases in prostate cancer patients and that bisphosphonates may also be employed more generally for the treatment of osteoblastic (osteosclerotic) metastases, in particular osteoblastic bone metastases, such as the osteoblastic metastases associated with prostate cancer and similar malignant diseases in mammals.

1-hydroxy-2(1H-imidazol-1-yl)-phosphono-ethyl phosphonic acid (zoledronic acid, zoledronate) is a third generation bisphosphonate compound. In animal models zoledronic acid shows high affinity to the mineralised bone matrix and inhibits osteoclastic bone resorption more effectively than earlier generation bisphosphonates, at doses that do not affect bone formation and mineralization and have no appreciable impact on renal function. This results in an improved ratio of antiresorptive versus renal effects (Green *et al.*, 1994; Green *et al.*, 1997). Zoledronic acid (ZOMETA™) is currently under regulatory review for the treatment of tumor-induced hypercalcemia (TIH) on the basis of safety and efficacy data in a dose finding study (Vigneron *et al.*, 1995) and two pivotal clinical trials (Mull *et al.*, 1999; O'Neill *et al.*, 1999), as well as supporting safety data from several other studies in cancer patients with bone metastases (van Valen *et al.*, 1999; Goas *et al.*, 1999; Borg *et al.*, 1999). The clinical studies demonstrate that the pharmacological action of zoledronic acid in reducing osteoclastic hyperactivity results in an effective clinical inhibition of bone resorption and calcium release into blood in TIH patients.

It has been found that an intravenously administered 4mg dose of zoledronic acid infused over an interval of approximately 15 minutes showed 1) improved clinical practicality, 2) potentially more reproducible infusion rate when using 100 ml over 15 min vs. lower volume infused over shorter period, 3) shows comparable efficacy to the current standard treatment, Aredia® (disodium pamidronate) 90 mg dosed over a period of 2-4 hours, and 4) 4 mg/15 minutes shows improved renal safety versus 4 mg/ 5 minutes and higher zoledronic acid dose/15 minutes. Thus in one embodiment, the invention is directed to a method of administering 2-(imidazol-1yl)-1-hydroxyethane-1,1-diphosphonic acid (zoledronic acid, zoledronate) to a patient in need of bisphosphonate treatment comprising intravenously administering 4mg of 2-(imidazol-1yl)-1-hydroxyethane-1,1-diphosphonic acid or a pharmaceutically acceptable salt thereof over a period of 15 minutes to a patient in need of said treatment.

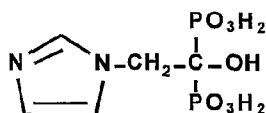
In another embodiment, the present invention relates to a method of treatment of bone metabolism diseases, e.g., tumour induced hypercalcemia (TIH), prosthesis loosening, treatment or reversal of angiogenesis associated with pathological conditions, e.g. tumour angiogenesis, said method comprising intravenously administering 4mg of 2-(imidazol-1yl)-1-hydroxyethane-1,1-diphosphonic acid or a pharmaceutically acceptable salt thereof over a period of 15 minutes to a patient in need of said treatment.

In a further embodiment, the present invention relates to a method of treatment of bone metastases, said method comprising intravenously administering 4mg of 2-(imidazol-1yl)-1-hydroxyethane-1,1-diphosphonic acid or a pharmaceutically acceptable salt thereof over a period of 15 minutes to a patient in need of said treatment.

In a still further embodiment, the present invention relates to a method of treatment or prevention of multiple myeloma, said method comprising intravenously administering 4mg of 2-(imidazol-1yl)-1-hydroxyethane-1,1-diphosphonic acid or a pharmaceutically acceptable salt thereof over a period of 15 minutes to a patient in need of said treatment.

In the present description the terms "treatment" or "treat" refer to both prophylactic or preventative treatment as well as curative or disease modifying treatment, including treatment of patients at risk of developing TIH, BM, or MM or suspected to have contracted the disease, e.g. TIH, as well as patients who are ill or have been diagnosed as suffering from a particular disease or medical condition treatable with bisphosphonates.

Zoledronic acid, chemically designated as 1-hydroxy-2-(imidazol-1-yl)ethane-1,1-diphosphonic acid having the structure



is known and can be prepared as described e.g. in US patent 4,939,130 (see also US patents 4,777,163 and 4,687,767), the contents of the latter three patents are hereby incorporated by reference.

Pharmaceutically acceptable salts of 1-hydroxy-2-(imidazol-1-yl)ethane-1,1-diphosphonic acid are preferably salts with bases, conveniently metal salts derived from groups

Ia, Ib, IIa and IIb of the Periodic Table of the Elements, including alkali metal salts, e.g. potassium and especially sodium salts, or alkaline earth metal salts, preferably calcium or magnesium salts, and also ammonium salts with ammonia or organic amines.

Especially preferred pharmaceutically acceptable salts are those where one, two, three or four, in particular one or two, of the acidic hydrogens of the bisphosphonic acid are replaced by a pharmaceutically acceptable cation, in particular sodium, potassium or ammonium, in first instance sodium.

A very preferred group of pharmaceutically acceptable salts is characterised by having one acidic hydrogen and one pharmaceutically acceptable cation, especially sodium, in each of the phosphonic acid groups.

Zoledronic acid can also be used in the form of its hydrates or it may include other solvents used for crystallisation.

The zoledronic acid is preferably administered in the form of pharmaceutical compositions that contain the 4 mg therapeutically effective amount optionally together with or in admixture with inorganic or organic, solid or liquid, pharmaceutically acceptable carriers which are suitable for intravenous administration.

The method according to the instant invention is for the intravenous administration of zoledronic acid.

The intravenous formulations used in the methods of the instant invention are injectable fluids which are preferably isotonic aqueous solutions which can be prepared before use by methods well known in the art, for example from lyophilised preparations which contain active ingredient alone or together with a pharmaceutically acceptable carrier. The pharmaceutical preparations may be sterilised and/or contain adjuncts, for example preservatives, stabilisers, wetting agents and/or emulsifiers, solubilisers, salts for regulating the osmotic pressure and/or buffers. Preferred intravenous infusion solutions are those containing 4 mg of zoledronic acid per unit dose in an infusion solution volume of from about 5 up to about 200 ml, preferably from about 50 to about 100ml and more preferably about 100 ml for infusion over a period of about 15 minutes plus or minus up to about 45 seconds.

Preferably, the compositions of the invention comprise a buffering agent. The type and amount of buffering agent may be selected in order to obtain a pH in the range of from 5 to

7, e.g., pH 5.9, when the composition of the invention is dissolved, e.g., in water. We have found that stability is best at these pH values. The pH may also be adjusted by using a basic solution, e.g., a sodium hydroxide solution. As a preferred buffering agent one may use trisodium citrate.

It is also preferred that the compositions of the invention comprise a bulking agent which preferably also acts as an isotonicising agent. Preferably, the bulking/isotonicising agent is chemically inert, has a low hygroscopicity and good bulking properties. The amount of bulking/isotonicising may be selected in order to obtain an isotonic solution when the composition of the invention is dissolved. For example the weight ratio of Zoledronic acid to the bulking/isotonicising agent is in the range of from 1:5 to 1:4000, e.g., 1:10 to 1:3000, e.g., 1:20 to 1:2500, e.g., 1:30 to 1:1000, e.g., 1:40 to 1:500, e.g., 1:50 to 1: 150. As a preferred bulking/isotonicising agent one may use mannitol.

The intravenous solution may be obtained by dissolving a pharmaceutical composition as described above into an appropriate amount of a biocompatible water-based solvent, water or saline for parenteral administration.

For treatment of tumor induced hypercalcemia, zoledronic acid is preferably administered one time in most patients. Repeat dosing, administered no sooner than 7 days post initial treatment, normally limited to one occurrence, may be used for improved control of the hypercalcemia. For the treatment and prevention of bone metastases, long-term administration of zoledronic acid is generally administered at 3 to 4-week intervals and at monthly intervals for patients with multiple myeloma although this can be more or less frequent depending upon individual circumstances. For example in one standard double blind clinical trial for Tumour Induced Hypercalcemia, 4 mg and 8 mg equivalents of Zoledronic acid delivered as a sodium salt of zoledronic acid are diluted with 50ml of an intravenous infusion solution (composition of the invention) and are delivered to a patient over a 15 minutes period once a day. Patients are retreated with an 8 mg dose if desired. Preferably, a minimum of 7 days, e.g., 14 days, should elapse before re-treatment to allow for full response to the initial dose.

The compositions of the invention may be prepared as follows. The required amount of isotonicising agent is dissolved in, e.g., 50 to 90%, of the total amount of biocompatible water-based solvent or water. Zoledronic acid is then suspended and dissolved by adding

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up to the final volume with biocompatible water-based solvent or water for parenteral use. Then the process is continued under aseptic conditions. The solution is sterilised and filled into 4 to 10 ml vials. In plastic vials, the solutions may be stored for a long-term period.

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Before storage, the content of the vials may also be dried, e.g., freeze-dried, according to a pre-programmed cycle. When the cycle is complete, the vials are stoppered after flushing with a gas, e.g., nitrogen or carbon dioxide, within a chamber. The vials are sealed, e.g., with aluminium caps, outside the sterile area. The lyophilisate
10 may then be used by re-dissolving the content of the vials into a solvent suitable for intravenous administration, e.g. saline.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and
15 "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

The reference to any prior art in this specification is not, and should not be taken
20 as, an acknowledgment or any form of suggestion that that prior art forms part of the common general knowledge in Australia.

The present invention is illustrated by the following examples.

25 Example 1 :

In a stainless steel kettle the required amount of mannitol is dissolved by stirring and under nitrogen flushing in approximately 70% of the total amount of water for injection. Zoledronic acid is suspended and dissolved by adding a 10% trisodium citrate
30 solution. After complete dissolution the pH-value is adjusted with 10% trisodium citrate solution to 5.9 – 6.1. The solution is then made up to the final volume with water for injection. The following procedure is carried out under aseptic conditions (In a grade A clean area): The solution is passed through a sterile membrane filter (0.22 micrometers pore size), and filled into 6 ml vials with a filling weight of 1.945 g (including an overfill of
35 3% of the solution to be lyophilised in order to compensate for the amount of reconstituted solution remaining in the vial after withdrawal). The overfill is selected according to USP. The vials are freeze-dried according to the following cycle :

Step	Time [min.]	Temperature [°C]	Pressure [mbar]
Begin freezing	30 min.	-20°C	--
Freezing	90 min.	-45°C	--
Freezing	150 min.	-45°C	--
equilibration time			
Begin primary drying	35 min.	-10°C	1500
Primary drying	85 min.	13°C	1500
Primary drying	480 min.	13°C	1500
Begin secondary drying	30 min.	30°C	420
Secondary drying	300 min.	30°C	420
Cooling down	30 min.	20°C	420
End of cycle	5 min.	20°C	420

When the cycle is complete, the vials are stoppered after flushing with nitrogen within the chamber. The vials are sealed with aluminium caps outside the sterile area (under LF). A solution for intravenous injection may be reconstituted by adding 5 ml of sterile water for injection USP to each vial. This dose is further diluted in 50 ml of sterile 0.9% Sodium Chloride, USP, or 5% Dextrose Injection, USP. If not used immediately, for microbiological integrity, the solution is refrigerated at, e.g., 36°- 46°F (2-8°C). The total time between reconstitution, dilution, storage in the refrigerator and end of administration does not preferably exceed 24 hours.

Examples 2 :

According to a similar processing as in example 1 the following composition may be obtained.

Compositions	
Zoledronic acid	4 mg
Mannitol, pyrogen-free	220.0 mg
Trisodium citrate	up to pH 5.9
Sodium hydroxide	-
Water for injection	up to 1.8 ml

Example 9 :

An 8 mg composition is prepared similarly as in example 1. The type and amounts of components are the same as for the 4 mg composition (example 7). Only amount of Zoledronic acid and trisodium citrate is doubled while the amount of mannitol is reduced down to 150 mg.

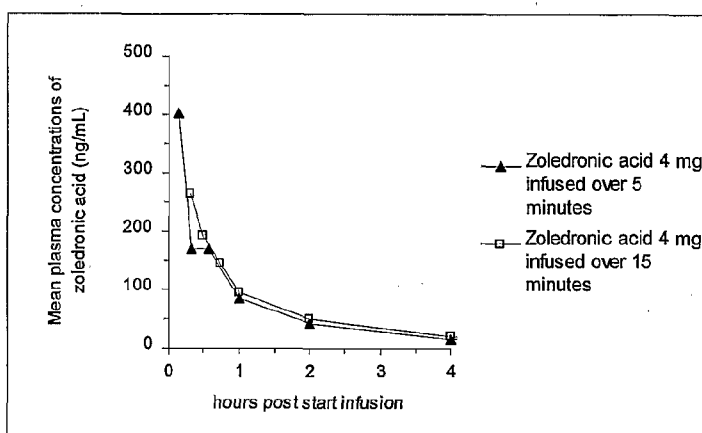
The Composition of Example 2 may be freeze dried and re-constituted as described in Example 1.

4 mg zoledronic acid is reconstituted in 100 ml of infusion solution. The solution is infused over a period of 15 minutes. This corresponds to an infusion rate of drug of 4 mg / 15 minutes = 0.27 mg/minute = 1 micromole/minute. The 4 mg dose, infused over 15 minutes, represents a more practical alternative to other bisphosphonate drugs, which are infused over a considerably longer period of time and at a higher infusion rate in terms of mass per unit time (mg/minute) and number of molecules per unit time (micromoles/minute), as tabulated below:

	Bisphosphonate Drug	
	zoledronic acid	pamidronate
Clinical dose (mg)	4	90
Infusion time (minutes) specified in label	15	120
Infusion rate		
mg/minute	0.27	0.75
micromoles/minute	1	2

1. The volume of 100 ml containing 4 mg zoledronic acid is infused over 15 minutes as an intravenous drip, which allows the drug to be administered at a uniform and precise rate. Clinical use of shorter infusion times of zoledronic acid, for example as an intravenous push of 5 minutes [Major P, Lortholary A, Hon J, et al., Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: a pooled analysis of two randomized, controlled clinical trials, J Clin Oncol 2001; 19: 558-567], may result in more variable infusion rates. Changing the infusion rate impacts the peak plasma concentrations achieved, as demonstrated in a pharmacokinetic study of zoledronic acid in cancer patients with bone metastases. Relevant data are shown in the figure below.

Plasma concentrations in patients after 4 mg zoledronic acid infused over 5 minutes and 15 minutes (mean data for n = 5 patients in 4 mg/5 min group, n = 7 patients in 4 mg/15 min group, study 503 [2])



The pharmacokinetic parameters derived from the individual patients' plasma concentration versus time curves, and urinary excretion of drug are tabulated below. Differences in mean C_{max} (maximum observed zoledronic acid concentration, at end of infusion) were statistically significant. Differences in AUC (area under zoledronic acid concentration versus time curve) and A_e (amount of drug excreted in urine) were not significant.

	Zoledronic acid 4 mg infused over 15 minutes (n=7)	Zoledronic acid 4 mg infused over 5 minutes (n=5)
C _{max} (ng/ml)	264 ± 86	403 ± 118
AUC 0-24 h (ngxh/ml)	420 ± 218	378 ± 116
A _e 0-24 h (% of dose)	37.4 ± 17.0	38.7 ± 6.34

The 4 mg dose of zoledronic acid has been determined to be clinically effective in several controlled trials in cancer patients, with placebo or the bisphosphonate pamidronate as comparator. Pertinent data attesting to zoledronic acid showing comparable efficacy to pamidronate and superior efficacy against placebo are summarized below.

	Percentage of patients showing a skeletal related adverse event		Statistical significance
	Zoledronic acid 4 mg	Comparator: Placebo or pamidronate	
Study 10: breast cancer patients	42%	47%	P>0.05
multiple myeloma patients	47%	49%	P>0.05
Study 11: hypercalcemic lung cancer patients	42%	48%	P = 0.036
hypercalcemic patients with other solid tumors	33%	46%	P = 0.047
Study 39: prostate cancer patients	33%	44%	P = 0.021

The dose of 4 mg zoledronic acid infused over 15 minutes offers a safety advantage in terms of renal tolerability over the shorter infusion time of 5 minutes. The lower incidence of renal adverse events with zoledronic acid infused over 15 minutes versus 5 minutes is summarized below. Renal adverse events are defined as increases in a patient's serum creatinine over baseline, by ≥ 0.5 mg/dL if baseline < 1.4 mg/dL, by ≥ 1 mg/dL if baseline ≥ 1.4 mg/dL, by ≥ 2 -fold irrespective of baseline value.

	zoledronic acid 4 mg	
	15 minutes infusion	5 minutes infusion
Study 10: breast cancer and multiple myeloma patients	24/272 patients 8.8%	36/272 patients 13.2%
Study 11: lung cancer patients	18/165 patients 10.9%	10/61 patients 16.4%
Study 39: prostate cancer patients	14/78 patients 15.2%	22/111 patients 19.8%

Zoledronic acid 4 mg infused over 15 minutes showed similar renal tolerability compared to pamidronate 90 mg infused over 2 hours, 8.8% versus 8.2%, respectively.

4 mg of zoledronic acid infused over 15 minutes versus higher doses of zoledronic acid, 8 mg and 16 mg results in improved renal safety without, surprisingly, losing clinical efficacy.

In summary, 4 mg zoledronic acid infused in a 100 mL volume over 15 minutes offers an input rate of drug into the patients' systemic circulation of 1 micromole per minute, which can be precisely administered and is considerably lower than the infusion rate used for other bisphosphonate drugs. The shorter duration of the infusion, 15 minutes for zoledronic acid versus 2 hours for pamidronate, offers a greater degree of flexibility and practicality in the clinical setting. The clinical studies attest to a clinical benefit in the choice of zoledronic acid 4 mg dose infused over 15 minutes in terms of improved renal tolerability versus a shorter infusion period of 5 minutes, but without impacting clinical efficacy, which is comparable to the current standard therapy pamidronate, and superior to placebo.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A method of administering 2-(imidazol-1yl)-1-hydroxyethane-1,1-diphosphonic acid to a patient in need of bisphosphonate treatment comprising intravenously administering 4 mg of 2-(imidazol-1yl)-1-hydroxyethane-1,1-diphosphonic acid or a pharmaceutically acceptable salt thereof over a period of 15 minutes to a patient in need of said treatment.
2. A method of treatment of bone metabolism diseases, said method comprising intravenously administering 4 mg of 2-(imidazol-1yl)-1-hydroxyethane-1,1-diphosphonic acid or a pharmaceutically acceptable salt thereof over a period of 15 minutes to a patient in need of said treatment.
3. A method according to claim 2 wherein said bone metabolism disease is tumour induced hypercalcemia.
4. A method of treatment of bone metastases, said method comprising intravenously administering 4 mg of 2-(imidazol-1yl)-1-hydroxyethane-1,1-diphosphonic acid or a pharmaceutically acceptable salt thereof over a period of 15 minutes to a patient in need of said treatment.
5. A method of treatment of multiple myeloma, said method comprising intravenously administering 4 mg of 2-(imidazol-1yl)-1-hydroxyethane-1,1-diphosphonic acid or a pharmaceutically acceptable salt thereof over a period of 15 minutes to a patient in need of said treatment.
6. A method according to claim 1 wherein said 4 mg of 2-(imidazol-1yl)-1-hydroxyethane-1,1-diphosphonic acid or a pharmaceutically acceptable salt thereof is administered in an infusion solution volume of from about 5 up to about 200 ml.
7. A method according to claim 6 wherein said infusion volume is from about 50 to about 100 ml.
8. A method according to claim 6 wherein said infusion volume is about 100 ml.
9. A method according to claim 1 wherein the 2-(imidazol-1yl)-1-hydroxyethane-1,1-diphosphonic acid is in the form of a pharmaceutically acceptable salt having one acidic hydrogen and one pharmaceutically acceptable cation in each of the phosphonic acid groups.

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10. A method according to claim 9 wherein said pharmaceutically acceptable cation is sodium.
11. Use of 2-(imidazol-1yl)-1-hydroxyethane-1,1-diphosphonic acid or a pharmaceutically acceptable salt thereof for the preparation of an intravenous medicament for the treatment of bone metabolism diseases, in which 4 mg of 2-(imidazol-1yl)-1-hydroxyethane-1,1-diphosphonic acid or a pharmaceutically acceptable salt thereof is administered intravenously over a period of 15 minutes.
12. Use of 2-(imidazol-1yl)-1-hydroxyethane-1,1-diphosphonic acid or a pharmaceutically acceptable salt thereof for the preparation of an intravenous medicament for the treatment of bone metastases, in which 4 mg of 2-(imidazol-1yl)-1-hydroxyethane-1,1-diphosphonic acid or a pharmaceutically acceptable salt thereof is administered intravenously over a period of 15 minutes.
13. Use of 2-(imidazol-1yl)-1-hydroxyethane-1,1-diphosphonic acid or a pharmaceutically acceptable salt thereof for the preparation of an intravenous medicament for the treatment of multiple myeloma, in which 4 mg of 2-(imidazol-1yl)-1-hydroxyethane-1,1-diphosphonic acid or a pharmaceutically acceptable salt thereof is administered intravenously over a period of 15 minutes.
14. A method according to any one of claims 1, 2, 4 and 5, substantially as hereinbefore described.
15. Use according to any one of claims 11 to 13, substantially as hereinbefore described.

DATED this 16th day of December, 2004

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