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(54) Title: USE OF ARGININE IN ENDOSCOPY AND OTHER MEDICAL PROCEDURES

(57) Abstract: A method for facilitating an *in vivo* procedure on an internal region of the body of a human subject, which region comprises muscle, wherein there is administered to part or all of the said region, before or during the procedure, arginine, a derivative thereof, or a pharmaceutically acceptable salt thereof, generally in a pharmaceutically acceptable carrier is disclosed together with the use of arginine, a derivative thereof, or pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in such a method. The procedure may be investigative and/or therapeutic, for example, surgical. Procedures include endoscopy, radiography, ultrasound, CT and NMR scans. The arginine reduces motility and/or causes relaxation of muscles hence facilitation the procedure.

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USE OF ARGININE IN ENDOSCOPY AND OTHER MEDICAL PROCEDURES

INTRODUCTION

The present invention relates to improvements to *in vivo*
5 procedures, especially endoscopy.

The present invention is concerned with procedures carried out on internal regions of the body that comprise muscle, both smooth muscle and striated muscle. Such procedures are
10 in particular procedures carried out on tracts, tubes, canals, cavities and organs that comprise muscle, for example, the vagina, cervix, uterus and Fallopian tubes, the urethra, ureter and bladder, and especially the gastrointestinal tract (GI tract).

15

BACKGROUND OF THE INVENTION

In vivo investigative techniques include radiography, ultrasound, CT and NMR scans, and endoscopy. The general techniques are well known, as are specialised applications,
20 for example, angiography and digital subtraction angiography. In many of the techniques contrast media are used to enhance the visualisation of the target site. All of the techniques are diagnostic. Some, in particular endoscopy, also enable biopsy samples to be obtained and therapeutic and surgical
25 procedures, to be carried out during the investigation.

The term "procedure" as used herein includes investigations and other procedures that are diagnostic and therapeutic and surgical procedures, including biopsy, which are carried out
30 *in situ*. A procedure may be exclusively investigative, therapeutic or surgical or may involve any combination thereof.

A medical problem often encountered by a person carrying out an *in vivo* procedure on a region of the body that comprises muscle is that of motility. Movement of muscle, for example, muscular tissue or a muscular organ, at or near the site of a procedure reduces the effectiveness of the procedure. Using the gastrointestinal tract (GI tract) as an example, there is a natural motility associated with the GI tract. It is generally described as movement of the muscular component of the digestive tube, and includes peristalsis and segmentation. Prior to an investigative or therapeutic, for example, surgical, procedure, the individual subject is normally asked to avoid food and, if required, to undergo a bowel preparation. The fasting period, the use of the bowel preparation or both can lead to the natural contractions becoming even more pronounced. Such enhanced natural motility must be distinguished from pathological conditions where hypermotility occurs.

In the case of an endoscopic procedure, the natural motility of the GI tract may cause difficulties, for example, in entering sphincters, in passing the endoscope through the tract or both. Contraction of a sphincter may make it difficult to pass an endoscope through the sphincter. If the natural motility of the GI tract is increased, for example, by one or more of fasting, the use of bowel preparations and the presence of disease, the problems are increased. Furthermore, during an endoscopic procedure, the presence of the endoscope itself may cause the gut, including sphincters, to contract, which causes difficulties, for example, for any one or more of the following: further passage of the endoscope, visualisation, and manipulations.

The problems caused by normal GI tract motility or hypermotility during procedures, for example, endoscopy, are

well known and various measures have been adopted in attempts to overcome the problem.

Two agents are commonly used intravenously to try to reduce gastric tract motility during procedures, but both have systemic effects and significant disadvantages. Buscopan (Trade Mark) comprises hyoscine butylbromide, an anticholinergic agent. It frequently causes side effects, for example, cramps, meteorism, pain, tachycardia and urine retention, and its use should be avoided in patients with glaucoma and prostate pathology. Glucagon, available under the Trade Mark Glucagen, is normally used as a treatment of hypoglycaemic episodes, but has also been used to reduce gastric tract motility, which use frequently results in nausea and vomiting.

SUMMARY OF THE INVENTION

The present invention provides a method for carrying out a procedure on an internal region of the body of a human subject, which internal region comprises muscle, which method comprises administering to part or all of the region an amount of the amino acid arginine, a derivative thereof, or a pharmaceutically acceptable salt of arginine or a derivative thereof effective to cause muscle in the treated region to relax, and carrying out the procedure while the muscle in the treated region is relaxed.

The present invention provides a method for carrying out a procedure on an internal region of the body of a human subject, which internal region comprises muscle, which method comprises administering to part or all of the region an amount of the amino acid arginine, a derivative thereof, or a pharmaceutically acceptable salt of arginine or a derivative thereof effective to reduce the motility of the treated

region, and carrying out the procedure while the motility of the treated region is reduced.

The present invention provides a method for carrying out a
5 procedure on an internal region of the body of a human
subject, which internal region comprises muscle, which method
comprises administering an effective amount of the amino acid
arginine, a derivative thereof, or a pharmaceutically
acceptable salt of arginine or a derivative thereof, to part
10 or all of the region, allowing muscle in the treated region
to relax, and carrying out the procedure while the muscle in
the treated region is relaxed.

The present invention provides a method for carrying out a
15 procedure on an internal region of the body of a human
subject, which internal region comprises muscle, which method
comprises administering an effective amount of the amino acid
arginine, a derivative thereof, or a pharmaceutically
acceptable salt of arginine or a derivative thereof, to part
20 or all of the region, allowing the motility of the treated
region to reduce, and carrying out the procedure while the
motility of the treated region is reduced.

The present invention provides use of the amino acid
25 arginine, a derivative thereof, or a pharmaceutically
acceptable salt of arginine or a derivative thereof for the
manufacture of a medicament for use in a method for carrying
out a procedure on an internal region of the body of a human
subject, which internal region comprises muscle, which method
30 comprises administering the amino acid arginine, a derivative
thereof, or a pharmaceutically acceptable salt of arginine or
a derivative thereof to part or all of the region in an
amount sufficient to cause muscle in the treated region to
relax, and carrying out the procedure while the muscle in the
35 treated region is relaxed.

The present invention provides use of the amino acid arginine, a derivative thereof, or a pharmaceutically acceptable salt of arginine or a derivative thereof for the manufacture of a medicament for use in a method for carrying out a procedure on an internal region of the body of a human subject, which internal region comprises muscle, which method comprises administering the amino acid arginine, a derivative thereof, or a pharmaceutically acceptable salt of arginine or a derivative thereof to part or all of the region to be treated in an amount sufficient to reduce the motility of the treated region, and carrying out the procedure while the motility of the treated region is reduced.

15 The present invention provides use of the amino acid arginine, a derivative thereof, or a pharmaceutically acceptable salt of arginine or a derivative thereof for the manufacture of a medicament for use in a method for carrying out a procedure on an internal region of the body of a human subject, which internal region comprises muscle, which method comprises administering the amino acid arginine, a derivative thereof, or a pharmaceutically acceptable salt of arginine or a derivative thereof, to part or all of the region, allowing muscle in the treated region to relax, and carrying out the procedure while the muscle in the treated region is relaxed.

The present invention provides use of the amino acid arginine, a derivative thereof, or a pharmaceutically acceptable salt of arginine or a derivative thereof for the manufacture of a medicament for use in a method for carrying out a procedure on an internal region of the body of a human subject, which internal region comprises muscle, which method comprises administering the amino acid arginine, a derivative thereof, or a pharmaceutically acceptable salt of arginine or

a derivative thereof, to part or all of the region, allowing the motility of the treated region to reduce, and carrying out the procedure while the motility of the treated region is reduced.

5

The present invention provides a method for reducing motility and/or for causing relaxation of muscle in an internal region of the body of a human subject, which internal region comprises muscle, during an *in vivo* procedure involving said
10 region, which comprises administering to part or all of said region, before or during the procedure, an effective amount of the amino acid arginine, a derivative thereof, or a pharmaceutically acceptable salt of arginine or a derivative thereof, generally in admixture with a pharmaceutically
15 acceptable carrier.

The present invention also provides a method for facilitating an *in vivo* procedure on an internal region of the body of a human subject, which internal region comprises muscle,
20 wherein there is administered to part or all of the region, before or during the procedure, an effective amount of the amino acid arginine, a derivative thereof, or a pharmaceutically acceptable salt of arginine or a derivative thereof, generally in admixture with a pharmaceutically
25 acceptable carrier.

The present invention also provides the use of arginine, a derivative thereof, or a pharmaceutically acceptable salt of arginine or a derivative thereof, for the manufacture of a
30 medicament for use in a method for reducing motility and/or causing relaxation of muscle in an internal region of the body of a human subject, which internal region comprises muscle, during an *in vivo* procedure involving the internal region, which method comprises administering the arginine,

derivative thereof, or pharmaceutically acceptable salt to part or all of the region, before or during the procedure.

The present invention also provides the use of arginine, a
5 derivative thereof, or a pharmaceutically acceptable salt of arginine or a derivative thereof for the manufacture of a medicament for use in a method for facilitating an *in vivo* procedure on a region of the body of a human subject, which internal region comprises muscle, which method comprises
10 administering the arginine, derivative thereof, or pharmaceutically acceptable salt to part or all of the internal region, before or during the procedure.

If the arginine, derivative thereof or pharmaceutically
15 acceptable salt is administered to the region before the *in vivo* procedure is carried out, it must be administered at such a time before the procedure that, when the procedure is carried out muscle in the region is relaxed, motility in the region is reduced, or both.

20 The arginine, derivative thereof, or pharmaceutically acceptable salt facilitates the *in vivo* procedure by reducing motility of muscle or causing relaxation of muscle, or both of the region of the body undergoing the procedure.

25 The *in vivo* procedure may be investigative, therapeutic or surgical, or may involve any combination thereof.

The term "arginine active substance" is used herein to denote
30 arginine, derivatives thereof and pharmaceutically acceptable salts of arginine and of derivatives thereof. Examples of derivatives and salts are given below. The arginine may be L-arginine, D-arginine or a mixture thereof. Derivatives and pharmaceutically acceptable salts of arginine and of arginine

derivatives are derivatives and salts of L-arginine, D-arginine or a mixture thereof.

An effective amount of an arginine active substance is an
5 amount that results in at least partial reduction in motility or at least partial relaxation of muscle. The muscle may be smooth muscle, or striated muscle, and may be a sphincter.

References to relaxation of muscle denote at least partial
10 relaxation. References to reduction of motility denote at least partial reduction in motility. Complete relaxation of muscle or reduction in motility may be produced by administration of the arginine active substance, but in most cases complete relaxation of muscle or reduction in motility
15 is not necessary and partial relaxation of muscle or reduction in motility is sufficient for the present invention.

According to the present invention, the arginine active
20 substance is administered locally, not systemically. The arginine active substance is delivered to all or part of the region of the body where the procedure is carried out. It will be understood that administration to all or part of a region of the body means administration to appropriate parts
25 of the body in that region.

The invention further provides the use or method according to the invention wherein the subject is a non-human animal other than a rodent. There is also provided a method or use
30 according to the invention wherein the subject is selected from the group consisting of animals used in food production, breeding animals, companion animals, horses, cats and dogs.

DETAILED DESCRIPTION OF THE INVENTION

The region of the body involved in an *in vivo* procedure according to the present invention is generally greater than the specific site that is the target of the procedure. For
5 example, in the case of an endoscopic procedure involving visualisation of the bile ducts, the site under investigation is the bile ducts. In such a procedure, the endoscope is passed from the mouth through the stomach to the duodenum, then to the sphincter of oddi and optionally through the
10 sphincter and into the bile ducts. The region of the body involved in the endoscopic procedure therefore includes more of the GI tract than just the site that is the specific target for investigation ie the bile ducts themselves. It includes the region of the GI tract from the mouth to the
15 bile ducts.

According to the present invention, the arginine active substance may be administered to any part or to all of the region involved in the procedure, which region comprises
20 muscle. In the present example, the region involved in the procedure is the region of the GI tract from the mouth to the bile ducts themselves, which region comprises muscle. The arginine active substance may be administered to any part of that region or to all of that region. Further details are
25 given below.

The same considerations apply to procedures involving other regions of the body that comprise muscle. For example, in the case of a procedure for example, endoscopy, that targets the
30 Fallopian tubes, the site of investigation or surgery is the Fallopian tubes themselves, but the region of the body involved in the procedure includes the vagina, the cervix, the uterus and the Fallopian tubes themselves. In the case of a procedure, for example, endoscopy, that targets a

ureter, the region of the body involved in the procedure includes the urethra, the bladder and the ureter. Both of these regions comprise muscle. In each case, the arginine active substance may be applied to part or to all of the
5 region involved in the procedure.

The same considerations also apply to other types of procedures, for example, other *in vivo* investigative procedures, for example, radiographic procedures, for
10 example, angiography, for example, digital subtraction angiography, ultrasound investigations, and CT and NMR scans. The arginine active substance may be administered to the appropriate region or to part of the region. For example, in the case of a radiographical examination of the GI tract that
15 involves the use of a contrast medium, the arginine active substance may be applied to all or part of the GI tract before administration of the contrast medium and carrying out the radiological investigation. In the case of an ultrasound investigation of an abdominal organ, for example, the liver
20 or the uterus, the region involved in the procedure is the abdomen, which includes the GI tract, movement of which can impair the investigation. In such a procedure, the arginine active substance may be administered to all or part of the GI tract before the ultrasound investigation to reduce the
25 motility of the gut and hence improve visualisation of the organ under investigation. The arginine active substance must be administered at such a time before the investigative procedure that muscle in the region is relaxed and/or motility is reduced when the investigation is carried out.
30 Although the procedure in question involves an internal region of the body, the measurements themselves may be recorded from outside of the body. This may be the case, for example, for an ultrasound scan.

The present invention is concerned with investigations and therapeutic and surgical procedures carried out on internal regions of the body that comprise muscle. As indicated above, the invention is particularly concerned with

5 investigations, surgery and therapeutic procedures carried out on tracts, tubes, canals, cavities and organs that comprise muscle, for example, procedures, especially endoscopy, carried out on the vagina, cervix, uterus and Fallopian tubes, of the urethra, ureter and bladder, and

10 especially of the gastrointestinal tract (GI tract).

The present invention may be regarded as an aid to *in vivo* diagnostic investigations and to therapeutic and surgical procedures when diminished motility is required, especially

15 in examination procedures and therapeutic and surgical, procedures carried out on the oesophagus, stomach, duodenum, small bowel and colon, particularly investigations involving radiological examination and also ultrasound, CT and NMR scans.

20

The present invention relates, for example, to endoscopy. Endoscopy is a general technique for inspection of internal cavities using an endoscope, which is generally a flexible fibre-optic device, that both illuminates and enables

25 inspection of the desired site. An endoscope may also comprise further means, for example, for administering a contrast agent. An endoscope may be used for carrying out biopsy or a surgical procedure, or both biopsy and surgery may be carried out during the same procedure. The use of

30 endoscopy has increased greatly in recent years with miniaturisation of and improvements in optical devices including cameras and surgical instrumentation used with endoscopes. Endoscopes now enable effective visualisation of

a variety of internal cavities and hence effective diagnosis and surgery.

Endoscopy may be non-invasive, the endoscope being inserted
5 into the body through a natural orifice, or it may be
invasive, the endoscope being inserted through a surgical
incision. The present invention is particularly concerned
with endoscopy of tracts, tubes, canals, cavities and organs
that comprise muscle, for example, endoscopy of the vagina,
10 cervix, uterus and Fallopian tubes, of the urethra, ureter
and bladder, and especially of the gastrointestinal tract (GI
tract).

Endoscopy of the upper part of the GI tract including the
15 oesophagus, stomach, duodenum, sphincter of oddi, pancreatic
and bile ducts is carried out *per os*. Endoscopy of the lower
GI tract including the anus, rectum, colon and ileum is
carried out *per anal canal*. Endoscopy of certain regions of
the GI tract is often referred to by specific terms. For
20 example, colonoscopy is endoscopy of the colon; sigmoidoscopy
is endoscopy of the sigmoid colon; proctoscopy is endoscopy
of the anal canal and rectum. Endoscopic retrograde
cholangiopancreatography (ERCP) is endoscopy of the
pancreatic and bile ducts via the sphincter of oddi.

25 In ERCP, a flexible endoscope is passed through the mouth and
down into the duodenum. A catheter is then passed through
the endoscope and inserted via the sphincter of oddi into the
pancreatic or bile ducts. A contrast agent is injected into
30 the catheter, which agent highlights the course and calibre
of the duct. Narrowing, stones or ductal tumours can be
identified using this procedure. Therapeutic and surgical
measures can also be undertaken at the time of ERCP to remove
stones in the bile ducts or to relieve obstructions in the

bile ducts, so that traditional open surgery can be avoided. ERCP is increasingly accepted as the diagnostic, therapeutic and surgical procedure of choice, for example, in identifying and removing gallstones in the bile duct.

5

Investigative, including diagnostic, therapeutic and surgical, endoscopic procedures in other parts of the GI tract and in other regions of the body, for example, on other tracts, tubes, canals, cavities and organs that comprise muscle, for example, procedures carried out on the vagina, cervix, uterus and Fallopian tubes, and on the urethra, ureter and bladder, are carried out analogously to ERCP, a contrast agent being used as appropriate and as required.

15 The invention includes endoscopic procedures and also other *in vivo* investigative procedures, for example, other radiographic techniques, for example, angiography, for example, digital subtraction angiography, and ultrasound investigations, CT and NMR scans. The arginine active
20 substance may be administered to the desired region or part of a region by whatever means is most appropriate. For example, for investigations of the female reproductive tract the active substance may be administered, for example, via a catheter or pessary or by local application, for example, in
25 the form of a cream gel or foam; for investigations of the urinary tract the active substance is generally administered via a catheter. When the arginine active substance is administered before the procedure is carried out, it must be administered at such a time that muscle in the region is
30 relaxed and/or motility in the region is reduced at the time when the procedure is carried out.

In endoscopy according to the present invention the individual subjected to the procedure is generally a mammal

and is especially a human. As mentioned above, the internal region of the body undergoing the endoscopic procedure is, for example, a tract, tube, canal, cavity or organ that comprises muscle. The endoscopic procedure may be, for
5 example, endoscopy of the vagina, cervix, uterus and Fallopian tubes (for example hysteroscopy, the examination of the inner cavity of the uterus through a fibre optic telescope inserted through the vagina and cervical canal), of the urethra, ureter and bladder, and all parts of the gastro-
10 intestinal tract.

As explained above, an endoscopic procedure on a particular site in the body generally involves a larger region that includes the specific site that is under investigation. For
15 example, in the case of ERCP site of the endoscopic procedure is the pancreatic or bile ducts. In carrying out ECRP, an endoscope is passed from the mouth through the stomach to the duodenum. The region of the body involved in the ERCP endoscopic procedure therefore includes more of the GI tract
20 than just the site that is the specific target for investigation, that is to say, the pancreatic and bile ducts. It also includes the region of the GI tract from the mouth to the duodenum.

25 The arginine active substance may be administered to all or part of the region of the body that is to undergo the chosen procedure. For example, in the case of ERCP, the arginine active substance may be applied directly to any one or more sites selected from the sphincter of oddi, the pancreatic
30 ducts and the bile ducts, to improve visualisation of and passage through those sites. Alternatively or in addition, the arginine active substance may be applied to other parts of the upper GI tract to assist the insertion of the

endoscope or any other tubing through those parts of the region en route to the target site.

The arginine active substance is advantageously administered
5 directly to the desired region via the endoscope itself or
via a separate catheter. For example, the active substance
can be sprayed from the endoscope or other catheter. Many
endoscopes comprise an integral working canal, for example,
for the administration of a contrast agent or to enable air
10 to be blown down to clear an area to assist passage of the
endoscope or to improve visibility.

The present invention relates, for example, to surgery. For
example, the invention relates to surgery on an internal
15 organ comprising muscle wherein one or more of reduction in
motility and muscle relaxation is desirable.

The invention also relates to surgery in the abdominal cavity
wherein one or more of relaxation of muscle and reduction in
20 motility, for example the gut, assists the surgical
procedure. If the arginine, derivative thereof or
pharmaceutically acceptable salt is administered before the
surgery is carried out, it must be administered to the
relevant region at such a time before surgery that, when the
25 surgery is carried out, muscle in the region is relaxed,
motility in the region is reduced or both.

The invention relates especially to surgery on the gut, but
also to surgery on other abdominal organs, for example the
30 female reproductive tract.

As indicated above, in the case of procedures involving other
parts of the body, the arginine active substance may be
administered to all or part of the appropriate region. For

example, in the case of a procedures that involves the female reproductive tract, the arginine active substance may be administered to all or part of that region of the body, for example, to any one or more of the vagina, the cervix, the uterus and the Fallopian tubes, or to a part thereof. In the case of a procedure, that targets the urinary system, the arginine active substance may be administered to all or part of the relevant region, for example to any one of more of the urethra, the bladder and the ureters, or to a part thereof.

10

The arginine active substance may be administered continuously during a procedure or as required. The latter is particularly useful in the case of endoscopy of the GI tract or other regions of the body as the investigator carrying out the endoscopy can readily determine during the procedure where and when motility is interfering adversely with the procedure.

15

Administration as required during a procedure is particularly useful in procedures involving the bile or pancreatic ducts, as the endoscope can be positioned suitably and the arginine active substance administered directly on to the sphincter of oddi, duodenal regions around the sphincter of oddi and/or into the ducts, greatly improving visualisation and passage of the apparatus, and also enabling biopsy and surgical manipulations. Administration of L-arginine directly to the duodenum gives a relaxation of the duodenum of up to about 60 minutes and enables a very clear view of, for example, the duodenum, sphincter of oddi and pancreatic and bile ducts.

20

25

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Such results are also obtained when the arginine active substance is applied to other parts to the GI tract, for example, directly to the colon during colonoscopy.

An alternative to direct administration is administration of the arginine active substance by a route and using a formulation that will result in release of the active substance at the appropriate region. For example, in the case of endoscopy of the GI tract, by the use of an oral pharmaceutical preparation that releases the active substance either substantially throughout the GI tract or that releases the active substance in a targeted manner at or near a specific region, for example, at or near the duodenum in the case of ERCP. Targeted delivery may be achieved using an appropriate coated or otherwise delayed release or targeted release pharmaceutical composition, for example, a tablet or capsule. Formulations for delayed and targeted release are known in the art. When the arginine active substance is administered before the procedure is carried out, it must be administered at such a time that muscle in the region is relaxed and/or motility in the region is reduced at the time when the procedure is carried out.

In the case of investigations of the female reproductive tract the active substance may be administered, for example, via a catheter or pessary or by local application, for example, in the form of a cream gel or foam; for investigations of the urinary tract the active substance is generally administered via a catheter. Again, when the arginine active substance is administered before the procedure is carried out, it must be administered at such a time that muscle in the region is relaxed and/or motility in the region is reduced at the time when the procedure is carried out.

The arginine active substance may be arginine itself, a pharmaceutically acceptable salt thereof, a derivative of arginine or a pharmaceutically acceptable salt of a

derivative. The arginine may be L-arginine, D-arginine or a mixture thereof.

Examples of pharmaceutically acceptable salts of arginine
5 include, arginine monohydrochloride, arginine free base, arginine aspartate salt, glutamyl arginine, arginine hydrochloride, arginine hydroxamate, arginine phosphate, argininic acid, arginine benzylidene, arginine diflavinate, arginine dipicrate and arginine picrate. The hydrochloride
10 salt is particularly preferred. A salt may be of L-arginine or D-arginine or of a mixture thereof.

Derivatives of arginine include, for example, esters, amides, carboxamido derivatives, amines, imines and imides. Esters
15 and amides may be formed at the terminal carboxy group, and carboxamido derivatives, amines, imines and imides at the alpha (peptide forming) amino group or at the guanidino group. Pharmaceutically acceptable salts of arginine derivatives are, for example, as described above for arginine
20 itself. Esters may be formed with aliphatic, aryl or heteroaryl groups. For example, esters include alkyl esters having from 1 to 4 carbon atoms in the alkyl moiety, for example, L-arginine methyl ester and the dihydrochloride thereof, L-arginine ethyl ester and the dihydrochloride
25 thereof, and esters with arylsulphonic acids, for example with p-toluene sulphonic acid, for example the L-arginine methyl ester p-toluenesulfonyl derivative. Further derivatives include those with carboxylic acids, for example, argininosuccinic acid, and derivatives with polyhydroxy
30 compounds, for example, with saccharides, for example, polysaccharides, for example, L-arginine agarose. L-arginine amides and derivatives and salts thereof include, for example, L-argininamide and the dihydrochloride thereof, L-arginin-N^G-amine and salts thereof, for example, the

- flavionate salt thereof, and amides formed with alkyl groups, especially those having from 1 to 4 carbons atoms, and with aryl and heteroaryl groups, for example, with naphthyl and substituted naphthyl groups, for example, alkyl and alkoxy, especially C1-C4-alkyl- and C1-C4-alkoxy-substituted naphthyl groups, and salts thereof, for example, L-arginine-4-methoxy- β -naphthylamide, L-arginine- β -naphthylamide and the hydrochloride thereof, and with nitroaniline, for example, L-arginine-p-nitroanilide and the dihydrochloride thereof.
- Pharmaceutically acceptable salts of L-arginine derivatives are also provided by the present invention. Corresponding derivatives and salts of derivatives of D-arginine may also be used in the present invention.
- Preferably, there is used L-arginine, D-arginine, L-arginine hydrochloride, D-arginine hydrochloride or a mixture of any two or more thereof.

- As explained above, in the present invention the active substance is administered locally, not systemically. The active substance is delivered to all or part of the region of the body involved in the procedure. As described above, when an endoscopic procedure is carried out, the arginine active substance may be delivered via the endoscope itself or via another catheter, which ensures delivery at the correct site and also enables delivery when and where required.

- An example of a preparation suitable for administration via an endoscope or via another catheter to the desired site is a solution or suspension of the arginine active substance in a pharmaceutically suitable liquid carrier, for example, in water, preferably water for injection, or a physiological saline, for example phosphate buffered saline or normal saline. A liquid preparation may be thickened to assist its

retention at the desired site, for example, using hydroxy methyl cellulose or another appropriate thickening agent.

The concentration of the arginine active substance in a liquid carrier may be determined on the basis of the desired total dose and an appropriate volume of liquid for the intended administration. For example, for administration to the duodenum or other parts of the GI tract a volume of up to about 150 ml, for example, up to about 100 ml may be used.

The volume is generally greater than 5 ml, for example, greater than 10 ml. For example, from 20 to 40 ml of liquid carrier may be used. Appropriate concentrations of arginine in a liquid carrier are, for example, 50 mg/ml or more, for example, 100 mg/ml or more, for example, 150 mg/ml or more, for example, 200 mg/ml or more, for example, 500 mg/ml or more. Generally at least 50 mg/ml will be used, for example, at least 100 mg/ml, for example, at least 150 mg/ml. Equivalent amounts of an arginine salt or an arginine derivative or pharmaceutically acceptable salt thereof should be used, that is to say, the amount of the derivative or salt should be such that amount of arginine provided is as set out above.

The total dose of the arginine active substance to be administered may be, for example, from 0.5 g to 20 g, for example, from 1 to 10 g for example, from 2 to 8 g, for example, from 3 to 6 g of arginine or the equivalent amount of a derivative or salt thereof,

When a dose of 3 g or 6 g of of L-arginine in solution in 20 ml or 40 ml, respectively, of normal saline was applied locally to the duodenum through an endoscope used for visualisation of the sphincter of oddi, a good response was reported for 13 of 15 patients, with relaxation of the

duodenum for up to 60 minutes and easy performance of the ERCP procedure.

The dosages and concentrations of arginine active substance mentioned above apply to arginine for application to a subject. The arginine active substance may however be provided in a more concentrated form and such a concentrate may be diluted to the desired concentration with saline, water or other carrier prior to use.

10

The invention also provides a pharmaceutical composition comprising arginine active substance in solution in a pharmaceutically suitable solvent, for example saline or water. Preferably the solution may contain a thickener and, more especially, the solution may be in the form of a concentrate for the manufacture of the final composition to be administered. Such a concentrate may comprise arginine at a concentration of at least 500 mg/ml and may be a saturated solution.

20

The invention further provides a solution for use in the treatment of a human subject, more especially in a method of the invention.

As indicated above, the arginine active substance may also be administered in the form of a preparation that is suitable for oral ingestion. In this case, the preparation may be a tablet, capsule or powder. In a preferred embodiment, the tablet or capsule is coated with an enteric coating that is selected so that it dissolves at a desired location in the gastrointestinal tract, for example, at the duodenum. A number of such enteric coatings are known. Many of these take the form of pH sensitive polymers. The polymer is coated onto the surface of the tablet and the product is released only

after the coating has dissolved. Enteric coatings that may be used in conjunction with the formulations of the invention include, for example, cellulose acetate 1,2 benzedi-
carboxylate, hexadecan-1-ol, cellulose ethyl ether, liquid
5 glucose, cellulose 2-hydroxyethylether, cellulose 2-hydroxypropylether, cellulose 2-hydroxypropyl methyl ether, cellulose hydrogen 1,2 benzene dicarboxylate 2-hydroxypropylmethyl ether, maltodextrin, cellulose methylether, polymethacrylates, shellac, confectioner's
10 sugar, titanium oxide, carnauba wax, microcrystalline wax, zein, gelatin, polyvinyl ethanol and cellulose carboxymethyl ether sodium salt. It is also possible to blend the arginine active substance with a polymer before coating the tablet. In this case the active ingredient is released at the desired
15 location and sustained or controlled release of the drug at the site can be achieved.

Drug delivery systems that are colon specific may also be used in conjunction with the present invention in order to
20 effect release of the drug in the colon. Drug delivery systems are known that effect selective targeting to the ascending, transverse or descending sections of the colon. For example, coatings are known that are degraded by colonic bacteria. The amount of the arginine, derivative thereof or
25 pharmaceutically acceptable salt thereof administered is preferably such that an effective quantity of the active substance reaches the rectum, anus or colon. In a preferred embodiment, from 0.1 mg to 5 g of arginine reach the rectum, anus or colon, more preferably from 10 mg to 1 g reach the
30 rectum, anus or colon, still more preferably 50 mg to 800 mg reach the rectum, anus or colon. Preferably, the requisite amount of the arginine active substance reaches the descending colon or the rectum. In a further embodiment, the pharmaceutically acceptable carrier is an enema solution.

The amount of the arginine present in a preparation for oral administration should be such that an effective amount is delivered to the desired site. Preferred doses of the
5 arginine active substance are set out above. When the arginine active substance is administered before the procedure is carried out, it must be administered at such a time that muscle in the region is relaxed and/or motility in the region is reduced at the time when the procedure is
10 carried out.

The present invention has been described in detail above in relation to endoscopy of the GI tract. The teachings may be applied, *mutatis mutandis*, to other endoscopic procedures and
15 also to other *in vivo* investigative procedures, for example, other radiographic techniques, for example, angiography, for example, digital subtraction angiography, and to ultrasound investigations, CT and NMR scans. The arginine active substance may be administered to the desired region or part
20 of a region by whatever means is most appropriate. For example, for investigations of the GI tract the arginine active substance may be administered, for example, via a catheter or oral preparation, for example, as described above; for investigations of the female reproductive tract
25 the active substance may be administered, for example, via a catheter or pessary or by local application, for example, in the form of a cream gel or foam; for investigations of the urinary tract the active substance is generally administered via a catheter.

30

The subject undergoing the procedure is generally a human but, in a variant of the invention, may be another animal other than a rodent, especially a mammal other than a rodent. A mammal may be a commercially reared animal, especially a

non-laboratory animal, for example, a bovine or ovine animal or a horse, or may be a companion animal or a pet, for example a cat or a dog. It may also be a sports animal or an animal reared in a zoo. A commercially reared animal may be
5 reared for its meat or milk, for its coat or skin, or for breeding, for example a key stud animal. The general statements made above in respect of the invention with reference to a human subject apply *mutatis mutandis* to the invention with reference to a non-human animal subject.
10 Appropriate adjustments of, for example, dosages may be required for a non-human animal subject.

The following non-limiting Examples illustrate the present invention.

15

EXAMPLES:

Formulation Examples:

Single use formulation:

3g of L-arginine was dissolved in 20ml normal saline with
20 stirring at room temperature until dissolution had occurred.

Larger scale stock solution formulation:

30g of L-arginine was dissolved in 200ml normal saline with
stirring at room temperature until dissolution had occurred.

25

Endoscope Procedure:

15 patients who were to undergo an ERCP (endoscopic retrograde cholangiopancreatography) procedure to visualise
30 site of the sphincter of oddi and the bile ducts were selected. The endoscope used was introduced into the duodenum of each patient in the usual manner but without the use of Buscopan or Glucogan, which would otherwise be administered

to reduce GI tract motility. The sphincter of oddi area-+ was visualised using the endoscope.

After visualising the sphincter of oddi area 3g L-arginine in
5 20ml normal saline or 6g L-arginine in 40ml of normal saline
were applied locally through the endoscope.

The detailed results showed that in one patient no effect was
observed and in another no clear judgement could be made. In
10 all the other 13 patients a good response was reported, with
relaxation of the duodenum for up to 60 minutes and easy
performance of the ERCP procedure.

The motility of the duodenum was seen to be either reduced,
15 diminished or stopped i.e. was not observed. The passage of
the endoscope tube through the sphincter of oddi was
described by the investigator as "easy" or "not difficult".
The observed clinical effects occurred rapidly after local
administration of the L-arginine solution.

CLAIMS:

1. Use of the amino acid arginine, a derivative thereof, or a pharmaceutically acceptable salt of arginine or a
5 derivative thereof for the manufacture of a medicament for use in a method for carrying out a procedure on an internal region of the body of a human subject, which internal region comprises muscle, which method comprises administering the amino acid arginine, a derivative thereof, or a
10 pharmaceutically acceptable salt of arginine or a derivative thereof to part or all of the region in an amount sufficient to cause muscle in the treated region to relax, and carrying out the procedure while the muscle in the treated region is relaxed.

15

2. Use of the amino acid arginine, a derivative thereof, or a pharmaceutically acceptable salt of arginine or a derivative thereof for the manufacture of a medicament for use in a method for carrying out a procedure on an internal
20 region of the body of a human subject, which internal region comprises muscle, which method comprises administering the amino acid arginine, a derivative thereof, or a pharmaceutically acceptable salt of arginine or a derivative thereof to part or all of the region to be treated in an
25 amount sufficient to reduce the motility of the treated region, and carrying out the procedure while the motility of the treated region is reduced.

3. Use of the amino acid arginine, a derivative thereof, or
30 a pharmaceutically acceptable salt of arginine or a derivative thereof for the manufacture of a medicament for use in a method for carrying out a procedure on an internal region of the body of a human subject, which internal region comprises muscle, which method comprises administering the

amino acid arginine, a derivative thereof, or a pharmaceutically acceptable salt of arginine or a derivative thereof, to part or all of the region, allowing muscle in the treated region to relax and carrying out the procedure while
5 the muscle in the treated region is relaxed.

4. Use of the amino acid arginine, a derivative thereof, or a pharmaceutically acceptable salt of arginine or a derivative thereof for the manufacture of a medicament for
10 use in a method for carrying out a procedure on an internal region of the body of a human subject, which internal region comprises muscle, which method comprises administering the amino acid arginine, a derivative thereof, or a pharmaceutically acceptable salt of arginine or a derivative
15 thereof, to part or all of the region, allowing the motility of the treated region to reduce, and carrying out the procedure while the motility of the treated region is reduced.

20 5. A method for carrying out a procedure on an internal region of the body of a human subject, which internal region comprises muscle, which method comprises administering to part or all of the region an amount of the amino acid arginine, a derivative thereof, or a pharmaceutically acceptable salt of arginine or a derivative thereof effective
25 to cause muscle in the treated region to relax, and carrying out the procedure while the muscle in the treated region is relaxed.

30 6. A method for carrying out a procedure on an internal region of the body of a human subject, which internal region comprises muscle, which method comprises administering to part or all of the region an amount of the amino acid arginine, a derivative thereof, or a pharmaceutically

acceptable salt of arginine or a derivative thereof effective to reduce the motility of the treated region, and carrying out the procedure while the motility of the treated region is reduced.

5

7. A method for carrying out a procedure on an internal region of the body of a human subject, which internal region comprises muscle, which method comprises administering an effective amount of the amino acid arginine, a derivative thereof, or a pharmaceutically acceptable salt of arginine or a derivative thereof, to part or all of the region, allowing muscle in the treated region to relax and carrying out the procedure while the muscle in the treated region is relaxed.

15 8. A method for carrying out a procedure on an internal region of the body of a human subject, which internal region comprises muscle, which method comprises administering an effective amount of the amino acid arginine, a derivative thereof, or a pharmaceutically acceptable salt of arginine or a derivative thereof, to part or all of the region, allowing the motility of the treated region to reduce, and carrying out the procedure while the motility of the treated region is reduced.

25 9. A method for reducing motility in an internal region of the body of a human subject, which internal region comprises muscle, during an *in vivo* procedure involving said region, which comprises administering to part or all of said region, before or during the procedure, an effective amount of the amino acid arginine, a derivative thereof, or a pharmaceutically acceptable salt of arginine or a derivative thereof, and wherein , when the arginine, derivative thereof or pharmaceutically suitable salt is administered before the procedure is carried out, it is administered at such a time

30

that motility in the region is reduced when the procedure is carried out.

10. A method for causing relaxation of muscle in an internal
5 region of the body of a human subject, which internal region
comprises muscle, during an *in vivo* procedure involving said
region, which comprises administering to part or all of said
region, before or during the procedure, an effective amount
of the amino acid arginine, a derivative thereof, or a
10 pharmaceutically acceptable salt of arginine or a derivative
thereof, and wherein, when the arginine, derivative thereof
or pharmaceutically suitable salt is administered before the
procedure is carried out, it is administered at such a time
that muscle in the region is relaxed when the procedure is
15 carried out.

11. A method for facilitating an *in vivo* procedure on an
internal region of the body of a human subject, which
internal region comprises muscle, wherein there is
20 administered to part or all of the region, before or during
the procedure, an effective amount of the amino acid
arginine, a derivative thereof, or a pharmaceutically
acceptable salt of arginine or a derivative thereof and
wherein, when the arginine, derivative thereof or
25 pharmaceutically suitable salt is administered before the
procedure is carried out, it is administered at such a time
that muscle in the region is relaxed: motility in the region
is reduced, or both, at the time when the procedure is
carried out.

30

12. Use of arginine, a derivative thereof, or a
pharmaceutically acceptable salt of arginine or a derivative
thereof, for the manufacture of a medicament for use in a
method for reducing motility and/or causing relaxation of

muscle in an internal region of the body of a human subject, which internal region comprises muscle, during an *in vivo* procedure involving the internal region, which method comprises administering to part or all of the region, before
5 or during the procedure, the arginine, derivative thereof, or pharmaceutically acceptable salt, and wherein, when the arginine, derivative thereof or pharmaceutically suitable salt is administered before the procedure is carried out, it is administered at such a time that muscle in the region is
10 relaxed and/or motility in the region is reduced at the time when the procedure is carried out.

13. Use of arginine, a derivative thereof, or a pharmaceutically acceptable salt of arginine or a derivative
15 thereof for the manufacture of a medicament for use in a method for facilitating an *in vivo* procedure on a region of the body of a human subject, which internal region comprises muscle, which method comprises administering to part or all of the internal region, before or during the procedure, the
20 arginine, derivative thereof, or pharmaceutically acceptable salt, and wherein, when the arginine, derivative thereof or pharmaceutically suitable salt is administered before the procedure is carried out, it is administered at such a time that muscle in the region is relaxed and/or motility in the
25 region is reduced at the time when the procedure is carried out.

14. A method as claimed in any one of claims 9 to 11 or use as claimed in any one of claims 1 to 8, 12 or 13, wherein the
30 muscle is smooth muscle or striated muscle.

15. A method or use as claimed in any one of claims 1 to 14, wherein the muscle is or comprises a sphincter.

16. A method or use as claimed in any one of claims 1 to 15, comprising any one or more procedures wherein the *in vivo* procedure is selected from the group consisting of investigative, therapeutic, and surgical procedures.

5

17. A method or use as claimed in claim 16, wherein a surgical procedure is biopsy.

18. A method or use as claimed in any one of claims 1 to 17,
10 wherein the procedure is carried out on a tract, tube, canal, cavity or organ.

19. A method or use as claimed in any one of claims 1 to 18,
wherein the region involved in the procedure is selected from
15 the group consisting of the vagina, cervix, uterus, Fallopian tubes, urethra, ureter, bladder, and the gastrointestinal tract or appropriate combinations thereof.

20. A method or use as claimed in any one of claims 1 to 19,
20 which wherein the *in vivo* procedure comprises endoscopy.

21. A method or use as claimed in claim 20, which comprises endoscopy of the oesophagus, stomach, duodenum, sphincter of oddi, pancreatic ducts, bile ducts, anus, rectum, colon or
25 ileum.

22. A method or use as claimed in claim 20, wherein the endoscopy is endoscopic retrograde cholangiopancreatography.

23. A method or use as claimed in any one of claims 1 to 22,
30 wherein the procedure involves radiological examination.

24. A method or use as claimed in any one of claims 1 to 23,

wherein the region to which the arginine, derivative thereof, or pharmaceutically acceptable salt is administered is or includes the site at which the procedure is carried out.

5 25. A method or use as claimed in any one of claims 1 to 24, wherein an endoscope or a catheter is used in carrying out the procedure at a selected site, and wherein the region to which the arginine, derivative thereof, or pharmaceutically acceptable salt is administered is or includes the region
10 through which the endoscope or catheter passes en route to the site undergoing the procedure.

26. A method or use as claimed in claim 24 or claim 25, wherein the procedure is endoscopic retrograde
15 cholangiopancreatography and the arginine, derivative thereof, or pharmaceutically acceptable salt is administered directly to the sphincter of oddi, to the duodenal regions, into the pancreatic ducts, into the bile ducts, or to any two or more of those sites of administration.

20 27. A method or use as claimed in any one of claims 1 to 26, wherein the arginine, derivative thereof or pharmaceutically acceptable salt is used in an amount that results in at least partial reduction in motility or at least partial
25 relaxation of muscle at said region.

28. A method or use as claimed in any one of claims 20 to 27, wherein the arginine, derivative thereof, or pharmaceutically acceptable salt is in a form suitable for
30 administration via an endoscope or another catheter.

29. A method or use as claimed in any one of claims 1 to 27,

wherein the arginine, derivative thereof, or pharmaceutically acceptable salt is in a form suitable for oral administration or for administration to the colon.

- 5 30. A method or use as claimed in any one of claims 1 to 29, wherein the arginine, derivative thereof, or pharmaceutically acceptable salt is in the form of a solution or suspension in a pharmaceutically suitable liquid carrier.
- 10 31. A method or use as claimed in claim 29, wherein the arginine, derivative thereof, or pharmaceutically acceptable salt is in a sustained release, controlled release or targeted release formulation.
- 15 32. A method or use as claimed in any one of claims 1 to 28, in a form suitable for administration to the vagina, cervix, uterus, Fallopian tubes, urethra, ureter or bladder.
- 20 33. A method or use as claimed in any one of claims 1 to 32, wherein the arginine is L-arginine, D-arginine, or a mixture thereof, and derivatives and pharmaceutically acceptable salts of arginine or arginine derivatives are derivatives and salts of L-arginine, D-arginine, or a mixture thereof.
- 25 34. A method or use as claimed in any one of claims 1 to 33, wherein L-arginine, L-arginine hydrochloride, D-arginine, D-arginine hydrochloride or a mixture of any two or more thereof is administered.
- 30 35. A method or use as claimed in any one of claims 1 to 34, wherein a derivative of arginine is an ester, amide, amine, imine, imide, or carboxamide derivative thereof.
36. A method or use as claimed in claim 35, wherein an

arginine derivative is an ester formed with an aliphatic, aryl or heteroaryl group, a derivative with a carboxylic acid, for example, argininosuccinic or a derivative with a polyhydroxy compound.

5

37. A method or use as claimed in claim 35, wherein an arginine derivative is an alkyl ester having from 1 to 4 carbon atoms in the alkyl moiety, an ester with an arylsulphonic acid, argininosuccinic acid, a derivative
10 formed with a polysaccharide, argininamide, arginin-N^G-amine, or an amide formed with an alkyl group having 1 to 4 carbon atoms, or with a naphthyl and or substituted naphthyl group.

38. A method or use as claimed in any one of claims 1 to 37
15 wherein the subject is a non-human animal other than a rodent.

39. A method or use as claimed in any one of claims 1 to 37 wherein the subject is selected from the group consisting of
20 animals used for food production, breeding animals, companion animals, horses, cats and dogs.

40. A pharmaceutical concentrate comprising arginine active substance in solution in a pharmaceutically suitable solvent.
25

41. A pharmaceutical concentrate as claimed in claim 40 wherein the concentrate comprises arginine at a concentration of at least 500 mg/ml.

30 42. A pharmaceutical concentrate as claimed in claim 40 or claim 41 further comprising a thickener.

INTERNATIONAL SEARCH REPORT

Inter I Application No

PC., 01/04014

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/198 A61B1/00 A61P41/00

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)

IPC 7 A61K A61B

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 practical, search terms used)

EPO-Internal, BIOSIS, MEDLINE, PAJ, WPI Data, CHEM ABS Data, PASCAL, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 595 753 A (HECHTMAN HERBERT B) 21 January 1997 (1997-01-21) abstract column 2, line 30 -column 3, line 15 ---	1-42
Y	US 5 827 889 A (CUNICO ROBERT) 27 October 1998 (1998-10-27) abstract column 1, line 65 -column 2, line 36; example 2 ---	1-42
Y	US 6 063 027 A (ALVING KJELL ET AL) 16 May 2000 (2000-05-16) column 2, line 60 - line 63 --- -/--	1-42



Further documents are listed in the continuation of box C.



Patent family members are listed in 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
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *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

24 January 2002

Date of mailing of the international search report

01/02/2002

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INTERNATIONAL SEARCH REPORT

Inte: il Application No

PC., -- 01/04014

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO.01 28538 A (BARRAS NORMAN ;NORGINE RES LTD (GB); HARVARD COLLEGE (US); HECHTMA) 26 April 2001 (2001-04-26) page 7, line 1 - line 29	40-42
Y,P	page 8, line 12 - line 25; claim 5	1-42
A	DOKITA S ET AL: "NG-NITRO-L-ARGININE INHIBITS NON-ADRENERGIC, NON-CHOLINERGIC RELAXATION IN RABBIT URETHRAL SMOOTH MUSCLE" LIFE SCIENCES, PERGAMON PRESS, OXFORD, GB, vol. 48, no. 25, 1991, pages 2429-2436, XP000670051 ISSN: 0024-3205 abstract	1-42
A	US 5 958 881 A (KORMAN LOUIS Y) 28 September 1999 (1999-09-28) abstract	1-42

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-42 relate to a large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only 1 compound claimed. Evidence is only given for L-arginine. It is not clear whether all derivatives of L-arginine, D-arginine and derivatives of D-arginine possess the same therapeutical effect.

Present claims 1-39 relate to a therapeutical application with reference to a result to be achieved, namely muscle relaxation, motility reduction. Consequently, the search has been carried out for those parts of the application which do appear to be clear (and concise), namely the use of L-arginine or D-arginine, or derivatives or salts thereof, for the manufacture of a medicament for therapeutical application or diagnostic method involving endoscopy or radiography.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Inter Application No
PCT, 01/04014

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5595753	A	21-01-1997	EP 0925046 A1 30-06-1999 WO 9632081 A1 17-10-1996
US 5827889	A	NONE	
US 6063027	A	16-05-2000	SE 503876 C2 23-09-1996 AT 191563 T 15-04-2000 AU 4127396 A 19-06-1996 DE 69516172 D1 11-05-2000 DE 69516172 T2 16-11-2000 DK 795130 T3 24-07-2000 EP 0795130 A1 17-09-1997 ES 2147308 T3 01-09-2000 GR 3033785 T3 31-10-2000 JP 10510052 T 29-09-1998 SE 9404161 A 31-05-1996 WO 9617244 A1 06-06-1996 US 6183416 B1 06-02-2001
WO 0128538	A	26-04-2001	AU 7809900 A 30-04-2001 WO 0128538 A2 26-04-2001
US 5958881	A	28-09-1999	AU 664850 B2 07-12-1995 DE 69231979 D1 06-09-2001 EP 0631503 A1 04-01-1995 JP 6507415 T 25-08-1994 US 5681816 A 28-10-1997 AU 2175692 A 21-12-1992 CA 2107884 A1 12-11-1992 ES 2162616 T3 01-01-2002 WO 9219261 A1 12-11-1992