Title: LIPOIC ACID FOR TREATING OR PREVENTING THREATENED MISCARRIAGE OR PRETERM DELIVERY

Abstract: The present invention relates to the use of lipoic acid, administered vaginally, for the treatment and/or prevention of threatened abortion or preterm birth in pregnant women with cervical shortening.
LIPOIC ACID FOR TREATING OR PREVENTING THREATENED MISCARRIAGE OR PRETERM DELIVERY

FIELD OF THE INVENTION
The present invention relates to the field of substances for pharmaceutical use, in particular it relates to a new medical use of lipoic acid.

BACKGROUND ART
a-lipoic acid (AL), or thioctic acid, is an endogenous fatty acid with antioxidant properties which acts as a scavenger of free radicals which are released at the extracellular level during inflammatory processes. Due to its molecular structure, lipoic acid is able to change from the oxidized form to the reduced form (AL/DHLA), participating in oxide-reduction reactions or in reactions with different radical species of oxygen [1]. Lipoic acid is present in the leaves of plants containing mitochondria and non-photosynthetic plant tissues such as potato tubers: even broccoli and spinach are particularly rich thereof, but the greatest alimentary source of AL are red meats and some offal. However, there are problems of bioavailability for the AL contained in food since it is present in a complexed form with difficult adsorption. For this reason, the dietary intake can benefit from an integration: the dosages may vary according to the individual characteristics, lifestyle, physical activity, exposure to sunlight and diet.

At an intracellular level, lipoic acid takes part in different antioxidative mechanisms such as the regeneration of reduced glutathione (GSH) and of ascorbic acid. At an extracellular level, it acts as scavenger of free radicals [2]. Lipoic acid is known to be a useful supplement for the treatment of Alzheimer, multiple sclerosis, diabetic neuropathy and other diseases [7-9].

Preterm birth (PB) is defined as birth before the 37th completed week of gestation. In developed countries, it occurs in 7.5% of all pregnancies, and is associated with high morbidity and neonatal mortality, since 1990 the incidence of PB has increased by about 20% due to the increase of the use of assisted reproduction techniques.

Given the importance of the several clinical and also socio-economic implications, in research, there are many studies aimed at understanding the risk factors and the physiopathological mechanisms involved. The mechanisms underlying preterm...
birth are manifold: Dudley et al. (J. of reproductive immunology. 1997, 36 (102), 93-109) in fact define such an event as a real syndrome, making specific reference to a complex inflammatory process. Particularly in the last 20 years, the role of the cervical length and of inflammatory interleukins has been specifically studied.

In physiological pregnancies, the cervical length is considered regular for values >35 mm, there are still uncertainties as to which is the cut-off for correctly identifying pregnancies at risk of PB, and currently based on the conclusions of the majority of works available in literature, a cervicometry of ≤ 30 mm is regarded as a threshold.

As described above, in addition to the ultrasound measurement of the cervix, another very thoroughly studied topic in recent years is that of pro-inflammatory cytokines. In fact, over the last 10 years many studies have shown an increase of the proinflammatory cytokine interleukin 6 (IL-6) at the level of cervico-vaginal secretions, of maternal serum and of the amniotic fluid in women with a risk of PB.[3]

In particular, the shortening and dilation processes of the cervix occur as a result of inflammatory processes involving important changes in the extracellular matrix of fibrous connective tissues [4]. For this reason, in case of threatened miscarriage or preterm delivery, the appropriate tocolytic therapies aimed at silencing the excessive uterine contractility should be associated with actions capable of opposing the morphological changes which take place on the fibrous connective tissues of the cervix.

In vitro tests on fragments of amniochorial membranes; after the pick-up, the fragments were placed in incubation with a control medium alone, or TNF alone, with or without a pretreatment with AL, demonstrated that pre-treatment with AL is able to inhibit both the weakening of membranes induced by TNF production and the release of MMP9 and cytokine-induced prostaglandin E2 [10-11]. A miscarriage or preterm delivery is a devastating event with social and health implications of great impact. Therefore, there is a clear need to identify new strategies for reducing the number of PB in women at risk.
SUMMARY OF THE INVENTION

The subject of the present invention is lipoic acid to be administered vaginally for use in the treatment and/or prevention of threatened miscarriage or preterm delivery, said lipoic acid in the form of α, β enantiomer or mixtures thereof and/or pharmaceutically acceptable organic or inorganic salts thereof.

The subject of the present invention is also a pharmaceutical composition to be administered vaginally, said composition having an acid pH; said composition including lipoic acid, in a dosage from 10 mg to 2 g but also from 0.1 mg to 2 g, and at least one other pharmaceutically acceptable ingredient for use in the treatment and/or prevention of threatened miscarriage or preterm delivery.

Vaginal administration has the following advantages compared to the usual oral administration: fast action, reduced dosage, better bioavailability. In fact, since vaginal administration prevents the hepatic metabolic processes (first step effect), it allows effective concentrations of lipoic acid to be achieved in the myometrium layer, in fetal membranes and in the uterine cervix. Systemic administration would not obtain similar results also due to a much more widespread distribution of the molecule in all of the organism sites. A further advantage of vaginal administration is represented by the absence of interaction with other substances (food, drinks) which are known to limit the intestinal absorption processes of lipoic acid, whose preferred supplementation is therefore between meals (C. H. Gleiter, Eur J ClinPharmacol 1996: 51:3-514). However, often the administration of lipoic acid supplements (commonly characterized by high dosages of such a substance) involves the onset of gastrointestinal disorders due to the acid and irritating nature of the lipoic acid itself. These issues lead patients to take such supplements with meals, thus limiting the pharmacokinetics and efficacy thereof.

In the prior art, it has already been assumed that the (dietary) supplementation with AL may be useful in the prevention of preterm premature rupture of the fetal membranes. In addition to this assumption, other studies show the ability of AL to interact with the prostanoid receptors EP2 and EP4 by stimulating the production of cAMP, a potent immunosuppressant. (Salinthone S et al. Journal of Neuroimmunology 2008, 1-2, 46-55). This could have an interesting implication in processes adapted to maintain the uterine quiescence, counteracting the
spontaneous preterm uterine contractions safely and free of side effects. The use of lipoic acid, according to the invention, in obstetrics would therefore oppose the common tocolytic agents currently representing the most common therapeutic approach against threatened miscarriage and preterm delivery and which have many limitations in terms of safety (Higby et al. AJOG, 1993, 168 (4), 1247-1 259).

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 shows the changes in cervical length between before and after treatment of two groups treated vaginally with AL and with placebo, respectively.

DETAILED DESCRIPTION OF THE INVENTION

According to the invention, it is preferred to administer lipoic acid for the treatment of threatened miscarriage or preterm delivery in patients with cervical shortening, that is, characterized by vaginal inflammatory and oxidative conditions due to changes in the vaginal cervix, uterine hypercontractility and/or placental detachment in pregnancy.

It is also preferred to administer lipoic acid to prevent threatened miscarriage or preterm delivery as a result of prenatal diagnostic procedures such as amniocentesis and chorionic villus sampling, assisted reproductive technologies and obstetric surgery.

The composition according to the invention is characterized by an acid pH (preferably 3.5-4.5), in order not to disrupt the physiological conditions of the vaginal environment.

Therefore, the composition of the invention is preferably in the form of vaginal suppositories, rigid or soft vaginal capsules, vaginal cream.

According to the invention, preferably stabilizers are selected from the group consisting of microcrystalline cellulose, sodium carboxymethyl cellulose, medium-chain triglycerides and sodium alginate.

According to the invention, preferably anti-agglomerant agents are selected from the group consisting of magnesium stearate and silicon dioxide.

According to the invention, preferably preservatives are selected from the group consisting of sorbic acid, benzoic acid, lactic acid, magnesium oxide.
According to the invention, preferably rebalancing agents are selected from the group consisting of Lactobacilli, potassium salts (i.e. potassium chloride), sodium hyaluronates.

Preferably, a composition according to the invention to be administered vaginally is in the form of a vaginal capsule or a vaginal ovule and includes lipoic acid in amounts from 10 mg to 800 mg, but also amounts from 0.1 mg to 800 mg, preferably from 5 mg to 200 mg, more preferably from 10 mg to 200 mg; even more preferably 10-50 mg. In trials using vaginal capsules containing 50 mg of lipoic acid, the patients reported bothersome itching and subsequent studies were conducted at lower doses with vaginal capsules containing 10 mg of lipoic acid which allows the itching to be reduced while maintaining the clinical efficacy. Said vaginal capsule preferably comprises an enclosure including gelatin or cellulose derivatives. Said vaginal capsule preferably having a total weight from 300 mg to 3 g.

Preferably, a composition according to the invention is in the form of a vaginal ovule and also includes, in addition to lipoic acid, at least one preservative and at least one rebalancing agent. Preferably, a vaginal ovule according to the invention includes, in addition to lipoic acid, lactic acid, EDTA, polyhexamethylene biguanide hydrochloride and potassium chloride.

Preferably, a composition for use according to the invention, said composition in the form of a vaginal capsule, comprises:

Lipoic acid 5-200 mg; preferably 10-200 mg; more preferably 10-50 mg
Magnesium stearate 2-50 mg;
Microcrystalline cellulose 100-600 mg;
Silicon dioxide 3-15 mg;
HPMC (hydroxypropylmethyl cellulose) capsule 80-150 mg.

Preferably, a composition for use according to the invention, said composition in the form of a vaginal ovule, comprises:

Lipoic acid 5-200 mg; preferably 10-200 mg; more preferably 10-50 mg
Lactic acid 0.5-10 mg
EDTA 1-10 mg
Polyhexamethylene biguanide hydrochloride 1-10 mg
Potassium chloride 2-20 mg  
Semisynthetic triglycerides a.n. to 2 g  

The present invention will be better understood in the light of the following embodiments.

EXPERIMENTAL PART

EXAMPLE 1 - FORMULATION in vaginal capsules:
Lipoic acid 50 mg  
Magnesium stearate 5 mg  
Microcrystalline cellulose 295 mg  
Silicon dioxide 5 mg  
HPMC (hydroxypropylmethyl cellulose) capsule 95 mg

EXAMPLE 2 - FORMULATION in vaginal ovules comprising lipoic acid, preservatives, emulsifiers and rebalancing agents.
Example of formulation:
Lipoic acid 50 mg  
Lactic acid 1 mg  
EDTA 3 mg  
Polyhexamethylene biguanide hydrochloride 3 mg  
Potassium chloride 4 mg  
Semisynthetic triglycerides a.n. to 2 g

EXAMPLE 3 - DESIGN OF CLINICAL TRIAL

TRIAL DESIGN
Randomized pilot trial, vaginal capsules according to example 1 vs. placebo  
Number of participants: 30 (15 per branch)

PRIMARY OBJECTIVE
In nulliparous patients with cervical length from 30 mm to 20 mm as measured between 24 and 30 weeks of gestation, the trial has the following objective:
- evaluating whether the administration of AL by the vaginal route is associated
  with a stabilization of the cervical shortening and with a reduction of the secretion
  of pro-inflammatory cytokines IL-6, IL1β and TNFa.

SECONDARY OBJECTIVES

- Gestation week at delivery
- Mode of delivery
- Apgar score, weight and gender of the child
- Vaginal itching/burning

INCLUSION CRITERIA

- Primigravid between 24 and 30 weeks of gestation
- Cervicometry from 30 mm to 20 mm
- Single pregnancy
- Intact membranes
- Ultrasound dating of pregnancy

EXCLUSION CRITERIA

- Rupture of membranes
- Proven fetal or chromosomal malformations
- Loss of blood from the genitals
- Contractions
- Therapy with progesterone

MATERIALS

The women enrolled were randomized into 2 groups:

- 15 were administered with vaginal capsules containing 50 mg AL (DAV), 1 per
day for 30 days
- 15 were administered with vaginal capsules containing placebo

Two visits were scheduled:

1) Enrolment, where cervicometry and vaginal swab are performed for dosing
the pro-inflammatory cytokines

2) At the end of the therapy, where cervicometry and vaginal swab are
repeated for dosing the pro-inflammatory cytokines
Preliminary results of the trial showed that vaginal treatment with AL causes a normalizing effect on the fibrous connective tissues of the cervix. In fact, in patients treated with AL there was a significant reduction of the cervical shortening processes than the placebo group TAB 1 and Fig. 1. This figure is probably due to the antioxidant action of AL which counteracts the tissue changes caused by reactive oxygen species released during the inflammatory processes.

<table>
<thead>
<tr>
<th></th>
<th>Cervicometry (mm)</th>
<th>Cervicometry (mm)</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>to</td>
<td>T1</td>
<td></td>
</tr>
<tr>
<td>DAV</td>
<td>24.5 ± 3.0</td>
<td>26.6 ± 1.9</td>
<td>0.016</td>
</tr>
<tr>
<td>Placebo</td>
<td>25.2 ± 3.0</td>
<td>23.8 ± 2.7</td>
<td>NS</td>
</tr>
</tbody>
</table>

The values of cervicometry in the two groups are referred to as ± SD means, and they were compared with a Student’s t-test. Differences associated with values of p < 0.05 between the two time points were considered significant.

Figure 1 shows the variations of the cervical length in the two groups before and after treatment.

In conclusion, the vaginal AL turns out to be an effective approach in clinical practice in obstetrics and gynecology in patients at risk for preterm birth.

The clinical observations of this trial showed that patients treated with 50 mg of AL vaginally reported an annoying itching. For this reason, subsequent studies described hereinafter were conducted at lower dose of AL.
EXAMPLE 4 - FORMULATION in vaginal capsules (DAV):

<table>
<thead>
<tr>
<th>Composition of one 400 mg capsule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha-lipoic acid (ALA)</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
</tr>
<tr>
<td>Magnesium stearate</td>
</tr>
<tr>
<td>Silicon dioxide</td>
</tr>
<tr>
<td>Hydroxypropyl methylcellulose</td>
</tr>
<tr>
<td>Titanium dioxide</td>
</tr>
</tbody>
</table>

EXAMPLE 5 - DESIGN OF CLINICAL TRIAL

5 TRIAL DESIGN

Randomized trial, vaginal capsules of example 4 vs. progesterone and placebo
Number of participants: 66 (27 medical device, 27 progesterone, 22 placebo)

PRIMARY OBJECTIVE

In primigravid patients between the 7th and 12th week of gestation, the trial had the following objective:
- evaluating whether the administration of 10 mg ALA vaginally is associated with the reabsorption of the subchorionic hematoma.

SECONDARY OBJECTIVES

Reduction or disappearance of:
- pelvic pain
- vaginal bleeding

INCLUSION CRITERIA

- Women aged 20-40
- Primigravid between 7th e and 12th weeks of gestation
- Presence of pelvic pain
- With or without moderate vaginal bleeding
- Presence of the subchorionic hematoma detected by ultrasound
EXCLUSION CRITERIA
- Absence of the fetus
- Absence of heartbeat
- Presence of uterine abnormalities
- Presence of fetal abnormalities
- Presence of multiple pregnancies
- Presence of pre-pregnancy or gestational abnormalities
- Diagnosis of allergic reaction to progesterone
- Presence of ongoing therapies with anticoagulants or antihypertensives
- Presence of karyotypic abnormalities

MATERIALS
The women enrolled to be treated with ALA or progesterone were randomized into 2 groups:
- 27 were administered with vaginal capsules containing 10 mg ALA 1 per day until resolution of the clinical condition
- 27 were administered with vaginal capsules containing 400 mg progesterone daily.

The women in the control group were those who refuse any medical treatment.

Three visits were scheduled:
1) Enrolment
2) 20 days after the first visit
3) 60 days after the first visit

In each visit, a "blinded" operator carried out the ultrasound examination to evaluate the subchorionic hematoma and the subjective (pelvic pain) and objective (vaginal bleeding) symptoms were recorded.

Results:
In the group of patients treated with vaginal ALA, the resorption of the subchorionic hematoma showed a statistically significant improvement ($p < 0.05$)
compared to that of the progesterone group and the control group. There were no significant differences between these two groups with reference to the absorption of the subchorionic hematoma, in particular:

<table>
<thead>
<tr>
<th>Improvement (%) mean ± st. error</th>
<th>ALA</th>
<th>Progesterone</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>83.9 ± 3.9</td>
<td>49.7 ± 2.7</td>
<td>48.6 ± 2.5</td>
</tr>
</tbody>
</table>

With reference to the disappearance of pelvic pain, a significant reduction was already observed at the second visit in the group treated with LA with respect to the other two (p < 0.05). In contrast, as regards vaginal bleeding, no significant differences were found between the three groups.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>2\textsuperscript{nd} visit</th>
<th>3\textsuperscript{rd} visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pel. pain</td>
<td>LA 100% Prog 100% Contr. 100%</td>
<td>ALA 0% Prog 14% Contr. 12%</td>
</tr>
<tr>
<td>Vaginal bleeding</td>
<td>LA 54% Prog 57% Contr. 65%</td>
<td>ALA 0% Prog 0% Contr. 12%</td>
</tr>
</tbody>
</table>

In the ALA group, a significant smaller number of abortions (p < 0.05) was observed with respect to those present in the progesterone and control groups.

<table>
<thead>
<tr>
<th>Spontaneous abortions</th>
<th>LA</th>
<th>Progesterone</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3</td>
<td>6</td>
<td>5</td>
</tr>
</tbody>
</table>

**EXAMPLE 6 - DESIGN OF CLINICAL TRIAL**

**TRIAL DESIGN**

Randomized trial, vaginal capsules of example 4 vs. progesterone and placebo

Number of participants: 120 (60 medical device, 60 progesterone)
PRIMARY OBJECTIVE
In primigravid patients between the 7th and 12th week of gestation, the trial had the following objective:
- evaluating whether the administration of 10mg ALA vaginally is associated with the reduction of the number of spontaneous abortions.

SECONDARY OBJECTIVES
Reduction or disappearance of symptoms related to the risk of spontaneous abortion after therapy

INCLUSION CRITERIA
- Women aged 20-40
- Primigravid between 7th e and 12th weeks of gestation
- Threat of spontaneous abortion suggested by the following symptoms:
Abdominal pain and presence of vaginal bleeding

EXCLUSION CRITERIA
- Absence of heartbeat
- Presence of uterine abnormalities
- Presence of fetal abnormalities
- Presence of multiple pregnancies
- Presence of pre-pregnancy or gestational abnormalities
- Diagnosis of allergic reaction to progesterone
- Presence of ongoing therapies with anticoagulants or antihypertensives
- Presence of karyotypic abnormalities

MATERIALS
The women enrolled to be treated with ALA or progesterone were randomized into 2 groups:
- 60 were administered with vaginal capsules containing 10 mg ALA 1 per day until resolution of the clinical condition
- 60 were administered with vaginal capsules containing 400 mg progesterone daily.
Three visits were scheduled:

1) Enrolment
2) 20 days after the first visit
3) 60 days after the first visit

Results:
In the group treated with AL, both a smaller number of abortions and persistence of symptoms post treatment were observed, in particular, the results obtained with AL are statistically significant \((p < 0.05)\) than those obtained with progesterone, in particular:

<table>
<thead>
<tr>
<th></th>
<th>ALA</th>
<th>Progesterone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abortion</td>
<td>15%</td>
<td>25%</td>
</tr>
<tr>
<td>Absence of symptoms</td>
<td>85%</td>
<td>75%</td>
</tr>
</tbody>
</table>

The dosage of ALA at 10 mg per vaginal route did not cause itching.
References


[9] US5728735


CLAIMS

1. Lipoic acid to be administered vaginally for use in the treatment and/or prevention of threatened miscarriage or preterm delivery, said lipoic acid in the form of an α or β enantiomer or mixtures thereof and/or pharmaceutically acceptable organic or inorganic salts thereof.

2. Lipoic acid according to claim 1 for use in the treatment of threatened miscarriage or preterm delivery characterized by vaginal inflammatory and oxidative conditions due to changes in the vaginal cervix, uterine hypercontractility and/or placental detachment in pregnancy.

3. Lipoic acid according to claim 1 for use in the prevention of threatened miscarriage or preterm delivery as a result of prenatal diagnostic procedures such as amniocentesis and chorionic villus sampling, assisted reproductive technologies and obstetric surgery.

4. A pharmaceutical composition for use according to any one of claims 1-3, said composition having an acid pH, said composition comprising lipoic acid in a dosage from 0.1 mg to 2 g and at least another pharmaceutically acceptable ingredient.

5. A composition according to claim 4, said composition having a pH from 3.5 to 4.5.

6. A pharmaceutical composition according to any one of claims 4-5, wherein said other pharmaceutically acceptable ingredient is selected from stabilizers, anti-agglomerant agents, emulsifiers, preservatives and rebalancing agents.

7. A pharmaceutical composition according to any one of claims 4-6, said composition in the form of vaginal ovules, rigid or soft vaginal capsules, vaginal cream.

8. A pharmaceutical composition according to claim 7 in the form of a vaginal capsule in which the lipoic acid is present in a dosage from 0.1 mg to 800 mg, preferably from 10 mg to 200 mg.

9. A composition according to claim 7 in the form of a vaginal capsule.
$*p = 0.016$ calculated between the mean values of cervical length at T1 and T0 in the group of DAV® vaginal capsules.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/385 A61P15/06
ADD.

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)
A61K

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

Electronic database consulted during the international search (name of database and, where practicable, search terms used)
EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
</table>
| A        | PADMANABHAN RENGASAMY ET AL: "Beneficial effect of supplemental lipopolysaccharide on diabetes-induced pregnancy loss in the mouse."
          | ANNALS OF THE NEW YORK ACADEMY OF SCIENCES
          | abstract
          | page 120, paragraph 2
          | -----
          | /-/- |

Date of the actual completion of the international search 5 April 2016
Date of mailing of the international search report 10/05/2016

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HN Rijswijk
Tel. (+31-70) 340-3040
Fax: (+31-70) 340-3016

Authorized officer
Col Iura, Al essandra

* 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 application or patent 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
  * 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

*I* document member of the same patent family

Further documents are listed in the continuation of Box C.

See patent family annex.
### DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>MOORE ROBERT M ET AL: &quot;Alpha-1 i po i c aci d inhi bits tumor necrosis factor-induced remodeling and weakening of human fetal membranes.&quot;, BIOLOGY OF REPRODUCTION APR 2009, vol. 80, no. 4, April 2009 (2009-04), pages 781-787, XP002743757</td>
<td>1-9</td>
</tr>
<tr>
<td>A</td>
<td>UA 17 059 U (KHARKIV MED ACAD POSTGRADUATE [UA]) 15 September 2006 (2006-09-15) the whole document</td>
<td>1-9</td>
</tr>
<tr>
<td>A</td>
<td>WO 03/047567 AI [DEGUSSA [DE]; SCHUHBAUER HANS [DE]; WINKLER STEPHAN [DE]; RUDHOLZNER M] 12 June 2003 (2003-06-12) claims 1, 2, 6</td>
<td>1-9</td>
</tr>
<tr>
<td>Patent document</td>
<td>Publication date</td>
<td>Patent family member(s)</td>
</tr>
<tr>
<td>-----------------</td>
<td>-----------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>UA 17059</td>
<td>15-09-2006</td>
<td>NONE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 1450789 AI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2006502245 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2004266858 AI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WO 03047567 AI</td>
</tr>
<tr>
<td>WO 2007138022</td>
<td>06-12-2007</td>
<td>AU 2007267159 AI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BR PI0712517 A2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2653403 AI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EA 200802398 AI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 2034974 A2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 5491859 B2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2009537611 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2014040434 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NZ 573756 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WO 2007138022 A2</td>
</tr>
</tbody>
</table>