Abstract:

Title: TREATMENT OF VAGINAL ATROPHY AS NOVEL INDICATION FOR MYRRH

The invention relates to a novel medical indication of myrrh, namely the treatment of vaginal atrophy as menopausal symptom. The invention further relates to a pharmaceutical preparation in vaginal dosage form for the treatment of vaginal atrophy and a method for preparing a pharmaceutical preparation against vaginal atrophy as menopausal symptom.
Treatment of vaginal atrophy as novel indication for myrrh

Specification

The instant invention relates to a novel indication for myrrh according to claim 1, a pharmaceutical preparation in vaginal dosage form according to claim 10, and a method for preparing a pharmaceutical preparation against menopausal symptoms according to the preamble of claim 13.

Myrrh Resin

Myrrh is the oleo-gum resin obtained from stems and branches of Commiphora molmol Engler and other related species of Commiphora other than Commiphora mukul. Commiphora mukul - although sharing the genus name - cannot be used for obtaining myrrh. Commiphora molmol Engler is sometimes also referred to as Commiphora myrrha or Commiphora myrrha (Nees) Engler. Suited related species of Commiphora molmol for obtaining myrrh are Commiphora abyssinica Engler and Commiphora schimperi Engler. Pharmacopoeia myrrh is generally obtained from Commiphora molmol Engler, but the other related species, in particular those referred to above, are also well suited.

For medical purposes, myrrh is used as powdered resin, capsules, myrrh tincture and other galenical preparations for topical use.

Myrrh can be separated into three components: volatile oil (ca. 2 to 10%), alcohol-soluble resin (ca. 25 to 40 %) and water-soluble gum.

The main constituents of myrrh essential oil are furanosesquiterpenes of various structural types together with sesquiterpenes. Furanosesquiterpenes are the source of its characteristic balsamic odour; a mixture of furanoeudesma-1,3-diene and lindestrene has the typical aroma of myrrh.

Myrrh essential oil is generally obtained by hydrodistillation, steam distillation, and solvent extraction. Extraction by carbon dioxide in the supercritical state is the state-of-the-art process that offers many advantages in obtaining volatile extracts. The mild extraction
conditions give assurance against chemical reactions not taking place during the process; i.e. no hydrolysis, oxidation, or isomerisation taking place. Other possible extraction agents include nitrogen, hexane, methane, and ethane.

Marongiu et al.: "Chemical Composition of the Essential Oil and Supercritical CO₂ Extract of Commiphora myrrha (Nees) Engl. and of Acorus calamus L", J. Agric. Food Chem. 53 (2005), 7939-7943 discloses the composition of myrrh extract obtained by different methods. The authors demonstrated that hydrodistillation (HD), steam distillation (SD) and supercritical extraction with carbon dioxide (SFE) yield similar results as far as main components and quantities extracted are concerned.


US 4,719,111 A discloses the external use of myrrh gum for treating decubitus ulcers.

US 4,592,912 A discloses the topical use for the relief of or for the prevention of muscular aches, pains, cramps and muscular spasms such as are found, for example, in overexerted muscles, misused muscles, headaches and back aches.

US 5,350,774 A describes the topical treatment of skin disorders with myrrh.

US 5,248,503 A discloses the utilization of myrrh as food or dietary supplement.

US 6,077,513 A discloses a pharmaceutical composition containing myrrh oil and myrrh resin as the active ingredients therein for treating schistosomiasis.

CN 1 679 687 A describes the use of a composition comprising seven substances of the traditional Chinese medicine against several diseases, namely vaginitis, cervical erosion, endometritis, hysteromyoma and adnexitis. However, this document does not teach or suggest the use of myrrh against other diseases or impaired states of a patient, like, e.g. vaginal atrophy.

Physiology of Menopausal Vaginal Symptoms
The menopause is defined as the permanent cessation of cyclical menstruation due to loss of ovarian follicular activity. The decline in estrogen concentration is associated with both acute and long-term effects. Established acute symptoms are vasomotor instability, manifesting as hot flushes and night sweats, and vaginal atrophy, manifesting as vaginal dryness, itching, burning, and discomfort.

Menopausal symptoms may be managed by using hormone replacement therapy (HRT) with estrogens, with or without progestogens. Adverse effects of HRT include an increased risk of breast cancer, ovarian and endometrial cancer, an increased risk of venous thromboembolism, stroke, dementia, gallstone formation and cholecystectomy. It is now generally recommended that menopausal HRT used to relieve vasomotor and vaginal symptoms should be given at the lowest effective dose for no longer than necessary. But to withdraw HRT means recurrence of menopausal symptoms.

Density of estrogen receptors is highest in endometrium and vagina. A drop in estrogen levels results in
- a decrease in mitotic activity, so the vaginal lining becomes thinner and more fragile;
- a drop in collagen content in the connective tissue;
- decreased blood flow and decreased vaginal lubrication;

leading to vaginal symptoms and findings of pallor, dryness and decreased rugosity of the vaginal mucosa.

US 2003/01 70325 A1 discloses compositions in gel or suppository form for the treatment of vaginal dryness. The compositions comprise herbal compounds with or without vitamin. However, this patent application does not suggest using extracts of myrrh for the treatment of vaginal dryness.

A non-hormonal effective treatment of vaginal atrophy as menopausal symptom is needed, as an alternative to HRT. It is an objective of the instant invention to provide an active ingredient for a pharmaceutical preparation or a medicinal product for such a treatment, a pharmaceutical preparation in a suitable dosage form as well as a method for preparing a pharmaceutical preparation against menopausal symptoms.

This objective is achieved by using myrrh in vaginal dosage form for the treatment of vaginal atrophy as menopausal symptom according to claim 1. In the patent and non-patent literature known to the inventor, no teaching or suggestion for such an indication of myrrh could be
found. This novel indication is surprising since vaginal atrophy as menopausal symptom is not related to bacteria and fungi against which myrrh has been used hitherto.

In other words, the myrrh is intended to be used for the treatment of vaginal atrophy and symptoms related therewith occurring (not exclusively but also) during menopause.

In an embodiment, the myrrh is the sole active ingredient within the claimed novel indication of myrrh. This means that pharmaceutical preparations or medicinal products comprise only myrrh as active pharmaceutical ingredient, but no other pharmaceutically active substances.

The term "myrrh" is to be understood as the oleo-gum resin originating from Commiphora species with the exception of Commiphora mukul. The myrrh used in connection to this invention is preferably pharmacopeia myrrh.

The term "menopausal symptoms" relates to all symptoms occurring in the menopause. Established acute symptoms are vasomotor instability, manifesting as hot flushes, and vaginal atrophy, manifesting as vaginal dryness, itching, burning, and discomfort.

In an embodiment, the myrrh is present in the form of a powdered resin, a myrrh tincture or an extract of myrrh. In doing so, the resin, tincture or extract are provided in vaginal dosage form, i.e. in a form suited for the topical application to the vagina of a patient to be treated. The resin tincture or extract can, e.g., be used to impregnate a tampon or another carrier suited for vaginal application.

In another embodiment, the extract of myrrh is a dry extract (preferably obtained by extraction of myrrh with an organic solvent) or an aqueous extract. In a further embodiment, the myrrh is used in pastry form. To obtain a pastry, myrrh resin is subjected to extraction with an organic solvent, for example ethanol, petroleum ether or ethyl acetate. The extract thus obtained is filtered and vacuum-concentrated to a pastry form. Thus, myrrh pastry is a filtered and concentrated form of a myrrh extract. The residue is again dissolved in alcohol (e.g., ethanol) or a mixture of alcohol and water, filtered and vacuum-concentrated.

In a further embodiment, the myrrh is used as lipophilic extract of myrrh, in particular obtained by extraction with liquid carbon dioxide in the supercritical state. Other standard extraction methods as explained above are also applicable.
In a further embodiment, the extract contains furanoeudesma-1,3-diene, lindestrene and curzerene as main ingredients. The according chemical structures of these compounds are displayed below:

![Chemical Structures]

Preferably, furanoeudesma-1,3-diene is present in the extract in an amount of more than 20%, in particular more than 25%, in particular more than 30% and very particular more than 35%. All percentages given in the present application are to be understood as percent by weight if not explicitly indicated otherwise.

In a further embodiment, the extract contains more than 10%, in particular more than 15%, in particular more than 20% and in particular more than 25% of curzerene.

In a further embodiment, the extract contains more than 5%, in particular more than 10%, in particular more than 15% of lindestrene.

In a further embodiment, the extract has a refractive index at 20 °C (measured with an Abbe refractometer) of 1.5 to 1.6, in particular of 1.51 to 1.55, in particular of 1.515 to 1.54, in particular of 1.517 to 1.537.

In a further embodiment, the extract has a density at 20 °C (measured with a pycnometer) of 1.0 to 2.0 g/cm³, in particular of 1.02 to 1.08 g/cm³, in particular of 1.025 to 1.075 g/cm³.

In a further embodiment, the myrrh is present in a semisolid dosage form for vaginal application, in particular as vaginal ointment, vaginal cream, or vaginal gel. In such semisolid preparations, oleaginous bases or water-soluble bases can be used. The semisolid preparations might be water-in-oil emulsions or oil-in-water emulsions.

In yet another embodiment, the myrrh is present in a liquid dosage form for vaginal application, in particular as vaginal liquid, vaginal emulsion, or vaginal suspension.

In another embodiment, the myrrh is present as vaginal foam or vaginal tampon.
In still another embodiment, the myrrh is present in a solid dosage form for vaginal application, in particular as vaginal tablet, vaginal capsule, or vaginal suppository.

Any of the afore-mentioned vaginal dosage forms enables a user to apply the myrrh at the location at which it can develop its activity against menopausal symptoms in a very well suited manner.

In a further embodiment, the solid dosage form, in particular the vaginal tablet, vaginal capsule, or vaginal suppository essentially consists of a fatty, oleaginous, or oil-type base and the myrrh. Cocoa butter and hard fat are members of this group of substances. Cocoa butter is an oleaginous base that softens at 30 °C and melts at about 34 °C, just below body temperature, thus representing an ideal suppository base. Other bases in this category include commercial products such as Fattibase (triglycerides from palm, palm kernel, and coconut oils with self-emulsifying glyceryl monostearate and polyoxyl stearate), Wecobee bases (triglycerides derived from coconut oil), Witepsol bases (triglycerides of saturated C12-,
C14 fatty acids with varying portions of the corresponding partial glycerides), Suppocire and Ovucire bases.

The inventor could already establish a synergistic effect of the combination of cocoa butter and myrrh. In particular, experiments indicate that constituents of cocoa butter and ingredients of myrrh essential oil show synergistic effects on mitotic activity, collagen metabolism, blood flow or lubrication when applied vaginally for treatment of vaginal atrophy. Thus, using cocoa butter as basic material even enhances the effectiveness of the myrrh.

It was found that a very well suited dosage for using the myrrh, in particular in form of a suppository, is daily, in particular once a day, in particular once a day at bed time. Such a dosage regime is sufficient to alleviate the menopausal symptoms, in particular vaginal atrophy.

The invention also relates to a pharmaceutical preparation or medicinal product in vaginal dosage form which is suited for the treatment of vaginal atrophy (in particular of vaginal atrophy as menopausal symptom), in particular a vaginal ointment, a vaginal cream, a vaginal gel, a vaginal liquid, a vaginal emulsion, a vaginal suspension, a vaginal foam, a vaginal tampon, a vaginal tablet, a vaginal capsule, or a vaginal suppository containing myrrh as the only pharmaceutical active ingredient. It is not known from prior art that myrrh alone (without any other pharmaceutically active substance) can have a positive effect on the symptoms related with vaginal atrophy.
In an embodiment, the pharmaceutical preparation is present in form of a vaginal tablet, vaginal capsule or vaginal suppository essentially consisting of a fatty, an oleaginous or an oil-type base material and myrrh according to the preceding explanations. Such a vaginal tablet, capsule or suppository is suitable for the treatment of menopausal symptoms, in particular for the treatment of vaginal atrophy and vaginal symptoms of dryness, itching, burning, and discomfort.

In an embodiment, the tablet, capsule or suppository has a weight of 0.5 to 5 g, in particular of 1 to 4 g, in particular of 2 to 3 g, in particular of 1.5 to 2.5 g, in particular of 1.7 to 1.9 g. 1.8 g is a particular well suited weight. Thereby, the myrrh is preferably present in the tablet, capsule or suppository in an amount of 0.1 to 10 %, in particular of 0.25 to 9 %, in particular of 0.5 to 8 %, in particular of 0.75 to 7 %, in particular of 1 to 6 %, in particular of 1.5 to 5 %, in particular of 2 to 4 %, in particular of 2.5 to 3 % based on the total weight of the tablet, capsule or suppository. An amount around 1 % of myrrh is particularly well suited.

The objective is also solved by a method for preparing a pharmaceutical preparation or medicinal product, respectively, against vaginal atrophy as menopausal symptom, having the following steps:

- melting a fatty, an oleaginous or an oil-type base at an elevated temperature above the melting temperature of this base material to obtain a melt,
- adding myrrh as the only pharmaceutically active ingredient to the melt in an amount of 0.1 to 10 % with respect to the sum of the base material and the myrrh so as to obtain a mixture of the base and the myrrh,
- stirring the mixture,
- pouring the mixture into at least one mould,
- cooling the mixture to room temperature,
- removing the solidified mixture from the mould.

By such a method, differently shaped pharmaceutical preparations or medicinal products against menopausal symptoms can be obtained. It should be noted that besides myrrh no other pharmaceutically active ingredient is used within the claimed method.

In an embodiment, the mould has a shape to form the mixture such that at least one vaginal tablet, capsule or suppository is obtained. Preferably, the mould forms the mixture in such a way that a plurality of tablets, capsules or suppositories is obtained. These tablets, capsules or suppositories can have the same size and/or shape or different shapes and/or sizes.
Thus, differently sized and/or shaped tablets, capsules or suppositories can be provided to address the individual needs of the users of this medical product.

Explained embodiments of the claimed use of myrrh are also applicable with respect to the claimed pharmaceutical preparation and the claimed method, and vice versa.

Furthermore, a method for treating the (female) human or animal body with myrrh to relieve menopausal symptoms, in particular to relieve vaginal atrophy, is hereby disclosed. Explained embodiments of the claimed use of myrrh or the claimed pharmaceutical preparation are also applicable with respect to this method.

Further details of the instant invention are explained in connection to the following examples which are, however, not to be construed in a limiting way.

A lipophilic extract of Commiphora myrrha, produced by supercritical CO₂ extraction, was used.

Vaginal suppositories were prepared using either hard fat or cocoa butter as suppository base.

Cocoa butter was melted at 50 °C. Under stirring, myrrh extract was added to a final concentration of 1% by weight of the total weight of the formula (mixture). Stirring was continued for several hours to obtain a stable crystalline form. The mixture was then poured into molds and cooled.

Hard fat was melted at 50 °C. Myrrh extract was added to a final concentration of 1% of the total weight of the formula to obtain a mixture. The mixture was poured into molds and cooled.

The suppositories weighed 2 grams each, containing 20 mg of myrrh extract each.

Both preparations (hard fat/cocoa butter) were tested in postmenopausal women (more than 2 years past last menstrual period) with vaginal symptoms of dryness, discomfort and itching. The vaginal suppositories were applied over a period of 14 consecutive days once a day, namely at bedtime each night.
Both preparations provided subjective and objective relief of menopausal symptoms, in particular vaginal symptoms due to vaginal atrophy. Colposcopy revealed an improved status of the vaginal mucosa.

Improvement of genital symptoms was more pronounced with the cocoa butter suppositories. Theobroma cocoa seeds contain polyphenols and flavonoids - substances with high antioxidation potential - and procyanidins which exhibit vascular effects. It appeared that in connection to the myrrh extract synergistic effects on mitotic activity, collagen metabolism, blood flow or lubrication occur when both substances are applied concomitantly for the treatment of vaginal atrophy.
Patent Claims


2. Myrrh for use according to claim 1, characterized in that the myrrh is present in the form of a powdered resin, a myrrh tincture or an extract of myrrh.

3. Myrrh for use according to claim 2, characterized in that the extract of myrrh is an aqueous extract, a dry extract, or a lipophilic extract.

4. Myrrh for use according to claim 2 or 3, characterized in that the myrrh tincture or the extract of myrrh contains furanoeudesma-1,3-diene, lindestrene and curzerene as main ingredients.

5. Myrrh for use according to any of the preceding claims, characterized in that it is present in a semisolid vaginal dosage form, in particular as ointment, cream, or gel.

6. Myrrh for use according to any of claims 1 to 4, characterized in that it is present in a liquid vaginal dosage form, in particular as liquid, emulsion, or suspension.

7. Myrrh for use according to any of claims 1 to 4, characterized in that it is present as vaginal foam or vaginal tampon.

8. Myrrh for use according to any of claims 1 to 4, characterized in that it is present in a solid vaginal dosage form, in particular as tablet, capsule, or suppository.

9. Myrrh for use according to any of the preceding claims, characterized in that it is to be used daily, in particular once a day.

10. Pharmaceutical preparation in vaginal dosage form for the treatment of vaginal atrophy, in particular a vaginal ointment, a vaginal cream, a vaginal gel, a vaginal liquid, a vaginal emulsion, a vaginal suspension, a vaginal foam, a vaginal tampon, a vaginal tablet, a vaginal capsule, or a vaginal suppository containing myrrh as only pharmaceutical active ingredient.
11. Pharmaceutical preparation according to claim 10, characterized in that it is present in form of a vaginal tablet, vaginal capsule or vaginal suppository and essentially consists of a fatty, an oleaginous or an oil-type base like cocoa butter, hard fat, or a semisynthetic triglyceride and myrrh.

12. Pharmaceutical preparation according to claim 11, characterized in that the tablet, capsule or suppository has a weight of 0.5 to 5 grams, wherein the content of myrrh is 0.1 to 10 percent by weight of the total weight of the tablet, capsule or suppository.

13. Method for preparing a pharmaceutical preparation against vaginal atrophy as menopausal symptom, characterized by the following steps:

- melting a fatty, an oleaginous or an oil-type base at an elevated temperature to obtain a melt,
- adding myrrh as only pharmaceutical ingredient to the melt in an amount of 0.1 to 10 percent by weight with respect to the sum of the fatty, oleaginous or oil-type base and the myrrh to obtain a mixture,
- stirring the mixture,
- pouring the mixture into at least one mould,
- cooling the mixture to room temperature,
- removing the solidified mixture from the mould.

14. Method according to claim 13, characterized in that the mould forms the mixture such that at least one vaginal tablet, vaginal capsule or vaginal suppository is obtained.
According to International Patent Classification (IPC) or to both national classification and IPC

**A. CLASSIFICATION OF SUBJECT MATTER**

INV. A61K36/328 A61K9/00 A61P15/12

**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 A61P

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal , BIOSIS, 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>
<tbody>
<tr>
<td>X</td>
<td>Wo 98/42188 Al (SQUI RES MERYL [US]) 1 October 1998 (1998-10-01) claims</td>
<td>1-14</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:

**A** document defining the general state of the art which is not considered to be of particular relevance

**E** earlier 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 (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

**Z** document member of the same patent family

Date of the actual completion of the international search: 25 April 2012

Date of mailing of the international search report: 08/05/2012

Name and mailing address of the ISA/
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer
Friederich Martin

Form PCT/ISA/210 (second sheet) (April 2003)
### 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>X</td>
<td>DATABASE WPI Week 201108 Thomson Sci enti f i c, London, GB; AN 2010-P07573 XP0026674663, &amp; CN 101 849 981 A (UNIV NANJING TRADITIONAL CHINESE MEDICIN) 6 October 2010 (2010-10-06) abstract</td>
<td>10-14</td>
</tr>
<tr>
<td>Patent document cited in search report</td>
<td>Publication date</td>
<td>Patent family member(s)</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>-----------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>CN 1679687</td>
<td>12-10-2005</td>
<td>NONE</td>
</tr>
<tr>
<td>AT 358418 T</td>
<td>07-12-2000</td>
<td></td>
</tr>
<tr>
<td>AU 727339 B2</td>
<td>20-10-1998</td>
<td></td>
</tr>
<tr>
<td>AU 6771898 A</td>
<td>31-07-2002</td>
<td></td>
</tr>
<tr>
<td>BR 9807892 A</td>
<td>22-02-2000</td>
<td></td>
</tr>
<tr>
<td>CA 2285394 A1</td>
<td>01-10-1998</td>
<td></td>
</tr>
<tr>
<td>CN 1258191 A</td>
<td>28-06-2000</td>
<td></td>
</tr>
<tr>
<td>CZ 9903368 A3</td>
<td>12-07-2000</td>
<td></td>
</tr>
<tr>
<td>DE 69837474 T2</td>
<td>13-12-2007</td>
<td></td>
</tr>
<tr>
<td>DK 0980203 T3</td>
<td>30-07-2007</td>
<td></td>
</tr>
<tr>
<td>EE 9900436 A</td>
<td>17-04-2000</td>
<td></td>
</tr>
<tr>
<td>ES 2285765 T3</td>
<td>16-11-2007</td>
<td></td>
</tr>
<tr>
<td>HU 0001379 A2</td>
<td>28-08-2000</td>
<td></td>
</tr>
<tr>
<td>IL 132003 A</td>
<td>31-08-2005</td>
<td></td>
</tr>
<tr>
<td>IS 5191 A</td>
<td>23-09-1999</td>
<td></td>
</tr>
<tr>
<td>JP 2000119188 A</td>
<td>25-04-2000</td>
<td></td>
</tr>
<tr>
<td>JP 2001527541 A</td>
<td>25-12-2001</td>
<td></td>
</tr>
<tr>
<td>NO 994639 A</td>
<td>24-11-1999</td>
<td></td>
</tr>
<tr>
<td>NZ 500002 A</td>
<td>28-09-2001</td>
<td></td>
</tr>
<tr>
<td>OA 11198 A</td>
<td>30-05-2003</td>
<td></td>
</tr>
<tr>
<td>PL 336168 A1</td>
<td>05-06-2000</td>
<td></td>
</tr>
<tr>
<td>SK 131899 A3</td>
<td>11-12-2000</td>
<td></td>
</tr>
<tr>
<td>TR 9902674 T2</td>
<td>21-02-2000</td>
<td></td>
</tr>
<tr>
<td>UA 65563 C2</td>
<td>15-08-2000</td>
<td></td>
</tr>
<tr>
<td>WO 9842188 A1</td>
<td>01-10-1998</td>
<td></td>
</tr>
<tr>
<td>CN 101057892 A</td>
<td>24-10-2007</td>
<td>NONE</td>
</tr>
<tr>
<td>CN 1559586 A</td>
<td>05-01-2005</td>
<td>NONE</td>
</tr>
<tr>
<td>ZA 200000192 A</td>
<td>27-09-2000</td>
<td>NONE</td>
</tr>
<tr>
<td>CN 101849981 A</td>
<td>06-10-2010</td>
<td>NONE</td>
</tr>
</tbody>
</table>