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(54) **Title**: ORAL COMBINATION DRUG FORMULATION COMPRISING A NON-STEROIDAL ANTI-INFLAMMATORY DRUG AND A COMPLEMENTARY LOW DOSE OF TRANEXAMIC ACID FOR THE TREATMENT OF MENSTRUAL PAIN ACCOMPANIED WITH EXCESSIVE MENSTRUAL BLOOD LOSS

(57) **Abstract**: The present invention relates to the relief of menstrual pain and the reduction of menstrual blood loss by an oral combination drug formulation comprising a non-steroidal anti-inflammatory drug (NSAID) and a complementary low-dose antifibrinolytic medication, tranexamic acid. This treatment can be used by women with painful menstrual periods (including those clinically diagnosed with dysmenorrhea) accompanied with heavy menstrual bleeding (including those clinically diagnosed with menorrhagia).

ORAL COMBINATION DRUG FORMULATION COMPRISING A NON-STEROIDAL ANTI-INFLAMMATORY DRUG AND A COMPLEMENTARY LOW DOSE OF TRANEXAMIC ACID FOR THE TREATMENT OF MENSTRUAL PAIN ACCOMPANIED WITH EXCESSIVE MENSTRUAL BLOOD LOSS

FIELD OF THE INVENTION

The present invention relates to the treatment of female menstrual disorders. More specifically, the present invention relates to the pharmacological treatment of menstrual pain accompanied with excessive menstrual blood loss. More specifically, the present invention relates to the pharmacological treatment of menstrual pain accompanied with excessive menstrual blood loss by administering an oral combination drug formulation comprising a non-steroidal anti-inflammatory drug (NSAID) and a complementary low dose of tranexamic acid.

BACKGROUND

Menstrual disorders affect the lives of millions of women. Painful menstrual periods associated with heavy menstrual bleeding often require medical attention and initiation of appropriate therapy.

Painful menstrual periods may be clinically diagnosed as primary or secondary dysmenorrhea. Primary dysmenorrhea is defined as painful menstrual period in women with normal pelvic anatomy. It is characterized by crampy pelvic pain beginning shortly before or at the onset of menstrual periods and lasting one to three days. Dysmenorrhea also may be secondary to pelvic organ pathology.[1] Reported dysmenorrhea prevalence rates range from 43% to 90%. The variability of these estimates is explained by differences in the methods of data collection, the definitions of dysmenorrhea and populations studied[2].

Heavy menstrual bleeding is defined as menorrhagia when the menstrual blood loss (MBL) exceeds 80 mL per menstrual cycle. In real-world practice, if a woman's periods are so heavy or so long that she finds them distressing she is experiencing heavy menstrual bleeding. One-third of all women report heavy menstrual bleeding at

some point in their lives, and in Western countries about 5% of reproductive-aged women seek treatment for it annually[3].

With the high prevalence of dysmenorrhea and menorrhagia, one may expect that a substantial number of women are suffering from both diseases concomitantly. Days of painful menstrual periods in conjunction with excessive MBL may also be experienced by women not clinically diagnosed with either condition, or diagnosed with only one of them (e.g., clinically diagnosed menorrhagia in the absence of dysmenorrhea; or clinically diagnosed dysmenorrhea in the absence of menorrhagia).

In North America and Europe, dysmenorrhea and menorrhagia are often treated by off-label use of approved hormonal contraceptives. For a number of women, the treatments may not be acceptable due to known contraindications, hormone-related adverse events and/or undesirable changes in the menstrual bleeding pattern, including unpredictable intra-cyclic bleeding, irregular menstrual periods and/or the development of amenorrhea[4, 5, 6] Due to known safety issues, danazol is rarely considered as a viable pharmacological treatment option. Surgical removal of the uterus (i.e., hysterectomy) may be considered for women with severe, refractory dysmenorrhea and menorrhagia. Yet, this is a radical treatment option with known undesirable consequences, including loss of fertility, surgical morbidity, as well as entailing high cost. There is limited evidence supporting minimally invasive methods of endometrial destruction as efficacious treatment options for dysmenorrhea and menorrhagia[1, 7].

Non-steroidal anti-inflammatory drugs (NSAIDs) are currently considered the most appropriate initial therapy for dysmenorrhea.[1,8,9,10,11,12,13,14,15,16] The following NSAIDs are commonly prescribed for the treatment of pain associated with dysmenorrhea: (1)Mefenamic acid, (Ponstel®); (2) Ibuprofen (Motrin®, Advil®); (3)Diclofenac potassium (Cataflam®); (4)Naproxen sodium (ANAPROX®/ANAPROX® DS); (5)Ketoprofen (Orudis®); (6) Meclofenamate sodium.[17,18,19,20,21,22,23] Ibuprofen, naproxen and ketoprofen are recommended drugs.[11,12] In the published meta-analysis, ibuprofen was singled out as the drug having the most favorable risk-benefit ratio.[16]

Oral NSAIDs have been shown to reduce MBL.[6,25,26] The NSAIDs' ability to reduce MBL is related to the established relationship of endomyometrial prostaglandins to the genesis of menorrhagia. The most extensively studied NSAIDs, the fenamates, inhibit prostaglandin synthesis and bind to prostaglandin receptors which are significantly increased in women with menorrhagia.[24]

Many patients desire greater reduction of the amount of menstrual flow than what is typically achievable using recommended doses of oral NSAIDs.[29] To ensure greater reduction of MBL, the maximal NSAID doses must often be adminitered.[4] This leads to undesirable side effects such as diarrhea, nausea, vomiting, stomach pain, constipation, and allergic reactions and is not optimal, particularly if a much lower NSAID dose is sufficient to alleviate menstrual pain. As an example, a high dose of ibuprofen (800 mg every 8 hours) has been recommended for MBL reduction[5], while a lower dose (400 mg every 4 hours as necessary for pain relief[19]) may be sufficient to alleviate menstrual pain. A recommendation in the FDA-approved class labeling for NSAIDs is to use the lowest effective dose for the shortest duration possible.[21]

In addition, NSAIDs demonstrate inferior efficacy in reducing MBL when compared to another drug widely used for treatment of menorrhagia, oral tranexamic acid. Oral tranexamic acid is marketed in the U.S. as Lysteda® and both within and outside the U.S. as Cyklokapron®. As is reported in the Lysteda label, tranexamic acid is a synthetic lysine amino acid derivative which diminishes the dissolution of hemostatic fibrin by plasmin. In the presence of tranexamic acid, the lysine receptor binding sites of plasmin for fibrin are occupied, preventing binding to fibrin monomers, thus preserving and stabilizing fibrin's matrix structure.[32] The antifibrinolytic activity of tranexamic acid results in inhibition of the dissolution of clots.[28] For many women, oral tranexamic acid is an efficacious treatment option. Clinical studies indicated that a 3900 mg/day regimen (marketed in the US as Lysteda) meets MBL reduction targets established by the FDA and significantly reduces limitations on social, leisure and physical activities.[32,36]

However, the treatment-induced changes in MBL established in the Lysteda clinical trials may be not satisfactory for some women, and many patients may desire even greater reduction of the amount of menstrual flow. As was noted in the medical

review of the Lysteda NDA, less than half (44%) of subjects returned to normal MBL after treatment (i.e., achieved a mean on-treatment MBL of less than 80 mL). There were no statistically significant differences between tranexamic acid and placebo treatment with regard to reduction of large stains, small and large clots as well as for changes in serum ferritin levels.[36]The latter endpoint is particularly meaningful for women with impaired iron status and/or clinically-diagnosed anemia frequently associated with menorrhagia.

In the evaluation of tranexamic acid in the treatment of menorrhagia performed in 2000 by the European Agency for the Evaluation of Medicinal Products (EMEA), a dose-dependent increase in efficacy was noted. The same review recommended a daily dose of 3-4 g/day and indicated that the risk of gastrointestinal adverse events is increased at 6 g/day.[34] While the FDA-approved Lysteda regimen (up to 3.9 g/day) is within the aforementioned recommended dosing range, certain Warnings and Precautions -- dose adjustment in women with renal impairment; increase in the risk of blood clots, stroke, or myocardial infarction in the event of concomitant therapy with hormonal contraceptives; the possibility of severe allergic reactions; visual or ocular adverse effects[6] -- reflect regulatory concerns regarding Lysteda's safety. In the risk-benefit assessment, the FDA medical reviewer suggested a 50% dose reduction for women who do not tolerate the common adverse events associated with the approved treatment regimen.[36]

A possibility of combining oral NSAID and oral tranexamic acid treatments has been suggested.[6] It may be assumed that the currently-approved doses of 3.9 mg/day for Lysteda (US) and 3.0 mg/day for Cyklokapron® (ex-US) would be used.[27,29] A combination oral tablet containing the standard doses of tranexamic acid (500 mg) and NSAID mefenamic acid (250 mg) is marketed in India (under Gynameno-Plus® and other trade names). For the treatment of primary dysmenorrhea, the mefenamic acid (Ponstel®) label recommends 500 mg as an initial dose followed by 250 mg every 6 hours, starting with the onset of bleeding and associated symptoms.[17] To comply with this recommendation, five Gynameno-Plus tablets must be taken daily. Therefore, the daily dose of co-administered tranexamic acid would be 2500mg (i.e. 65% and 85% of Lysteda and Cyklokapron approved doses, respectively). These treatment modalities do not take into consideration substantial contribution of the

NSAID component to the MBL reduction. As a result, they use doses of tranexamic acid which are much greater than needed for adequate control of excessive MBL resulting in increased incidence of adverse events.

Taken together, the clinical evidence indicates that the efficacy of oral NSAIDs in the treatment of dysmenorrhea accompanied with heavy menstrual bleeding cannot ensure adequate reduction of MBL. Due to safety issues reflected in relevant FDA guidance, an increase in an NSAID dose cannot be considered as an acceptable option. The efficacy of oral tranexamic acid in the reduction of MBL must also be weighed against the potentially disturbing side effects associated with this medication. When administered concomitantly via the conventional oral route at approved doses, the combination of an NSAID and tranexamic acid may raise safety concerns.

SUMMARY OF THE INVENTION

The present invention provides a method for effectively relieving menstrual pain and reducing excessive menstrual blood loss (MBL) without the undesirable side effects of currently recommended doses for oral medications by providing for an oral combination drug formulation comprising (i) a first therapeutically effective dose of a non-steroidal anti-inflammatory drug (NSAID), wherein said NSAID is able to reduce the volume of MBL, and (ii) a second complementary low dose of tranexamic acid. In a preferred embodiment, the dose of tranexamic acid is in the range from 50 mg to 425 mg per oral combination drug formulation. In the most preferred embodiment, the dose of tranexamic acid is in the range from 150 mg to 250 mg per oral combination drug formulation.

The present invention takes advantage of the ability of certain NSAIDs to reduce excessive MBL and of the different mechanisms of action between NSAIDs and tranexamic acid in MBL reduction and allows for the use of lower doses of tranexamic acid as compared to those currently employed. Due to combining MBL-reducing NSAIDs with tranexamic acid, the present invention also avoids the need to increase the doses of NSAIDs above doses which are efficacious for pain relief.

As compared to the currently available treatments, oral combination drug formulations of the present invention provide increased efficacy in the reduction of MBL in women suffering from painful menstrual periods accompanied by excessive MBL.

According to the present invention, an effective MBL reduction is achievable with a relatively low complementary daily dose of tranexamic acid, ranging from 10% to 55%, preferably ranging from 10% to 33% of the currently used oral dose of tranexamic acid (marketed in the US as Lysteda®). According to the present invention, a complementary dose of up to 2125 mg daily, preferably up to 1300 mg daily, most preferably ranging from 600 mg to 1000 mg daily (as opposed to the Lysteda's 3900 mg/day dose), is used for desirable MBL reduction.

According to the present invention, the dose selection of an NSAID and tranexamic acid takes into account the efficacy of a given NSAID in reducing the volume of MBL. For NSAIDs which cause reduction in the volume of MBL, the dose of co-administered tranexamic acid can be substantially lowered. Different mechanisms of the MBL-reducing action (e.g., inhibition of prostaglandin synthesis and binding to prostaglandin receptors by NSAID; reduction of plasminogen activator and plasmin levels by tranexamic acid) result in at least an additive effect of the two components of the oral combination drug formulations of the present invention. The appreciable contribution of the NSAID component to the MBL reduction dictates the selection of both NSAID and tranexamic acid doses. Relative severity of menstrual pain and the amount of MBL in the target population must also be taken into account. For example, in women with severe dysmenorrhea and relatively modest MBL, addition of a very small dose of tranexamic acid to the potent dose of NSAID should be considered. If, however, menstrual pain is less than severe and the volume of MBL is high, then a relatively small dose of NSAID is combined with a slightly greater complementary dose of tranexamic acid. In any case, the goal is an effective treatment of both conditions with an appropriate dose of each component. The method of the present invention ensures achievement of the clinical targets established in the treatment of menstrual pain and excessive MBL.

The critical aspect of the method of the present invention is the use of a complementary low dose of tranexamic acid. Data from the Lysteda® clinical program suggests 40% as a desirable treatment-induced decrease in the MBL.[36] An approximate 40% decrease in MBL was also considered as clinically relevant in the scientific evaluation of tranexamic acid in the treatment of menorrhagia performed in 2000 by the European Agency for the Evaluation of Medicinal Products, EMEA. The same review indicated a dose-dependent increase of efficacy of tranexamic acid.[34] Dose-dependent percent decrease in MBL is supported by the Lysteda clinical data: a mean percent change in MBL for 1950 mg/day regimen was approximately 25% vs. 39% for the 3900 mg/day dose. [36]

Across a number of evaluated studies, an overall mean percent reduction in MBL for NSAIDs was close to 30%.[27]Therefore, an additional 10% decrease in MBL may be considered as an appropriate target for the complementary dose of tranexamic acid. Assuming proportionality across the entire tranexamic acid dose range, it may be hypothesized that up to 1000 mg of tranexamic acid daily may be sufficient to achieve this target. To accommodate the possibility of a less-than-expected effect of NSAID on the MBL, the more conservative estimate would be a complementary dose of up to 1300 mg/day, or 33% of the currently used Lysteda dose. To ensure additional reduction of the severe menstrual blood loss (MBL), the most conservative estimate would be a complementary dose of up to 2125 mg/day, or 55% of the currently used Lysteda dose.

The MBL reduction targets must be adjusted for females suffering from both menstrual pain and excessive MBL when the latter alone would not be clinically diagnosed as menorrhagia. The data from the Lysteda clinical program suggests 25% as an adequate treatment-induced decrease in the MBL in women with excessive MBL when pretreatment (baseline) MBL is relatively modest (less than 100 mL per menstrual cycle).[38] Such a percent decrease in MBL must be adequate for women with no clinical diagnosis related to menorrhagia and would allow for a lower complementary dose of tranexamic acid (possibly, up to 10%-15% of the daily dose of Lysteda).

Specific examples of the calculation of complementary doses of tranexamic acid for individual NSAIDs (based on historical data) are presented in one of the following sections.

While the exact doses for each drug useful in the method of the invention are going to be determined in clinical trials, the possibility of a substantial dose decrease, relative to the currently employed doses of oral tranexamic acid is surprising and new. Also surprising and new is the possibility of reduced doses of an NSAID when compared to the doses recommended for women with painful menstrual periods accompanied with excessive MBL: no NSAID dose increase or smaller NSAID dose increase is needed according to the present invention to ensure adequate MBL reduction in addition to effective pain relief.

While the optimal treatment duration will be determined during clinical trials, it is expected that the drug administration has to start at the onset of the menstrual period and last for several days, until the end of the menstrual period or at least until the end of painful and/or heavy menstrual bleeding.

Reduced oral doses of NSAID and tranexamic acid used according to the present invention lead to a lower incidence of adverse events, such as diarrhea, nausea, vomiting, stomach pain, upset stomach, constipation, heartburn, allergic reactions, disturbance of color, sharpness, or field of vision, etc. The reduced complementary dose of tranexamic acid may also eliminate the risks of systemic toxicity and thrombloembolism associated with its oral administration.

The oral combination drug formulations of the present invention allows to achieve high efficacy in the management of menstrual pain accompanied with excessive MBL and a decrease in drug-related adverse events, as well as the convenience of a single drug formulation.

DETAILS OF THE INVENTION

Definitions:

Menstrual flow is defined as encompassing menstrual blood and/or menstrual fluid.

Menstrual pain relief is defined as a decrease in the severity of menstrual pain when compared to the pre-treatment conditions. Menstrual pain relief may be complete (when a woman does not experience any pain) or partial (when a woman experiences less severe pain).

A therapeutically effective dose/amount of NSAID is defined as the amount of oral NSAID that results in significant (at least, 20%) changes in a 4-point verbal rating scale ranging from 0 (no pain) to 3 (severe pain) and/or a 100-mm visual analog scale of severity of the menstrual pain (see reference 43) when compared to the pre-treatment conditions.

A therapeutically effective dose/amount of tranexamic acid is defined as the amount of the drug that results in a significant (at least, 10%) change in the volume of menstrual blood loss (MBL) when compared to the pre-treatment conditions.

- The present invention provides a method for relieving menstrual pain and reducing menstrual blood loss (MBL) in a female by administering to the female an oral combination drug formulation comprising (i) a first therapeutically effective dose of a non-steroidal anti-inflammatory drug (NSAID), wherein said NSAID is able to reduce the volume of MBL, and (ii) a second complementary low dose of tranexamic acid.
- In a preferred embodiment, the dose of tranexamic acid is in the range from 50 mg to 425 mg, most preferably from 150 mg to 250 mg, per oral combination drug formulation.
- The total daily dose of tranexamic acid does not exceed 2125 mg.
- In a preferred embodiment, the total daily dose of tranexamic acid does not exceed 1300 mg, and is most preferably ranging from 600 mg to 1000 mg.
- The oral combination drug formulation of the present invention can be administered to females, e.g., one to six times per day.
- The oral combination drug formulation of the invention can be administered to females suffering from menstrual pain accompanied with excessive MBL from the

onset of menstrual bleeding until the resolution of related symptoms or the end of the menstrual period.

- Non-limiting examples of useful oral drug formulations useful in the method of the present invention include oral tablet, oral capsule and oral caplet.

- The NSAIDs useful in the formulations of the present invention have proven analgesic efficacy and/or an indication for the treatment of menstrual pain and are also be able to reduce the volume of MBL. Non-limiting examples of useful NSAIDs include, e.g., ibuprofen, naproxen, diclofenac, ketoprofen, mefenamic acid, and metabolites thereof.

-Preferably, NSAID doses range from 5 mg to 1000 mg per oral combination drug formulation.

- In one embodiment, the NSAID is ibuprofen. Preferably, the dose of ibuprofen is ranging from 100 mg to 800 mg per oral combination drug formulation.

- In another embodiment, the NSAID is naproxen. Preferably, the dose of naproxen is ranging from 150 mg to 600 mg per oral combination drug formulation.

- In yet another embodiment, the NSAID is diclofenac. Preferably, the dose of diclofenac is ranging from 5 mg to 50 mg per oral combination drug formulation.

- In a further embodiment, the NSAID is ketoprofen. Preferably, the dose of ketoprofen is ranging from 5 mg to 50 mg per oral combination drug formulation.

- In one embodiment, the NSAID is mefenamic acid. Preferably, the dose of mefenamic acid is ranging from 50 mg to 500 mg per oral combination drug formulation.

- In certain embodiments, the method of the invention is used to treat females clinically diagnosed with primary dysmenorrhea.

- In certain embodiments, the method of the invention is used to treat females clinically diagnosed with secondary dysmenorrhea.

- In certain embodiments, the method of the invention is used to treat females with no clinical diagnosis related to primary dysmenorrhea or secondary dysmenorrhea, but who perceive their menstrual periods to be painful.

- In certain embodiments, the method of the invention is used to treat females with menstrual bleeding of less than 80 mL per menstrual cycle.

- In certain embodiments, the method of the invention is used to treat females with menstrual bleeding of more than 80 mL per menstrual cycle.

- In certain embodiments, the method of the invention is used to treat females clinically diagnosed with menorrhagia.

- In certain embodiments, the method of the invention is used to treat females clinically diagnosed with idiopathic menorrhagia.

- In certain embodiments, the method of the invention is used to treat females clinically diagnosed with cyclic heavy menstrual bleeding.

- In certain embodiments, the method of the invention is used to treat females clinically diagnosed with dysfunctional uterine bleeding.

- In certain embodiments, the method of the invention is used to treat females with no clinical diagnosis related to menorrhagia, idiopathic menorrhagia, cyclic heavy menstrual bleeding, or dysfunctional uterine bleeding, but who perceive their menstrual periods to be heavy.

- In certain embodiments, the method of the invention is used to treat females clinically diagnosed with anemia.

-In a preferred embodiment, an oral combination drug formulation consists of 400 mg ibuprofen and 150-200 mg of tranexamic acid; this oral combination drug formulation is administered four times daily to treat females clinically diagnosed with primary or secondary dysmenorrhea and clinically diagnosed with menorrhagia.

-In another preferred embodiment, an oral combination drug formulation consists of 200 mg ibuprofen and 200-250 mg tranexamic acid; this oral combination drug formulation is administered three times daily to treat females with no clinical diagnosis related to primary dysmenorrhea or secondary dysmenorrhea and with no clinical diagnosis related to menorrhagia.

The active compounds of the present invention can be formulated in an oral combination drug formulation in combination with one or more pharmaceutically acceptable carriers and/or excipients such as, e.g., stabilizers, lubricants, diluents, flavorants, colorants, buffers, and disintegrants. Suitable pharmaceutically acceptable carriers include any and all conventional solvents (such as, e.g., water, physiological solution, dextrose, glycerol, ethanol, and the like, as well as combinations thereof), wetting agents, emulgators, buffers, conservants, antioxidants, dispersion media, fillers, solid carriers, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, as well as other well-known agents which enhance the shelf life or effectiveness of one or more of the active components of the composition.

Examples of such useful substances can be found e.g. in the book Remington: the science and practice of pharmacy. Lippincott Williams & Wilkins 2005. Except insofar as any conventional media or agent is incompatible with the active ingredients, use thereof in compositions of the present invention is contemplated.

Oral combination drug formulations of this invention may be formulated to modify and control the distribution of the NSAID and/or tranexamic acid present in a composition upon administration to the female; such controlled release formulations are well known and widely practiced in the art. In particular, the controlled release formulation may be an extended release formulation, which can reduce the required frequency of administration by maintaining the concentration of the active substances in the composition at desired levels. Any suitable extended release delivery system may be used. Some exemplary methods and technologies useful for implementing controlled release pharmaceutical formulations, and particularly extended-release formulations, are discussed in the following publications: Chasin M, Langer RS Biodegradable polymers as drug delivery systems. New York: M. Dekker 1990; Park K et al. Biodegradable hydrogels for drug delivery. Lancaster, PA: Technomic Pub 1993; Wise DL Handbook of pharmaceutical controlled release technology. New York: Marcel Dekker 2000; Li XP, Jasti BR Design of controlled release drug delivery systems. New York: McGraw-Hill 2006; Benita S Microencapsulation: methods and industrial applications. New York: Taylor & Francis 2006; and Rathbone MJ Modified-release drug delivery technology. New York: Informa Healthcare 2008.

It will be readily evident to the one skilled in the art that the various approaches useful in preparing pharmaceutical formulations, as described herein, and other approaches known in the art, may be usefully combined in a single oral combination drug formulation.

EXAMPLES

The present invention is also described and demonstrated by way of the following examples. However, the use of these and other examples anywhere in the specification is illustrative only and in no way limits the scope and meaning of the invention or of any exemplified term. Likewise, the invention is not limited to any

particular preferred embodiments described here. Indeed, many modifications and variations of the invention may be apparent to those skilled in the art upon reading this specification, and such variations can be made without departing from the invention in spirit or in scope. The invention is therefore to be limited only by the terms of the appended claims along with the full scope of equivalents to which those claims are entitled.

General Considerations. Determination of a complementary dose of tranexamic acid in oral combination drug formulation provided in the Examples, below, are based on the MBL reduction targets established by the FDA[36] in the treatment of menorrhagia as well as the MBL-reducing potency of an NSAID selected for the inclusion in the combination drug formulation.

The efficacy metrics reported for the oral tranexamic acid formulation (3900 mg daily dose, marketed in the US as Lysteda®) may serve as appropriate benchmarks.

Data from the Lysteda clinical program suggests 40% as a desirable treatment-induced decrease in the MBL in women with menorrhagia.[32] An approximate 40% decrease in MBL was also considered as clinically relevant in the scientific evaluation of oral tranexamic acid in the treatment of menorrhagia performed in 2000 by the European Agency for the Evaluation of Medicinal Products, EMEA. The same review indicated a dose-dependent increase in the efficacy of tranexamic acid.[34] A dose-dependent reduction in MBL is also evident from the Lysteda clinical study: the mean percent change in MBL for the 1950 mg/day regimen was approximately 25% vs. 39% for the 3900 mg/day dose. [36]

The data from the Lysteda clinical program also suggests 25% as an adequate treatment-induced decrease in the MBL in women with excessive MBL when pretreatment (baseline) MBL is relatively modest (less than 100 mL per menstrual cycle).[38] Such a decrease in MBL must be adequate for women with no clinical diagnosis related to menorrhagia.

The estimates below are based on data from individual clinical studies. Use of averages across all studies for any particular NSAID may also be considered.

Alternatively, a specially designed study may be conducted to evaluate MBL reduction induced by an NSAID selected for the oral drug formulation in combination with tranexamic acid.

Example 1. One clinical study evaluated effect on MBL of 400 mg of ibuprofen administered four times daily. A 32% reduction in MBL was reported.[27,39] A complementary reduction of MBL (necessary to reach the 40% MBL reduction target in women clinically diagnosed with menorrhagia) would be 8%, or about one-third of the effect observed for the 1950 mg tranexamic acid daily dose as reported in the Lysteda label.[32] One-third of that dose (approximately 650 mg) would be an adequate daily supplement of tranexamic acid. The combined oral formulation would then consist of 400 mg of ibuprofen and 150-200 mg of tranexamic acid with a four times/day dosing schedule.

This oral combination drug formulation may be considered for women clinically diagnosed with primary or secondary dysmenorrhea and clinically diagnosed with menorrhagia.

Example 2. Another clinical study evaluated effect on MBL of 200 mg of ibuprofen administered three times daily. A 16% reduction in MBL was reported.[27,40] A complementary reduction of MBL (necessary to reach the 25% MBL reduction target in women with relatively modest baseline MBL) would be 8%, or about one-third of the effect observed for the 1950 mg tranexamic acid daily dose as reported in the Lysteda label.[32] One-third of that dose (approximately 650 mg) would be an adequate daily supplement of tranexamic acid. The combined oral formulation would then consist of 200 mg of ibuprofen and 200-250 mg of tranexamic acid with a three times/day dosing schedule.

This oral combination drug formulation may be considered for women with no clinical diagnosis related to dysmenorrhea and menorrhagia.

Example 3. Another clinical study evaluated effect on MBL of 50 mg of diclofenac sodium administered four times daily on Day 1 and three times on the following four days of the menstrual period. A 24% reduction in MBL was reported.[27,41] A

complementary reduction of MBL (necessary to reach the 40% MBL reduction target in women clinically diagnosed with menorrhagia) would be 16%, or about two-thirds of the effect observed for the 1950 mg of tranexamic acid daily dose as reported in the Lysteda label.[32] Two-thirds of that dose (approximately 1300 mg) would be an adequate daily supplement of tranexamic acid. The combined oral formulation would then consist of 50 mg of diclofenac sodium and 325 mg of tranexamic acid with a four times/day dosing schedule.

This oral combination drug formulation may be considered for women clinically diagnosed with primary or secondary dysmenorrhea and clinically diagnosed with menorrhagia.

Example 4. Another clinical study evaluated effect on MBL of 500 mg of mefenamic acid administered three times daily during the menstrual period. A 30% reduction in MBL was reported for women clinically diagnosed with menorrhagia (baseline MBL > 80 mL)[27,42] A complementary reduction of MBL (necessary to reach the 40% MBL reduction target in women clinically diagnosed with menorrhagia) would be 10%, or about two-fifths of the effect observed for the 1950 mg tranexamic acid daily dose as reported in the Lysteda label.[32] Two-fifths of that dose (approximately 800 mg) would be an adequate daily supplement of tranexamic acid. The combined oral formulation would then consist of 500 mg of mefenamic acid and 250-300 mg of tranexamic acid with a three times/day dosing schedule.

This oral combination drug formulation may be considered for women clinically diagnosed with primary or secondary dysmenorrhea and clinically diagnosed with menorrhagia.

Example 5. The study referenced in the previous example also evaluated the effect on MBL of 500 mg of mefenamic acid administered three times daily during the menstrual period in women with no clinical diagnosis of menorrhagia (baseline MBL < 80 mL). A 19% reduction in MBL was reported.[27,42] A complementary reduction of MBL (necessary to reach the 25% MBL reduction target in women with relatively modest baseline MBL) would be 6%, or about one-fourth of the effect observed for the 1950 mg tranexamic acid daily dose as reported in the Lysteda label.[32] One-fourth

of that dose (approximately 500 mg) would be an adequate daily supplement of tranexamic acid. The combined oral formulation would then consist of 500 mg of mefenamic acid and 150-200 mg of tranexamic acid with a three times/day dosing schedule.

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This oral combination drug formulation may be considered for women with no clinical diagnosis related to dysmenorrhea and menorrhagia.

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* * *

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description. Such modifications are intended to fall within the scope of the appended claims.

All patents, applications, publications, test methods, literature, and other materials cited herein are hereby incorporated by reference in their entirety as if physically present in this specification.

CLAIMS

1. A method for relieving menstrual pain and reducing menstrual blood loss in a female by administering to the female an oral combination drug formulation comprising (i) a first therapeutically effective dose of a non-steroidal anti-inflammatory drug (NSAID), wherein said NSAID is able to reduce the volume of menstrual blood loss, and (ii) a second complementary low dose of tranexamic acid.

2. A method for relieving menstrual pain and reducing menstrual blood loss in a female by administering to the female an oral combination drug formulation comprising (i) a first therapeutically effective amount of a non-steroidal anti-inflammatory drug (NSAID), wherein said NSAID is able to reduce the volume of menstrual blood loss, and (ii) a second complementary low dose of tranexamic acid, wherein the dose of tranexamic acid is in the range from 50 mg to 425 mg per oral combination drug formulation.

3. The method according to claim 1 or 2, wherein the total daily dose of tranexamic acid does not exceed 2125 mg.

4. The method according to claim 1 or 2, wherein the total daily dose of tranexamic acid does not exceed 1300 mg.

5. The method according to claim 1 or 2, wherein the total daily dose of tranexamic acid ranges from 600 mg to 1000 mg.

6. The method according to claim 1 or 2, wherein the oral combination drug formulation is selected from the group consisting of oral tablet, oral capsule and oral caplet.

7. The method according to claim 1 or 2, wherein the NSAID is selected from the group consisting of ibuprofen, naproxen, diclofenac, ketoprofen, mefenamic acid, and metabolites thereof.

8. The method according to claim 7, wherein the NSAID is ibuprofen.

9. The method according to claim 7, wherein the NSAID is naproxen.

10. The method according to claim 7, wherein the NSAID is diclofenac.

11. The method according to claim 7, wherein the NSAID is ketoprofen.

12. The method according to claim 7, wherein the NSAID is mefenamic acid.

13. The method according to any one of claims 1-2, wherein the dose of NSAID is ranging from 5 mg to 1000 mg per oral combination drug formulation.

14. The method according to claim 8, wherein the dose of ibuprofen is ranging from 100 mg to 800 mg per oral combination drug formulation.

15. The method according to claim 9, wherein the dose of naproxen is ranging from 150 mg to 600 mg per oral combination drug formulation.

16. The method according to claim 10, wherein the dose of diclofenac is ranging from 5 mg to 50 mg per oral combination drug formulation.

17. The method according to claim 11, wherein the dose of ketoprofen is ranging from 5 mg to 50 mg per oral combination drug formulation.

18. The method according to claim 12, wherein the dose of mefenamic acid is ranging from 50 mg to 500 mg per oral combination drug formulation.

19. The method according to claim 1, wherein the dose of tranexamic acid is ranging from 50 mg to 425 mg per oral combination drug formulation.

20. The method according to claim 1 or 2, wherein the female has a condition selected from the group consisting of primary dysmenorrhea, secondary dysmenorrhea, menorrhagia, idiopathic menorrhagia, cyclic heavy menstrual bleeding, dysfunctional uterine bleeding, and anemia.

21. The method according to claim 1 or 2, wherein the female has menstrual bleeding of less than 80 ml per menstrual cycle.

22. The method according to claim 1 or 2, wherein the female has menstrual bleeding of more than 80 ml per menstrual cycle.

23. The method according to claim 1 or 2, wherein the oral combination drug formulation is administered from the onset of menstrual bleeding until the resolution of related symptoms.

24. The method according to claim 1 or 2, wherein the oral combination drug formulation is administered from the onset of menstrual bleeding until the end of the menstrual period.

25. The method according to claim 1 or 2, wherein the oral combination drug formulation is administered one to six times per day.

AMENDED CLAIMS
received by the International Bureau on 03 May 2012

1. A method for relieving menstrual pain and reducing menstrual blood loss in a female by administering to the female an oral combination drug formulation comprising (i) a first therapeutically effective dose of a non-steroidal anti-inflammatory drug (NSAID), wherein said NSAID is able to reduce the volume of menstrual blood loss, and (ii) a second complementary low dose of tranexamic acid.

2. A method for relieving menstrual pain and reducing menstrual blood loss in a female by administering to the female an oral combination drug formulation comprising (i) a first therapeutically effective amount of a non-steroidal anti-inflammatory drug (NSAID), wherein said NSAID is able to reduce the volume of menstrual blood loss, and (ii) a second complementary low dose of tranexamic acid, wherein the dose of tranexamic acid is in the range from 50 mg to 425 mg per oral combination drug formulation.

3. The method according to claim 1 or 2, wherein the total daily dose of tranexamic acid does not exceed 2125 mg.

4. The method according to claim 1 or 2, wherein the total daily dose of tranexamic acid does not exceed 1300 mg.

5. The method according to claim 1 or 2, wherein the total daily dose of tranexamic acid ranges from 600 mg to 1000 mg.

6. The method according to claim 1 or 2, wherein the oral combination drug formulation is selected from the group consisting of oral tablet, oral capsule and oral caplet.

7. The method according to claim 1 or 2, wherein the NSAID is selected from the group consisting of ibuprofen, naproxen, diclofenac, ketoprofen, mefenamic acid, and metabolites thereof.

8. The method according to claim 7, wherein the NSAID is ibuprofen.

9. The method according to claim 7, wherein the NSAID is naproxen.

10. The method according to claim 7, wherein the NSAID is diclofenac.

11. The method according to claim 7, wherein the NSAID is ketoprofen.

12. The method according to claim 7, wherein the NSAID is mefenamic acid.

13. The method according to any one of claims 1-2, wherein the dose of NSAID is ranging from 5 mg to 1000 mg per oral combination drug formulation.

14. The method according to claim 8, wherein the dose of ibuprofen is ranging from 100 mg to 800 mg per oral combination drug formulation.

15. The method according to claim 9, wherein the dose of naproxen is ranging from 150 mg to 600 mg per oral combination drug formulation.

16. The method according to claim 10, wherein the dose of diclofenac is ranging from 5 mg to 50 mg per oral combination drug formulation.

17. The method according to claim 11, wherein the dose of ketoprofen is ranging from 5 mg to 50 mg per oral combination drug formulation.

18. The method according to claim 12, wherein the dose of mefenamic acid is ranging from 50 mg to 500 mg per oral combination drug formulation.

19. The method according to claim 1, wherein the dose of tranexamic acid is ranging from 50 mg to 425 mg per oral combination drug formulation.

20. The method according to claim 1 or 2, wherein the female has a condition selected from the group consisting of primary dysmenorrhea, secondary dysmenorrhea, menorrhagia, idiopathic menorrhagia, cyclic heavy menstrual bleeding, dysfunctional uterine bleeding, and anemia.

21. The method according to claim 1 or 2, wherein the female has menstrual bleeding of less than 80 ml per menstrual cycle.

22. The method according to claim 1 or 2, wherein the female has menstrual bleeding of more than 80 ml per menstrual cycle.

23. The method according to claim 1 or 2, wherein the oral combination drug formulation is administered from the onset of menstrual bleeding until the resolution of related symptoms.

24. The method according to claim 1 or 2, wherein the oral combination drug formulation is administered from the onset of menstrual bleeding until the end of the menstrual period.

25. The method according to claim 1 or 2, wherein the oral combination drug formulation is administered one to six times per day.

26. A method for relieving menstrual pain and reducing menstrual blood loss in a female by administering to the female an oral combination drug formulation comprising (i) a first therapeutically effective dose of a non-steroidal anti-inflammatory drug (NSAID), wherein said dose of NSAID is able to significantly reduce menstrual pain and is also able to reduce the volume of menstrual blood loss, and (ii) a second complementary dose of tranexamic acid, wherein the dose of tranexamic acid is selected based on the contribution of the NSAID to the reduction of menstrual blood loss.

27. A method for relieving menstrual pain and reducing menstrual blood loss in a female by administering to the female an oral combination drug formulation comprising (i) a first therapeutically effective dose of a non-steroidal anti-inflammatory drug (NSAID), wherein said dose of NSAID is able to significantly reduce menstrual pain and is also able to reduce the volume of menstrual blood loss, and (ii) a second complementary dose of tranexamic acid, wherein the dose of tranexamic acid is in the range from 150 mg to 250 mg per oral combination drug formulation.

28. The method according to claim 26 or 27, wherein the total daily dose of tranexamic acid is determined

a) based on the difference between the desired percent (%) reduction in menstrual blood loss and the percent (%) reduction in menstrual blood loss achievable with the selected dose of the NSAID and

b) based on the assumptions that (i) efficacy of tranexamic acid in reduction of menstrual blood loss is dose-dependent and (ii) approximately 40% reduction of menstrual blood loss is achievable with a daily dose of 3900 mg of tranexamic acid, when used without NSAID.

29. The method according to claim 26 or 27, which method results in at least 40% decrease in menstrual blood loss when administered to the female having menorrhagia.

30. The method according to claim 26 or 27, which method results in at least 25% decrease in menstrual blood loss when administered to the female with no clinical diagnosis related to menorrhagia.

31. The method according to claim 26 or 27, wherein the total daily dose of tranexamic acid is ranging from 600 mg to 1000 mg.

32. The method according to claim 31, wherein the total daily dose of tranexamic acid is approximately 800 mg.

33. The method according to claim 31, wherein the total daily dose of tranexamic acid is approximately 650 mg.

34. The method according to claim 26 or 27, wherein the total daily dose of tranexamic acid is ranging from 390 mg to 585 mg.

35. The method according to claim 26 , wherein the dose of tranexamic acid is ranging from 250 mg to 300 mg per oral combination drug formulation.

36. The method according to claim 26 or 27, wherein the NSAID has proven analgesic efficacy and/or an indication for the treatment of menstrual pain.

37. The method according to claim 26 or 27, wherein the NSAID is selected from the group consisting of ibuprofen, naproxen, diclofenac, ketoprofen, mefenamic acid, and metabolites thereof.

38. The method according to claim 37, wherein the oral combination drug formulation comprises 400 mg of ibuprofen and 150-200 mg of tranexamic acid.

39. The method according to claim 38, wherein the oral combination drug formulation is administered four times daily to the female clinically diagnosed with primary or secondary dysmenorrhea and clinically diagnosed with menorrhagia.

40. The method according to claim 37, wherein the oral combination drug formulation comprises 200 mg of ibuprofen and 200-250 mg of tranexamic acid.

41. The method according to claim 40, wherein the oral combination drug formulation is administered three times daily to treat the female with no clinical diagnosis related to dysmenorrhea and menorrhagia.

42. An orally administrable pharmaceutical composition comprising (i) a first therapeutically effective dose of a non-steroidal anti-inflammatory drug (NSAID), wherein said dose of NSAID is able to significantly reduce menstrual pain and is also able to reduce the volume of menstrual blood loss, and (ii) a second complementary low dose of tranexamic acid, wherein the dose of tranexamic acid is selected based on the contribution of the NSAID to the reduction of menstrual blood loss.

43. The composition according to claim 42, wherein the dose of tranexamic acid is in the range from 150 mg to 250 mg.

44. The composition according to claim 42 which is an oral tablet, oral capsule or oral caplet.

45. The composition according to claim 42, wherein the NSAID has proven analgesic efficacy and/or an indication for the treatment of menstrual pain.

46. The composition according to claim 42, wherein the NSAID is selected from the group consisting of ibuprofen, naproxen, diclofenac, ketoprofen, mefenamic acid, and metabolites thereof.

47. The composition according to claim 46, wherein the composition comprises 400 mg of ibuprofen and 150-200 mg of tranexamic acid.

48. The composition according to claim 46, wherein the composition comprises 200 mg of ibuprofen and 200-250 mg of tranexamic acid.

49. The composition according to claim 42, wherein the dose of tranexamic acid is ranging from 250 mg to 300 mg.

50. The composition according to claim 46, wherein the composition comprises 500 mg of mefenamic acid and 150-200 mg of tranexamic acid.

51. The composition according to claim 46, wherein the composition comprises 500 mg of mefenamic acid and 250-300 mg of tranexamic acid.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 11/60643

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 9/00 (2012.01)
USPC - 424/400
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)
USPC-424/400

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC-514/370, 567 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Dialog Web, Google Scholar, tranexamic, ibuprofen, naproxen, diclofenac, keptoprofen, mefenamic, menstrual bleeding, dysmenorrhea, menorrhagia, dysfunctional uterine bleeding, anemia, non-streroidal anti-inflammatory drugs, antifibrinolytic

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	Natesan et al. Improved Rp- Hplc Method for the Simultaneous Estimation of Tranexamic Acid and Mefenamic Acid in Tablet Dosage Form. Pharm Anal Acta, 20 February 2011, Vol 2, Iss 1, pg 1-6, entire document, esp pg 1, para 3	1, 6-7, 12-13, 18, 20 ---------- 2-5, 8-11, 14-17, 19, 21-25
Y	US 2010/0143468 A1 (Moore et al.) 10 June 2010 (10.06.2010) entire document esp para [0004], [0009], [0015], [0029], [0044]-[0052], [0072], [0107], [0133]	2-4, 19, 21-25
Y	US 7,351,740 B2 (Zerangue et al.) 01 April 2008 (01.04.2008) entire document esp. col 43, ln 24-25, ln 50-59; col 44, ln 56-60	5, 8-11, 14-17
Y	US 2004/0186180 A1 (Gelotte et al.) 23 September 2004 (23.09.2004) entire document esp. para[0002], [0024], [0032]	16-17

☐ Further documents are listed in the continuation of Box C. ☐

* 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
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
08 March 2012 (08.03.2012)	26 MAR 2012
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)