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Lysteda® for Heavy Menstrual Bleeding

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Abstract
Lysteda®, a novel formulation of tranexamic acid, is an antifibrinolytic medication recently approved by the Food and Drug Administration (FDA) for the treatment of heavy menstrual bleeding. Tranexamic acid has been shown to significantly reduce menstrual blood loss while simultaneously allowing a woman to safely become pregnant. The major advantage of Lysteda® (an oral modified-release formulation of tranexamic acid) compared to oral immediate-release tranexamic acid, is the decreased occurrence of gastrointestinal side effects. As there are no therapeutic equivalents to Lysteda® for heavy menstrual bleeding, it is important for pharmacists to be able to counsel patients appropriately on the specific dosing regimen and side effects of this new product.

Objectives
1. Describe the mechanism of action of Lysteda®.
2. Compare and contrast treatment options for heavy menstrual bleeding.
3. List the side effects and warnings associated with Lysteda®.
4. Explain important patient counseling information.

Introduction
During normal menstruation women lose approximately 35-45 mL of blood every 21 to 35 days. The amount of blood lost with each menstrual cycle varies between women and throughout an individual's life. The American Congress of Obstetricians and Gynecologists define menorrhagia, or heavy menstrual bleeding (HMB), as the "loss of 80 mL or more of blood per cycle or bleeding that lasts for more than seven days," however it can also be diagnosed based on a patient's perception of excessive bleeding and interference with physical, social, and/or emotional quality of life. Lysteda® (Ferring Pharmaceuticals Inc., Parsippany, N.J.) is the only non-hormonal medication approved to treat cyclic HMB in the United States. Immediate-release tranexamic acid (TA) has been utilized in Europe, Canada, Asia and Australia for over 30 years to decrease menstrual blood loss, and it is even available over-the-counter in select countries. The antifibrinolytic, Lysteda®, made its debut on the U.S. market in July 2010. With approximately 27 percent of women experiencing a decreased quality of life due to HMB, Lysteda® has the potential to greatly impact a significant number of women. To differentiate the modified- and immediate-release forms of tranexamic acid, we will refer to the modified-release form as Lysteda® and the immediate-release form as TA throughout the remainder of this article.

Pathophysiology
Fibrinolysis, or dissolution of a clot, begins when endothelial cells release tissue plasminogen activator (tPA). TPA facilitates the binding of plasminogen to lysine binding sites on fibrin, resulting in the conversion of plasminogen to plasmin. Plasmin is ultimately responsible for degrading clots, and in the uterus, the result is menstrual bleeding. Regulatory mechanisms usually control fibrinolysis, but when they fail, excessive uterine fibrinolysis may occur and lead to HMB. Tranexamic acid, a synthetic lysine analog, decreases menstrual blood loss by reversibly blocking the lysine binding site on plasminogen, preventing the formation of plasmin and subsequent fibrinolysis. HMB may be due to a specific biological cause such as uterine polyps, fibroids, endometriosis, von Willebrand's disease or hemophilia; however, half of all women with HMB suffer from idiopathic HMB. Idiopathic HMB is attributed to elevated levels of endometrial tPA and plasmin compared to women with normal bleeding, making antifibrinolytic medications such as Lysteda® an ideal treatment option.

Review of Other Treatment Options for HMB
Lysteda® is a unique and effective way of treating menorrhagia. However, because this non-hormonal treatment option was recently FDA approved and is the first of its kind, many health care professionals may not feel comfortable counseling patients on this new medication. With Lysteda® costing nearly $170 for a five day supply of 30 tablets, physicians and patients must consider the price of Lysteda® compared to more traditional medications. The unique qualities of Lysteda® may be worth the price in patients who refuse, have failed or cannot tolerate traditional therapies.

One of the first questions considered upon treating menorrhagia is whether the woman wishes to preserve long-term fertility. If she does not wish to preserve long-term fertility, she may consider one of two primary surgical procedures: hysterectomy or endometrial ablation. Hysterectomies are becoming much less common as second-generation endometrial ablation becomes more advanced. These surgical procedures are very effective for menorrhagia, but are becoming less practical as medications become more effective, while providing the opportunity for continued fertility.

If a woman wishes to preserve her fertility long term, hormonal therapy (including hormonal contraceptives or cyclic
progesterone) and non-steroidal anti-inflammatory drugs (NSAIDs) are traditional options.

It has been long established that the best nonsurgical treatment option for HMB is the levonorgestrel-containing intrauterine device (LNG-IUD).\(^8,10,11\) It ranks higher than all other medical treatments when considering effectiveness, side effects and length of treatment.\(^11\) The LNG-IUD is the first-line therapy in treating menorrhagia as outlined by Britain’s National Institute for Health and Clinical Excellence (NICE) guidelines for HMB released in January of 2007.\(^10\) Women must be fitted for the IUD by a doctor or specially trained nurse and, after insertion, the IUD should be replaced every five years. This system works by releasing 20 mcg of levonorgestrel, a synthetic progesterone, every 24 hours.\(^1\) This product suppresses endometrial growth, which causes endometrial glands to atrophy.\(^8\) Some irregular spotting may occur within the first few months and approximately 25 percent of users develop amenorrhea, but overall patient satisfaction is high.\(^1,13\) There is a small chance of uterine perforation at the time of placement. Common side effects include headache, breast tenderness and acne.\(^12,13\)

Combined hormonal contraceptives (CHCs) reduce menstrual blood loss by approximately 40 percent.\(^8,9\) On March 14, 2012, the four-phase oral contraceptive Natazia\(^\circledR\) (estradiol valerate and estradiol valerate/dienogest), became the first and only FDA approved CHC for the treatment of HMB.\(^14\) CHCs are administered in either a cyclic or continuous manner and, like LNG-IUDs, they prevent proliferation of the endometrium.\(^8,9,12\) Continuous administration products (meaning no inert or hormone-free interval) may improve bleeding patterns and other symptoms associated with menstruation, but the patient may also experience some breakthrough bleeding.\(^8,9\) Although these drugs generally do not appear to pose a risk with long-term use, it should be noted that they are not recommended in some patient populations, such as smokers older than 35 years, as they increase the risk of venous thromboembolism, stroke or heart attack.\(^1,8,10\) Common side effects associated with CHCs include headache, mood changes, nausea, fluid retention and breast tenderness.\(^12\)

Like the other hormonal options, cyclically administered oral progestins prevent the proliferation of the endometrium and may cause amenorrhea, which may be a desired effect in patients with HMB.\(^9,13\) Although the cyclically administered oral progestins are not FDA-labeled contraceptives, they may affect a woman’s ability to become pregnant. Progestins may result in weight gain, bloating, breast tenderness, headaches, acne and, possibly, depression.\(^13\)

Many women will initially attempt to treat heavy and painful periods on their own, making NSAIDS a popular choice. NSAIDs are the most common medications used for HMB in women who do not want hormone therapy or wish to become pregnant. By inhibiting the formation of Prostaglandins E and I\(_2\), which appear to be elevated during menstruation and endometrial shedding, NSAIDs are able to reduce blood flow.\(^1\) Another benefit of NSAIDs is the additional analgesic properties they provide. Because NSAIDs are only taken during menstruation, the gastrointestinal side effects commonly associated with long-term NSAID use are of little concern. Clinical efficacy between different NSAIDs appears to be similar.\(^8\) According to the NICE guidelines, NSAIDs are preferred over TA in patients experiencing HMB with dysmenorrhea, due to the cost and analgesic effects.\(^12\) However, Lysteda\(^\circledR\) is an option for HMB in women wishing to avoid hormonal therapy and either cannot tolerate or are refractory to NSAID therapy.

### Efficacy of Tranexamic Acid and Clinical Trials

In regards to efficacy, clinical trials performed by Lukes, et al. and Freeman, et al. have demonstrated favorable outcomes in terms of the ability of Lysteda\(^\circledR\) to both reduce menstrual blood loss and improve quality of life in women suffering from HMB.\(^3,15\) In 2010, a double-blind, randomized con-

### Table 1. Treatment Options for HMB.\(^3,10,12\)

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Decrease in Bleeding (%)</th>
<th>Eliminate long-term fertility</th>
<th>Contraceptive Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hysterectomy</td>
<td>100</td>
<td>Yes</td>
<td>--------</td>
</tr>
<tr>
<td>Endometrial Ablation</td>
<td>80-94</td>
<td>Yes</td>
<td>--------</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PHARMACOLOGICAL</th>
<th>Type</th>
<th>Class</th>
<th>NICE Guidelines</th>
<th>Decrease in Bleeding (%)</th>
<th>Eliminate long-term fertility</th>
<th>Contraceptive Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormonal</td>
<td>LNG-IUD</td>
<td>1st Line</td>
<td></td>
<td>79-97</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Oral Progestin</td>
<td>3rd Line</td>
<td></td>
<td>87</td>
<td>No</td>
<td>Possible</td>
</tr>
<tr>
<td></td>
<td>COCs</td>
<td>2nd Line</td>
<td></td>
<td>20-50</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>GnRH analogues</td>
<td>Other</td>
<td></td>
<td>&gt;90</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Non-hormonal</td>
<td>NSAIDs</td>
<td>2nd Line</td>
<td></td>
<td>20-50</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Tranexamic Acid</td>
<td>2nd Line</td>
<td></td>
<td>20-60</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Lysteda(^\circledR)</td>
<td>N/A</td>
<td></td>
<td>40</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
controlled trial conducted by Lukes, et al. evaluated the effects of TA in adult women with HMB. Women free of uterine abnormalities experiencing an average blood loss of at least 80 mL per menstrual cycle were randomized to receive either 3.9 g/day TA or placebo. Participating women received treatment at the onset of menses for up to five days each menstrual cycle and were studied over the course of six cycles. Menstrual blood was collected and measured to determine a mean reduction in blood loss. Furthermore, improvements in quality of life were assessed based on participant responses to the Menorrhagia Impact Questionnaire (MIQ), a six-question questionnaire designed to evaluate HMB-related limitations on daily activities and detect patient perceived changes in blood loss.

At the conclusion of the trial, a significant reduction in menstrual blood loss in the modified intent-to-treat population (-69.6 mL; -40.4 percent) as compared to placebo (-12.6 mL; -8.2 percent; p<0.001) was found. Furthermore, researchers found a significant reduction in MIQ scores on limitation in social, leisure and physical activities in the TA group compared to placebo (p<0.001). However, it should be noted that the study was five participants short of meeting power, as there were only 115 participants in the modified intent-to-treat receiving TA instead of the calculated 120 participants.

Similar results were found in an analogous study performed by Freeman, et al. in which women with an average menstrual blood loss of at least 80 mL per cycle were randomized to receive either 3.9 g/day TA or placebo. By the conclusion of the trial, the modified intent-to-treat population consisted of 112 subjects in the treatment group and 67 subjects in the placebo group, which was sufficient to meet power. In terms of results, experimenters found a 38.6 percent (-65.3 mL) reduction from baseline in menstrual blood loss in participants receiving TA compared to placebo (-1.9 percent; -3.0 mL; p<0.0001).

**Long-Term Safety and Health-Related Quality of Life**

The long-term safety and health-related quality of life (HRQoL) of Lysteda was examined in a multi-center, open-label trial lasting 27 months (HRQoL evaluated during the first 15 months) and included 62 sites within the United States. Patients aged 18 to 49 years old with a history of HMB were diagnosed with HMB based on the medical judgment of study investigators. The intent-to-treat population included 723 patients, with 239 patients completing all 27 months. The most common reasons for withdrawing from the study were not related to the treatment (29 percent failed to return and 22 percent had unrelated requests). Eleven percent of patients reported treatment-emergent adverse effects (TEAEs) that the investigators considered related to Lysteda. Gastrointestinal side effects were reported by 102 patients and no patients developed a venous thromboembolism (VTE) or pulmonary embolism (PE) during the study. Serious TEAEs were reported by 28 women and two women had life-threatening TEAEs, however the two events were related to other health issues and not Lysteda. Fourteen women became pregnant and no fetal abnormalities reported eye issues, but only one patient had to withdraw due to severe blurred vision, which completely returned to normal upon discontinuation of Lysteda.

HRQoL was measured using the Short Form 36 Health Survey (SF-36), a general health assessment tool, and the Ruta Menorrhagia Questionnaire (RMQ), a disease specific tool. Both showed statistically and clinically significant improvements mentally, emotionally and physically starting with the first cycle of treatment and persisting throughout treatment.

This study had a few major drawbacks. First of all, the investigators subjectively determined causality between the adverse effects and medication use. Secondly, they decided the significance of reported adverse events, resulting in possibly biased results. Finally, they did not report the number of patients included in the 15 month HRQoL portion of the study. Overall, this study concluded that gastrointestinal issues with Lysteda occur at rates lower than reported with TA and demonstrated no increased risk of developing thromboembolism due to Lysteda use, however there is a small risk of serious ophthalmic issues.

**Pharmacist Information and Patient Counseling**

The main advantage of Lysteda over TA is a decreased occurrence of gastrointestinal side effects such as nausea, vomiting, diarrhea and dyspepsia, resulting in greater tolerability and patient compliance. The most common side effects reported with Lysteda are those associated with menstruation, including menstrual discomfort, headache and back pain. However, these side effects may be reduced with concurrent use of acetaminophen, ibuprofen or naproxen. The most serious adverse effects possible with Lysteda are thromboembolisms and ocular disturbances. To avoid an excessive risk of thrombosis, it is contraindicated in patients with active, history of, or other risk factors for thromboembolism. Additionally, Lysteda should not be used concomitantly with CHCs or hormone replacement therapy. It is also important to warn patients of possible visual changes which will reverse upon discontinuation of the medication.

The recommended dosage of Lysteda is 1300 mg (two 650 mg tablets) taken three times per day, with doses separated by six hours. It can be taken with or without food. Dose adjustments are required in patients with a serum creatinine greater than 1.4 mg/dL (Table 2). Women should be instructed to begin taking Lysteda at the onset of menses, and continue use for a maximum of five days throughout menstruation. Since Lysteda is only intended to be taken during menstruation, pharmacists should remind patients not to take it continuously throughout the month, as is common with other treatments.

Finally, since patients may confuse Lysteda with more traditional hormonal treatments for HMB, pharmacists should explain that Lysteda is a non-hormonal medication and has no effect on fertility. Therefore, women may become pregnant and should be instructed to use barrier forms of contraception if necessary. Other counseling points include educat-
ing women on ways to manage premenstrual symptoms, such as drinking plenty of water, getting adequate rest and avoiding excessive salt and caffeine intake.

Conclusion
Heavy menstrual bleeding is a troublesome condition that interferes with the lives of approximately 27 percent of women. To date, there are several treatment options available to reduce bleeding, such as hormones, NSAIDS, Lysteda® and surgery in severe cases. The non-hormonal Lysteda® may help women effectively reduce menstrual bleeding without interfering with the ability to conceive. With Lysteda®, women can expect to see an approximate 40 percent reduction in bleeding while experiencing only the mild side effects associated with menstruation. Furthermore, Lysteda® has demonstrated a favorable safety profile and has not been associated with any serious adverse events. Since it was only recently introduced to the U.S. market in July 2010, much of the medical community remains unfamiliar with Lysteda®, however, it is an additional, effective, non-hormonal treatment option for women suffering from HMB.

References

Table 2. Renal Dose Adjustments for Lysteda®

<table>
<thead>
<tr>
<th>Serum Creatinine (mg/dL)</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1.4</td>
<td>1300 mg TID</td>
</tr>
<tr>
<td>1.5 - 2.8</td>
<td>1300 mg BID</td>
</tr>
<tr>
<td>2.9 - 5.7</td>
<td>1300 mg daily</td>
</tr>
<tr>
<td>≥ 5.8</td>
<td>650 mg daily</td>
</tr>
</tbody>
</table>
Assessment Questions

1. Idiopathic heavy menstrual bleeding (HMB) is due to:
   a. Excessive fibrin
   b. Reduced lysine
   c. Intrauterine devices (IUDs)
   d. Elevated endometrial tPA and plasmin

2. Lysteda® reduces menstrual blood loss by:
   a. Blocking lysine binding sites on plasminogen
   b. Preventing synthesis of lysine
   c. Increasing plasmin levels
   d. Reducing endometrial tPA

3. Lysteda can treat HMB caused by:
   a. Idiopathic causes
   b. Endometriosis
   c. von Willebrand's disease
   d. A and B
   e. B and C

4. The most effective non-surgical treatment for HMB is:
   a. Natazia®
   b. Levonorgestrel-containing intrauterine device (LNG-IUD)
   c. Lysteda®
   d. Ibuprofen

5. FDA approved treatment options for HMB include:
   a. Lysteda®
   b. Natazia®
   c. Advil®
   d. A and B
   e. All of the above

6. Lysteda reduced menstrual blood flow by approximately ____.
   a. 20%
   b. 40%
   c. 60%
   d. 80%

7. What is the major advantage of Lysteda® over tranexamic acid?
   a. Increased effectiveness
   b. Reduced side effects
   c. Easier administration
   d. Reduced menstrual cramping

8. What serious side effect(s) is a concern with Lysteda®?
   a. Amenorrhea
   b. Ophthalmic issues
   c. Nausea and vomiting
   d. A and C

9. What is the recommended dose of Lysteda® in a young, healthy female?
   a. 650 mg daily
   b. 1300 mg daily for 21 days
   c. 1300 mg TID for a maximum of 5 days
   d. 1300 mg as needed for heavy menstruation

10. Lysteda® can safely be taken concomitantly with which medication(s)?
    a. Advil®
    b. Lo Loestrin Fe®
    c. Premarin®
    d. B and C
    e. All of the above
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CEUs: 0.1

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City: State: Zip:

Phone: E-mail:

Pharmacy License #: State: ONU Alumni? Y N

Program Content: Strongly Disagree Strongly Agree

1. The program objectives were clear. 1 2 3 4 5

2. The program met the stated goals and objectives:

   Describe the mechanism of action of Lysteda®. 1 2 3 4 5

   Compare and contrast treatment options for heavy menstrual bleeding. 1 2 3 4 5

   List the side effects and warnings associated with Lysteda®. 1 2 3 4 5

   Explain important patient counseling information. 1 2 3 4 5

3. The program met your educational needs. 1 2 3 4 5

4. Content of the program was interesting. 1 2 3 4 5

5. Material presented was relevant to my practice. 1 2 3 4 5

6. Comment/Suggestions for future programs:

Thank you!

Answers to Assessment Questions—Please Circle Your Answer


Any questions/comments regarding this continuing education program can be directed to Lynn Bedford, Advanced Administrative Assistant for the Office of Continuing Education (email: l-bedford@onu.edu, phone 419-772-1871).

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