

A PATIENT GUIDE TO THE LIXELLE® β 2-MICROGLOBULIN APHERESIS COLUMN

Humanitarian Use Device

Authorized by Federal (USA) law for use in the treatment of patients with clinically diagnosed dialysis-related amyloidosis (DRA).

The effectiveness of this device for this use has not been demonstrated.

CAUTION: Federal (US) law restricts this device to sale by or on the order of a physician.

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I. Key medical terms

The following terms are used in this guide or may be used by your physician in discussing your condition and possible treatments for your condition.

Activities of Daily Living (ADL) - term used to refer to daily self-care activities within an individual's place of residence, in outdoor environments, or both. The ability to perform ADLs is a measurement of the functional status of a person,

Adsorption - is the adhesion of atoms, ions, or molecules from a gas, liquid, or dissolved solid to a surface

Air embolism: - entry of air into your bloodstream

Amyloid fibrils – protein deposits that form in your body due to Dialysis-Related Amyloidosis (DRA)

Anemia - not enough iron in your blood or loss of blood

Anticoagulation - blood thinning

Anti-hypertensive medications - medications for lowering high blood pressure

Arrhythmia - irregular heartbeat

Bolus - a rapid injection

Bone cyst - non-cancerous, fluid-containing growths found in bones

Carpal Tunnel Syndrome - a condition that causes tingling, pain, numbness, and other symptoms in the hand and wrist

End Stage Renal Disease (ESRD) – complete loss of kidney function

Extracorporeal - blood is taken outside the body for treatment

Hypersensitivity reaction - allergic reaction

Hypotension - low blood pressure

Infection - illness caused by bacteria or viruses.

Myocardial infarction - a heart attack: complete or partial blockage of one of the arteries in your heart.

Prolonged bleeding (at blood access site(s)) - bleeding at the site where the intravenous device or catheter is placed that continues in excess of 20 minutes after removal of the needle.

Plasma - the liquid part of the blood which does not contain the blood cells

Serum albumin - a particular type of protein in your blood. There are many types of proteins in your blood. A brief decrease in serum albumin does not usually cause serious adverse effects, but if it needs to be treated, your doctor will add an albumin solution to your blood.

Serum protein - proteins in your blood. There are many types of proteins in your blood. A brief decrease in serum proteins does not usually cause serious adverse effects, but if it needs to be treated, your doctor can provide these by an intravenous route or change your diet.

Thrombocytopenia - a persistent decrease in the platelets in your blood. Platelets help your blood clot.

Transient - temporary, brief.

II. How this guide can help you

This Patient Guide provides basic information to respond to general questions which you are likely to have about treatment with the Lixelle[®] column. Please feel free to discuss this information with your doctor who is familiar with your specific medical condition. Treatment with this medical device must be prescribed by a physician and used by medical professionals who have been trained in its specific use.

III. Why you are considered a candidate for treatment with the Lixelle® column

You have been diagnosed with dialysis-related amyloidosis (DRA). DRA is a complication that affects patients with end stage renal disease (ESRD) who have been receiving hemodialysis treatment for a long time (typically 5 years or more). Hemodialysis is not able to remove all of the substances from your blood due to limitations of the dialyzer filter. One molecule that is not removed very well is β 2-microglobulin (β 2m). The normal kidney filters and removes excess proteins such as β 2m from the blood, keeping blood levels of such proteins normal. When the kidney fails to function properly, β 2m builds up in the blood and may form deposits called amyloid fibrils that deposit in various areas of your body and may cause pain, stiffness and lack of mobility. Patients with DRA may have joint pain, back pain, carpal tunnel syndrome or an increase in the rate of bone cysts and fractures.

In summary, you are being considered as a candidate to receive therapy with the Lixelle® column because you have been diagnosed with DRA and other treatment options are limited for this condition.

IV. Indications for Treatment with the Lixelle® β 2m Apheresis Column

The Lixelle® β 2-microglobulin apheresis column is indicated for the treatment of patients with clinically-diagnosed dialysis-related amyloidosis (DRA).

If you meet this condition (criterion) and, after reading this guide and discussing it with your physician, you choose to receive this therapy, you will be closely followed by the medical team, including checking for various symptoms that can occur during Lixelle® column therapy.

V. Contraindications for Treatment with the Lixelle® β 2m Apheresis Column

Below are the medical conditions and circumstances that would not allow your doctor to treat you with the Lixelle® column:

- (1) Your doctor believes that because you have certain conditions related to blood clotting (such as severe anemia, severe bleeding, severe stomach ulcers) or because you are receiving medications that reduce the amount of available vitamin K (an important blood clotting factor) it will not be possible to give you medications that thin the blood (called anticoagulants) and prevent blood clotting during the procedure.
- (2) Your doctor believes that you cannot tolerate therapy with a machine that temporarily removes large amounts of blood from your body because you have a medical condition (such as poor heart function), current or recent heart attack (also called acute myocardial infarction), abnormal heart rhythm, recent or current stroke, or severe uncontrollable low blood pressure (hypotension) or
- (3) You are allergic to parts of the Lixelle[®] column including cellulose or heparin (a blood thinner).

VI. Alternatives

The best treatment option for patients with DRA is a kidney transplant, which cures ESRD and gives the patient a normal functioning kidney, which is able to filter and remove β 2m from the blood. Sometimes surgery is used to remove amyloid deposits from the joints, but this does not reduce the levels of β 2m in your blood and it does not cure DRA. Other treatments, including a specific kind of dialysis called hemodiafiltration, and hemodialysis treatments extended over a long period of time (such as overnight) are options for increased removal of β 2-microglobulin, but these treatments are not widely available in the United States.

As you consider therapy with the Lixelle[®] column, you should discuss all other possible treatments for your disease with your physician.

VII. What is the Lixelle[®] β 2m Apheresis Column?

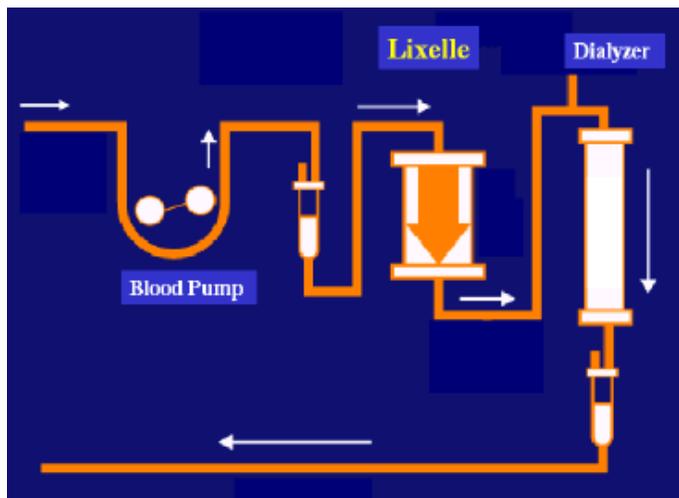
Lixelle[®] β 2m Apheresis Column is a sterile, plastic column containing round cellulose beads with small holes (pores). The pores and surface chemicals on the Lixelle[®] column adsorb (or remove) β 2m from your blood. It is used at the same time as your hemodialysis treatment. The column has been especially designed to remove β 2m, but to leave behind other substances that your body needs to remain healthy. The column is available in three (3) sizes. Your doctor will choose the column that works best for you, considering your size and

medical condition.

Three sizes of the Lixelle® column



Lixelle® column connected to the dialyzer



VIII. How is Treatment with the Lixelle® column performed?

The Lixelle® β 2m Apheresis column is attached to the dialysis circuit in front of the dialyzer. The blood passes through the column, β 2m is adsorbed selectively, and the filtered blood is then returned to you after it exits the dialyzer.

Lixelle® treatment will occur at the same time as your dialysis treatments, generally at least 3

times per week. The flow rate through the Lixelle[®] column must be slower than the blood flow rates that are used for most dialyzers, therefore, your dialysis treatments will have to be extended when you are being treated with Lixelle[®]. Your doctor will determine how long your treatments need to be in order to ensure that you receive adequate dialysis treatment.

X. Use of Lixelle[®] column to treat patients with DRA

The Lixelle[®] column has been used to treat patients with DRA in Japan since 1994. Published studies^{1,2,3,4} describe treatment of approximately 100 patients with the device.

Several studies have been done which show that the Lixelle[®] column can reduce the amounts of β 2m in patients' blood. In these studies, many study subjects experienced a decrease in pain and stiffness and an improved ability to perform their activities of daily living (such as eating, dressing, bathing, toileting, and personal grooming). Other findings in these studies included a decrease in bone cyst formation and improved grip and pinch strength.

After the Lixelle[®] column was approved for the treatment of DRA in Japan, a post-market study was performed to collect information on the safety of the Lixelle[®] column. This study included 183 patients who had a total of 13,476 treatments at 58 centers in Japan.. The most common adverse events (safety problems) seen in the study were temporary decrease in blood pressure (hypotension), heart palpitations, pain, fatigue, anemia, nausea/vomiting, and chills/shivering. Most of these adverse reactions are common for patients undergoing dialysis or any extracorporeal therapy, but combined usage with Lixelle[®] column may increase the frequency at which these side effects occur.

¹ Gejyo F, Kawaguchi Y, Hara S. Arresting Dialysis related amyloidosis: a prospective, multicenter controlled trial of direct hemoperfusion with a β 2-microglobulin adsorption column. *Artif. Organs.* 2004; 28(4): 371-380.

² Abe T., Uchita K., Orita H. Effect of β 2-microglobulin adsorption column on dialysis related amyloidosis. *Kidney Int.* 2003; 64:1522-28.

³ Yamamoto , Y., Hirawa N, Yamaguchi S., Ogawa N., Takeda H., Shibuya K., Kawahara K., Kojima H., Dobashi Y., Fujita M., Azusima K., Miyazaki N., Kobayashi M., Kobayashi C., Fujiwara A., Yuto J., Saka S., Yatsu, K., Toya Y., Yasuda G., Ohnishi T., Umemura S. Long term efficacy and safety of the small-sized β 2-microglobulin adsorption column for dialysis-related amyloidosis. *Therap. Apheresis Dialy.*; 2011; 15(5): 466-474.

⁴ Kuragano T., Inoue T., Yoh K., Shin J., Fujita Y., Yoshiya K., Kim J., Sakai R., Sekita K., Goto T., Fukagawa M., Nakanishi T. Effectiveness of β 2-microglobulin adsorption column in treating dialysis-related amyloidosis: A multicenter study. *Blood Purif.* 2011; 32:317-322.

XI. Safety of treatment with the Lixelle[®] column

Note: A detailed explanation of risks and adverse reactions associated with treatment with the Lixelle[®] column should be provided by your physician.

Adverse Reactions (Side Effects)

Most of the adverse reactions are common for patients undergoing dialysis or any extracorporeal therapy, but combined usage with Lixelle[®] column may increase the frequency at which these side effects occur. Among these adverse reactions, hypotension and anemia are reported to be more frequent when Lixelle[®] is used. Other adverse reactions that may occur include decreased blood volume, nausea/vomiting, chills/shivering, fatigue/malaise, heart palpitations, decrease in blood platelets, worsening of joint pain, shortness of breath, chest discomfort, high blood pressure, abdominal pain, and throat pain.

There are other side effects which you may experience which are also experienced in other extracorporeal therapies, such as hemodialysis. These include abnormal heart rhythms, muscle cramping, itching, headache, dizziness/fainting, damage to blood cells, hematoma (swelling filled with blood) formation at needle insertion sites, infection, anaphylaxis/allergic reactions, and removal of other useful substances from the blood.

Some of the adverse events (side effects) are explained in greater detail below:

Hypotension or low blood pressure is the most common adverse reaction. If you have a hypotensive reaction during your treatment, it can be corrected by temporarily stopping your treatment, placing your head down and raising your legs, and, in some cases, giving you I.V. fluids. In most cases, the hypotension will go away and your treatment can continue. Your doctor may decide to use a smaller column if you experience low blood pressure during treatment. This may resolve the problem.

Anemia may occur because more blood is being removed from your body during Lixelle[®] treatment, as compared to a standard hemodialysis treatment. As a result, your doctor may

increase the dose of your medications that are used to prevent the problem. In this case, your doctor will discuss with you the potential side effects of this increase in medications.

Stopping the procedure resolves most adverse reactions or complications that may occur during treatment with the Lixelle[®] column.

In addition to β 2-microglobulin, other substances are removed by the Lixelle[®] column. The effect of removing these other substances is unknown. Your doctor will closely monitor your blood chemistry levels (such as salt, potassium, and other electrolytes) and may take action if your blood chemistry levels are changing too much as a result of Lixelle[®] treatment. These actions may include using a smaller column, prescribing additional medications, or stopping treatment with Lixelle[®].

No studies have been done to test the safety of the Lixelle[®] column for pregnant women or their unborn babies. Therefore, probable benefit for this patient population is unknown and there may be unknown adverse reactions for the woman or her unborn baby associated with the use of the device during pregnancy. Also, probable benefit and the effects of treatment are not known for patients with liver or thyroid disease, patients with cancer, and for pediatric (age 21 or less) patients.

XII. What you can do to minimize adverse reactions

1. Continue to follow your doctor's advice regarding what you should do before, during and after your hemodialysis treatments.
2. Consult with your doctor which size of Lixelle[®] column would be most appropriate for you, considering the risks and benefits of each.
3. Do not perform strenuous exercise on the day of your procedure.
4. Avoid activities increasing the risk of physical injury for 24 hours after your treatment because of the blood thinning medication used.
5. Sexually active women of childbearing potential should use oral, implantable, or barrier methods of birth control (e.g., birth control pills, intrauterine device,

condoms) during treatment with the Lixelle[®] column to prevent pregnancy and any adverse reaction that may harm an unborn child.

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