BELOTERO BALANCE® (+) Lidocaine
Patient Information Guide

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This guide will help you decide whether treatment with BELOTERO BALANCE® (+) Lidocaine (herein after referred to as BELOTERO BALANCE® (+)) is right for you. This information does not take the place of a discussion with your doctor. This guide will answer some questions you may have about BELOTERO BALANCE® (+) treatment.

- Only you and your doctor can decide whether BELOTERO BALANCE® (+) is right for you. Other treatments are available to correct wrinkles and folds and you may discuss these treatment options with your doctor.
- Please read all the information in this guide and discuss any questions with your doctor before you are treated with BELOTERO BALANCE® (+).

Please keep this information. You may want to read it again.

GLOSSARY

Adverse event	Undesirable side effects
Allergic Reaction	Allergic reactions occur when a person's immune system (needed to fight infections) over reacts to substances that are harmless in most people. Symptoms can include a rash, sneezing, itching, congestion, or difficulty breathing.
Anaphylatic Shock	A severe allergic reaction with lip swelling and difficulty breathing; this is a medical emergency.
Anesthetic	A substance that blocks the sensation of pain.
Dermal Filler	A substance that is injected in the skin to create a smoother and/or fuller appearance in the face.
Edema	Swelling
Erythema	Redness
Granuloma	Small lump under the skin due to an immune response
Hematoma	Collection of blood under the skin
Hyaluronic Acid (HA)	A naturally occurring substance in the skin that forms some of its structure.
Hyaluronidase	A substance that breaks down hyaluronic acid (HA)
Induration	Firmness of the skin from swelling or inflammation
Injection Site Reactions	Reactions that occur at the site of an injection. For dermal fillers, this can include bruising, change in skin color, change in firmness, itching, lumps, pain or tenderness, redness, and swelling.
Keloid	A thick scar that is larger than the injury that caused it
Lidocaine	A type of anesthetic drug that can be used to block the sensation of pain.
Nasolabial Fold (NLF)	The creases that extend from the corner of the nose to the corner of the mouth
Necrosis	Local death of the skin
Nodules	Lumps under the skin (e.g cyst-like) that can be felt with the fingers
Quincke's edema	Swelling of the skin or mucous membranes, similar to an allergic reaction or hives
Pustule	A small skin bump with pus
Split Face Design	A type of clinical study in which half of the face is treated one way and the other half is treated a different way
Streptococcus equi	A type of bacterium that is used to make hyaluronic acid.
Touch-up	An additional injection, performed 2 to 4 weeks after the initial injection. Some patients may require a touch-up treatment to achieve the desired aesthetic results.
Topical	Any drug or product that is applied to the outside of the skin.
Tyndall effect	Bluish skin discoloraton in the area of treatment
Vascular occlusion	Blockage of a blood vessel
Vascular compromise	A situation in which an area does not receive sufficient blood flow.

Note that terms in the glossary are underlined throughout this document.

ABOUT BELOTERO BALANCE® (+)

Caution: Federal (USA) law restricts this device to sale by or on the order of a physician or other licensed healthcare practitioner.

What is BELOTERO BALANCE® (+)?

BELOTERO BALANCE® (+) is a clear, hyaluronic acid gel and a small quantity of an anaesthetic (lidocaine), to reduce the sensation of pain and the chemical BDDE to make it last longer. Hyaluronic acid is a naturally occurring substance in the body. One of the natural functions of hyaluronic acid in the skin is to provide firmness and hold water in the deep portions of the skin (dermis). Lidocaine helps to improve the comfort of the injection.

What is BELOTERO BALANCE® (+) use for?

BELOTERO BALANCE® (+) is used to smooth out and fill in moderate to severe folds or wrinkles, such as the creases that extend from the corner of the nose to the corner of the mouth (nasolabial folds) as shown in Figure 1 below.

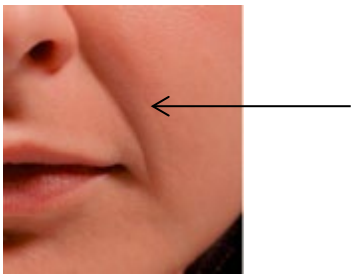


Figure 1. Facial Nasolabial Fold

Why add Lidocaine to BELOTERO BALANCE®?

An anesthetic medicine (lidocaine) was added to BELOTERO BALANCE® to reduce pain and discomfort during and after injection.

HOW IS BELOTERO BALANCE® (+) ADMINISTERED?

Your doctor will inject a small amount of BELOTERO BALANCE® (+) into the skin with a small needle. A 'touch-up' injection is often given two weeks after the first injection to get the optimal smoothing and rounding of skin or to make the effect last longer. You and your doctor will decide whether a second 'touch-up' injection is needed later on. In one study, 40 out of 52 (77%) patients had a second injection of BELOTERO BALANCE® (+) at the two week visit.

SAFETY INFORMATION

Who should not use BELOTERO BALANCE® (+)?

You should not use BELOTERO BALANCE® (+) if you have severe allergies or a history of allergic reactions to hyaluronic acid, local anesthetics such as lidocaine, or to small amounts of protein from bacteria. Injections in such patients could result in allergic reactions, anaphylactic shock, or death.

If you are unsure about this, talk about the details of your medical history with your doctor and the risks versus the benefits of using BELOTERO BALANCE® (+).

Warning: One of the risks with using BELOTERO BALANCE® (+) is unintentional injection into a blood vessel. The chances of this happening are very small, but if it does happen, the complications can be serious, and may be permanent. These complications, which have been reported for facial injections, can include vision abnormalities, blindness, stroke, temporary scabs, or permanent scarring of the skin. If you have changes in your vision, signs of a stroke (including sudden difficulty speaking, numbness or weaknesses in your face, arms, or legs, difficulty walking, face drooping, severe headache, dizziness, or confusion), white appearance of the skin, or unusual pain during or shortly after treatment, you should notify your health care practitioner immediately.

Do not use BELOTERO BALANCE® (+) if you have an allergic reaction to lidocaine or similar anesthetics.

If you easily develop big scars or keloids on your skin do not use BELOTERO BALANCE® (+) because you will most likely get a scar where BELOTERO BALANCE® (+) is injected.

What are precautions to consider?

- Injection site reactions to BELOTERO BALANCE® (+) injection include the following: swelling, bruising, redness, pain, rash, development of small bumps, inflammation, itching, and discomfort. One out of two (50%) subjects had at least one of these reactions after injection of BELOTERO BALANCE®. In 9 out of 10 people these reactions are not serious and go away within 1 to 2 weeks. There is a small chance that they will last longer than 2 weeks in some people.
- Do not use BELOTERO BALANCE® (+) if you have a skin infection or inflammation such as a pimple, cyst, cold sore, or rash at the injection site. Skin infections or inflammations increase the risk of infection from an injection. Wait until the infection is cleared up before using BELOTERO BALANCE® (+).
- Until any initial swelling and redness have gone away and needle entrance sites have healed you should minimize exposure of the treated area to excessive sun, heat, UV lamp exposure, Turkish bath, and extreme cold weather.
- BELOTERO BALANCE® (+) should only be used by a health care professional trained in the correct procedure to inject dermal fillers and who completely understands the entire package insert and physician label.
- BELOTERO BALANCE® (+) has not been evaluated in pregnant women, lactating women who are breast feeding, or in subjects less than 22 years of age.

- Patients who bleed easily or are taking aspirin or other drugs which prevent blood clotting (blood thinners) may have a greater risk for bleeding and/or bruising at the site where BELOTERO BALANCE® (+) is injected.
- Radiation therapy or drugs which decrease your immunity or resistance to infections, such as chemotherapy and immune suppressing drugs, may increase your risk of infection from an injection of BELOTERO BALANCE® (+).
- Laser treatments, chemical peels, or other procedures performed on your skin after treatment with BELOTERO BALANCE® (+), may increase the risk that you will have a reaction at the injection site.
- Discuss with your doctor all questions you may have about the risks from using BELOTERO BALANCE® (+) in relation to any of the above precautions and/or warnings concerning the use of BELOTERO BALANCE® (+).

Have there been side effects (adverse events) reported in clinical studies?

- **Main Clinical Study of BELOTERO BALANCE®**

In the main clinical study of BELOTERO BALANCE®, three out of 118 patients treated (2.5%) had at least one side effect that was not at the injection site. The non-injection site adverse events included moderate hives-like reaction, mild herpes simplex, and mild headache. Since each patient was injected with Belotero® on one side of the face and collagen on the other side of the face, the cause of these events could not be determined.

In darker skinned individuals, four out of 93 patients (4.3%) had side effects that were not in the injection site. These were moderate headache, moderate swelling on the side of the nose, moderate cold sore, moderate lip numbness, and mild lip dryness.

BELOTERO BALANCE® is a prescription medical device and should only be administered by a trained physician. BELOTERO BALANCE® has not been evaluated in pregnant women, lactating women who are breastfeeding, or in subjects less than 21 years of age.

Injection Site Reactions:

Injection site reactions to BELOTERO BALANCE® are common. In three US clinical studies, more than half of all subjects injected with BELOTERO BALANCE® had one or more injection site reactions. All subjects were asked to keep a daily diary to record any injection site reaction, how severe the reaction was, how long it lasted and how fast it improved. Table 1 below lists the reactions that were reported by patients during the studies, the number of patients who had them, and the maximal severity of the reactions.

Table 1 Number of Subjects with Injection Site Reactions to BELOTERO BALANCE® and Maximal Severity of Reactions*

	Number of Subjects who had Reactions and the Maximum Severity of the Reactions (out of 211 subjects total)			
Injection Site Response	**Total**	**Mild**	**Moderate**	**Severe**
Swelling	145 (68.7%)	60 (28.4%)	65 (30.8%)	20 (9.5%)
Nodule (lump under the skin)	92 (43.6%)	46 (21.8%)	37 (17.5%)	9 (4.3%)
Bruising	115 (54.5%)	46 (21.8%)	51 (24.2%)	18 (8.5%)
Induration (hardening of the tissue)	107 (50.7%)	52 (24.6%)	45 (21.3%)	10 (4.7%)
Erythema (redness)	109 (51.7%)	55 (26.1%)	48 (22.7%)	6 (2.8%)
Pain	103 (48.8%)	68 (32.2%)	26 (12.3%)	9 (4.3%)
Discoloration	61 (28.9%)	32 (15.2%)	25 (11.8%)	4 (1.9%)
Pruritus (itching)	46 (21.8%)	37 (17.5%)	9 (4.3%)	0 (0%)
*Reported by patients				

Swelling (145 out of 211 subjects), bruising (115 out of 211 subjects), redness (109 out of 211 subjects), and induration or hardening of the tissue (107 out of 211 subjects) were the four most commonly reported skin reactions to BELOTERO BALANCE®. These occurred in more than half of all subjects.

Table 2 shows how long each skin reaction lasted after injection of BELOTERO BALANCE® and for how many patients, as reported in the patient diaries.

Table 2 Duration of Injection Site Skin Reactions

	Number of Subjects who had Skin Reactions and # of days Each Skin Reaction Lasted (out of 211 subjects total)			
Injection Site Reaction	≤ 3 days	4 – 7 days	8 – 14 days	>14 days
Swelling	66 (31.3%)	51 (24.2%)	17 (8.1%)	11 (5.2%)
Nodule (lump under the skin)	27 (12.8%)	31 (14.7%)	17 (8.1%)	17 (8.1%)
Bruising	29 (13.7%)	46 (21.8%)	34 (16.1%)	6 (2.8%)
Induration (Hardening of the Tissue)	46 (21.8%)	29 (13.7%)	20 (9.5%)	12 (5.7%)
Erythema (Redness)	66 (31.3%)	27 (12.8%)	10 (4.7%)	6 (2.8%)
Pain	72 (34.1%)	22 (10.4%)	4 (1.9%)	5 (2.4%)
Discoloration	24 (11.4%)	14 (6.6%)	17 (8.1%)	6 (2.8%)
Pruritus (Itching)	32 (15.2%)	8 (3.8%)	3 (1.4%)	3 (1.4%)

The results showed that:

- The majority of skin reactions resolve by 1 week after injection
- Injection site reactions in 9 out of 10 (90%) subjects lasted less than 2 weeks.
- Swelling, pain, and redness lasted less than 3 days in one third of patients in the study.
- Skin discoloration, “dent” in the skin, bruising, swelling, and nodules may last longer than 2 weeks in approximately 1 out of 10 people treated in the study.

During the clinical studies for BELOTERO BALANCE®, the physicians recorded reactions to BELOTERO BALANCE® that were seen at each visit during the study. Table 3 presents the reactions that were recorded by the physician during the study.

Table 3 Reactions Recorded by the Physician

Description of Reaction	BELOTERO BALANCE® Maximum Reaction Severity (out of 211 subjects total)			
	Total	Mild	Moderate	Severe
Any Reaction	189 (89.6%)			
Injection Site Swelling	135 (64.0%)	55 (26.1%)	60 (28.4%)	20 (9.5%)
Injection Site Induration (Hardening)	104 (49.3%)	50 (23.7%)	44 (20.9%)	10 (4.7%)
Injection Site Bruising	104 (49.3%)	40 (19.0%)	49 (23.2%)	15 (7.1%)
Injection Site Erythema (Redness)	102 (48.3%)	53 (25.1%)	44 (20.9%)	5 (2.4%)
Injection Site Pain	95 (45.0%)	63 (29.9%)	24 (11.4%)	8 (3.8%)
Injection Site Nodule (lump under the skin)	91 (43.1%)	46 (21.8%)	36 (17.1%)	9 (4.3%)
Injection Site Discoloration	61 (28.9%)	33 (15.6%)	24 (11.4%)	4 (1.9%)
Injection Site Pruritus (Itching)	44 (20.9%)	35 (16.6%)	9 (4.3%)	0 (0%)
Application Site Exfoliation (Skin Peeling)	6 (2.8%)	4 (1.9%)	1 (0.5%)	1 (0.5%)
Injection Site Rash	5 (2.4%)	3 (1.4%)	2 (0.9%)	0 (0%)

- **Study Evaluating Pain Reduction Between BELOTERO BALANCE® to BELOTERO BALANCE® (+)**

In the study of 52 patients comparing pain reduction between BELOTERO BALANCE® to BELOTERO BALANCE® (+), there were a total of five unwanted side effects of which two were related to treatment. Of the events related to treatment, one of these was headache, which resolved in one day; and the other was skin tightness which resolved in twenty days. All side effects were mild in intensity. There were no serious side effects in this study.

Injection Site Reactions:

A total of 41 of the 52 (79%) of people treated in the study reported at least one injection site reaction during the 6 week study period. The most common injection site reactions in the nasolabial fold treated with BELOTERO BALANCE® (+) were swelling (31 of the 52; 60%), redness (26 of the 52; 50%), firmness (25 of the 52; 48%), tenderness (25 of the 52; 48%), bruising (22 of the 52; 42%) or lumps/bumps (16 of the 52; 31%). Most side effects occur shortly after injection and went away within few weeks.

A total of 45 of the 52 (87%) of people treated in the study reported at least one injection site reaction during the 6 week study period for BELOTERO BALANCE®. The most common injection site reactions in the nasolabial fold treated with BELOTERO BALANCE® were tenderness (32 of the 52; 62%), swelling (31of the 52; 60%), firmness (25 of the 52; 48%), bruising (25 of the 52; 48%), redness (23 of the 52; 44%), lumps/bumps (22 of the 52; 42%) or pain (19 of the 52; 37%). Most side effects occur shortly after injection and went away within few weeks.
With the exception of injection site pain, the most common injection site reactions (swelling, redness, firmness, bruising, lumps/bumps) observed in this study are similar to the total number observed in main study (Table 3).

Have there been unwanted side effects reported from use of this product from regular use, outside of clinical trials?

The following unwanted side effects were reported after the product was approved for use. Because it is not known how many people have been treated with this product since it was approved, it is not possible to estimate reliably what percent of patients have had each of these side effects.

These side effects are listed here because they are serious or because they might have been caused by Belotero Balance®:

- Allergic reactions including localized swelling of the skin and soft tissues, possibly including the airway opening (Quincke's edema);
- A severe allergic reaction which needs medical treatment right away (Anaphylactic shock)
- Uneven sides of the face
- Bruising
- Bumps/Lumps
- Discoloration
- Swelling (Edema)
- Redness (Erythema)
- Firm, inflamed bump under the skin (Granuloma)
- Collection of blood under the skin (Hematoma)
- Hives
- Firmness of the skin from swelling or inflammation (Indurations)
- Infection
- Inflammation
- Movement of the filler to another area in the skin where it was not injected
- Numbness
- Blockage of a blood vessel (Vascular Occlusion)
- Death of an area of skin (Necrosis)
- Solid or cyst like bumps under the skin (Nodules)
- Pain
- Small skin lesion with pus (Pustule)

Delayed-onset inflammation near the site of dermal filler injections is one of the known adverse events associated with dermal fillers. Cases of delayed-onset inflammation have been reported to occur at the dermal filler treatment site following viral or bacterial illnesses or infections, vaccinations, or dental procedures. Typically, the reported inflammation was responsive to treatment or resolved on its own.

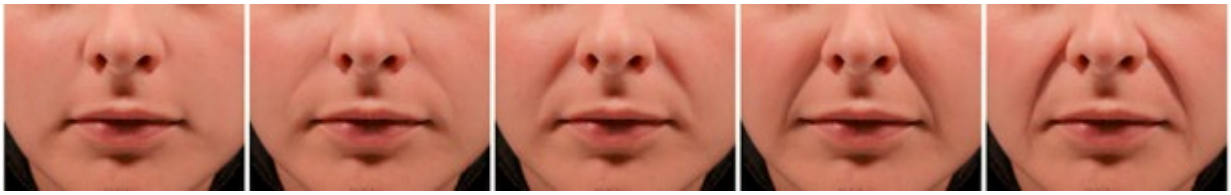
Based on information reported to Merz about the use of BELOTERO BALANCE®, your physician may recommend additional treatments after BELOTERO BALANCE®: antibiotics, anti-inflammatories, corticosteroids, antihistamines, pain medications, hyaluronidase, massage, warm compress, surgical removal, and drainage.

This information is not medical advice and is not intended to be read as medical advice. You should discuss with your doctor what treatments are right for you, if any.

BENEFITS OF BELOTERO BALANCE® (+)

BELOTERO BALANCE® (+) smooths, adds volume, and fills out folds in the skin such as the nasolabial fold. The photos below in Figure 2 show variations in the appearance of the facial nasolabial folds from extremely deep (#4) on the far right to absent (#0) on the far left. You and your doctor will decide how much smoothing is right for you to get the desired effect.

Figure 2 Gradation of Facial Nasolabial Fold Appearance from Absent, #0 (Far Left) to Extreme, #4 on the Far Right



0 – Absent	1 – Mild	2 – Moderate	3 – Severe	4 – Extreme
No visible fold; continuous skin line	Shallow but visible fold with a slight indentation; minor facial feature	Moderate deep folds; clear feature visible at normal appearance but not when stretched	Very long and deep folds; prominent facial feature; less than 2 mm visible fold when stretched.	Extremely deep and long folds, detrimental to facial appearance; 2 to 4 mm V-shaped fold when stretched.

How long does BELOTERO BALANCE® last?

The filling effect of BELOTERO BALANCE® lasts about 6 months and then slowly goes away. The photographs in Figure 2 show the rating scale used during the studies to rate the appearance of nasolabial folds. In clinical trials, 170 out of 211 (81%) of people treated in clinical studies had visible changes that were at least 2 scores better, when rated using this scale. For example, a subject that started the study with a wrinkle rating of 3 (severe) would be rated either 0 (absent) or 1 (mild). The appearance of the folds over time as the filling and smoothing effect of BELOTERO BALANCE® wears off is illustrated in Figure 2 generally moving from left to right on the scale.

Clinical Trials with BELOTERO BALANCE® and BELOTERO BALANCE® (+)

- **BELOTERO BALANCE®**

Three clinical trials were conducted in the United States which evaluated the safety and effectiveness of BELOTERO BALANCE® for a period of 24 weeks, in a total of 211 adult subjects, 18 to 75 years of age. The subjects consisted of both light and dark skin types and approximately 90% (9 out of 10) were female. In these studies an optional touch-up injection of a lesser volume of BELOTERO BALANCE® was given to almost all subjects about 2 weeks after the first treatment.

The results indicated that BELOTERO BALANCE® when injected into the skin, was clinically effective for filling and smoothing the nasolabial folds on the face. The smoothing and filling effects of BELOTERO BALANCE® on the nasolabial fold were similar in light skin and dark skin type subjects.

The only adverse events or side effects that were related to injection of BELOTERO BALANCE® were skin reactions at the injection site. These occurred in one-third to one-half of all subjects. None was serious and most were gone in 1 to 2 weeks (see SAFETY above).

- **BELOTERO BALANCE® (+)**

One additional clinical trial was conducted in the United States which evaluated reduction in pain of BELOTERO BALANCE® (+) compared to BELOTERO BALANCE® for a period of 6 weeks.

In this study, BELOTERO BALANCE® (+) was shown to have an effect on reducing pain. 52 patients received an average of 1.50 mL of BELOTERO BALANCE® on one side of the face and an average of 1.59 mL of BELOTERO BALANCE® (+) on the other side of the face (split-face design). Patients rated their pain on a scale of 0 to 10. On the scale, 0 is no pain and 10 was very severe pain. Immediately after injection, patients rated their pain about 5.94 on a scale of 0 to 10 for the side of the face injected with BELOTERO BALANCE® compared to 3.07 on the same scale for the side of the face treated with BELOTERO BALANCE® (+). Thirty (30) minutes after treatment, patients rated their pain about 2.31 for the side of the face injected with BELOTERO BALANCE® compared to 0.73 for the side of the face treated with BELOTERO BALANCE® (+). Sixty (60) minutes after treatment patients rated their pain about 0.71 for the side of the face injected with BELOTERO BALANCE® compared to 0.28 for the side of the face treated with BELOTERO BALANCE® (+).

Patients were asked to compare their week 6 photographs to their baseline photographs. Patients rated their treatment based upon the global aesthetic improvement scale (GAIS). 77% of the nasolabial folds (NLF) treated with BELOTERO BALANCE® and BELOTERO BALANCE® (+) demonstrated improvement on the GAIS. Subjects also scored their entire face using the FACE-Q questionnaire of nasolabial folds lines. Overall, patients were satisfied with NLF treatment using both BELOTERO BALANCE® and BELOTERO BALANCE® (+) in the split-face design. Finally, patients were assessed their approximate age after treatment of the nasolabial folds. 78.4% of patients indicated that they look younger when comparing their looks from baseline to Week 6, with the median FACE-Q age VAS scores of approximately 5 years younger after treatment of their nasolabial folds.

ABOUT THE PROCEDURE

Do the injections hurt?

Injections may cause some discomfort during and after the procedure. BELOTERO BALANCE® (+) contains the anesthetic lidocaine, which can reduce the sensation of pain. You and your doctor may also decide to numb the treatment area with a topical or injected anesthetic to further reduce your discomfort.

What can I expect to happen at a treatment session?

Note that each doctor may have a different process for assessing and treating patients. The following is an example of what you would experience with a typical procedure:

Before Treatment:

- Your doctor will answer all your questions and prepare you for the treatment. You can use the space at the end of this Guide to write down your questions before you see your doctor.
- Your doctor will ask you questions about your medical history. You should inform your doctor about any medicines and nutritional supplements that you are taking.
- Your doctor will clean the area where the injections will be given.
- You and your doctor will determine if a topical or local anesthetic is needed.

During Treatment:

- Your doctor will inject small amounts of BELOTERO BALANCE® (+) into the skin using a thin needle until you have received the amount of visible change.
- Your doctor may gently massage the treatment area to ensure the product is evenly distributed.

After Treatment:

- Your health care provider will give you specific after treatment care instructions.
- If you have changes in your vision, signs of a stroke (including sudden difficulty speaking, numbness or weakness in your face, arms, or legs, difficulty walking, face drooping, severe headache, dizziness, or confusion), white appearance of the skin, or unusual pain during or shortly after treatment, you should notify your health care practitioner immediately.
- Within the first 12-24 hours, patients should avoid touching/pressing treated parts of the face, applying make-up to treated parts of the face, strenuous exercise, and consuming alcoholic beverages. Patients should also avoid taking anti-coagulation, anti-platelet, or thrombolytic medications, aspirin or non-steroidal anti-inflammatory drugs or other substances known to increase coagulation time for three days after treatment.
- Your doctor may periodically apply an ice pack to the treatment area to help reduce swelling.

How many treatments are required to get the look I want?

The number of treatments required to get the look you want depends on your face and your personal treatment plan. Your doctor will decide with you the number of treatment sessions you will need and the amount of BELOTERO BALANCE® (+) you will need at each treatment session. A touch-up treatment may be required to get the desired outcome.

How do I decide about using BELOTERO BALANCE® (+)?

Ask your doctor if you will benefit from treatment with BELOTERO BALANCE® (+). If you and your doctor decide that BELOTERO BALANCE® (+) is for you, you will then talk about your complete medical history with your doctor. It is important to tell your doctor everything in your medical history, about all medicines and supplements that you are taking, any past and present allergies and their seriousness, and all current or past medical conditions you have had. Your doctor will discuss what your chances are for getting any of the side effects from injection of BELOTERO BALANCE® (+) and how serious they may be.

WHERE DO I GO FOR MORE INFORMATION?

For further information please call Merz North America at (844) 469-6379.

QUESTIONS FOR MY DOCTOR

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