BELOTERO BALANCE® Patient Information Guide

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This guide will help you decide whether treatment with 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®.

GLOSSARY

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.
Anaphylaxis	A severe allergic reaction which needs medical treatment right away.
Anesthetic	A substance that reduces sensitivity to pain.
Dermal Filler	A substance that is injected in the skin to create a smoother and/or fuller appearance in the face.
Hyaluronic Acid (HA)	A naturally occurring substance found in the human body which helps keep the skin moisturized and soft.
Injection Site Reactions	Reactions which can be expected after injection of a dermal filler. It includes bruising, change in skin color, firmness, itching, lumps/bumps, pain, redness, swelling, and tenderness. Injection site reactions can also be called common treatment reactions.
Keloid	A thick, tough scar
Nasolabial Fold (NLF)	The creases that extend from the corner of the nose to the corner of the mouth
Split Face Design	Clinical study where patients received BELOTERO BALANCE® on one side of the face and BELOTERO BALANCE® (+) on the other side of the face.
Streptococcus equi	Bacterial which does not cause illness in people, used to make the 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	A cream or ointment applied on top of the skin and affecting only the area to which is it is applied.
Vascular compromise	A situation where there is a decrease of blood flow through blood vessels.

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.

PATIENT INFORMATION SHEET

BEFORE USING BELOTERO BALANCE®, PLEASE READ THE FOLLOWING INFORMATION THOROUGHLY.

Please direct any questions to Merz North America, Inc, Raleigh, NC 27615; (1-844-469-6379)

WHAT IS BELOTERO BALANCE®?

BELOTERO BALANCE® is a clear, hyaluronic acid gel 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 help retain natural moisture and softness.

WHAT IS BELOTERO BALANCE® USED 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.

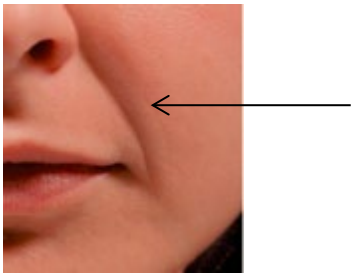


Figure 1. Facial Nasolabial Fold

HOW IS BELOTERO BALANCE® ADMINISTERED?

Your doctor will inject a small amount of BELOTERO BALANCE® into the skin using a small needle. The doctor may first inject a local anesthetic such as lidocaine to numb the area.

A "touch up" injection is often given 2 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, 67 out of 93 subjects had a second injection of BELOTERO BALANCE®. In another study, 103 out of 118 subjects were given a second injection.

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.
- 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 puncture sites have healed you should minimize exposure of the treated area to excessive sun, heat, UV lamp exposure, Turkish baths and extreme cold weather.
- BELOTERO BALANCE® should only be used by a physician 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 21 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 anti-cancer 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 ADVERSE EVENTS (SIDE EFFECTS) REPORTED IN CLINICAL STUDIES?

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

In the main clinical study, 3/118 (2.5%) subjects had at least one non- injection site adverse event. The non-injection site AEs included moderate hives-like reaction, mild herpes simplex, and mild headache. Since each patient received BELOTERO BALANCE® and Collagen Control, the cause of these events could not be determined. In the Fitzpatrick IV, V, VI (individuals with darker skin) study 4/93 (4.3%) subjects experienced 5 non-injection site AEs. 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 (Solid Raised Area)	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 (Solid Raised Area)	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 are gone within one week.
- 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 subjects 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.

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	MODERAT	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 (Raised, Hard Area)	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%)

Have there been <u>unwanted side effects</u> 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, anti-histamines, pain medications, hyaluronidase, massage, warm compress, surgical removal, and drainage.

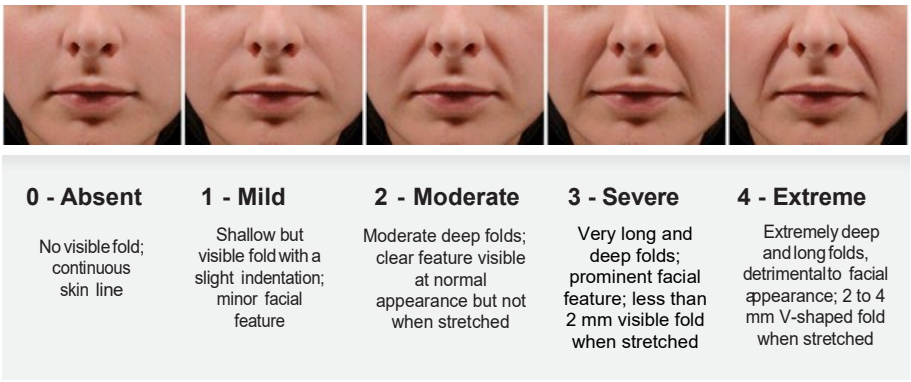
This information is not medical advice and is not intended to be read as medical advice. You should discuss with your doctor what treatments are right for you, if any.

WHAT ARE THE BENEFITS OF USING BELOTERO BALANCE®?

Hyaluronic acid is a naturally occurring substance in the body. One of the natural functions of hyaluronic acid is to help provide structural form and shape to the external features of the body. This property of hyaluronic acid is the basis for BELOTERO BALANCE®'s effectiveness as a dermal filler.

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



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%) subjects still demonstrated an effect of at least 2 points on the rating scale 6 months after an initial BELOTERO BALANCE® treatment and one touch-up treatment. 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®

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) subjects 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).

ABOUT THE PROCEDURE

DO THE INJECTIONS HURT?

Injections may cause some discomfort during and after the procedure. 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.
- 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 desired correction.
- 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 and what products to use or avoid after treatment.
- 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 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 GET MORE INFORMATION?

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

QUESTIONS FOR MY DOCTOR

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