

Public Assessment Report

NABOTA

INFORMASI PRODUK

Nama obat	: NABOTA
Bentuk sediaan	: Serbuk Injeksi
Zat aktif	: Tiap vial mengandung Botulinum toxin type A 100 U
Kemasan	: NABOTA vacuum dried powder for injection 100 Units (Clostridium botulinum toxin type A) (Reconstitute by diluting with preservative-free, sterile saline solution to make 100U/2.5 mL (4U/0.1 mL) Using a sterile 30-gauge needle)
Pendaftar	: PT. Daewoong Biologics Indonesia
Produsen	: Daewoong Pharmaceuticals Co., Ltd, Hyangnam, Republic of Korea
Kategori Registrasi	: Perubahan dan/atau penambahan indikasi dan/atau posologi baru
Indikasi yang diajukan:	: <u>Glabellar lines</u> <i>Temporary improvement in the appearance of moderate to severe glabella lines (vertical lines between the eyebrows) associated with corrugator muscle and/or procerus muscle activities, in adults aged between 20 to 65.</i> <u>Focal upper limb spasticity</u> <i>Upper limb spasticity associated with stroke in adults aged over 18 years.</i> <u>Lateral canthal lines (crow's feet lines)</u> <i>Temporary improvement in the appearance of moderate to severe lateral canthal lines (crow's feet lines) associated with orbicularis oculi muscle activity in adults aged 18 to 65 years.</i> <u>Blepharospasm.</u> <i>Treatment of benign essential blepharospasm in adults aged over 18 years.</i> <u>Benign masseter muscle hypertrophy (square jaw)</u> <i>Temporary improvement in marked* to very marked** benign masseter muscle hypertrophy in adults aged 18 to 65 years.</i> <i>*Marked: At rest, the lower face contour, including the masseter muscle, jaw, and jawline, is square, and the surface of the masseter muscle is severely convex. At maximum clenching, the lower face contour shows a severe difference compared to at rest, and the masseter muscle mass is firm or hard and palpable.</i> <i>** Very marked: At rest, the lower face contour, including the masseter muscle, jaw, and jawline, is trapezoidal, and the surface of the masseter muscle is severely convex. At maximum clenching, the lower face contour shows a severe difference compared to at rest, and the masseter muscle is hard and palpable.</i>
Posologi yang diajukan	: <u>Glabellar lines</u> <i>Reconstitute by diluting with preservative-free, sterile saline solution to make 100U/2.5 mL (4U/0.1 mL). Using a sterile 30-gauge needle, inject a dose of 0.1 mL into each of the 5 injection sites: 2 injections in each corrugator muscle and 1 injection in the procerus muscle for a total dose of 20 Units. In order to reduce the complication of ptosis, injections near the levator palpebrae superioris muscle must be avoided, particularly in patients with larger brow-depressor complexes (depressor supercilii). Injections into inner corrugators muscle and central eyebrow should be placed at least 1 cm above the bony</i>

supraorbital ridge.

Careful attention should be paid to avoid injection of this product into the blood vessel. The thumb or index finger should be placed firmly below the orbital rim in order to prevent extravasation below the orbital rim. The needle should be oriented superiorly and medially during the injection and careful attention should be paid to inject accurate volume.

Glabella facial lines arise from the activity of corrugator muscle and orbicularis oculi muscle. These muscles move the brow medially, and the procerus muscle and depressor supercilii muscle pull the brow inferiorly. This creates a frown or “furrowed brow”. The location, size, and use of the muscles vary markedly among individuals. An effective dose for facial lines is determined by gross observation of the patient’s ability to activate the superficial muscles injected. Each treatment lasts approximately three to four months. More frequent injection of this product is not recommended because the safety and efficacy are not established.

Typically the initial doses of botulinum toxin induce chemical denervation of the injected muscles one to two days after injection, increasing in intensity during the first week.



Focal upper limb spasticity

The exact dosage and number of injection sites may be tailored to the individual based on the size, number and location of the muscles involved, the severity of spasticity, the presence of local muscle weakness, and the patient's response to previous treatment. Clinical improvement of spasticity was observed within 4 weeks after injection, which lasted for 8 and 12 weeks.

The injection doses in the clinical study are as follows:

<i>Muscle</i>	<i>Total dose</i>	<i>Number of sites</i>
<i>Biceps brachii</i>	<i>100 – 200 units</i>	<i>Up to 4 sites</i>
<i>Flexor digitorum profundus</i>	<i>15 – 50 units</i>	<i>1 or 2 sites</i>
<i>Flexor digitorum sublimis</i>	<i>15 – 50 units</i>	<i>1 or 2 sites</i>
<i>Flexor carpi ulnaris</i>	<i>10 – 50 units</i>	<i>1 or 2 sites</i>
<i>Flexor carpi radialis</i>	<i>15 – 60 units</i>	<i>1 or 2 sites</i>

In the clinical study, doses ranging up to 360 units were divided among selected muscles. A sterile 24-30 gauge needle is used for superficial muscles, and a needle of appropriate length is used for muscle tissues. Localization of the involved muscles with techniques such as electromyographic guidance or nerve stimulation is recommended.

Lateral canthal lines (crow's feet lines)

Lateral canthal lines arise largely from the activity of the orbicularis oculi muscles, which are around the eyes and responsible for blinking and eyelid closure. Forceful contraction of the orbicularis oculi results in lateral and radially oriented folds (crow's feet lines), which originate from the lateral canthus. The distribution of these radial lines differs among patients. Injections should be given with the needle bevel tip pointed up and oriented away from the

eye. Using a 30-33 gauge needle, inject a dose of 0.1 mL (4 U) into 3 sites per side (a total of 6 sites and 24 units for both sides) in the lateral orbicularis oculi muscle. The first injection should be approximately 1.5-2.0 cm temporal to the lateral canthus and just temporal to the orbital rim. If the lines in the lateral canthus at maximum smile are above and below the lateral canthus, inject as shown in the figure.



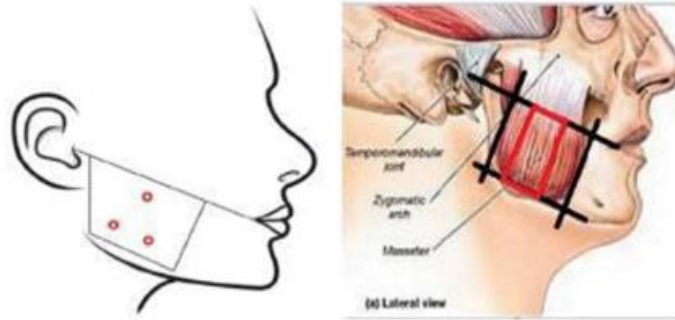
The duration of effect of NABOTA for lateral canthal lines is approximately 3 months. The safety and efficacy of the injection interval have not been clinically evaluated.

Blepharospasm

For blepharospasm, reconstitute by dilution (see Dilution Table) and inject using a sterile 27-30 gauge needle without electromyographic indicator. The recommended initial dose for injection into the medial and lateral pretarsal orbicularis oculi of the upper lid and into the lateral pretarsal orbicularis oculi of the lower lid is 2.5 U (0.1 mL at each site). If blepharospasm blocks vision, injections into the medial corrugator supercilii muscle and superolateral portion of orbicularis oculi are possible. At repeat treatment sessions, the same dose as the most recent total injection dose may be injected up to 5 U per injection site (a total of 50 U). The safety and efficacy of a single dose of NABOTA were assessed for blepharospasm for 12 weeks. The safety and efficacy of the injection interval have not been clinically evaluated.

Benign masseter muscle hypertrophy

Inject a dose of 0.2 mL (8 U) into each of 3 sites on each side of the bilateral masseter muscles (a total of 6 sites and 1.2 mL (48 U) for both sides) using a 30-33 gauge needle. Before the injection, palpate the masseter muscle to mark the anterior and posterior borders when the patient clenches their teeth. Consider the anterior and posterior borders as left and right boundaries, respectively. Consider the line from tragus to angle of mouth to be a superior border and the mandible border line to be an inferior border and mark a zone 1 cm inside each border. Inject into 2 sites in the inferior border of the mandible and 1 site above them corresponding to a vertex of an imaginary triangle around the most prominent bulges within the rectangle imagined by the borders (a total of 3 sites). The injection sites should be 1 cm apart. Make sure to carefully administer the product 1 cm inward from the left/right and anterior/posterior borderlines after determining the injection sites by identifying the location of the masseter muscles and referring to the figure below, as the administration may cause discomfort in chewing and changes in facial expression when smiling. Be careful to avoid injection into the muscles around the mouth.



Injection sites of botulinum toxin for MMH and anatomical image of masseter muscle.

PENGANTAR

Toksin botulinum tipe A merupakan toksin yang dihasilkan oleh *Clostridium botulinum* dan diketahui dapat menghambat pelepasan asetilkolin, yaitu suatu neurotransmitter, sehingga menyebabkan relaksasi otot. Toksin botulinum tipe A digunakan secara luas tidak hanya untuk tujuan terapeutik, tetapi juga untuk tujuan kosmetik, dengan penggunaannya yang terus meningkat.

ASPEK MUTU

Tidak ada evaluasi aspek mutu pada pengajuan registrasi variasi ini.

ASPEK KHASIAT DAN KEAMANAN

Studi Non Klinik

N/A

Studi Klinik

1. Untuk mendukung registrasi penambahan indikasi dan posologi baru Nabota sesuai yang diajukan, diserahkan data sebagai berikut:
 - Indikasi *focal upper limb spasticity*: studi DW_DWP450002 (Fase III)
 - Indikasi *lateral canthal lines (crow's feet lines)*: studi DW_DWP450005 (fase II/III)
 - Indikasi *blepharospasm*: DW_DWP450007 (fase II/III)
 - Indikasi *benign masseter muscle hypertrophy (square jaw)*:
 - Studi DW_DWP450008 (fase II)
 - Studi DW_DWP450301 (CORE study)
 - Studi DW_DWP450301 (OLE study)
 - Dokumen Perencanaan Manajemen Risiko (RMP)
2. Indikasi *focal upper limb spasticity*
 - Studi klinik DW_DWP450002 (n=197) yang dilakukan pada subjek dewasa dengan post stroke upper limb spasticity menunjukkan hasil efikasi dan keamanan Nabota yang sebanding dengan Botox:
 - Efikasi Nabota vs. Botox yang dinilai dari perbedaan perubahan *Modified Ashworth Scale (MAS)* pada *muscle tension values of the wrist flexor* adalah sebesar 0,0129 (95%CI: -0,2062 - 0,2319), memenuhi kriteria non-inferioritas (batas atas 95%CI dari perbedaan perubahan MAS antara obat uji dan pembanding lebih kecil dari 0,45).
 - Data keamanan menunjukkan profil keamanan Nabota dapat ditoleransi dengan baik dan sebanding dengan Botox. *Adverse Drug Reaction (ADR)* yang dilaporkan terjadi selama studi adalah *muscular weakness*, *muscle atrophy*, dan *pain extremity* masing-masing 1 subjek (1,03%) pada kelompok Nabota, sedangkan pada kelompok Botox, *muscular weakness* dilaporkan terjadi pada 2 subjek (2,04%), *dysphagia* dan *asthenia* masing-masing pada 1 subjek (1,03%). semua ADR dikategorikan sebagai *moderate* atau *mild*.
3. Indikasi *lateral canthal lines (crow's feet lines)*
 - Studi klinik fase III DW_DWP450005 (n=203) yang dilakukan pada subjek dewasa dengan moderate atau severe crow's feet lines menunjukkan hasil efikasi dan keamanan Nabota yang sebanding dengan Botox:
 - Efikasi Nabota vs. Botox yang dinilai dari perbedaan *Crow's feet line improvement rate at maximum smile* pada minggu ke-4 adalah sebesar -2,46% (95% CI: -0,91% - 5,83%), memenuhi

kriteria non-inferioritas (batas bawah 95%CI dari perbedaan *Improvement rate* antara obat uji dan pembandingan adalah lebih besar dari -15%).

- Data keamanan menunjukkan bahwa AE terkait tempat penyuntikan dilaporkan terjadi pada 1 subjek (0,49%) di masing-masing kelompok, yaitu *pruritus* di kelompok Nabota dan *tenderness* di kelompok Botox. Kedua AE tersebut dikategorikan sebagai *mild*. Sebanyak 28 AE yang tidak terkait tempat penyuntikan dilaporkan terjadi pada 20 subjek (9,80%). AE yang paling sering dilaporkan terjadi adalah *viral upper respiratory tract infection* pada 5 subjek (2,45%), diikuti oleh *myalgia* dan *cough* pada masing-masing 2 subjek (0,98%). Semua AE tersebut dianggap tidak terkait dengan pengobatan.

4. Indikasi *blepharospasm*

- Studi klinik DW_DWP450007 fase III (n=207) yang merupakan studi lanjutan dari DW_DWP450007 fase II dan dilakukan pada subjek dewasa dengan essential blepharospasm menunjukkan hasil efikasi dan keamanan Nabota yang sebanding dengan Botox:
 - Efikasi Nabota vs. Botox yang dinilai dari perbedaan *Improvement rate in severity of spasms* berdasarkan *Scott's scale* adalah 0,04% (95% CI: -5,21% - 5,29%), memenuhi kriteria non-inferioritas (batas bawah 95%CI dari perbedaan *improvement rate* antara obat uji dan pembandingan lebih besar dari -10).
 - Data keamanan menunjukkan:
 - Kejadian TEAE yang dilaporkan selama studi adalah sebesar 39,32% pada kelompok Nabota dan 27,43% pada kelompok Botox. Sebagian besar TEAE yang dilaporkan bersifat *mild*, yaitu 33,33% pada kelompok Nabota dan 25,66% pada kelompok Botox.
 - Kejadian ADR yang dilaporkan selama studi adalah 11,97% pada kelompok Nabota dan 13,27% pada kelompok Botox.
 - Kejadian SAE yang dilaporkan selama studi adalah 3,42% pada kelompok Nabota dan 0,88% pada kelompok Botox.
 - Tidak terdapat perbedaan yang signifikan secara statistik pada kejadian AE, ADR, dan SAE antara kelompok Nabota dan Botox (p-values lebih besar dari 0,05).

5. Indikasi *benign masseter muscle hypertrophy (square jaw)*:

- Hasil studi klinik fase II DW_DWP450008 (n=90) yang dilakukan pada subjek dewasa dengan *benign masseteric hypertrophy (square jaw)* yang bertujuan untuk menentukan dosis efektif Nabota, menunjukkan:
 - Efikasi obat meningkat dengan meningkatnya dosis Nabota yang diberikan, dengan nilai *mean changes in bilateral masseter muscle thickness at maximum clenching* pada minggu ke-12 setelah pemberian obat adalah -1,91±1,63 mm pada kelompok Nabota 24 U, -2,42±1,11 mm pada kelompok Nabota 48 U, -3,07±0,83 mm pada kelompok Nabota 72 U, dan -3,38±1,16 mm pada kelompok Nabota 96 U.
 - Keamanan Nabota sampai dosis maksimum yang diberikan (96 U) dapat ditoleransi dan tidak terlihat tren peningkatan kejadian TEAE yang bergantung dosis. Masing-masing 1 ADR (5,56%) dilaporkan terjadi pada kelompok Nabota 48 U dan 96 U.
 - Berdasarkan hasil tersebut, ditetapkan dosis efektif Nabota pada rentang 72 U-96 U.
- Studi klinik fase III DW_DWP450301 (CORE study) (n=180) yang dilakukan pada subjek dewasa dengan *benign masseteric hypertrophy (square jaw)* menggunakan Nabota dibandingkan dengan plasebo, menunjukkan hasil:
 - Efikasi Nabota lebih baik dibandingkan plasebo. *Mean changes in bilateral masseter muscle thickness at maximum clenching* pada minggu ke-12 setelah pemberian obat adalah -3,38±0,14 mm pada kelompok Nabota dan -0,49±0,14 mm pada kelompok plasebo. LS mean difference pada *mean change in bilateral masseter muscle thickness* antara kedua kelompok adalah -2,89±0,20 mm (95% CI: -3,28,-2,50) (p lebih kecil dari 0,0001).
 - Data keamanan menunjukkan:
 - Kejadian AE yang dilaporkan lebih rendah pada kelompok Nabota dibandingkan kelompok plasebo (13,19% vs. 22,47%), sedangkan kejadian ADR dilaporkan lebih tinggi pada kelompok Nabota dibandingkan kelompok plasebo (5,49% vs. 2,25%). Semua ADR merupakan AE lokal terkait penyuntikan. Tidak ada SAE terkait obat yang dilaporkan.
 - AE yang paling sering dilaporkan pada kelompok Nabota adalah mastication disorder (5,49%) yang dikategorikan sebagai *mild* dan diklasifikasikan sebagai AE lokal terkait

penyuntikan (ADR). AE yang paling sering dilaporkan pada kelompok plasebo adalah dysmenorrhoea (3,37%), yang dikategorikan sebagai *mild*.

- Studi klinik fase III DW_DWP450301 (OLE study) (n=113) adalah studi open label yang merupakan lanjutan dari CORE study, dimana pasien yang telah mendapatkan Nabota (n=47) dan plasebo (n=66) pada CORE study, diberikan Nabota selama OLE study. Hasil studi menunjukkan:

- Semua parameter efikasi menunjukkan hasil yang lebih baik pada kelompok Nabota dibandingkan kelompok plasebo, meliputi parameter *bilateral masseter muscle thickness at maximum clenching*, *bilateral masseter muscle thickness at rest*, *percent change from baseline in lower face volume*, *overall subject satisfaction at all measurement time points*, *proportion of subjects with MMHS* kurang atau sama dengan 3 *at all measurement time points*, dan *mean change in bilateral masseter muscle thickness at maximum clenching*.

- Data keamanan menunjukkan bahwa kejadian ADR yang dilaporkan pada kelompok Nabota adalah 5.49% selama CORE study dan 4.17% setelah diberikan Nabota pada OLE study, sedangkan kejadian ADR yang dilaporkan pada kelompok plasebo adalah 2,25% selama CORE study dan 7,58% setelah diberikan Nabota pada OLE study.

6. Berdasarkan dokumen RMP versi 4.0 tahun 2021, perencanaan manajemen risiko yang diajukan untuk penggunaan Botulinum toxin type A pada focal upper limb spasticity, lateral canthal lines (crow's feet lines), blepharospasm, dan benign masseter muscle hypertrophy (square jaw) dipertimbangkan dapat diterima. Aktivitas farmakovigilans tambahan yang direncanakan mencakup pemantauan keamanan terkait eye disorders (mencakup eyelid ptosis, brow ptosis, blepharospasm, muscle twitching; blurred vision, diplopia dan muscle wasting).

EVALUASI

Penilaian Manfaat-Risiko

Nabota adalah produk sediaan botulinum toxin tipe A yang bekerja dengan menghambat pelepasan asetilkolin sehingga otot menjadi relaks. Nabota terdaftar dengan bentuk sediaan serbuk injeksi mengandung eksipien terdiri atas Sodium chloride dan Human Albumin. Produk ini disimpan pada suhu 2°C to 8°C pada kondisi penyimpanan sampai 36 bulan.

Berdasarkan data khasiat dan keamanan yang diperoleh dari hasil studi klinik, Nabota memiliki efek yang menguntungkan, efek yang tidak menguntungkan, ketidakpastian dan keterbatasan sebagai berikut :

a. Aspek menguntungkan

- i. Data keamanan menunjukkan profil keamanan Nabota dapat ditoleransi dengan baik dan sebanding dengan Botox.
- ii. ADR (*Adverse Drug Reaction*) yang dilaporkan selama studi pada kelompok Nabota meliputi: muscular weakness, muscle atrophy, dan pain extremity masing-masing 1 subjek (1,03%).
- iii. Pada kelompok Botox, ADR yang dilaporkan meliputi: muscular weakness pada 2 subjek (2,04%), dysphagia dan asthenia masing-masing pada 1 subjek (1,03%).
- iv. Semua ADR (*Adverse Drug Reaction*) dikategorikan sebagai mild atau moderate
- v. AE (*Adverse Event*) terkait tempat penyuntikan, dilaporkan pada 1 subjek (0,49%) di masing-masing kelompok: pruritus pada Nabota dan tenderness pada Botox. Kedua AE ini dikategorikan sebagai mild.
- vi. AE (*Adverse Event*) tidak terkait tempat penyuntikan, Sebanyak 28 AE dilaporkan pada 20 subjek (9,80%), AE yang paling sering terjadi adalah viral upper respiratory tract infection pada 5 subjek (2,45%), diikuti oleh myalgia dan cough masing-masing pada 2 subjek (0,98%).
- vii. TEAE (*Treatment Emergent Adverse Events*), Terjadi pada 39,32% subjek di kelompok Nabota dan 27,43% pada kelompok Botox, Sebagian besar TEAE bersifat mild: 33,33% (Nabota) dan 25,66% (Botox).
- viii. Kejadian ADR keseluruhan, dilaporkan sebesar 11,97% pada Nabota dan 13,27% pada Botox.
- ix. SAE (Serious Adverse Events (SAE), Dilaporkan sebesar 3,42% pada Nabota dan 0,88% pada Botox, Meskipun numerik lebih tinggi pada Nabota, perbedaan tidak signifikan secara statistik ($p > 0,05$).
- x. Tidak terdapat perbedaan yang signifikan secara statistik pada kejadian AE, ADR, dan SAE antara kelompok Nabota dan Botox ($p > 0,05$).
- xi. Nabota dapat ditoleransi sampai dosis maksimum yang diberikan (96 U) tanpa tren peningkatan TEAE yang bergantung dosis.

b. Apek tidak menguntungkan

- i. Profil efek samping yang paling sering dilaporkan selama pengobatan dengan jumlah persentasi $\geq 1\%$ dan $< 10\%$ yaitu gangguan pada sistem otot dan jaringan (kelemahan otot, gangguan mengunyah, nyeri pada anggota tubuh bagian atas, penurunan massa otot), area penyuntikan (nyeri, memar, bengkak , dan peradangan pada lokasi injeksi), Gangguan pada mata dan adnexa (kelopak mata terkulai (ptosis), gangguan fungsi wajah (kenaikan alis), gangguan saraf (pusing).

c. Ketidakpastian dan keterbatasan

- i. Belum ada studi pada wanita hamil dan menyusui.
- ii. Belum ada studi pada anak-anak dan remaja usia < 20 tahun.

Kesimpulan evaluasi manfaat-risiko:

Secara keseluruhan Nabota menunjukkan kemafaatan dalam menghambat pelepasan asetilkolin sehingga otot menjadi relaks pada pasien. Risiko penggunaan minimal, dapat diprediksi dan tidak ada issue keamanan.

KEPUTUSAN

Mempertimbangkan data khasiat dan keamanan tersebut di atas, diputuskan registrasi indication dan posology NABOTA Serbuk injeksi dapat **diterima** sebagai berikut:

Indication

THERAPEUTIC INDICATION

1. Glabellar lines

Temporary improvement in the appearance of moderate to severe glabella lines (vertical lines between the eyebrows) associated with corrugator muscle and/or procerus muscle activities, in adults aged between 20 to 65.

2. Focal upper limb spasticity

Upper limb spasticity associated with stroke in adults aged over 18 years.

3. Lateral canthal lines (crow's feet lines)

Temporary improvement in the appearance of moderate to severe lateral canthal lines (crow's feet lines) associated with orbicularis oculi muscle activity in adults aged 18 to 65 years.

4. Blepharospasm

Treatment of benign essential blepharospasm in adults aged over 18 years.

5. Benign masseter muscle hypertrophy (square jaw)

Temporary improvement in marked to very marked** benign masseter muscle hypertrophy in adults aged 18 to 65 years.*

***Marked:**

At rest, the lower face contour, including the masseter muscle, jaw, and jawline, is square, and the surface of the masseter muscle is severely convex. At maximum clenching, the lower face contour shows a severe difference compared to at rest, and the masseter muscle mass is firm or hard and palpable.

**** Very marked:**

At rest, the lower face contour, including the masseter muscle, jaw, and jawline, is trapezoidal, and the surface of the masseter muscle is severely convex. At maximum clenching, the lower face contour shows a severe difference compared to at rest, and the masseter muscle is hard and palpable.

Posology

1. Glabella lines

Reconstitute by diluting with preservative-free, sterile saline solution to make 100U/2.5 mL (4U/0.1 mL) Using a sterile 30-gauge needle, inject a dose of 0.1 mL into each of the 5 injection sites: 2 injections in each corrugator muscle and 1 injection in the procerus muscle for a total dose of 20 Units. In order to reduce the complication of ptosis, injections near the levator palpebrae superioris muscle must be avoided, particularly in patients with larger brow-depressor complexes (depressor supercilii). Injections into inner corrugators muscle and central eyebrow should be placed at least 1 cm above the bony supraorbital ridge. Careful attention should be paid to avoid injection of this product into the blood vessel. The thumb or index finger should be placed firmly below the orbital rim in order to prevent extravasation below the orbital rim. The needle should be oriented superiorly and medially during the injection and careful attention should be paid to inject accurate volume.

Glabella facial lines arise from the activity of corrugator muscle and orbicularis oculi muscle. These muscles move the brow medially, and the procerus muscle and depressor supercilii muscle pull the brow inferiorly. This creates a frown or "furrowed brow". The location, size, and use of the muscles vary markedly among individuals. An effective dose for facial lines is determined by gross observation of the patient's ability to activate the superficial muscles injected. Each treatment lasts approximately three to four months. More frequent injection of this product is not recommended because the safety and efficacy are not established.

Typically the initial doses of botulinum toxin induce chemical denervation of the injected muscles one to two days after injection, increasing in intensity during the first week.

2. Focal upper limb spasticity

The exact dosage and number of injection sites may be tailored to the individual based on the size, number and location of the muscles involved, the severity of spasticity, the presence of local muscle weakness, and the patient's response to previous treatment. Clinical improvement of spasticity was observed within 4 weeks after injection, which lasted for 8 and 12 weeks.

The injection doses in the clinical study are as follows:

Muscle	Total dose	Number of sites
Biceps brachii	100 – 200 units	Up to 4 sites
Flexor digitorum profundus	15 – 50 units	1 or 2 sites
Flexor digitorum sublimis	15 – 50 units	1 or 2 sites
Flexor carpi ulnaris	10 – 50 units	1 or 2 sites
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In the clinical study, doses ranging up to 360 units were divided among selected muscles. A sterile 24-30 gauge needle is used for superficial muscles, and a needle of appropriate length is used for muscle tissues. Localization of the involved muscles with techniques such as electromyographic guidance or nerve stimulation is recommended.

Lateral canthal lines (crow's feet lines)

Lateral canthal lines arise largely from the activity of the orbicularis oculi muscles, which are around the eyes and responsible for blinking and eyelid closure. Forceful contraction of the orbicularis oculi results in lateral and radially oriented folds (crow's feet lines), which originate from the lateral canthus. The distribution of these radial lines differs among patients. Injections should be given with the needle bevel tip pointed up and oriented away from the eye. Using a 30-33 gauge needle, inject a dose of 0.1 mL (4 U) into 3 sites per side (a total of 6 sites and 24 units for both sides) in the lateral orbicularis oculi muscle. The first injection should be approximately 1.5-2.0 cm temporal to the lateral canthus and just temporal to the orbital rim. If the lines in the lateral canthus at maximum smile are above and below the lateral canthus, inject as shown in the figure.



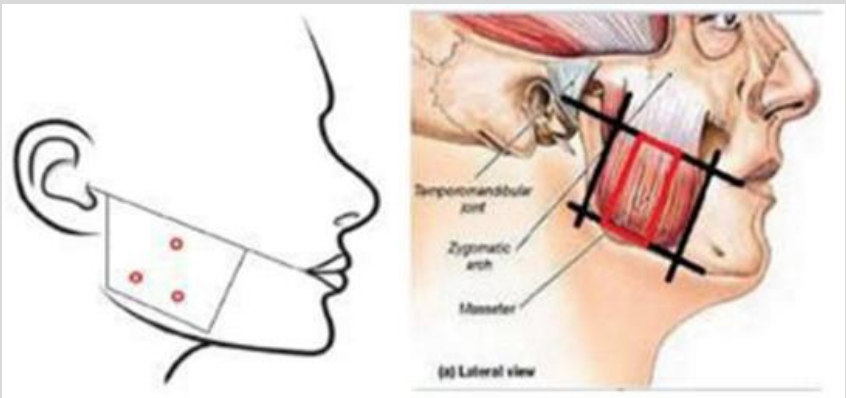
The duration of effect of NABOTA for lateral canthal lines is approximately 3 months. The safety and efficacy of the injection interval have not been clinically evaluated.

Blepharospasm

For blepharospasm, reconstitute by dilution (see Dilution Table) and inject using a sterile 27-30 gauge needle without electromyographic indicator. The recommended initial dose for injection into the medial and lateral pretarsal orbicularis oculi of the upper lid and into the lateral pretarsal orbicularis oculi of the lower lid is 2.5 U (0.1 mL at each site). If blepharospasm blocks vision, injections into the medial corrugator supercilii muscle and superolateral portion of orbicularis oculi are possible. At repeat treatment sessions, the same dose as the most recent total injection dose may be injected up to 5 U per injection site (a total of 50 U). The safety and efficacy of a single dose of NABOTA were assessed for blepharospasm for 12 weeks. The safety and efficacy of the injection interval have not been clinically evaluated.

Benign masseter muscle hypertrophy

Inject a dose of 0.2 mL (8 U) into each of 3 sites on each side of the bilateral masseter muscles (a total of 6 sites and 1.2 mL (48 U) for both sides) using a 30-33 gauge needle. Before the injection, palpate the masseter muscle to mark the anterior and posterior borders when the patient clenches their teeth. Consider the anterior and posterior borders as left and right boundaries, respectively. Consider the line from tragus to angle of mouth to be a superior border and the mandible border line to be an inferior border and mark a zone 1 cm inside each border. Inject into 2 sites in the inferior border of the mandible and 1 site above them corresponding to a vertex of an imaginary triangle around the most prominent bulges within the rectangle imagined by the borders (a total of 3 sites). The injection sites should be 1 cm apart. Make sure to carefully administer the product 1 cm inward from the left/right and anterior/posterior borderlines after determining the injection sites by identifying the location of the masseter muscles and referring to the figure below, as the administration may cause discomfort in chewing and changes in facial expression when smiling. Be careful to avoid injection into the muscles around the mouth.



Injection sites of botulinum toxin for MMH and anatomical image of masseter muscle.