DAEWOONG

NABOTA® inj.

Botulinum Toxin Type A
50, 100, 200 Units

Globally Exporting
Botulinum Toxin Type A!

NABOTA®
Features & Benefits

1 Patented Technology

- ▶ NABOTA® was developed with Daewoong's 30 years of experience in biotechnology.
- ▶ NABOTA® ensures the quality of international standards via its own patented purification process.
  → Patent registration KR 10-1339349 (Patented in 2013)

2 Reduced Impurity

- ▶ NABOTA® is a highly purified product manufactured with a patented purification process from which impurities are removed as much as possible.

3 Overseas Expansion

- ▶ Excellence in the quality of NABOTA® has led to contracts to export the finished product to about 90 countries including the United States and 28 European countries.

Bio Product Development
HISTORY

Starting from 1984, Daewoong Pharm developed NABOTA® with technology of approximately 30 years' bio product experience and patented manufacturing technique.

2001

Launched EASYEF®

The first new bio medicine in Korea

Developed Easyef of the same structure and activity as EGF existing in a body. Patent registration in 16 countries such as USA, Europe, Japan, Canada and China.

2008

Launched EPOSIS®

Recombinant human Erythropoetin

Effective improvement in anemia of chronic renal failure. Which features easy injection with prefilled syringe

2011

Launched CARETROPIN®

Recombinant human growth hormone

High quality product manufactured with patent technology, Which received 'Korea Star Award' with first Korea self-development cartridge syringe.

2013

Launched NOVOSIS®

Recombinant human BMP-2 protein

New-concept bio fusion medical device which grafts synthetic bone onto rhBMP-2, osteogenic Protein.

2014

Launched NABOTA® 100 Units

2015

Launched NABOTA® 50 Units

2015

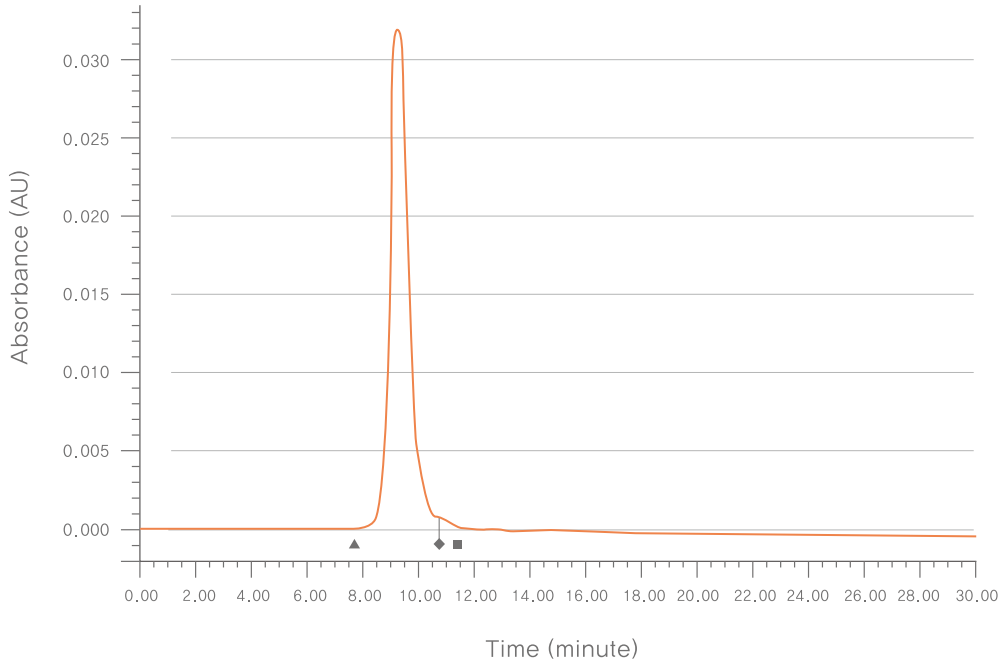
Launched NABOTA® 200 Units

1. USA IND approval(100units)
2. High purity with patent manufacturing process and 30 year biotechnology experience
3. Diversified dosages for the convenience of doctors and patients

NABOTA®

is botulinum toxin product with high purity.

High purity with patented technology



✓ NABOTA® is the product of high purity manufactured by its own patented purification process.[1]

(Patent registration KR. 10-1339349)

✓ NABOTA® is botulinum toxin with high purity manufactured by efficient process.[1]

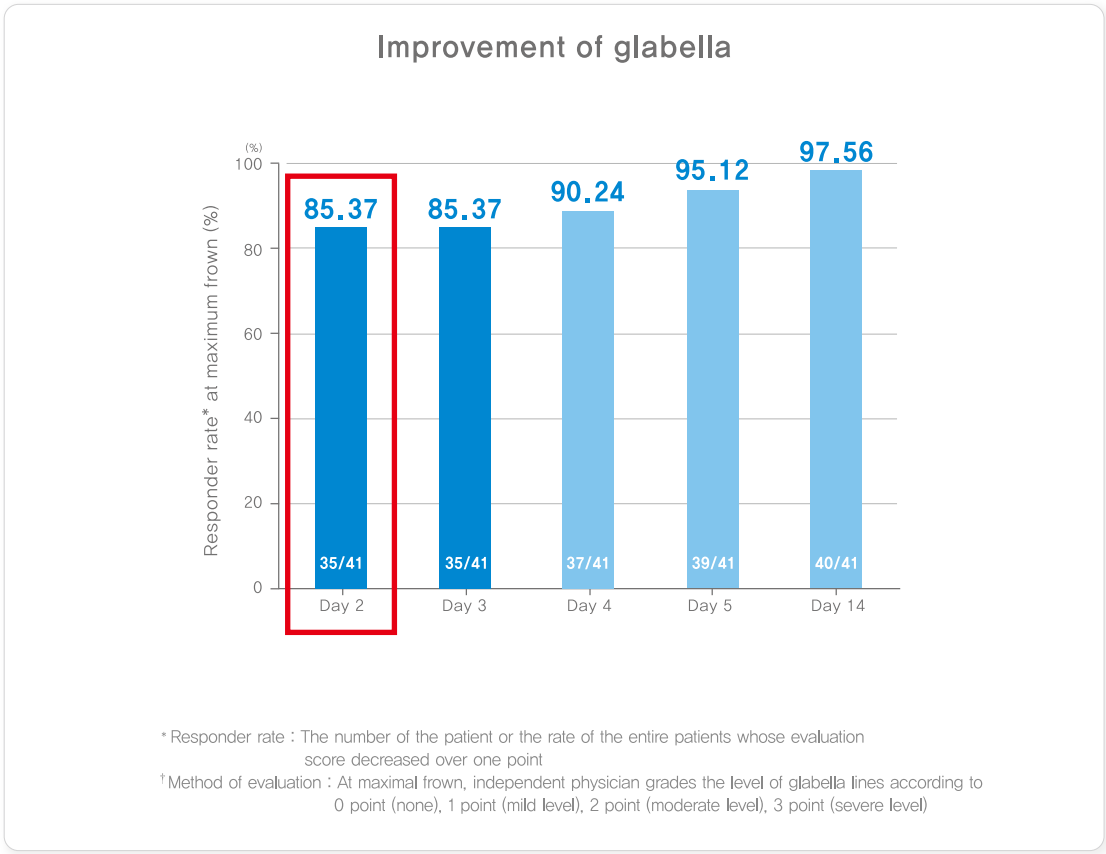
▲Botulinum toxin 900 kDa detection peak start point
◆Botulinum toxin 900 kDa detection peak end point
■Size variant end point

Ref. 1. Korean Intellectual Property Office: Registration No. 10-1339349.

NABOTA®

demonstrates a rapid onset of improvement effects in glabella lines.

Rapid improvement in glabella lines (phase Ⅳ)



* Responder rate : The number of the patient or the rate of the entire patients whose evaluation score decreased over one point

† Method of evaluation : At maximal frown, independent physician grades the level of glabella lines according to 0 point (none), 1 point (mild level), 2 point (moderate level), 3 point (severe level)

⇒ NABOTA® shows improvement effects in glabella lines **after two days** of injection.
(Improvement rate : 85.37%)

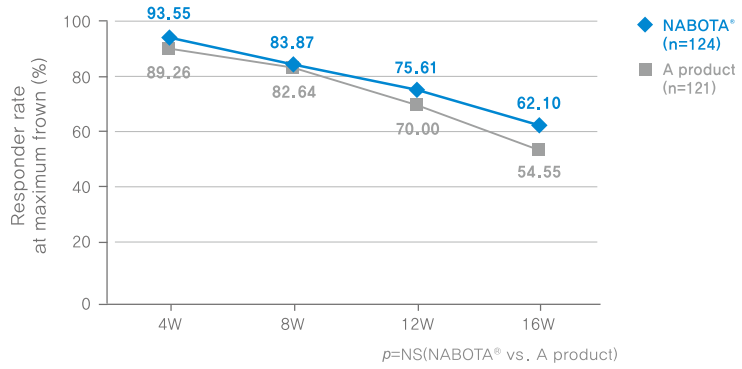
- Objective : to evaluate effectiveness and safety of NABOTA® in glabella lines
- Subjects : participants with glabella lines of at least moderate severity at maximum frown(n=44)
- Methods : single group, open, single center, phase Ⅳ in Korea
  intramuscular inject of total 20U in 5 sites(0.1mL(4U) per sites) in the glabella lines
  evaluate improvement rate and safety in glabella lines at 2, 3, 4, 5, 14 days after injection.
  – evaluation variable: improvement rate when maxiamal frown and rest
  (The group decreased over one point in facial wrinkle scale),
  onset time, rate, and adverse reaction when maximal frown and rest.

Ref. Data on file, Daewoong.

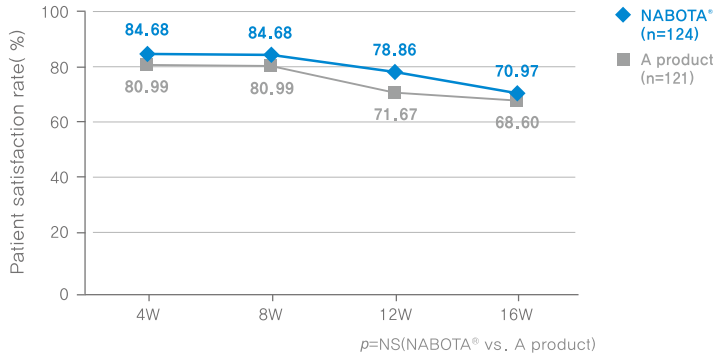
NABOTA®
is effective in improving glabella lines.

Improvement in glabella lines (phase Ⅲ)

Improvement rate of glabella lines



Patient satisfaction



†Responder rate: percentage of subjects with a score of none(0) or mild(1).
– Method of evaluation : Investigator assessed the glabella line severity at maximum frown using a four-point scale: 0=none, 1=mild, 2=moderate, 3=severe

†Satisfaction rate: percentage of subjects who scored more than six point(satisfied or very satisfied)
– Method of evaluation : satisfaction was assessed using the following seven-category scale: 1=very dissatisfied, 2=dissatisfied, 3=somewhat dissatisfied, 4=indifferent, 5=somewhat satisfied, 6=satisfied, 7=very satisfied.

⇒ NABOTA® demonstrates an improvement effect in glabella lines and high patient satisfaction.
⇒ NABOTA® demonstrates to be non-inferior when compared with A product.

- Objective : to compare the efficacy and safety of NABOTA® with A company product for the treatment of glabella lines
- Subjects : participants with glabella lines of at least moderate severity at maximum frown (N=268)
- Methods : prospective, double-blinded, randomized, active-controlled, phase Ⅲ study
  test product : NABOTA®, control product: A company product
  intramuscular injection of total 20U in 5 sites(0.1mL(4U)per sites) of glabella line and evaluate 4, 8,12,16 week after injection
  – evaluation variable : improvement rate evaluated by physicians, improvement rate evaluated by external researcher, improvement rate evaluated by patients, patient's satisfaction etc.

Ref. Won CH, et al. *Int J Dermatol*. 2015;54(2):227-234.

NABOTA® did not form antibody in the phase Ⅲ.

Antibody is not formed in glabella lines.

Time (from injection)	−1 week	16 week ± 1 week
Antibody formed (n*)	0	0

*n=Number of patients with antibody formed

⇒ Tested for 16 weeks to check if the patients have antibody after NABOTA® injection.
All patients did not have new antibody after 16 weeks with **small doses of 20 units.**[1]

- Objective: to perform Botulinum toxin type A antibody testing.
- Subjects: participants with glabella lines of at least moderate severity at maximum frown(n=135)
- Methods: active controlled, double blind, randomized, multicenter, phase Ⅲ upon screening visit and closing visit of patients, to collect 12 ml blood each, separate serum and analyze antibody formation with mouse bioassay(MBA)

Antibody is not formed in post stroke upper limb spasticity.

Time (from injection)	−2 week	12 week
Antibody formed (n*)	0	0

*n=Number of patients with antibody formed

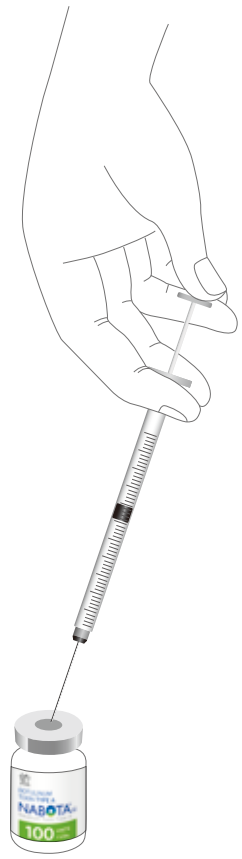
⇒ Tested for 12 weeks to check if the patients have antibody after NABOTA® injection.
All patients did not have new antibody after 12 weeks with **large doses of 360 units.**[2]

- Objective: to perform botulinum toxin type A antibody testing.
- Subjects: adult participants with post stroke upper limb spasticity(n=197)
- Methods: active controlled, double blinded, randomized, multicenter, phase Ⅲ upon screening visit and closing visit of patients to collect 12 ml blood each separate serum and analyze antibody formation with mouse bioassay(MBA)

Ref. 1.Won CH, et al. *Int J Dermatol*. 2015;54(2):227–234.
2.H.S. Nam et al. / Journal of the Neurological Sciences 357 [2015]192–197

NABOTA®
Reconstitution and Dilution Technique

NABOTA® reconstitution and dilution[1]



1. Using an appropriate syringe, draw nonpreserved sterile saline (see dilution table bellow). 0.9% Sodium Chloride is the recommended diluent.
2. Insert the needle and slowly inject the saline into the NABOTA® vial in which vacuum is present.
3. Inject slowly and avoid forming bubbles.
4. Gently mix lyophilized NABOTA® until it is completely clear and no particles are visible.
5. Record the date and time of reconstitution. The solution should be administered within 24 hours after reconstitution.
6. Reconstituted product should be stored in a refrigerator (2~8℃).

[Dilution Table]

Diluent Added (0.9% Sodium Chloride)			Resulting Dose (U/0.1 mL)
NABOTA® 50U	NABOTA® 100U	NABOTA® 200U	
0.5 mL	1.0 mL	2.0 mL	10.0 U
1.0 mL	2.0 mL	4.0 mL	5.0 U
1.25 mL	2.5 mL	5.0 mL	4.0 U
2.0 mL	4.0 mL	8.0 mL	2.5 U
4.0 mL	8.0 mL	16.0 mL	1.25 U

Ref. 1. Nabota product information.

NABOTA®
Injection

Glabella Lines

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.

Ref. Nabota product information_MFDS

NABOTA® inj.

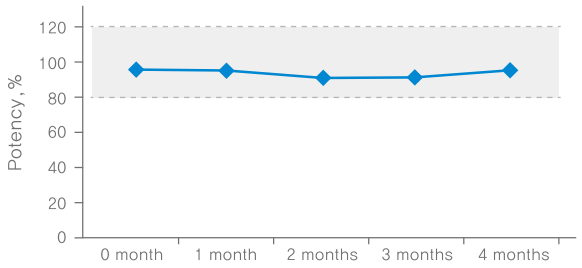
Botulinum Toxin Type A

NABOTA®

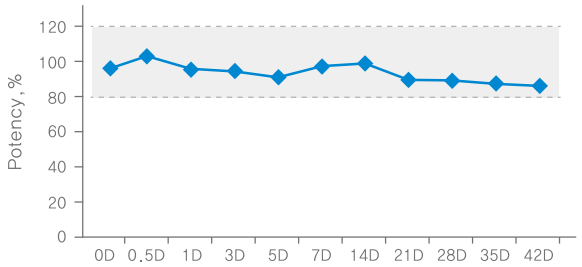
The potency of NABOTA® was proven to be effective when stored in freezer for up to 4 months, room temperature for up to 5 weeks and repetition of freezing/thawing carried out up to 4 times after reconstitution.

Stability after dilution[1]

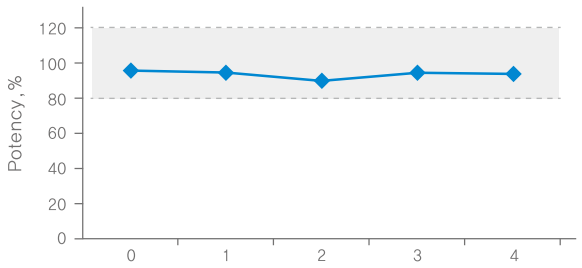
Stability at freezing temperature after dilution (-15~-25℃)



Stability at room temperature after dilution (15~25℃)



Stability after repetitive freezing/thawing after dilution (-15~-25℃/2~8℃)



* Cycle : regarded freezing (7days = −15 ~ −25, 7days) and thawing(2~8℃, 48 hours) of solution as 1 cycle, repeated the cycle 4 times.
※ Among the items of quality assurance test, potency test standard was 80~125%[2] of contrast potency of NABOTA® 100U
※ Korean registration storage requirements of NABOTA®: Use within 24 hours after dilution, keep diluted solution refrigerated (2~8℃)[3]

- Objective : to study the duration of stability of NABOTA® 100U maintained at room temperature, freezing and freezing/thawing after dilution, through animal potency test.
- Methods : conducted potency test using 3 batches of NABOTA® 100U finished products, and measured the average value as potency. confirmed the stability of 100U NABOTA® diluted in saline through animal potency test at room temperature, freezing and repetition of freezing/thawing conditions.

Ref.
1. Data on file, Daewoong.
2. Botulinum toxin investigation data establishment guideline_2014 MFDS Guideline.
3. Nabota product information _ MFDS.