HUGEL

A New Horizon of Botulinum Toxin Type A

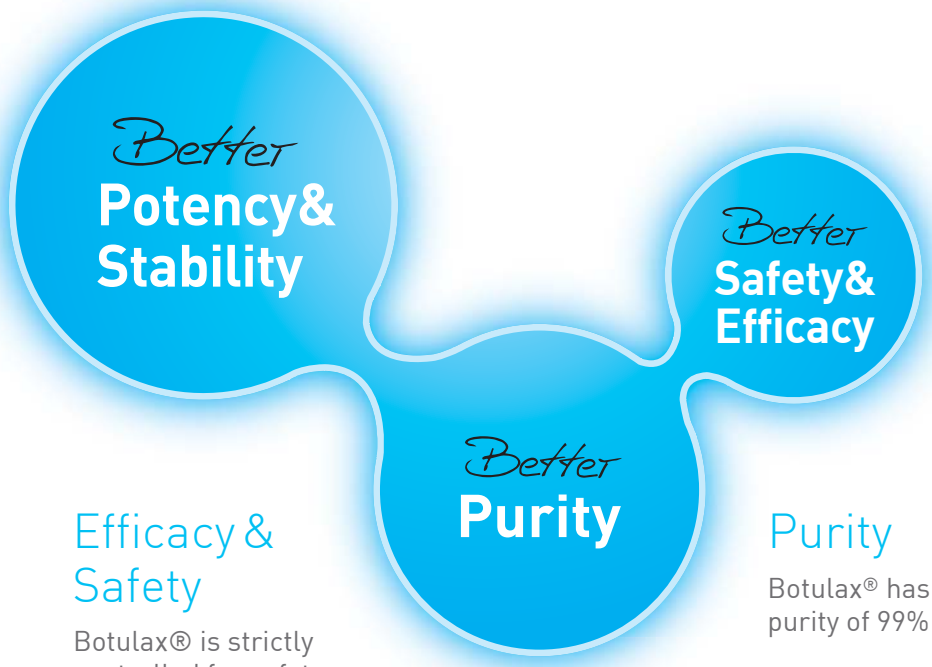
Botulax®

Botulinum Toxin Type A

"Hugel keeps evolving into a top-tier pharmaceutical company that meets the needs of both aesthetic and pharmaceutical market providing botulinum toxin, HA filler and medical devices with high quality."

Advantages of Botulax®

"3 Better"



Efficacy & Safety

Botulax® is strictly controlled for safety and high & stable potency

Purity

Botulax® has purity of 99%

Product Specifications

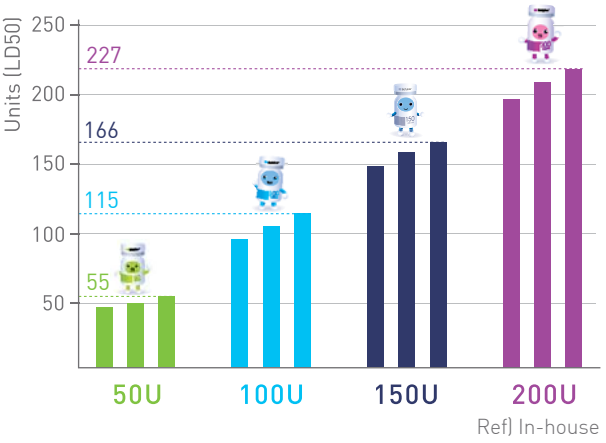
	Botulax® 50U	Botulax® 100U	Botulax® 200U	Botulax® 150U
Active Ingredient	*Clostridium botulinum* toxin type A			
Complex Size	900 kDa			
Appearance	Freeze-dried white powder			
Potency	KFDA / In-house 40-62 / 45-55	KFDA / In-house 80-125 / 95-115	KFDA / In-house 160-250 / 195-240	KFDA / In-house 120-188 / 142-172
Protein (ng/ Vial)	< 2.5	< 5	< 10	< 7.5
Endotoxin Level (EU/ Vial)	KFDA / In-house < 0.5 / < 0.175	KFDA / In-house < 1.0 / < 0.175		
pH	6.5±0.5			
Moisture	Less than 3%			
Storage	2-8°C			
Expiration	36 months from the date of manufacture			24 months

Quality & Stability

Specialized Quality Control

Botulax® keeps stabilized potency in each product followed by strict quality control.

SPECIFICATIONS / TYPE	KFDA	In-house
Botulax® 50U	40-62	45-55
Botulax® 100U	80-125	95-115
Botulax® 150U	120-188	142-172
Botulax® 200U	160-250	195-240

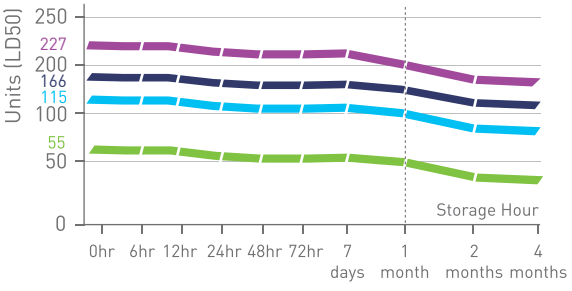


Ref) In-house

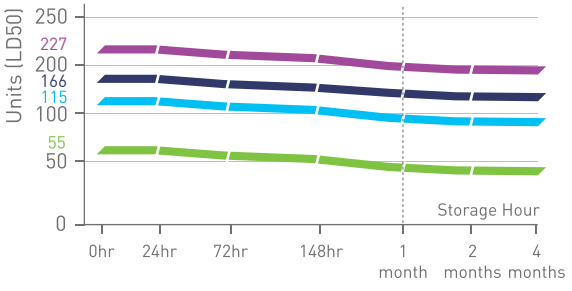
Stability after Reconstitution

Botulax® shows stable potency under the condition of cold storage or freezer after reconstitution.

Cold Storage after Reconstitution



Freezer Storage after Reconstitution



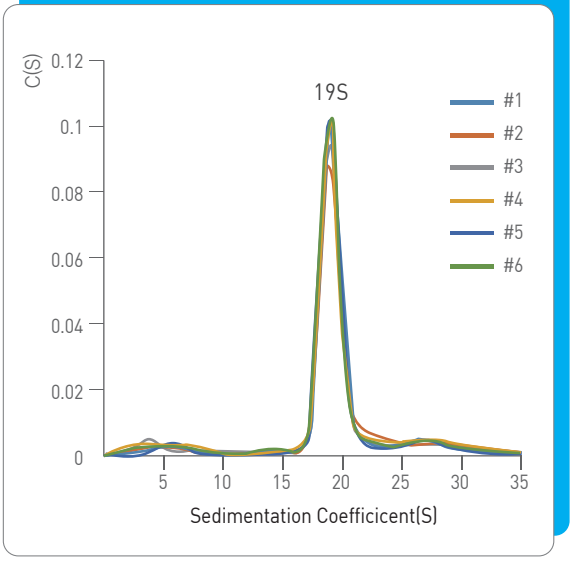
Ref) In-house

* It is recommended to use **Botulax®** within 24 hours after reconstitution followed by directions for the use of medicine.

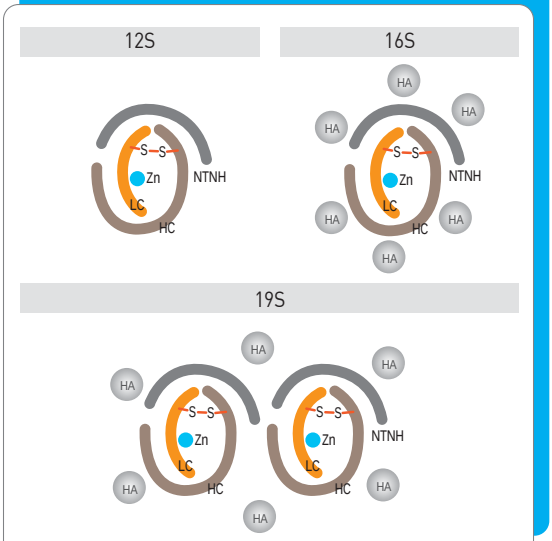
Purity

Botulax® is a highly purified product

•• Sedimentation Coefficient of BoNT/A Complex by Analytical Ultracentrifugation(AUC)



•• BTXN's Serotypes – A, B, C1, C2, D, E, F, G



The toxin complex of Botulinum Toxin Type A exist in type of 19S (900 kDa), 16S (500 kDa), and 12S (300 kDa) depending on the molecular weight.**

** Putnam F.W., Lamanna, C. and Sharp, D.O. Physicochemical Properties of Crystalline Clostridium Type A Toxin, J. Biol. Chern, 176, 401-412, 1948. Wagman, J. and Bateman, J.B., The Behavior of the Botulinus Toxins in the Ultracentrifuge. Arch. Biochem. Biophys. 31, 424-430, 1951.

Using SE-HPLC, undiluted toxin complex solution was analyzed which resulted in purity of over 99%.

•• Purity by Size Exclusion High Performance Liquid Chromatography(SE-HPLC)

```
================================================================================
                          Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=278 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]       [min]  mAU   *s   [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  20.005 MM T  0.6484   56.16814    1.44366   0.4931
   2  22.139 MM T  1.7743 1.13355e4   106.48115  99.5069
```

Safety & Efficacy

According to several clinical trials, the SAFETY & EFFICACY of **Botulax®** have been successfully proved compared with Botox® (Allergan Inc., USA).

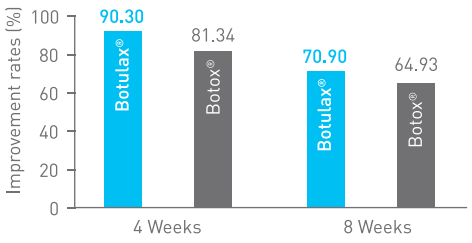
Clinical Study for Glabellar Lines

Comparative clinical study of **Botulax®** with Botox® for the improvement in **Glabellar Lines**[1)]

Improvement in Glabellar Lines at Maximum Frown

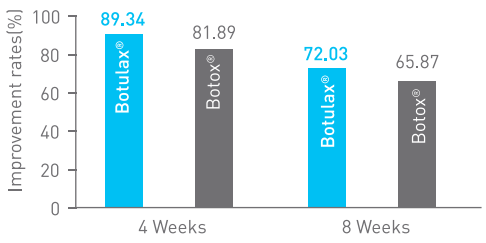
FAS (Full Analysis Set)

	Botulax®	Botox®
FAS	N=134	N=134



PPS (Per-Protocol Set)

	Botulax®	Botox®
PPS	N=122	N=127



Subjects

Two hundred seventy two (272) healthy male/ female adult patients aged between 18 and 65 with moderate to severe glabellar lines at maximum frown

Methodology

A multicenter, double-blind, randomized, active-controlled comparative, Phase Ⅲ clinical trial

Safety

There was no noticeable difference in the safety profile between **Botulax®** and Botox®.

Conclusion

This clinical trial proved that the glabellar line improvement effect of **Botulax®** is not inferior to that of Botox® in patients with moderate to severe glabellar lines. **Therefore, Botulax® is considered to be an effective and safe treatment option other than Botox®.**

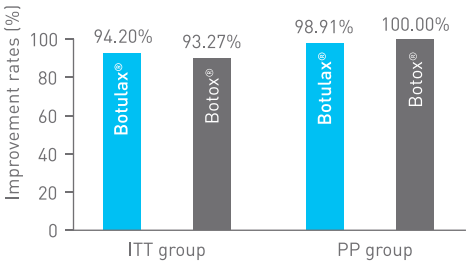
Ref. 1) clinical study results of Hugel Inc.

Clinical study for Blepharospasm

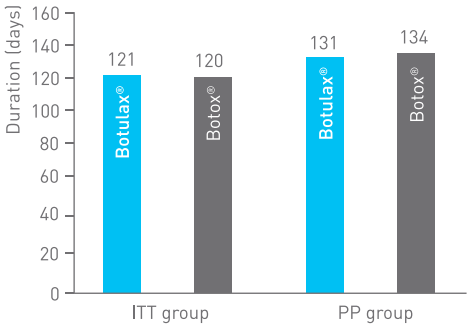
Comparative clinical study of **Botulax®** with Botox® for the treatment of **Essential Blepharospasm**[2)]

Effectiveness after Administration

	Botulax®	Botox®
ITT group	N=121	N=104
PP group	N=92	N=82



Duration after Administration



* ITT: Intention To Treat * PP: Per- Protocol

Subjects

Two hundred twenty five (225) patients diagnosed as essential blepharospasm and grade 2 to 4 spasms (Scott Method)

Methodology

A multi-center, double-blind, randomized, active-controlled comparative, Phase Ⅲ clinical trial

Safety

No clinically significant adverse event was observed.

Conclusion

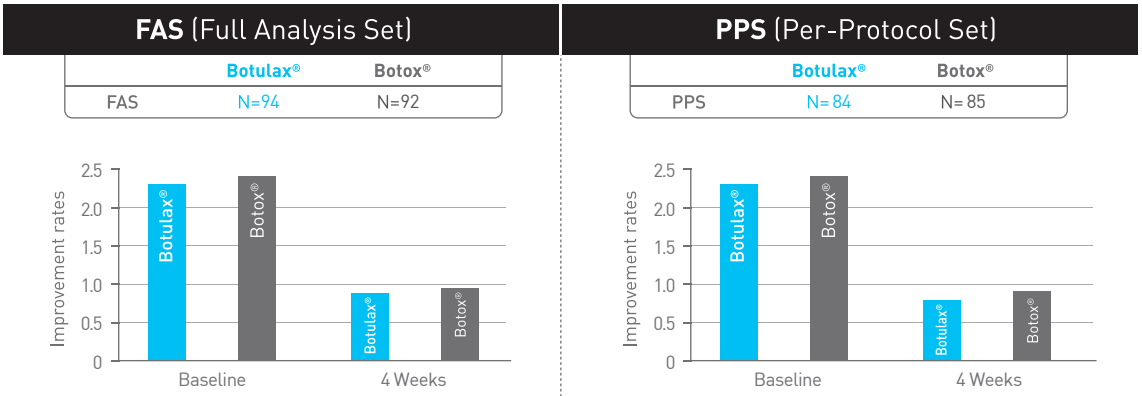
The efficacy of **Botulax®** is not inferior to that of Botox®.
Botulax® is considered to be effective and safe in treating essential blepharospasm.

Ref. 2) clinical study results of Hugel Inc.

Clinical Study for Post Stroke Upper Limb Spasticity

Comparative clinical study of **Botulax®** with Botox® for the improvement in **Post Stroke Upper Limb Spasticity**[3)]

Muscle tone improvement for patients with Post Stroke Upper Limb Spasticity



Subjects

One hundred eighty six (186) patients aged 20 or above who were diagnosed with stroke and have MAS score of ≥ 2 points for focal muscular spasticity in wrist flexor and ≥ 1point for muscular spasticity of one or more in elbow flexor and finger flexor

Methodology

A multicenter, double-blind, randomized, active drug controlled comparative, Phase Ⅲ clinical trial

Safety

No clinically significant adverse event was observed.

Conclusion

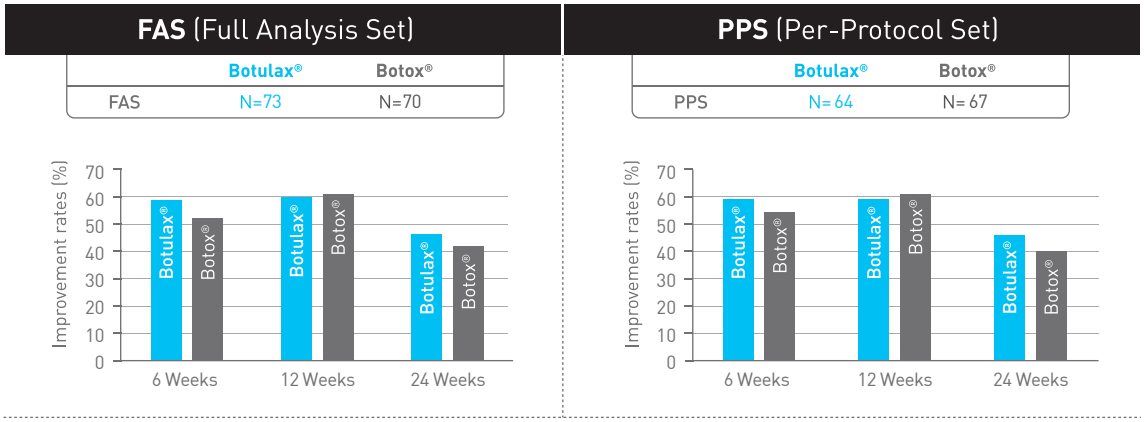
Results from this study demonstrated non-inferiority of **Botulax®** to Botox® in terms of the muscle tone improvement for patients with post stroke upper limb spasticity, as well as comparative equivalence in safety. **Therefore, Botulax® is considered to be an effective and safe treatment option for patients with post stroke upper limb spasticity.**

Ref. 3) clinical study results of Hugel Inc.

Clinical Study for Children with Cerebral Palsy

Comparative clinical study of **Botulax®** with Botox® for the improvement in **Children with Cerebral Palsy**[4)]

Improvement in Children with Cerebral Palsy



Subjects

144 cases of dynamic equinus foot deformity in children with cerebral palsy (study group: 72 cases, control group: 72 cases) and the patients diagnosed as GMFCS (Gross Motor Function Classification System) Level Ⅰ, Ⅱ or Ⅲ.

Methodology

Double-blinded, randomized, active control comparative, multicenter-designed, Phase Ⅲ clinical trial.

Safety

In analysis for safety assessment, differences between the Botulax Inj.® group and the Botox Inj.® group were not statistically significant.

Conclusion

Non-inferiority was demonstrated for Botulax Inj.® used for treatment of equinus deformity in children with cerebral palsy to Botox Inj.® in terms of the responder rate (the proportion of subjects with a 2 or more points increase in the PRS at Week 12 post-dose from baseline).

Ref. 4) clinical study results of Hugel Inc.

Publications

- Yang, K.Y., Kim, M.J., Ju, J.S., Park, S.K., Lee, C.G., Kim, S.T., Bae, Y.C. & Ahn, D.K. (2016). *Antinociceptive Effects of Botulinum toxin type A on Trigeminal Neuropathic Pain.* J Dent Res 2016;95(1):1183-90.
- Lee, I.H., Kim, N.H., Park, R.H., Park, J.B. & Ahn, T.J. (2016). *Botulinum Toxin Type A for Treatment of Masseter Hypertrophy: Volumetric Analysis of Masseter Muscle Reduction over Time.* Aesthetic Plast Surg 2016;22(2):79-86.
- Lee, J.H., Jung, S.K., Baik, J.S. & Yang, S.W. (2015). *Comparative Study of Hugel-tox® versus Botox® for the Treatment of Essential Blepharospasm.* J Korean Ophthalmol Soc 2015;56(6):811-814.
- Hyun, M.Y., Kim, B.J., Lee, C.J. & Kim, J.W. (2014). *Radiation-induced Alopecia Treated with Botulinum Toxin Type A Injection.* Plastic Reconstructive Surgery Global Open 2014;2:e226.
- Yang, K.Y., Mun, H.J., Park, K.D., Kim, M.J., Ju, J.S., Kim, S.T., Bae, Y.C. & Ahn, D.K. (2015). *Blockade of spinal glutamate recycling produces paradoxical antinociception in rats with orofacial inflammatory pain.* Neuro-Psychopharmacology & Biological Psychiatry 57 (2015) 100–109.
- Lee, H.H., Kim, S.T., Lee, K.J. & Baik, H.S. (2015). *Effect of a Second Injection of Botulinum Toxin on Lower Facial Contouring, as Evaluated Using 3-Dimensional Laser Scanning.* Dermatol Surg 2015;0:1–6.
- Kim, B.J., Kwon, H.H., Park, S.Y., Min, S.U., Yoon, J.Y., Park, Y.M., Seo, S.H., Ahn, J.Y., Lee, H.K. & Suh, D.H. (2014). *Double-blind, randomized non-inferiority trial of a novel botulinum toxin A processed from the strain CBFC26, compared with onabotulinumtoxin A in the treatment of glabellar lines.* European Academy of Dermatology and Venereology.
- Kim, H.J., Lee, G.W., Kim, M.J., Yang, K.Y., Kim, S.T., Bae, Y.C. & Ahn, D.K. (2015). *Antinociceptive Effects of Transcytosed Botulinum Neurotoxin Type A on Trigeminal Nociception in Rats.* Korean J Physiol Pharmacol Vol 19: 349-355.
- Kim, M.J., Cho, J.H., Kim, H.J., Yang, K.Y., Ju, J.S., Lee, M.K., Park, M.K. & Ahn, D.K. (2015). *Botulinum Toxin Type A Attenuates Activation of Glial Cells in Rat Medullary Dorsal Horn with CFA-induced Inflammatory Pain.* International Journal of Oral Biology, Vol. 40, No. 2 June 30 2015, p. 71-77.
- Al-Farhan, A. H. (2014). *Evaluation of Botox Treatment for Patients with Primary Axillary Hyperhidrosis in Basrah.* Basrah Journal Original Article Of Surgery Bas J Surg, June, 20, 2014.
- Jeong, H.S., Lee, B.H., Sung, H.M., Park, S.Y., Ahn, D.K., Jung, M.S. & Suh, I.S. (2015). *Effect of Botulinum Toxin Type A on Differentiation of Fibroblasts Derived from Scar Tissue.* American Society of Plastic Surgeons.
- Park, S.Y., Kim, B.J., Min, S.G., Yoon, J.Y., Kwon, H.H., Park, Y.M., Seo, S.H., Ahn, J.Y., Lee, H.K. & Suh, D.H. (2012). *Comparison of Onabotulinumtoxin A and Neurotoxin from CBFC26 strain (Botulax®) and their efficacy in relation to horizontal wrinkles on bridge of nose.* Korean Dermatological Association, The 64th Annual Meeting in 2012.

Global Product

Botulax® is being introduced to Korea, Japan, Southeast Asia(Thailand, etc.), Europe(Ukraine, etc.), Russia, South and Central America(Brazil, etc.).

Botulax® is also being sold worldwide under the names of Regenox®, Zentox®, Reage®, Magnion®, Hugel Toxin®, Juvenlife®, Botulim®, and Botoshot®.

Botulax®

Botulinum Toxin Type A

Manufactured and distributed by HUGEL

Hugel, Inc. 16F, 514, Seolleung-ro, Gangnam-gu, Seoul, Korea
T 82.2.6900.9108 **F** 82.2.534.7518
www.hugel.co.kr / globalbusiness@hugel.co.kr

BTX-BR180308ENG