Package leaflet: Information for the user

BOTOX, 50 Allergan Units, Powder for Solution for Injection
BOTOX, 100 Allergan Units, Powder for Solution for Injection
BOTOX, 200 Allergan Units, Powder for Solution for Injection

Botulinum toxin type A

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What BOTOX is and what it is used for

BOTOX is a muscle relaxant used to treat a number of conditions within the body. It contains the active substance Botulinum toxin type A and is injected into either the muscles, the bladder wall or deep into the skin. It works by partially blocking the nerve impulses to any muscles that have been injected and reduces excessive contractions of these muscles.

When injected into the skin, BOTOX works on sweat glands to reduce the amount of sweat produced. When injected into the bladder wall, BOTOX works on the bladder muscle to reduce leakage of urine (urinary incontinence). In the case of chronic migraine, it is thought that BOTOX may block pain signals which indirectly block the development of a migraine. However, the way BOTOX works in chronic migraine is not fully established.

1) BOTOX can be injected directly into the muscles, and can be used to treat the following conditions:
   - **persistent muscle spasms** in the **ankle and foot** in **children** aged two years or older with cerebral palsy, who can walk. BOTOX is used to support rehabilitation therapy;
   - **persistent muscle spasms** in the **wrist** and **hand** of **adult** patients who have suffered a stroke;
   - **persistent muscle spasms** in the **ankle and foot** of **adult** patients who have suffered a stroke;
   - **persistent muscle spasms** in the **eyelid** and **face** of **adult** patients;
   - **persistent muscle spasms** in the **neck** and **shoulders** of **adult** patients;

2) BOTOX is used to **reduce** the symptoms of **chronic migraine in adults** who have had headaches on 15 or more days each month of which at least 8 days are with migraine and who have not responded well to other preventative migraine medications.

Chronic migraine is a disease affecting the nervous system. Patients usually suffer from head pain which is often accompanied by excessive sensitivity to light, loud sounds or smells/odours, as well as nausea and/or vomiting. These headaches occur on **15 or more days** each month.

3) When injected into the bladder wall, BOTOX works on the bladder muscle to reduce leakage of urine (urinary incontinence) and control the following conditions in adults:
   - **overactive bladder with leakage of urine**, the sudden urge to empty your bladder and needing to go to the toilet more than usual when another drug (called an anticholinergic) did not help;
   - **leakage of urine** due to bladder problems associated with spinal cord injury or multiple sclerosis.

4) In adults, BOTOX can be injected deep into the skin and can work on sweat glands to reduce **excessive sweating** of the **armpits**, which affects the activities of daily living when other local treatments do not help.

2. What you need to know before you use BOTOX

Do not use BOTOX

- if you are **allergic** (hypersensitive) to botulinum toxin type A or any of the other ingredients of this medicine (listed in section 6);
- if you have an **infection** at the proposed **site of injection**;
- when you are being treated for leakage of urine and have either a urinary tract infection or a sudden inability to empty your bladder (and are not regularly using a catheter);
- if you are being treated for leakage of urine and are not willing to begin using a catheter if required.

Warnings and precautions

Talk to your doctor or pharmacist before using BOTOX:
- if you **have ever had problems with swallowing or food or liquid accidentally going into your lungs, especially if you will be treated for persistent muscle spasms in the neck and shoulders;**
- if you are **over 65 years of age** and have other **serious illnesses**;
- if you suffer from any other **muscle problems** or chronic diseases affecting your muscles (such as myasthenia gravis or Eaton Lambert Syndrome);
- if you suffer from certain **diseases** affecting your **nervous system** (such as amyotrophic lateral sclerosis or motor neuropathy);
- if you have significant **weakness** or **wasting of the muscles** which your doctor plans to inject;
- if you have had any **surgery** or **injury** that may have changed the muscle to be injected in some way;
- if you have had any **problems with injections** (such as fainting) in the past;
- if you have **inflammation in the muscles** or **skin** area where your doctor plans to inject;
- if you suffer from cardiovascular disease (disease of the heart or blood vessels);
- if you suffer of have suffered from seizures;
- if you have an eye disease called closed-angle **glaucoma** (high pressure in the eye) or were told you are at risk for developing this type of glaucoma;
- if you are about to be treated for overactive bladder with leakage of urine and you are a male with signs and symptoms of urinary obstruction, such as difficulty in passing urine or a weak or interrupted stream.

After you have been given BOTOX

You or your caregiver should contact your doctor and seek medical attention immediately if you experience any of the following:

- **difficulty in breathing, swallowing, or speaking;**
- **hives**, **swelling** including swelling of the face or throat, **wheezing**, feeling **faint** and shortness of **breath** (possible symptoms of severe allergic reaction).

General precautions

As with any injection, it is possible for the procedure to result in infection, pain, swelling, abnormal skin sensations (e.g. tingling or numbness), decreased skin sensation, tenderness, redness, bleeding/bruising at the site of injection and a drop in blood pressure or fainting; this may be the consequence of pain and/or anxiety associated with injection.

Adverse reactions possibly related to the spread of toxin distant from the site of administration have been reported with botulinum toxin (e.g. muscle weakness, difficulty swallowing or unwanted food or liquid in the airways). These side effects can be mild to severe, may require treatment and in some cases may be fatal. This is a particular risk for patients with an underlying illness that makes them susceptible to these symptoms.

Severe and/or immediate allergic reactions have been reported, the symptoms of which may include hives, swelling of the face or throat, shortness of breath, wheezing and fainting. Delayed allergic reactions (serum sickness) have also been reported, which may include symptoms such as fever, joint pain, and skin rash.

Side effects related to the cardiovascular system, including irregular heartbeat and heart attacks, have also been seen in patients treated with BOTOX, sometimes with a fatal outcome. However there was a prior history of cardiac risk factors in some of these patients.

Seizures have been reported in adults and children treated with BOTOX, mostly in patients who are more prone to seizures. It is not known if BOTOX is the cause of these seizures. Seizures that were reported in children were mostly in cerebral palsy patients treated for persistent muscle spasms.
If you are given BOTOX too often or the dose is too high, you may experience muscle weakness and adverse reactions related to the spread of toxin, or your body may start producing some antibodies, which can reduce the effect of BOTOX.

When BOTOX is used in the treatment of a condition that it is not listed in this leaflet, it could result in serious reactions, particularly in patients who already experience difficulty in swallowing or have significant debility.

If you have not done much exercise for a long time before receiving BOTOX treatment, then after your injections you should start any activity gradually.

It is unlikely that this medicine will improve the range of motion of joints where the surrounding muscle has lost its ability to stretch.

BOTOX should not be used when treating persistent post-stroke ankle muscle spasms in adults if it is not expected to result in improvement in function (e.g. walking) or symptoms (e.g. pain) or to help with patient care. If your stroke was more than 2 years ago or if your ankle muscle spasm is less severe, improvements related to activities such as walking may be limited. Furthermore, for patients who may be more likely to fall, your doctor will judge if this treatment is suitable.

BOTOX should only be used for the treatment of post-stroke ankle and foot muscle spasms following evaluation by health care professionals experienced in the management of the rehabilitation of post-stroke patients.

When BOTOX is used in the treatment of persistent muscle spasms in the eyelid, it could make your eyes blink less often, which may harm the surface of your eyes. In order to prevent this, you may need treatment with eye drops, ointments, soft contact lenses or even protective covering which closes the eye. Your doctor will tell you if this is required.

When BOTOX is used to control the leakage of urine, your doctor will give you antibiotics before and after the treatment to help prevent urinary tract infection.

You will be seen by your doctor approximately 2 weeks after the injection, if you were not using a catheter before the injection. You will be asked to pass urine and will then have the volume of urine left in your bladder measured using ultrasound. Your doctor will decide if you need to return for the same test during the next 12 weeks. You must contact your doctor if at any time you are unable to pass urine because it is possible that you may need to start using a catheter. In patients with leakage of urine due to bladder problems associated with spinal cord injury or multiple sclerosis, approximately one third who were not using a catheter before treatment may need to use a catheter after treatment. In patients with leakage of urine due to overactive bladder, approximately 6 out of 100 patients may need to use a catheter after treatment.

Other medicines with BOTOX

Tell your doctor or pharmacist if:
- you are using any **antibiotics** (used to treat infections), anticholinesterase medicines, or **muscle relaxants**. Some of these medicines may increase the effect of BOTOX.
- you have recently been injected with a **medicine containing a botulinum toxin** (the active substance of BOTOX), as this may increase the effect of BOTOX too much.
- you are using any anti-platelet (aspirin-like products) and/or anti-coagulants (blood thinners).

Tell your doctor or pharmacist if you are taking or have recently taken or might take any other medicine.

Pregnancy and breast-feeding

The use of BOTOX is not recommended during pregnancy and in women of childbearing potential not using contraception unless clearly necessary. BOTOX is not recommended in breast-feeding women. If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine.

Driving and using machines

BOTOX may cause dizziness, sleepiness, tiredness or problems with your vision. If you experience any of these effects, do not drive or use any machines. If you are not sure, ask your doctor for advice.

BOTOX contains sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially “sodium free”.

3. How to use BOTOX

BOTOX must only be injected by doctors with specific skills and experience on how to use the medicine.

BOTOX should only be prescribed for you for chronic migraine if you have been diagnosed by a neurologist who is a specialist in this area. BOTOX should be administered under the supervision of a neurologist. BOTOX is not used for acute migraine, chronic tension type headaches or patients with medication overuse headache.

Method and route of administration

BOTOX is injected into your muscles (intramuscularly), into the bladder wall via a specific instrument (cystoscope) to inject into the bladder or into the skin (intradermally). It is injected directly into the affected area of your body; your doctor will usually **inject BOTOX into several sites within each affected area**.

General information about dosage

- The number of injections per muscle and the dose vary depending on the indication. Therefore, your doctor will decide how much, how often, and in which muscle(s) BOTOX will be given to you. It is recommended that your doctor uses the lowest effective dose.
- Dosages for older people are the same as for other adults.

The dosage of BOTOX and the duration of its effect will vary depending on the condition for which you are treated. Below are details corresponding to each condition.
The safety and effectiveness of BOTOX has been established in children/adolescents over the age of two years for the treatment of persistent muscle spasms in the ankle and foot. associated with cerebral palsy.

Limited information is available on the use of BOTOX in the following conditions in children/adolescents over the age of 12 years. No recommendation on dosage can be made for these indications.

Persistent muscle spasms in the eyelid and face	12 years
Persistent muscle spasms in neck and shoulder	12 years
Excessive sweating of the armpits	12 years (limited experience in adolescents between 12 and 17 years)

Dosage

The dosage of BOTOX and the duration of its effect will vary depending on the condition for which you are treated. Below are details corresponding to each condition.

Indication	**Maximum dose (Units per affected area)**		**Minimal time between treatments**
	First treatment	**Following treatments**	
Persistent muscle spasms in the ankle and foot in children who have cerebral plasy	**Ankle & foot:** 4 to 8 Units/kg or 300 Units, whichever is lower	When treating the ankle & foot of both legs the maximum dose is not to exceed the lower of 10 Units/kg or 340 Units	12 weeks*

Persistent muscle spasms in the wrist and hand of adult patients who have had a stroke	The exact dosage and number of injection sites per hand/wrist is tailored to individual needs up to a maximum of 240 Units	The exact dosage and number of injection sites is tailored to individual needs up to a maximum of 240 Units	12 weeks
Persistent muscle spasms in the ankle and foot of adult patients who have had a stroke	Your doctor may give multiple injections in the affected muscles. The total dose is 300 Units to 400 Units divided among up to 6 muscles for each treatment session	The total dose is 300 Units to 400 Units divided among up to 6 muscles for each treatment session	12 weeks
Persistent muscle spasms of the eyelid and face	1.25-2.5 Units per injection site. Up to 25 Units per eye for eye spasms.	Up to 100 Units for spasms of the eye.	3 months for spasms of the eye.
Persistent muscle spasms of the neck and shoulders	200 Units No more than 50 Units should be given at any one site	Up to 300 Units	10 weeks
Headache in adults who have chronic migraine	155 to 195 Units No more than 5 Units should be given at any one site	155 to 195 Units	12 weeks
Overactive bladder with leakage of urine	100 Units	100 Units	3 months
Leakage of urine due to bladder problems associated with spinal cord injury or multiple sclerosis in adult patients	200 Units	200 Units	3 months
Excessive sweating of the armpits	50 Units per armpit	50 Units per armpit	16 weeks

** The doctor may select a dose that would mean the treatment may be up to 6 months apart.*

Time to Improvement and Duration of Effect

For **persistent muscle spasms in the ankle and foot in children two years and older**, the improvement usually appears within the first 2 weeks after the injection.

For **persistent muscle spasms in the wrist and hand of adult patients who have had a stroke,** you will usually see an improvement within the first 2 weeks after the injection. The maximum effect is usually seen about 4 to 6 weeks after treatment.

For **persistent muscle spasms in the ankle and foot of adult patients who have had a stroke,** when the effect starts to wear off, you can have the treatment again if needed, but not more often than every 12 weeks.

For **persistent muscle spasms of the eyelid and face**, you will usually see an improvement within 3 days after the injection and maximum effect is usually seen after 1 to 2 weeks.

For **persistent muscle spasms of the neck and shoulders,** you will usually see an improvement within 2 weeks after the injection. The maximum effect is usually seen about 6 weeks after treatment.

For **leakage of urine due to overactive bladder,** you will usually see an improvement within 2 weeks after the injection. Typically the effect lasts approximately 6-7 months after the injection.

For **leakage of urine due to bladder problems associated with spinal cord injury or multiple sclerosis,** you will usually see an improvement within 2 weeks after the injection. Typically the effect lasts approximately 8-9 months after the injection.

For **excessive sweating of the armpits**, you will usually see an improvement within the first week after injection. On average the effect usually lasts 7.5 months after the first injection with approximately 1 out of 4 patients still experiencing the effect after one year.

If you have received more BOTOX than you should

The signs of too much BOTOX may not appear for several days after the injection. Should you swallow BOTOX or have it accidentally injected, you should see your doctor who might keep you under observation for several weeks.

If you have received too much BOTOX, you may have any of the following symptoms and you must contact your doctor immediately. He/she will decide if you have to go to hospital:
- muscle weakness which could be local or distant from the site of injection;
- difficulty in breathing, swallowing or speaking due to muscle paralysis;
- food or liquid accidentally going into your lungs which might cause pneumonia (infection of the lungs) due to muscle paralysis;
- drooping of the eyelids, double vision;
- generalised weakness.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. In general, side effects occur within the first few days following injection.
They usually last only for a short time, but they may last for several months and in rare cases, longer.

IF YOU HAVE ANY DIFFICULTY IN <u>BREATHING</u>, <u>SWALLOWING</u> OR <u>SPEAKING</u> AFTER RECEIVING BOTOX, CONTACT YOUR DOCTOR IMMEDIATELY.

If you experience <u>hives</u>, <u>swelling</u> including swelling of the face or throat, <u>wheezing</u>, feeling <u>faint</u> and shortness of <u>breath</u>, contact your doctor immediately.

The side effects are classified into the following categories, depending on how often they occur:

Very common	may affect more than 1 in 10 people
Common	may affect up to 1 in 10 people
Uncommon	may affect up to 1 in 100 people
Rare	may affect up to 1 in 1,000 people
Very rare	may affect up to 1 in 10,000 people
Not known	cannot be estimated from the available data

Below are lists of side effects which vary depending on the part of the body where BOTOX is injected. If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Injections for children with persistent muscle spasms in the ankle and foot

Common	rash, problems with walking, stretching or tearing of ligaments, shallow wound to the skin, pain where the injection was given.
Uncommon	Muscle weakness.

There have been rare spontaneous reports of death sometimes associated with aspiration pneumonia in children with severe cerebral palsy after treatment with BOTOX.

Injections in the wrist and hand of adult patients who have had a stroke

Common	Pain in the hand and fingers, nausea, swelling of the extremities such as the hands and feet, tiredness, muscle weakness

Injections in the ankle and foot of adult patients who have had a stroke

Common	Rash, joint pain or inflammation, stiff or sore muscles, muscle weakness, swelling of the extremities such as the hands and feet, fall.

Injections in the eyelid and face

Very Common	Drooping of the eyelid.
Common	Pinpoint damage of the cornea (transparent surface covering the front of the eye), difficulty in completely closing the eye, dry eyes, sensitivity to light, eye irritation, overflow of tears, bruising under the skin, skin irritation, swelling of the face.
Uncommon	Dizziness, weakness of the face muscles, droop of the muscles on one side of the face, inflammation of the cornea (transparent surface covering the front of the eye), abnormal turning of the eyelids outwards or inwards, double vision, difficulties in seeing clearly, blurred vision, rash, tiredness.
Rare	Swelling of the eyelid.
Very Rare	Ulcer, damage to the cornea (transparent surface covering the front of the eye).

Injections in the neck and shoulder

Very Common	Difficulty in swallowing, muscle weakness, pain.
Common	Swelling and irritation inside the nose (rhinitis), blocked or runny nose, cough, sore throat, tickle or irritation in the throat, dizziness, increased muscle tension (cramps), decreased skin sensation, sleepiness, headache, dry mouth, nausea, stiff or sore muscles, feeling of weakness, flu syndrome, feeling generally unwell.
Uncommon	Double vision, fever, drooping of the eyelid, shortness of breath, changes in your voice.

Injections in the head and neck for the treatment of headache in patients who suffer from chronic migraine

Common	Headache, migraine and worsening of migraine, weakness of the face muscles, drooping of the eyelid, rash, itching, neck pain, muscle pain, muscle spasm, muscle stiffness, muscle tightness, muscle weakness, pain where the injection was given.
Uncommon	Difficulty in swallowing, skin pain, jaw pain.
Not known	Mephisto sign (raising of the outer eyebrows)

Injections in the bladder wall for leakage of urine due to overactive bladder

Very Common	Urinary tract infection, painful urination after the injection*.
Common	Bacteria in the urine, inability to empty your bladder (urinary retention), incomplete emptying of the bladder, frequent daytime urination, white blood cells in the urine, blood in the urine after the injection**.

** This side effect may also be related to the injection procedure.*
***This side effect is only related to the injection procedure.*

Injections in the bladder wall of adult patients for leakage of urine due to bladder problems associated with spinal cord injury or multiple sclerosis

Very Common	Urinary tract infection, inability to empty your bladder (urinary retention).
Common	Difficulty in sleeping (insomnia), constipation, muscle weakness, muscle spasm, blood in the urine after the injection*, painful urination after the injection*, bulge in the bladder wall (bladder diverticulum), tiredness, problems with walking (gait disturbance), possible uncontrolled reflex reaction of your body (e.g. profuse sweating, throbbing headache or increase in pulse rate) around the time of the injection (autonomic dysreflexia)*, fall.

**Some of these common side effects may also be related to the injection procedure.*

Injections in the bladder wall of paediatric patients for leakage of urine due to bladder problems associated with spina bifida, spinal cord injury or transverse myelitis

Very Common	Bacteria in the urine
Common	Urinary tract infection, white blood cells in the urine, blood in the urine after the injection, pain in the bladder after the injection.*

**This side effect is only related to the injection procedure.*

Injections for excessive sweating of the armpits

Very Common	Injection site pain.
Common	Headache, numbness, hot flushes, increased sweating at sites other than the armpit, abnormal skin odour, itching, lump under the skin, hair loss, pain in the extremities such as the hands and fingers, pain, reactions and swelling, bleeding or burning and increased sensitivity where the injection was given, general weakness.
Uncommon	Nausea, muscle weakness, feeling of weakness, muscle pain, problem with the joints.

The following list describes **additional side effects** reported for BOTOX, in any disease, since it has been marketed:

- allergic reaction, including reactions to injected proteins or serum;
- swelling of the deeper layers of the skin;
- hives;
- eating disorders, loss of appetite;

- nerve damage (brachial plexopathy);
- voice and speech problems;
- droop of the muscles on one side of the face;
- weakness of the face muscles;
- decreased skin sensation;
- muscle weakness;
- chronic disease affecting the muscles (myasthenia gravis);
- difficulty moving the arm and shoulder;
- numbness;
- pain/numbness/or weakness starting from the spine;
- seizures and fainting;
- increase in eye pressure;
- strabismus (crossed-eyes);
- blurred vision;
- difficulties in seeing clearly;
- decreased hearing;
- noises in the ear;
- feeling of dizziness or “spinning” (vertigo);
- heart problems including heart attack;
- aspiration pneumonia (lung inflammation caused by accidentally breathing in food, drink, saliva or vomit);
- breathing problems, respiratory depression and/or respiratory failure;
- abdominal pain;
- diarrhoea, constipation;
- dry mouth;
- difficulty swallowing;
- nausea, vomiting;
- hair loss;
- itching;
- different types of red blotchy skin rashes;
- excessive sweating;
- loss of eyelashes/eyebrows;
- muscles pain, loss of nerve supply to/shrinkage of injected muscle;
- feeling generally unwell;
- fever,
- dry eye (associated with injections around the eyes),
- localised muscle twitching/involuntary muscle contractions
- Swelling of the eyelid.

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via:

Ireland
HPRA Pharmacovigilance
Website: www.hpra.ie

Malta
ADR Reporting
Website: www.medicinesauthority.gov.mt/adrportal

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store BOTOX

Keep out of the sight and reach of children.

Your doctor should not use BOTOX after the expiry date which is stated on the label after 'EXP'. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C – 8°C), or store in a freezer (-5°C to -20°C).
After the solution is made up, immediate use of the solution is recommended; however it can be stored for up to 24 hours in a refrigerator (2°C – 8°C).

6. Contents of the pack and other information

What BOTOX contains

- The active substance is: Botulinum toxin type A from Clostridium botulinum. Each vial contains either 50, 100 or 200 Allergan Units of Botulinum toxin type A.
- The other ingredients are human albumin and sodium chloride.

What BOTOX looks like and contents of the pack

BOTOX is presented as a thin white powder that may be difficult to see on the bottom of a transparent glass vial. Prior to injection, the product must be dissolved in a sterile unpreserved normal saline solution (0.9% sodium chloride solution for injection).
Each pack contains 1, 2, 3 or 6 vials. In addition, the 50 and 100 Allergan Units of Botulinum toxin type A may also be presented in packs of 10 vials.
Not all pack sizes may be marketed.

Marketing Authorisation Holder

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The following information is intended for medical or healthcare professionals only:

Please refer to the Summary of Product Characteristics for complete prescribing information for BOTOX.
Botulinum toxin units are not interchangeable from one product to another. Doses recommended in Allergan Units are different from other botulinum toxin preparations.
BOTOX should only be given by physicians with appropriate qualifications, and expertise in the treatment and the use of the required equipment.

Chronic migraine should be diagnosed by, and BOTOX should be exclusively administered under, the supervision of neurologists who are experts in the treatment of chronic migraine.

BOTOX is indicated for the management of: focal spasticity of the ankle and foot in paediatric patients, two years of age or older; focal spasticity of the wrist and hand in adult post stroke patients; focal spasticity of the ankle and foot in adult post stroke patients; blepharospasm, hemifacial spasm and associated focal dystonias; cervical dystonia (spasmodic torticollis); symptom relief in adults fulfilling criteria for chronic migraine (headaches on ≥15 days per month of which at least 8 days with migraine) in patients who have responded inadequately or are intolerant of prophylactic migraine medications; idiopathic overactive bladder with symptoms of urinary incontinence, urgency and frequency in adult patients who have an inadequate response to, or are intolerant of, anticholinergic medication; urinary incontinence in adults with neurogenic detrusor overactivity due to stable sub-cervical spinal cord injury or multiple sclerosis and persistent severe primary hyperhidrosis of the axillae, which interferes with the activities of daily living and is resistant to topical treatment.

The safety and effectiveness of BOTOX in indications other than those described for the paediatric population in section 4.1 of the Summary of Product Characteristics have not been established. No recommendation on posology can be made for indications other than paediatric focal spasticity associated with cerebral palsy . Currently available data per indication are described in section 4.2, 4.4, 4.8 and 5.1 of the Summary of Product Characteristics, as shown in the table below.

Blepharospasm/Hemifacial spasm	12 years (see section 4.4 and 4.8)
Cervical dystonia	12 years (see section 4.4 and 4.8)
Focal spasticity in paediatric patients	2 years (see section 4.2, 4.4 and 4.8)
Primary hyperhidrosis of the axillae	12 years (limited experience in adolescents between 12 and 17 years, see section 4.4, 4.8 and 5.1)

No specific dose adjustment is required for use in the elderly. Initial dosing should begin at the lowest recommended dose for the specific indication. For repeat injections the lowest effective dose with the longest clinically indicated interval between injections is recommended. Elderly patients with significant medical history and concomitant medications should be treated with caution.
Generally valid optimum dose levels and number of injection sites per muscle have not been established for all indications. In these cases, individual treatment regimens should therefore be drawn up by the physician. Optimum dose levels should be determined by titration but the recommended maximum dose should not be exceeded. As with any drug treatment, initial dosing in a naïve patient should begin at the lowest effective dose.

Posology and method of administration (please refer to section 4.2 and 4.4 of the SPC for further information):

Focal spasticity of the lower limb in paediatric patients:
The recommended dose for treating paediatric lower limb spasticity is 4 Units/kg to 8 Units/kg body weight or 300 U, whichever is lower, divided among the affected muscles. When treating both lower limbs, the total dose should not exceed the lower of 10 Units/kg body weight or 340 Units, in a 12 week interval.

Muscles Injected	BOTOX 4 Units/kg* (maximum Units per muscle)	BOTOX 8 Units/kg** (maximum Units per muscle)	Number of Injection Sites
Ankle Muscles Gastrocnemius medial head	1 Unit/kg (37.5 Units)	2 Units/kg (75 Units)	2
Gastrocnemius lateral head	1 Unit/kg (37.5 Units)	2 Units/kg (75 Units)	2
Soleus	1 Unit/kg (37.5 Units)	2 Units/kg (75 Units)	2
Tibialis Posterior	1 Unit/kg (37.5 Units)	2 Units/kg (75 Units)	2

* did not exceed a total dose of 150 Units

** did not exceed a total dose of 300 Units

Focal upper & lower limb spasticity associated with stroke:

BOTOX is a treatment of focal spasticity that has only been studied in association with usual standard of care regimens, and is not intended as a replacement for these treatment modalities. BOTOX is not likely to be effective in improving range of motion at a joint affected by a fixed contracture.

Focal upper limb spasticity associated with stroke:

Muscle	Recommended Dose; Number of Sites
Forearm	
Pronator quadratus	10 – 50 Units; 1 site
Wrist	
Flexor carpi radialis	15 – 60 Units; 1-2 sites
Flexor carpi ulnaris	10 – 50 Units; 1-2 sites
Fingers/Hand	
Flexor digitorum profundus	15 – 50 Units; 1-2 sites
Flexor digitorum sublimis/superficialis	15 – 50 Units; 1-2 sites
Lumbricals*	5 – 10 Units;1 site
Interossei*	5 – 10 Units;1 site
Thumb	
Adductor pollicis	20 Units; 1-2 sites
Flexor pollicis longus	20 Units; 1-2 sites
Flexor pollicis brevis	5 – 25 Units; 1 site
Opponens pollicis	5 – 25 Units; 1 site

*When injecting both lumbricals and/or interossei, the recommended maximum dose is 50 U per hand.

The recommended dose for treating adult upper limb spasticity is up to 240 Units divided among the affected muscles as listed in the above table. The maximum dose at one treatment is 240 Units.

The exact dosage and number of injection sites should be tailored to the individual based on the size, number and location of muscles involved, the severity of spasticity, presence of local muscle weakness, and the patient response to previous treatment.

Focal lower limb spasticity associated with stroke:

Muscle	Recommended Dose Total Dosage; Number of Sites
Gastrocnemius Medial head	75 Units; 3 sites

Lateral head	75 Units; 3 sites
Soleus	75 Units; 3 sites
Tibialis Posterior	75 Units; 3 sites
Flexor hallucis longus	50 Units; 2 sites
Flexor digitorum longus	50 Units; 2 sites
Flexor digitorum brevis	25 Units; 1 site

The recommended dose for treating adult lower limb spasticity involving the ankle and foot is 300 Units to 400 Units divided among up to 6 muscles.

Blepharospasm/hemifacial spasm:

Muscles	Dose selection
Medial and lateral orbicularis oculi of the upper lid and the lateral orbicularis oculi of the lower lid. Additional sites in the brow area, the lateral orbicularis and in the upper facial area may also be injected if spasms here interfere with vision. Patients with hemifacial spasm or VIIth nerve disorders should be treated as for unilateral blepharospasm, with other affected facial muscles (e.g. zygomaticus major, orbicularis oris) being injected as needed.	Initial recommended 1.25-2.5 Units injected into the medial and lateral orbicularis oculi of the upper lid and the lateral orbicularis oculi of the lower lid. The initial dose should not exceed 25 Units per eye. The total dosing should not exceed 100 Units every 12 weeks.

Reduced blinking following botulinum toxin injection into the orbicularis muscle can lead to corneal pathology. Careful testing of corneal sensation in eyes previously operated upon, avoidance of injection into the lower lid area to avoid ectropion, and vigorous treatment of any epithelial defect should be employed. This may require protective drops, ointment, therapeutic soft contact lenses, or closure of the eye by patching or other means.

Cervical dystonia:

Muscles	Dose selection
Sternocleidomastoid, levator scapulae, scalene, splenius capitis, semispinalis, longissimus and/or the trapezius muscle(s).	No more than 50 Units should be given at any one site. No more than 100 Units should be given to the sternomastoid. No more than 200 Units total should be injected for the first course of therapy, with adjustments made in subsequent courses dependent on the initial response. A total dose of 300 Units at any one sitting should not be exceeded.

The list of muscles is not exhaustive as any of the muscles responsible for controlling head position may be involved and therefore require treatment.

Chronic Migraine

The recommended reconstituted BOTOX dose for treating chronic migraine is 155 Units to 195 Units administered intramuscularly (IM) using a 30-gauge, 0.5 inch needle as 0.1 ml (5 Units) injections to 31 and up to 39 sites. Injections should be divided across 7 specific head/neck muscle areas as specified in the table below. A 1-inch needle may be needed in the neck region for patients with extremely thick neck muscles. With the exception of the procerus muscle, which should be injected at 1 site (midline), all muscles should be injected bilaterally with half the number of injections sites administered to the left, and half to the right side of the head and neck. If there is a predominant pain location(s), additional injections to one or both sides may be administered in up to 3 specific muscle

groups (occipitalis, temporalis, and trapezius), up to the maximum dose per muscle as indicated in the table below.

	Recommended Dose
Head/Neck Area	**Total Dosage (number of sites[a])**
Corrugator[b]	10 Units (2 sites)
Procerus	5 Units (1 site)
Frontalis[b]	20 Units (4 sites)
Temporalis[b]	40 Units (8 sites) up to 50 Units (up to 10 sites)
Occipitalis[b]	30 Units (6 sites) up to 40 Units (up to 8 sites)
Cervical Paraspinal Muscle Group[b]	20 Units (4 sites)
Trapezius[b]	30 Units (6 sites) up to 50 Units (up to 10 sites)
Total Dose Range:	**155 Units to 195 Units 31 to 39 sites**

[a]1 IM injection site = 0.1 ml = 5 Units BOTOX
[b]Dose distributed bilaterally

Urinary incontinence due to overactive bladder
The recommended dose is 100 Units of BOTOX as 0.5 ml (5 Units) injections across 20 sites in the detrusor, avoiding the trigone and base.

Urinary incontinence due to neurogenic detrusor overactivity:
The recommended dose is 200 Units of BOTOX as 1 ml (~6.7 Units) injections across 30 sites in the detrusor, avoiding the trigone and base.

Primary hyperhidrosis of the axillae:

Injection sites	Dose selection
Multiple sites approximately 1-2 cm apart within the hyperhidrotic area of each axilla	Doses other than 50 Units per axilla have not been studied and therefore cannot be recommended.

Medical history and physical examination, along with specific additional investigations as required, should be performed to exclude potential causes of secondary hyperhidrosis (e.g. hyperthyroidism, phaeochromocytoma). This will avoid symptomatic treatment of hyperhidrosis without the diagnosis and/or treatment of underlying disease.

For all indications:
Side effects related to spread of toxin distant from the site of administration have been reported, sometimes resulting in death, which in some cases was associated with dysphagia, pneumonia and/or significant debility. The symptoms are consistent with the mechanism of action of botulinum toxin and have been reported hours to weeks after injection. The risk of symptoms is probably greatest in patients who have underlying conditions and comorbidities that would predispose them to these symptoms, including children and adults treated for spasticity, and are treated with high doses.

Patients treated with therapeutic doses may also experience exaggerated muscle weakness. Pneumothorax associated with injection procedure has been reported following administration of BOTOX near the thorax. Caution is warranted when injecting in proximity to the lung, particularly the apices or other vulnerable anatomic structures.

Serious adverse events including fatal outcomes have been reported in patients who had received off-label injections of BOTOX directly into salivary glands, the oro-lingual-pharyngeal region, oesophagus and stomach. Some patients had pre-existing dysphagia or significant debility.

There have been rare spontaneous reports of death sometimes associated with aspiration pneumonia in children with severe cerebral palsy after treatment with botulinum toxin, including following off-label use (e.g. neck area). Extreme caution should be exercised when treating paediatric patients who have significant neurologic debility, dysphagia, or have a recent history of aspiration pneumonia or lung disease. Treatment in patients with poor underlying health status should be administered only if the potential benefit to the individual patient is considered to outweigh the risks.

An anaphylactic reaction may occur very rarely after injection of botulinum toxin. Epinephrine (adrenaline) and other anti-anaphylactic measures should therefore be available.

Refer to the Summary of Product Characteristics for complete information for BOTOX.

In case of treatment failure after the first treatment session, i.e. absence, at one month after injection, of significant clinical improvement from baseline, the following actions should be taken:

- Clinical verification, which may include electromyographic examination in a specialist setting, of the action of the toxin on the injected muscle(s);
- Analysis of the causes of failure, e.g. bad selection of muscles to be injected, insufficient dose, poor injection technique, appearance of fixed contracture, antagonist muscles too weak, formation of toxin-neutralising antibodies;
- Re-evaluation of the appropriateness of treatment with botulinum toxin type A;
- In the absence of any undesirable effects secondary to the first treatment session, instigate a second treatment session as following: i) adjust the dose, taking into account the analysis of the earlier treatment failure; ii) use EMG; and iii) maintain a three-month interval between the two treatment sessions.

In the event of treatment failure or diminished effect following repeat injections alternative treatment methods should be employed.

Reconstitution of the medicinal product:

If different vial sizes of BOTOX are being used as part of one injection procedure, care should be taken to use the correct amount of diluent when reconstituting a particular number of units per 0.1 ml. The amount of diluent varies between BOTOX 50 Allergan Units, BOTOX 100 Allergan Units and BOTOX 200 Allergan Units. Each syringe should be labelled accordingly.

It is good practice to perform vial reconstitution and syringe preparation over plastic-lined paper towels to catch any spillage. BOTOX must only be reconstituted with sterile unpreserved normal saline solution (0.9% sodium chloride solution for injection). The appropriate amount of diluent (see dilution instructions or table below) should be drawn up into a syringe.

Dilution instructions for treatment of urinary incontinence due to overactive bladder:

It is recommended that a 100 Unit or two 50 Unit vials are used for convenience of reconstitution.

Should you need to use a 200 Unit vial, reconstitute **a 200 Unit vial** of BOTOX with 8 ml of sterile unpreserved normal saline solution (0.9% sodium chloride solution for injection) and mix the vial gently. Draw 4 ml from the vial into a 10 ml syringe. Complete the reconstitution by adding 6 ml of sterile unpreserved normal saline solution (0.9% sodium chloride solution for injection) into the 10 ml syringe and mix gently. This will result in a 10 ml syringe containing a total of 100 Units of reconstituted BOTOX. Use immediately after reconstitution in the syringe. Dispose of any unused saline.

Reconstitute **a 100 Unit vial** of BOTOX with 10 ml of sterile unpreserved normal saline solution

(0.9% sodium chloride solution for injection) and mix gently. Draw the 10 ml from the vial into a 10 ml syringe. This will result in a 10 ml syringe containing a total of 100 Units of reconstituted BOTOX. Use immediately after reconstitution in the syringe. Dispose of any unused saline.

Reconstitute **two 50 Unit vials** of BOTOX, each with 5 ml of sterile unpreserved normal saline solution (0.9% sodium chloride solution for injection) and mix each vial gently. Draw the 5 ml from each vial into a single 10 ml syringe. This will result in a single 10 ml syringe containing a total of 100 Units of reconstituted BOTOX. Use immediately after reconstitution in the syringe. Dispose of any unused saline.

This product is for single use only and any unused reconstituted product should be disposed of.

Dilution instructions for treatment of urinary incontinence due to neurogenic detrusor overactivity:

It is recommended that a 200 Unit or two 100 Unit vials are used for convenience of reconstitution
Reconstitute **a 200 Unit vial** of BOTOX with 6 ml of sterile unpreserved normal saline solution (0.9% sodium chloride solution for injection) and mix the vial gently. Draw 2 ml from the vial into each of three 10 ml syringes. Complete the reconstitution by adding 8 ml of sterile unpreserved normal saline solution (0.9% sodium chloride solution for injection) into each of the 10 ml syringes, and mix gently. This will result in three 10 ml syringes containing a total of 200 Units of reconstituted BOTOX. Use immediately after reconstitution in the syringe. Dispose of any unused saline.

Reconstitute **two 100 Unit vials** of BOTOX, each with 6 ml of sterile unpreserved normal saline solution (0.9% sodium chloride solution for injection) and mix the vials gently. Draw 4 ml from each vial into each of two 10 ml syringes. Draw the remaining 2 ml from each vial into a third 10 ml syringe. Complete the reconstitution by adding 6 ml of sterile unpreserved normal saline solution (0.9% sodium chloride solution for injection) into each of the 10 ml syringes, and mix gently. This will result in three 10 ml syringes containing a total of 200 Units of reconstituted BOTOX. Use immediately after reconstitution in the syringe. Dispose of any unused saline.

Should you need to use 50 Unit vials, reconstitute **four 50 Unit vials** of BOTOX, each with 3 ml of sterile unpreserved normal saline solution (0.9% sodium chloride solution for injection) and mix the vials gently. Draw 3 ml from the first vial and 1 ml from the second vial into one 10 ml syringe. Draw 3 ml from the third vial and 1 ml from the fourth vial into a second 10 ml syringe. Draw the remaining 2 ml from the second and fourth vials into a third 10 ml syringe. Complete the reconstitution by adding 6 ml of sterile unpreserved normal saline solution (0.9% sodium chloride solution for injection) into each of the three 10 ml syringes, and mix gently. This will result in three 10 ml syringes containing a total of 200 Units of reconstituted BOTOX. Use immediately after reconstitution in the syringe. Dispose of any unused saline.

Dilution table for BOTOX 50, 100 and 200 Allergan Units vial size for all other indications:

	50 Unit vial	100 Unit vial	200 Unit vial
Resulting dose (Units per 0.1 ml)	Amount of diluent (sterile unpreserved normal saline solution (0.9% sodium chloride solution for injection)) added in a 50 Unit vial	Amount of diluent (sterile unpreserved normal saline solution (0.9% sodium chloride solution for injection)) added in a 100 Unit vial	Amount of diluent (sterile unpreserved normal saline solution (0.9% sodium chloride solution for injection)) added in a 200 Unit vial
20 Units	0.25 ml	0.5 ml	1 ml
10 Units	0.5 ml	1 ml	2 ml
5 Units	1 ml	2 ml	4 ml
2.5 Units	2 ml	4 ml	8 ml
1.25 Units	4 ml	8 ml	N/A

This product is for single use only and any unused solution should be discarded.

Since BOTOX is denatured by bubbling or similar vigorous agitation, inject the diluent gently into the vial. Discard the vial if a vacuum does not pull the diluent into the vial. Reconstituted BOTOX is a clear colourless to slightly yellow solution free of particulate matter. The reconstituted solution should be visually inspected for clarity and absence of particles prior to use. When reconstituted in the vial, BOTOX may be stored in a refrigerator (2°C - 8°C) for up to 24 hours prior to use. If further diluted in a syringe, for intradetrusor injection, it should be used immediately.

Potency studies have demonstrated that the product may be stored for up to 5 days at 2 – 8°C following reconstitution. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution/dilution (etc) has taken place in controlled and validated aseptic conditions. The date and time of reconstitution should be recorded on the space of the label.

Procedure to follow for safe disposal of vials, syringes and materials used
Medicines should not be disposed of via wastewater or household waste. For safe disposal, unused vials should be reconstituted with a small amount of water and then autoclaved. Any used vials, syringes, and spillages etc. should be autoclaved, or the residual BOTOX inactivated using dilute hypochlorite solution (0.5%) for 5 minutes. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

Identification of the product
In order to verify receipt of actual BOTOX product from Allergan, look for a tamper-evident seal that contains a translucent silver Allergan logo on the top and bottom flaps of the BOTOX cartons, and a holographic film on the vial label. In order to see this film, examine the vial under a desk lamp or fluorescent light source. Rotating the vial back and forth between your fingers, look for horizontal lines of rainbow colour on the label and confirm that the name “Allergan” appears within the rainbow lines.

Do not use the product and contact your local Allergan office for additional information if:

- the horizontal lines of rainbow colour or the word “Allergan” are not present on the vial label
- the tamper-evident seal is not intact and present on both ends of the carton
- the translucent silver Allergan logo on the seal is not clearly visible or has a black circle with a diagonal line through it (i.e., prohibition sign)

Additionally, Allergan has created detachable stickers on the BOTOX vial label, which include the lot number and expiry date of the product you have received. These stickers can be peeled off and placed in your patient’s clinical file for traceability purposes. Note that once you remove the sticker off the BOTOX vial label, the word “USED” will show, which is to provide you with further assurance that you are using an authentic BOTOX product manufactured by Allergan.