PACKAGE LEAFLET: **ALLERGAN®**
INFORMATION FOR THE USER

BOTOX

100 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, or to give a temporary improvement in the appearance of vertical lines between the eyebrows seen at maximum frown (glabellar lines) or fan-shaped lines from the corner of the eyes seen at maximum smile (crow's feet lines) or forehead lines seen at maximum raised eyebrows. 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 control the following conditions:
    - **Persistent muscle spasms** in the leg in **children** aged two years or older with cerebral palsy, who can walk, BOTOX is used to control **foot deformity** caused by the persistent muscle spasms in the legs. **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.

5) BOTOX is used for the temporary improvement in the appearance of:
- vertical lines between the eyebrows seen at maximum frown and/or,
- fan-shaped lines from the corner of the eyes seen at maximum smile and/or,
- forehead lines seen at maximum raised eyebrows,

when the severity of the facial lines has an important psychological impact in **adult** patients.

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;
- if you are to be treated for facial lines and have been diagnosed with myasthenia gravis or Lambert-Eaton Syndrome (chronic diseases affecting the muscles).

Warnings and precautions

Talk to your doctor or pharmacist before using BOTOX:
- if you have had any problems in the past with previous botulinum injections;
- 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 Lambert-Eaton 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 an operation or injured your head, neck or chest;
- if you will have an operation soon;
- 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 or 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). Very rarely, an allergic reaction can occur after the injection of botulinum toxin.

Inform your doctor if you are being treated for facial lines and you see no significant improvement one month after your first course of treatment.

General precautions

As with any injection, it is possible for the procedure to result in infection, pain, swelling, burning and stinging, increased sensitivity, tenderness, redness, and/or bleeding/bruising at the site of 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). 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 in the legs.

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. To limit this risk, the interval between two treatments must not be less than three months depending on the indication.

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.

The use of BOTOX for the treatment of vertical lines between the eyebrows seen at maximum frown (glabellar lines) or fan-shaped lines from the corner of the eyes seen at maximum smile (crow's feet lines) or forehead lines seen at maximum raised eyebrows is not recommended in individuals under 18 years. There is limited experience of using BOTOX in patients older than 65 years. Drooping of the eyelid may occur after treatment.

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 for leakage of urine 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) including aminoglycoside antibiotics and spectinomycin, 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, 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 generalised and/or specific muscular weakness, 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.

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 indications; 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 foot deformity caused by muscle spasms in the legs, associated with Cerebral Palsy.

Foot deformity caused by muscle spasms in the legs of children who have Cerebral Palsy	2 years

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

Indication	**Maximum dose (Units per affected area)**		**Minimal time between treatments**
	First treatment	**Following treatments**	
Persistent muscle spasms in the legs of children who have cerebral palsy	4 Units/kg (hemiplegia) 6 Units/kg (diplegia)	4 Units/kg (hemiplegia) 6 Units/kg (diplegia)	3 months*
Persistent muscle spasms in the wrist and hand of patients who have had a stroke	The exact dosage and number of injection sites per hand/wrist is tailored to individual needs up	The exact dosage and number of injection sites is tailored to individual needs up to a maximum of 240 Units	12 weeks

	to a maximum of 240 Units		
Persistent muscle spasms in the ankle and foot of 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	25 Units per eye	Up to 100 Units	3 months
Persistent muscle spasms of the neck and shoulders	200 Units	Up to 300 Units	10 weeks
Headache in adults who have chronic migraine	155 to 195 Units	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	200 Units	200 Units	3 months
Excessive sweating of the armpits	50 Units per armpit	50 Units per armpit	16 weeks
Vertical lines between the eyebrows seen at maximum frown (glabellar lines)	4 Units per injection site (maximum total dose of 20 Units)	4 Units per injection site (maximum total dose of 20 Units)	3 months
Fan-shaped lines from the corner of the eyes seen at maximum smile (crow's feet lines)	4 Units per injection site (maximum total dose of 24 Units)	4 Units per injection site (maximum total dose of 24 Units)	3 months
Forehead lines seen at maximum raised eyebrows	4 Units per injection site (maximum total dose of 20 Units)	4 Units per injection site (maximum total dose of 20 Units)	3 months
The total dose for treatment of forehead lines (20 Units) in conjunction with glabellar lines (20 Units) is 40 Units. If you are treated for all 3 facial lines at the same time (fan-shaped lines from the corner of the eyes seen at maximum smile, vertical lines between the eyebrows seen at maximum frown, and forehead lines seen at maximum raised eyebrows) you will receive a total dose of 64 Units.			

** 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 legs of children who have cerebral palsy**, the improvement usually appears within the first 2 weeks after the injection.

For **persistent muscle spasms in the wrist and hand of 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 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.

For **vertical lines between the eyebrows (glabellar lines)**, you will usually see an improvement within 1 week after treatment, the maximum effect being observed 5 to 6 weeks after injection. The treatment effect has been demonstrated for up to 4 months after injection.

For **fan-shaped lines from the corner of the eyes (crow's feet lines)**, you will usually see an improvement within 1 week after treatment. The treatment effect has been demonstrated for up to 4 months after injection.

For **forehead lines seen at maximum raised eyebrows**, you will usually see an improvement within 1 week after treatment. The treatment effect has been demonstrated for up to 4 months after injection.

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

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 in the legs of children with cerebral palsy

Very Common	Viral infection, ear infection.
Common	Sleepiness, problems with walking, numbness, rash, muscle pain, muscle weakness, pain in the extremities such as the hands and fingers, urinary incontinence (leakage of urine), feeling generally unwell, pain where the injection was given, feeling of weakness, fall.

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 patients who have had a stroke

Common	Increased muscle tension, bruising and bleeding under the skin causing red patches (ecchymosis or purpura), pain in the hand and fingers, muscle weakness, pain where the injection was given, fever, flu syndrome, bleeding or burning where the injection was given.
Uncommon	Depression, difficulty in sleeping (insomnia), decreased skin sensation, headache, numbness, lack of coordination of movements, loss of memory, feeling of dizziness or "spinning" (vertigo), fall in blood pressure on standing up which causes dizziness, light headedness or fainting, nausea, numbness around the mouth, inflammation of the skin (dermatitis), itching, rash, joint pain or inflammation, general weakness, pain, increased sensitivity where the injection was given, feeling generally unwell, swelling of the extremities such as the hands and feet.

Some of these uncommon side effects may also be related to your disease.

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

Common	Rash, joint pain or inflammation, stiff or sore muscles, muscular 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, 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.

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 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 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.

Injections for the temporary improvement of vertical lines between the eyebrows at maximum frown, also known as glabellar lines

Common	Headaches, drooping eye lid, skin redness, localised muscle weakness, face pain, numbness, nausea (feeling sick), skin tightness, injection site swelling, injection site pain, bruising under the skin, injection site irritation.
Uncommon	Infection, anxiety, dizziness, inflammation of the eyelid, eye pain, visual disturbance, blurred vision, dry mouth, swelling (face, eyelid, around the eyes), sensitivity to light, itching, dry skin, muscle twitching, flu syndrome, lack of strength, fever.

These adverse reactions may be related to treatment, injection technique or both.

Injections for the temporary improvement in the fan-shaped lines from the corner of the eyes, when treated with or without vertical lines between the eyebrows seen at frown

Common	Injection site haematoma*.
Uncommon	Eyelid swelling, injection site bleeding*, injection site pain*, injection site tingling or numbness.

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

Injections for the temporary improvement in the forehead lines and vertical lines between the eyebrows seen at frown when treated with or without the fan-shaped lines from the corner of the eyes

Common	Headaches, drooping eyelid[1], skin tightness, drooping eyebrow[2], injection site bruising*, injection site haematoma*
Uncommon	Injection site pain*.

1.The median time to onset of drooping eyelid was 9 days following treatment
2. The median time to onset of drooping eyebrow was 5 days following treatment
*Some of these side effects may also be related to the injection procedure.

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;
- drooping eyelid
- difficulty in completely closing the eye
- strabismus (crossed eyes/squint);
- 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);
- shortness of breath;
- breathing problems, respiratory depression and/or respiratory failure;
- abdominal pain;
- diarrhoea, constipation;
- dry mouth;
- difficulty swallowing;
- nausea, vomiting;
- hair loss;
- drooping eyebrow
- itching;
- rash;
- different types of red blotchy skin rashes;
- psoriasis-like skin patches (red, thick, dry and scaly);
- excessive sweating;
- loss of eyelashes/eyebrows;
- muscles pain, loss of nerve supply to/shrinkage of injected muscle;
- malaise;
- 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, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. 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 100 Allergan Units of botulinum toxin type A.
- The other ingredients are human albumin and sodium chloride.

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially "sodium free".

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 sterile unpreserved normal saline solution (0.9% sodium chloride solution for injection).
Each pack contains 1, 2, 3, 6 or 10 vials.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Allergan Pharmaceuticals Ireland
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Ireland

This leaflet was last revised in September 2020.

(THIS IS A MEDICAMENT)

- Medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.

Keep medicament out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists

ALLERGAN®
Westport, Co. Mayo, Ireland

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.
BOTOX should only be given by physicians with appropriate qualifications, and expertise in the treatment and the use of the required equipment.

Botulinum toxin units are not interchangeable from one product to another. Doses recommended in Allergan Units are different from other botulinum toxin preparations.

BOTOX is indicated for the management of: blepharospasm, hemifacial spasm and associated focal dystonias; cervical dystonia (spasmodic torticollis); focal spasticity associated with dynamic equinus foot deformity due to spasticity in ambulant paediatric cerebral palsy patients, two years of age or older; focal spasticity of the wrist and hand in adult post stroke patients; focal spasticity of the ankle in adult post stroke patients; persistent severe primary hyperhidrosis of the axillae, which interferes with the activities of daily living and is resistant to topical treatment; 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 or 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 and urinary incontinence in adults with neurogenic detrusor overactivity due to stable sub-cervical spinal cord injury or multiple sclerosis.

BOTOX is indicated for the temporary improvement in the appearance of:

- moderate to severe vertical lines between the eyebrows seen at maximum frown (glabellar lines) and/or
- moderate to severe lateral canthal lines (crow's feet lines) seen at maximum smile and/or
- moderate to severe forehead lines seen at maximum eyebrow elevation,

when the severity of the facial lines has an important psychological impact in adult patients.

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 focal spasticity associated with paediatric 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 associated with paediatric cerebral palsy	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 associated with paediatric cerebral palsy:

Muscles	Dose selection
Medial and lateral heads of the affected gastrocnemius muscle.	Hemiplegia: Initial recommended 4 Units/kg body weight in the affected limb. Diplegia: Initial recommended 6 Units/kg body weight divided between the affected limbs. The total dose should not exceed 200 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:

Muscles	Dose selection; Number of Sites
Flexor digitorum profundus	15 – 50 Units; 1-2 sites
Flexor digitorum sublimis	15 – 50 Units; 1-2 sites
Flexor carpi radialis	15 – 60 Units; 1-2 sites
Flexor carpi ulnaris	10 – 50 Units; 1-2 sites
Adductor Pollicis	20 Units; 1-2 sites
Flexor Pollicis Longus	20 Units; 1-2 sites

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 Lateral head	 75 Units; 3 sites 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

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.

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.

Glabellar lines (moderate or severe vertical lines) seen at maximum frown:

Injection sites	Dose
5 injection sites: 2 injections in each corrugator muscle and 1 injection in the procerus muscle	0.1 mL (4 Units) into each of 5 injection sites for a total dose of 20 Units.

BOTOX is for intramuscular use (injected into muscles).
Before injection, the thumb or index finger is to 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. In order to reduce the risk of eyelid ptosis, the maximum dose of 4 Units for each injection site as well as the number of injection sites should not be exceeded. In addition, injections near the levator palpebrae superioris muscle must be avoided, particularly in patients with larger brow-depressor complexes (depressor supercilii). Injections in the corrugator muscle must be made into the central part of that muscle, a distance of at least 1 cm above the arch of the eyebrows.

Crow's feet lines (moderate or severe lateral canthal lines) seen at maximum smile:

Injection sites	Dose
6 injection sites: 3 injection sites per side in the lateral orbicularis oculi muscle	0.1 mL (4 Units) into each of 6 injection sites for a total dose of 24 Units.

BOTOX is for intramuscular use (injected into muscles).

Injections for crow's feet lines should be given with the needle tip bevel up and oriented away from the eye. In order to reduce the risk of eyelid ptosis, the maximum dose of 4 Units for each injection site as well as the number of injection sites should not be exceeded. In addition, injections should be made temporal to the orbital rim, thereby maintaining a safe distance from the muscle controlling eyelid elevation.

Forehead lines (moderate or severe lines) seen at maximum eyebrow elevation:

Injection sites	Dose
5 injection sites: To identify the location of the appropriate injection sites in the frontalis muscle, the overall relationship between the size of the subject's forehead, and the distribution of frontalis muscle activity should be assessed.	0.1 mL (4 Units) into each of 5 injection sites for a total dose of 20 Units.

BOTOX is for intramuscular use (injected into muscles).
The total dose for treatment of forehead lines (20 Units) in conjunction with glabellar lines (20 Units) is 40 Units/1.0mL.
For simultaneous treatment of forehead lines with glabellar lines and crow's feet lines, the total dose is 64 Units, comprised of 20 Units for forehead lines, 20 Units for glabellar lines, and 24 Units for crow's feet lines.

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 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 (for the treatment of glabellar lines, consider adjusting the dose up to 40 or 50 units), 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:
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 table below) should be drawn up into a syringe.

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

Dilution table for BOTOX 100 Allergan Units vial size for all other indications:

	100 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 100 Unit vial**
20 Units	**0.5 ml**
10 Units	**1 ml**
5 Units	**2 ml**
4 Units	**2.5 ml**
2.5 Units	**4 ml**
1.25 Units	**8 ml**

The central part of the rubber cap has to be cleaned with alcohol

This product is for single patient treatment only during a single session. 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. Microbiological and potency studies have demonstrated that the product may be stored for up to 5 days at 2°C - 8°C following reconstitution. Since the product does not contain a preservative, 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°C - 8°C. 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.

Recommendations in the event of an accident when handling botulinum toxin.
In the event of an accident when the product is being handled, whether in the vacuum-dried state or reconstituted, the appropriate measures described below must be initiated immediately.

- Any spillage must be wiped up: either with an absorbent material soaked in a solution of sodium hypochlorite (Javel solution) in the case of the vacuum-dried product, or with a dry absorbent material in the case of the reconstituted product.

- Contaminated surfaces must be cleaned with an absorbent material soaked in a solution of sodium hypochlorite (Javel solution) and then dried.

- If a vial is broken, proceed as stated above, carefully collect up the pieces of glass and wipe up the product, avoiding cutting the skin.

- If splashed onto the skin, wash with a solution of sodium hypochlorite (Javel solution) and then rinse thoroughly with plenty of water.

- If splashed into the eyes, flush thoroughly with plenty of water or with an ophthalmic eyewash solution.

- If the operator injures himself (cuts, pricks himself), proceed as above and take the appropriate medical steps according to the dose injected.

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.

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