Public Assessment Report

Decentralised Procedure

TWINJECT 0.15MG/0.15ML SOLUTION FOR INJECTION
TWINJECT 0.30MG/0.30ML SOLUTION FOR INJECTION

UK/H/1231/001-2/DC
UK licence no: PL 00039/0733-4

Shionogi Ireland
TWINJECT 0.15MG/0.15ML SOLUTION FOR INJECTION
TWINJECT 0.30MG/0.30ML SOLUTION FOR INJECTION

LAY SUMMARY

On 26th August 2010, Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Germany, Greece, Finland, France, Italy, Luxembourg, Malta, the Netherlands, Norway, Poland, Portugal, Romania, Spain, Slovenia, the Slovak Republic and the UK agreed to grant marketing authorisations to Shionogi Ireland for the medicinal products Twinject 0.15mg/0.15ml and 0.30mg/0.30ml Solution for Injection (PL 00039/0733-4; UK/H/1231/001-2/DC). The licences were granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After the national phase, licences were granted in the UK on 17th September 2010.

Twinject 0.15mg/0.15ml and 0.30mg/0.30ml Solution for Injection contain adrenaline and help treat life-threatening allergic reactions, by reducing swelling, relaxing muscles in the lungs to help breathing and by making the blood vessels smaller, to increase blood pressure.

Allergic reactions can be caused by stinging and biting insects or other animals, food, medicines, exercise, or sometimes the cause is not known. Life-threatening allergic reactions may make it difficult to breathe and can cause wheezing, sneezing, hoarseness, hives, itching, swelling, skin redness, fast heartbeat, weak pulse, feeling very anxious, confusion, stomach pain, losing control of urine or bowel movements (incontinence), faintness, or “passing out” (unconsciousness).

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Twinject 0.15mg/0.15ml and 0.30mg/0.30ml Solution for Injection outweigh the risks, hence Marketing Authorisations have been granted.
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## Module 1

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<td><strong>Type of Application</strong></td>
<td>Well-established use application, Article 10a</td>
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<tr>
<td><strong>Strength</strong></td>
<td>0.15mg/0.15ml and 0.30mg/0.30ml</td>
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<tr>
<td><strong>MA Holder</strong></td>
<td>Shionogi Ireland, 145 Lakeview Drive, Airside Business Park, Swords, County Dublin, Ireland</td>
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<tr>
<td><strong>RMS</strong></td>
<td>UK</td>
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<td><strong>CMS</strong></td>
<td>Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Germany, Greece, Finland, France, Italy, Luxembourg, Malta, the Netherlands, Norway, Poland, Portugal, Romania, Spain, Slovenia, the Slovak Republic</td>
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<td><strong>Procedure Number</strong></td>
<td>UK/H/1231/001-2/DC</td>
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<td><strong>Timetable</strong></td>
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Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Twinject 0.15 mg/ 0.15 ml Solution for Injection in a pre-filled syringe

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
1 ml of solution for injection contains 1 mg of adrenaline (epinephrine)

One dose contains 0.15 mg (0.15ml) of adrenaline.

The pre-filled syringe may deliver two doses of 0.15 mg (0.15 ml) of adrenaline.

Excipients: Sodium bisulphite (E222)
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Solution for injection (injection) in pre-filled syringe.
Clear colourless solution practically free from particles.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Emergency treatment for acute allergic reactions (anaphylaxis) caused by foods, drugs, latex, insect bites or stings, and other allergens as well as exercise-induced or idiopathic anaphylaxis.

4.2 Posology and method of administration
Use by the intramuscular route.
In a significant proportion of patients (e.g. the overweight), the route of injection will be subcutaneous.

Dosage
The usual paediatric dose for allergic emergencies is 0.15 mg adrenaline for intramuscular use depending upon the body weight of the patient (0.01 mg/kg body weight). However, the prescribing physician has the option of prescribing more or less than these amounts based on careful assessment of each of individual patient and recognising the life-threatening nature of the reaction for which this is being prescribed. The physician should consider using other forms of injectable adrenaline if lower doses are felt to be necessary for small children.

Children weighing between 15 and 30 kg body weight:
The usual dose is 0.15 mg (per injection) into the anterolateral (outer side) aspect of the thigh (intramuscular use).

The first dose is delivered automatically after the patient prepares the Twinject for firing.
In case of a prolonged or biphasic reaction, Twinject is designed to deliver a second manual dose of 0.15 mg (0.15 ml) adrenaline. The unit contains one needle to be used for both injections.

Children under 15 kg body weight:
Twinject is designed to deliver a single dose of 0.15 mg of adrenaline. A dosage below 0.15 mg cannot be administered with sufficient accuracy in children weighing less than 15 kg and use is therefore not recommended unless in a life-threatening situation and under medical advice.

Adults, adolescents, and children weighing more than 30 kg:
It is recommended to use the adult formulation dosed at 0.3 mg.

Method of administration
A first auto-dose is available from Twinject for immediate use when the first signs and symptoms of anaphylaxis appear. These may occur within minutes of exposure to the allergen and are most commonly manifested by urticaria, flushing or angioedema; more severe reactions involve the circulatory and respiratory systems.
A second manual dose is available from the Twinject in case the symptoms persist (or worsen) approximately 5 minutes after the first administration, and if the patient has not yet reached an emergency medical facility for treatment.

The second dose is available for manual injection by the patient following a partial disassembly of Twinject.

Please refer to section 6.6 for detailed instructions for use.

4.3 Contraindications
Hypersensitivity to adrenaline, sodium bisulphite or to any of the excipients (see section 4.4 for further information on sulphites). However, there are no absolute contraindications to the use of Twinject during an allergic emergency.

Clinical conditions where special precautions are advised and drug interactions are listed in sections 4.4 and 4.5, respectively.

4.4 Special warnings and precautions for use
Twinject is not intended as a substitute for immediate medical care. In conjunction with the administration of adrenaline, the patient should always seek appropriate medical care. The patient or caregiver should seek emergency medical assistance immediately after administering the first dose in order to have close monitoring of the anaphylactic episode and further treatment as required.

The physician who prescribes Twinject should review the content of this SPC in detail with the patient. This review should include thorough instruction in the correct method of administration. The accompanying patient information leaflet and wrap label should also be reviewed with the patient.

The physician should regularly review the use of the Twinject and ensure that the patient and carers have access to a training demonstrator to familiarise themselves with its use. A needle-free demonstrator is available.

Twinject should only be injected into the anterolateral (outer side) aspect of the thigh. Accidental injection into the hands or feet may result in loss of blood flow to the affected area and should be avoided. Do not inject into the buttock. If there is an accidental injection into these areas, advise the patient to inform the healthcare provider of the accidental injection when he/she goes to the nearest emergency room for further treatment of anaphylaxis.

Avoid possible inadvertent intravascular administration. Large doses or accidental intravenous injection of adrenaline may result in cerebral haemorrhage due to a sharp rise in blood pressure. Do not inject intravenously. Rapidly acting vasodilators can counteract the marked pressor effects of adrenaline if there is such inadvertent administration.

Twinject is not suitable for patients, or caregivers, with such disabilities as severe debilitating arthritis of the hands, because the use of this product requires some manual dexterity to administer.

There is a risk of adverse reactions following adrenaline administration in patients with hyperthyroidism, cardiovascular disease (severe angina pectoris, obstructive cardiomyopathy and ventricular arrhythmia and hypertension), phaeochromocytoma, high intraocular pressure, severe renal impairment, prostatic adenoma leading to residual urine, hypercalcaemia, hypokalaemia, diabetes, or in elderly or pregnant patients.

Adrenaline should be used with caution in patients with heart disease e.g. coronary heart and cardiac muscle diseases, cor pulmonale, cardiac arrhythmias or tachycardia. In such patients, adrenaline may precipitate or aggravate angina pectoris as well as produce ventricular arrhythmias.

Patients with diabetes may develop increased blood glucose levels following adrenaline administration.

Patients with Parkinson’s disease may notice a temporary worsening of symptoms.

Twinject contains sodium bisulphite (E222), which may rarely cause severe hypersensitivity reactions including anaphylactic symptoms and bronchospasm, especially in those with a history of asthma.
Patients with these conditions must be carefully instructed in regard to the circumstances under which Twinject should be used.

In the event of a life-threatening allergic reaction, Twinject can be used even if the patient is allergic to sulphites.

Twinject contains less than 1 mmol sodium per 0.15 ml.

4.5 Interaction with other medicinal products and other forms of interaction

The effects of adrenaline may be potentiated by tricyclic antidepressants mixed noradrenergic-serotonergic antidepressants like venlafaxine, sibutramine or milnacipran and monoamine oxidase (MAO) inhibitors (sudden blood pressure increase and possible cardiac arrhythmia), catechol-O-methyl-transferase (COMT) blocking agents, thyroid hormones, theophylline, oxytocin, parasympatholytics, certain antihistamines (diphenhydramine, chlorpheniramine), levodopa and alcohol.

Severe hypertension and bradycardia may occur when adrenaline is administered with non-selective beta-blocking medicinal products.

Concurrent therapy with sympathomimetics may potentiate the effects of adrenaline.

Use Twinject with caution in patients receiving medicinal products that may sensitise the heart to arrhythmias, e.g. digitalis, quinidine and halogenated anaesthetics.

The pressor effects of adrenaline may be counteracted by administration of rapidly acting vasodilators or alpha adrenergic blocking medicinal products (resulting in a decrease in blood pressure). The cardiostimulating and bronchodilating effects can be antagonised by beta-blocking agents, especially non-selective beta-blockers.

Adrenaline inhibits insulin secretion, thus increasing the blood glucose level. Therefore, diabetic patients may require upward adjustment of their insulin or other hypoglycaemic therapy.

4.6 Pregnancy and lactation

There are no adequate or well-controlled studies of adrenaline in pregnant women. Adrenaline should only be used in pregnancy if the potential benefit justifies the potential risk to the fetus. Adrenaline crosses the placenta and could lead to fetal hypoxia, spontaneous abortion or both.

Adrenaline is not orally bioavailable; any adrenaline excreted in breast milk would not be expected to have any effect on the nursing infant.

4.7 Effects on ability to drive and use machines

Adrenaline has no or negligible influence on the ability to drive and use machines. However it is recommended that patients should not drive or use machines following administration of adrenaline, since patients will be affected by symptoms of the anaphylactic shock.

4.8 Undesirable effects

The occurrence of undesirable effects depends on the sensitivity of the individual patient and the dose applied. The adverse reactions due to adrenaline are listed below, however their frequencies cannot be estimated from the available data:

- Metabolism and nutrition disorders: hyperglycaemia, hypokalaemia, metabolic acidosis
- Psychiatric disorders: anxiety, hallucinations, nervousness
- Nervous system disorders: mydriasis, tremor, headache, asthenia
- Cardiac disorders: syncopes, palpitation, tachycardia, dizziness, angina pectoris, hypertension
- Vascular disorders: vascular constriction, peripheral coldness
- Respiratory, thoracic and mediastinal disorders: respiratory difficulty, pulmonary oedema
- Gastrointestinal disorders: nausea, vomiting
- Musculoskeletal, connective tissue and bone disorders: weakness
- Renal and urinary disorders: urinary retention, renal impairment
- General disorders and administration site conditions: pallor, hyperhidrosis
Adverse reactions that may occur at higher doses or in susceptible individuals are cardiac arrhythmias (ventricular fibrillation/cardiac arrest), sudden rise of blood pressure (sometimes leading to cerebral haemorrhage), as well as vasoconstriction (e.g. in the skin, mucous tissues and kidneys)

Twinject contains a sulphite that may cause allergic-type reactions including anaphylactic reactions or life-threatening or less severe asthmatic episodes in certain susceptible patients.

4.9 Overdose

Adrenaline is rapidly inactivated in the body, and treatment following overdose with adrenaline is primarily supportive.

Overdose or accidental intravascular injection of adrenaline may cause cerebral haemorrhage from a sudden rise of blood pressure. Death may result from acute pulmonary oedema arising from peripheral vascular constriction and cardiac stimulation.

The pressor effects of adrenaline may be counteracted by rapidly acting vasodilators or alpha-adrenergic blocking medicinal products. Should prolonged hypotension follow such measures, it may be necessary to administer another pressor medicinal product, such as noradrenaline.

Acute pulmonary oedema with respiratory discomfort following adrenaline (epinephrine) overdose should be managed by administration of a rapidly acting alpha-adrenergic blocking medicinal product such as phentolamine and/or with intermittent positive pressure respiration.

Overdose sometimes results in extreme pallor and coldness of the skin, metabolic acidosis, and kidney failure. Suitable corrective measures must be taken in such situations.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: adrenergic and dopaminergic agents, adrenaline.
ATC code: C01 CA 24

Adrenaline is a naturally-occurring catecholamine secreted by the adrenal medulla in response to exertion or stress. It is a sympathomimetic amine which is a potent stimulant of both alpha and beta adrenergic receptors and its effects on target organs are, therefore, complex. It is the medicinal product of choice to provide rapid relief of hypersensitivity reactions to allergies or to idiopathic or exercise induced anaphylaxis.

If a clinical effect is not achieved, more than one injection is recommended after 5 minutes or sooner. Approximately 20% of patients require more than one adrenaline injection.

Adrenaline has a strong vasoconstrictor action through alpha-adrenergic stimulation. This activity counteracts the vasodilatation and increased vascular permeability leading to loss of intravascular fluid and subsequent hypotension, which are the major pharmacotoxicological features in anaphylactic shock.

Through its stimulation of bronchial beta adrenergic receptors, adrenaline has a powerful bronchodilator action that alleviates bronchospasm, wheezing and dyspnoea.

Adrenaline also alleviates pruritus, urticaria and angioedema, and may be effective in relieving gastrointestinal and genitourinary symptoms of anaphylaxis because of its relaxing effects on the smooth muscle of the stomach, intestine, uterus and urinary bladder.
5.2 Pharmacokinetic properties
Adrenaline is rapidly inactivated in the body, mostly in the liver by the enzymes COMT and MAO. Much of a dose of adrenaline is excreted as metabolites in urine. The plasma half-life is about 2-3 minutes. However, when given by subcutaneous or intramuscular injection, local vasoconstriction may delay absorption so that the effects may last longer than the half-life suggests.

5.3 Preclinical safety data
No relevant mutagenic or carcinogenic properties have been demonstrated with adrenaline. At high doses (100 times the human dose), adrenaline has teratogenic effects in mice, rats, hamsters and chickens. At doses in the range of clinical doses, fetal hypoxia resulting in fetal death has been observed following i.v. administration in monkeys.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Sodium chloride
Chlorobutanol hemihydrate
Sodium bisulphite (E222)
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
18 months.

6.4 Special precautions for storage
Do not store above 25°C.
Do not refrigerate or freeze.
Store in the original package to protect from light. Adrenaline is light sensitive. Patients should periodically check the solution in Twinject for any discolouration. If the solution is coloured the patient should replace their Twinject.

6.5 Nature and contents of container
A pre-filled syringe consisting of a Type I borosilicate glass cartridge, closed with an aluminum cap (containing a chlorobutyl rubber cap) and a chlorobutyl rubber insert plunger. The drug product and primary packaging configuration is fitted with a polypropylene needle hub, stainless steel needle and a clear polyethylene needle shield, in a measuring device (auto injector) dual dose product, containing 1.1 ml adrenaline.

The pre-filled syringe is assembled into a plexi-glass assembly then placed in a polypropylene carrying case in a carton.

Pack sizes: Single Carton, containing one 0.15 mg unit or Two-Pack Carton, containing two 0.15 mg units and a demonstrator.

Not all pack sizes may be marketed.
6.6 Special precautions for disposal

Instructions for use:
For single use only (two doses of 0.15 mg are available with each Twinject).

Actual demonstration of the injection technique by a physician or a pharmacist is recommended. A demonstrator that does not contain a needle or adrenaline is available for this purpose.

FIRST DOSE
STEP A
Remove the Twinject from the green carrying case.
• Pull off first GREEN end cap [labelled 1] to see a RED tip. Never put thumb, finger, or hand over the RED tip.

* Pull off second GREEN end cap [labelled 2].

STEP B
• Put the RED tip against the middle of the outer side of the thigh (upper leg) as shown. Twinject can be used through clothes, even thick ones such as jeans.
• Press down hard until the needle enters the thigh (upper leg) through the skin. Hold it in place while slowly counting to 10.

• Remove the Twinject from the thigh.
• Check the RED tip; if the needle is exposed the dose was received. If the needle is not visible, First Dose step B should be repeated. Make sure both green caps labelled 1 and 2 have been removed prior to repeating step B.

At this stage the patient should get emergency medical help right away.
He should prepare himself for the second dose.

SECOND DOSE PREPARATION
STEP A
• Carefully grasp the red tip avoiding the needle. Unscrew the body of the Twinject unit until the cap is fully loosened from the body. Carefully pull the body away from the cap avoiding touching or bending of the exposed needle.

STEP B
• Grab the BLUE plastic to pull the syringe out of the barrel (do not touch the needle).

STEP C
• Pull the YELLOW collar off the plunger. Be careful not to pull up on the plunger while removing the YELLOW collar.

PAUSE HERE

The patient and/or care-giver should pay special attention to the potential risks to the patient if the needle becomes contaminated between the two injections (for example by falling on the floor), as well as to the risk of a needle-stick injury to others. It is therefore necessary that the patient and/or care-giver handle the syringe very carefully to ensure that the needle does not come into contact with any other surface. Also, other people present should be warned about the presence of an exposed needle.
STEP D (SECOND DOSE ADMINISTRATION)
If the patient symptoms have not improved within about 5 minutes of the first injection, the second dose should be injected.

- Put the needle into the middle of the outer side of the thigh (upper leg), through the skin, as shown.
- Push the plunger down all the way until it cannot go any further.

- Remove the Twinject syringe from the skin.

The remaining volume (approximately 0.8 ml) in the syringe after the two fixed doses cannot be further administered and the syringe should be discarded as instructed (see section 6.6).

In cases where the second dose has not been administered, the syringe (including unused adrenaline) should also be discarded.

After use, do not attempt to replace the needle cover.

With one half of the carrying case lying on a flat surface, slide the syringe, needle first, into the carrying case.

Put the other half of the carrying case on and close it.

Replace the used Twinject as soon as possible.

The used product should be handed to the attending paramedics or given to the pharmacist when the replacement product is obtained.

7 MARKETING AUTHORISATION HOLDER
Shionogi Ireland
145 Lakeview Drive
Airside Business Park
Swords
County Dublin
Ireland

8 MARKETING AUTHORISATION NUMBER(S)
PL 00039/0733

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
17/09/2010

10 DATE OF REVISION OF THE TEXT
17/09/2010
NAME OF THE MEDICINAL PRODUCT
Twinject 0.3 mg/0.3 ml Solution for Injection in a pre-filled syringe

QUALITATIVE AND QUANTITATIVE COMPOSITION
1 ml of solution for injection contains 1 mg of adrenaline (epinephrine)

One dose contains 0.3 mg (0.3ml) of adrenaline.

The pre-filled syringe may deliver two doses of 0.3 mg (0.3 ml) of adrenaline.

Excipients: Sodium bisulphite (E222)
For a full list of excipients, see section 6.1.

PHARMACEUTICAL FORM
Solution for injection (injection) in pre-filled syringe.
Clear colourless solution practically free from particles.

CLINICAL PARTICULARS

Therapeutic indications
Emergency treatment for acute allergic reactions (anaphylaxis) caused by foods, drugs, latex, insect bites or stings, and other allergens as well as exercise-induced or idiopathic anaphylaxis.

Posology and method of administration
Use by the intramuscular route.
In a significant proportion of patients (e.g. the overweight), the route of injection will be subcutaneous.

Dosage
Adults, adolescents, and children weighing more than 30 kg:
The usual dose is 0.3 mg (per injection) into the anterolateral (outer side) aspect of the thigh (intramuscular use).

The first dose is delivered automatically after the patient prepares the Twinject for firing.
In case of a prolonged or biphasic reaction, Twinject is designed to deliver a second manual dose of 0.3 mg (0.3 ml) adrenaline. The unit contains one needle to be used for both injections.

Children weighing between 15 and 30 kg body weight:
It is recommended to use the paediatric formulation dosed at 0.15 mg.

Method of administration
A first auto-dose is available from Twinject for immediate use when the first signs and symptoms of anaphylaxis appear. These may occur within minutes of exposure to the allergen and are most commonly manifested by urticaria, flushing or angioedema; more severe reactions involve the circulatory and respiratory systems.

A second manual dose is available from the Twinject in case the symptoms persist (or worsen) approximately 5 minutes after the first administration, and if the patient has not yet reached an emergency medical facility for treatment.

The second dose is available for manual injection by the patient following a partial disassembly of Twinject.

Please refer to section 6.6 for detailed instructions for use.

Contraindications
Hypersensitivity to adrenaline, sodium bisulphite or to any of the excipients (see section 4.4 for further information on sulphites). However, there are no absolute contraindications to the use of Twinject during an allergic emergency.

Clinical conditions where special precautions are advised and drug interactions are listed in sections 4.4 and 4.5, respectively.
4.4 Special warnings and precautions for use

Twinject is not intended as a substitute for immediate medical care. In conjunction with the administration of adrenaline, the patient should always seek appropriate medical care. The patient should seek emergency medical assistance immediately after administering the first dose in order to have close monitoring of the anaphylactic episode and further treatment as required.

The physician who prescribes Twinject should review the content of this SPC in detail with the patient. This review should include thorough instruction in the correct method of administration. The accompanying patient information leaflet and wrap label should also be reviewed with the patient.

The physician should regularly review the use of the Twinject and ensure that the patient and carers have access to a training demonstrator to familiarise themselves with its use. A needle-free demonstrator is available.

Twinject should only be injected into the anterolateral (outer side) aspect of the thigh. Accidental injection into the hands or feet may result in loss of blood flow to the affected area and should be avoided. Do not inject into the buttock. If there is an accidental injection into these areas, advise the patient to inform the healthcare provider of the accidental injection when he/she goes to the nearest emergency room for further treatment of anaphylaxis.

Avoid possible inadvertent intravascular administration. Large doses or accidental intravenous injection of adrenaline may result in cerebral haemorrhage due to a sharp rise in blood pressure. Do not inject intravenously. Rapidly acting vasodilators can counteract the marked pressor effects of adrenaline if there is such inadvertent administration.

Twinject is not suitable for patients, or caregivers, with such disabilities as severe debilitating arthritis of the hands, because the use of this product requires some manual dexterity to administer.

There is a risk of adverse reactions following adrenaline administration in patients with hyperthyroidism, cardiovascular disease (severe angina pectoris, obstructive cardiomyopathy and ventricular arrhythmia and hypertension), phaeochromocytoma, high intraocular pressure, severe renal impairment, prostatic adenoma leading to residual urine, hypercalcaemia, hypokalaemia, diabetes, or in elderly or pregnant patients.

Adrenaline should be used with caution in patients with heart disease e.g coronary heart and cardiac muscle diseases, cor pulmonale, cardiac arrhythmias or tachycardia. In such patients, adrenaline may precipitate or aggravate angina pectoris as well as produce ventricular arrhythmias.

Patients with diabetes may develop increased blood glucose levels following adrenaline administration.

Patients with Parkinson’s disease may notice a temporary worsening of symptoms.

Twinject contains sodium bisulphite (E222), which may rarely cause severe hypersensitivity reactions including anaphylactic symptoms and bronchospasm, especially in those with a history of asthma. Patients with these conditions must be carefully instructed in regard to the circumstances under which Twinject should be used.

In the event of a life-threatening allergic reaction, Twinject can be used even if the patient is allergic to sulphites.

Twinject contains less than 1 mmol sodium per 0.3 ml.

4.5 Interaction with other medicinal products and other forms of interaction

The effects of adrenaline may be potentiated by tricyclic antidepressants mixed noradrenergic-serotonergic antidepressants like venlafaxine, sibutramine or milnacipran and monoamine oxidase (MAO) inhibitors (sudden blood pressure increase and possible cardiac arrhythmia), catechol-O-methyl-transferase (COMT) blocking agents, thyroid hormones, theophylline, oxytocin, parasympatholytics, certain antihistamines (diphenhydramine, chlorpheniramine), levodopa and alcohol.

Severe hypertension and bradycardia may occur when adrenaline is administered with non-selective beta-blocking medicinal products.
Concurrent therapy with sympathomimetics may potentiate the effects of adrenaline.

Use Twinject with caution in patients receiving medicinal products that may sensitize the heart to arrhythmias, e.g. digitalis, quinidine and halogenated anaesthetics.

The pressor effects of adrenaline may be counteracted by administration of rapidly acting vasodilators or alpha adrenergic blocking medicinal products (resulting in a decrease in blood pressure). The cardiostimulating and bronchodilating effects can be antagonised by beta-blocking agents, especially non-selective beta-blockers.

Adrenaline inhibits insulin secretion, thus increasing the blood glucose level. Therefore, diabetic patients may require upward adjustment of their insulin or other hypoglycaemic therapy.

4.6 Pregnancy and lactation

There are no adequate or well-controlled studies of adrenaline in pregnant women. Adrenaline should only be used in pregnancy if the potential benefit justifies the potential risk to the fetus. Adrenaline crosses the placenta and could lead to fetal hypoxia, spontaneous abortion or both.

Adrenaline is not orally bioavailable; any adrenaline excreted in breast milk would not be expected to have any effect on the nursing infant.

4.7 Effects on ability to drive and use machines

Adrenaline has no or negligible influence on the ability to drive and use machines. However it is recommended that patients should not drive or use machines following administration of adrenaline, since patients will be affected by symptoms of the anaphylactic shock.

4.8 Undesirable effects

The occurrence of undesirable effects depends on the sensitivity of the individual patient and the dose applied. The adverse reactions due to adrenaline are listed below, however their frequencies cannot be estimated from the available data:

- Metabolism and nutrition disorders: hyperglycaemia, hypokalaemia, metabolic acidosis
- Psychiatric disorders: anxiety, hallucinations, nervousness
- Nervous system disorders: mydriasis, tremor, headache, asthenia
- Cardiac disorders: syncope, palpitation, tachycardia, dizziness, angina pectoris, hypertension
- Vascular disorders: vascular constriction, peripheral coldness
- Respiratory, thoracic and mediastinal disorders: respiratory difficulty, pulmonary oedema
- Gastrointestinal disorders: nausea, vomiting
- Musculoskeletal, connective tissue and bone disorders: weakness
- Renal and urinary disorders: urinary retention, renal impairment
- General disorders and administration site conditions: pallor, hyperhidrosis

Adverse reactions that may occur at higher doses or in susceptible individuals are cardiac arrhythmias (ventricular fibrillation / cardiac arrest), sudden rise of blood pressure (sometimes leading to cerebral haemorrhage), as well as vasoconstriction (e.g. in the skin, mucous tissues and kidneys)

Twinject contains a sulphite that may cause allergic-type reactions including anaphylactic reactions or life-threatening or less severe asthmatic episodes in certain susceptible patients.

4.9 Overdose

Adrenaline is rapidly inactivated in the body, and treatment following overdose with adrenaline is primarily supportive.

Overdose or accidental intravascular injection of adrenaline may cause cerebral haemorrhage from a sudden rise of blood pressure. Death may result from acute pulmonary oedema arising from peripheral vascular constriction and cardiac stimulation.

The pressor effects of adrenaline may be counteracted by rapidly acting vasodilators or alpha-adrenergic blocking medicinal products. Should prolonged hypotension follow such measures, it may be necessary to administer another pressor medicinal product, such as noradrenaline.
Acute pulmonary oedema with respiratory discomfort following adrenaline (epinephrine) overdose should be managed by administration of a rapidly acting alpha-adrenergic blocking medicinal product such as phentolamine and/or with intermittent positive pressure respiration.

Adrenaline overdose may also result in transient bradycardia followed by tachycardia; these can be followed by potentially fatal cardiac arrhythmias.

Premature ventricular contractions may appear within one minute after injection and may be followed by multifocal ventricular tachycardia (presumably rhythm). Subsidence of the ventricular effects may be followed by atrial tachycardia and occasionally by atrioventricular block. Treatment of arrhythmias consists of administration of beta-adrenergic blocking medicinal products. These must be preceded or accompanied by an alpha-adrenergic blocker to control the alpha-mediated effects on the peripheral circulation.

Overdose sometimes results in extreme pallor and coldness of the skin, metabolic acidosis, and kidney failure. Suitable corrective measures must be taken in such situations.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: adrenergic and dopaminergic agents, adrenaline.
ATC code: C01 CA 24

Adrenaline is a naturally-occurring catecholamine secreted by the adrenal medulla in response to exertion or stress. It is a sympathomimetic amine which is a potent stimulant of both alpha and beta adrenergic receptors and its effects on target organs are, therefore, complex. It is the medicinal product of choice to provide rapid relief of hypersensitivity reactions to allergies or to idiopathic or exercise induced anaphylaxis.

If a clinical effect is not achieved, more than one injection is recommended after 5 minutes or sooner. Approximately 20% of patients may require more than one adrenaline injection.

Adrenaline has a strong vasoconstrictor action through alpha-adrenergic stimulation. This activity counteracts the vasodilatation and increased vascular permeability leading to loss of intravascular fluid and subsequent hypotension, which are the major pharmacotoxicological features in anaphylactic shock.

Through its stimulation of bronchial beta adrenergic receptors, adrenaline has a powerful bronchodilator action that alleviates bronchospasm, wheezing and dyspnoea.

Adrenaline also alleviates pruritus, urticaria and angioedema, and may be effective in relieving gastrointestinal and genitourinary symptoms of anaphylaxis because of its relaxing effects on the smooth muscle of the stomach, intestine, uterus and urinary bladder.

5.2 Pharmacokinetic properties
Adrenaline is rapidly inactivated in the body, mostly in the liver by the enzymes COMT and MAO. Much of a dose of adrenaline is excreted as metabolites in urine. The plasma half-life is about 2-3 minutes. However, when given by subcutaneous or intramuscular injection, local vasoconstriction may delay absorption so that the effects may last longer than the half-life suggests.

5.3 Preclinical safety data
No relevant mutagenic or carcinogenic properties have been demonstrated with adrenaline. At high doses (100 times the human dose), adrenaline has teratogenic effects in mice, rats, hamsters and chickens. At doses in the range of clinical doses, fetal hypoxia resulting in fetal death has been observed following i.v. administration in monkeys.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Sodium chloride
Chlorobutanol hemihydrate
Sodium bisulphite (E222)
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
6.2 Incompatibilities
Not applicable.

6.3 Shelf life
18 months.

6.4 Special precautions for storage
Do not store above 25ºC.
Do not refrigerate or freeze.
Store in the original package to protect from light.
Adrenaline is light sensitive. Patients should periodically check the solution in Twinject for any discolouration. If the solution is coloured the patient should replace their Twinject.

6.5 Nature and contents of container
A pre-filled syringe consisting of a Type I borosilicate glass cartridge, closed with an aluminium cap (containing a chlorobutyl rubber cap) and a chlorobutyl rubber insert plunger. The drug product and primary packaging configuration is fitted with a polypropylene needle hub, stainless steel needle and a clear polyethylene needle shield, in a measuring device (auto injector) dual dose product, containing 1.1 ml adrenaline.

The pre-filled syringe is assembled into a plexi-glass assembly then placed in a polypropylene carrying case in a carton.

Pack sizes: Single Carton, containing one 0.3 mg unit or Two-Pack Carton, containing two 0.3 mg units and a demonstrator.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Instructions for use:
For single use only (two doses of 0.3 mg are available with each Twinject).

Actual demonstration of the injection technique by a physician or a pharmacist is recommended. A demonstrator that does not contain a needle or adrenaline is available for this purpose.

FIRST DOSE
STEP A
Remove the Twinject from the blue carrying case.
• Pull off first GREEN end cap [labelled 1] to see a RED tip. Never put thumb, finger, or hand over the RED tip.

• Pull off second GREEN end cap [labelled 2].
PAR Twinject 0.15mg/0.15ml and 0.30mg/0.30ml Solution for Injection

STEP B
- Put the RED tip against the middle of the outer side of the thigh (upper leg) as shown. Twinject can be used through clothes, even thick ones such as jeans.
- Press down hard until the needle enters the thigh (upper leg) through the skin. Hold it in place while slowly counting to 10.

• Remove the Twinject from the thigh.
• Check the RED tip; if the needle is exposed the dose was received. If the needle is not visible, First Dose step B should be repeated. Make sure both green caps labelled 1 and 2 have been removed prior to repeating step B.

At this stage the patient should get emergency medical help right away. He should prepare himself for the second dose.

SECOND DOSE PREPARATION
STEP A
- Carefully grasp the red tip avoiding the needle. Unscrew the body of the Twinject unit until the cap is fully loosened from the body. Carefully pull the body away from the cap avoiding touching or bending of the exposed needle.

STEP B
- Grab the BLUE plastic to pull the syringe out of the barrel (do not touch the needle).
STEP C
• Pull the YELLOW collar off the plunger. Be careful not to pull up on the plunger while removing the YELLOW collar.

PAUSE HERE

The patient and/or care-giver should pay special attention to the potential risks to the patient if the needle becomes contaminated between the two injections (for example by falling on the floor), as well as to the risk of a needle-stick injury to others. It is therefore necessary that the patient and/or care-giver handle the syringe very carefully to ensure that the needle does not come into contact with any other surface. Also, other people present should be warned about the presence of an exposed needle.

STEP D (SECOND DOSE ADMINISTRATION)
If the patient symptoms have not improved within about 5 minutes of the first injection, the second dose should be injected.

• Put the needle into the middle of the outer side of the thigh (upper leg), through the skin, as shown.
• Push the plunger down all the way until it cannot go any further.

• Remove the Twinject syringe from the skin.

The remaining volume (approximately 0.5 ml) in the syringe after the two fixed doses cannot be further administered and the syringe should be discarded as instructed (see section 6.6).

In cases where the second dose has not been administered, the syringe (including unused adrenaline) should also be discarded.

After use, do not attempt to replace the needle cover.

With one half of the carrying case lying on a flat surface, slide the syringe, needle first, into the carrying case.

Put the other half of the carrying case on and close it.

Replace the used Twinject as soon as possible.

The used product should be handed to the attending paramedics or given to the pharmacist when the replacement product is obtained.
MARKETING AUTHORISATION HOLDER
Shionogi Ireland
145 Lakeview Drive
Airside Business Park
Swords
County Dublin
Ireland

MARKETING AUTHORISATION NUMBER(S)
PL 00039/0734

DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
17/09/2010

DATE OF REVISION OF THE TEXT
17/09/2010
Module 3

PACKAGE LEAFLET: INFORMATION FOR THE USER

Twinject 0.15 mg/0.15 ml solution for injection in pre-filled syringe
Adrenaline (epinephrine)

Read all of this leaflet carefully before you start using this medicine.
- 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. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- 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.

In this leaflet:
1. What Twinject is and what it is used for
2. Before you use Twinject
3. How to use Twinject
4. Possible side effects
5. How to store Twinject
6. Further information

1. WHAT TWINJECT IS AND WHAT IT IS USED FOR

Twinject contains adrenaline. Adrenaline helps treat life-threatening allergic reactions, by reducing swelling, relaxing muscles in the lungs to help breathing and by making the blood vessels smaller, to increase blood pressure.

Allergic reactions can be caused by stinging and biting insects or other animals, food, medicines, exercise, or sometimes the cause is not known.

Life-threatening allergic reactions may make it difficult to breathe and can cause wheezing, sneezing, hoarseness, hives, itching, swelling, skin redness, fast heartbeat, weak pulse, feeling very anxious, confusion, stomach pain, losing control of urine or bowel movements (incontinence), faintness, or “passing out” (unconsciousness).

The amount of adrenaline in this Twinject is enough to treat a child weighing between 15 and 30 kg.

2. BEFORE YOU USE TWINJECT

Do not use Twinject
- if the patient is allergic (hypersensitive) to adrenaline, sodium bisulphite or to any of the other ingredients of Twinject (see Section 6 'What Twinject contains').

However if the allergic reaction being treated is life-threatening Twinject can still be used.

Take special care with Twinject
Tell your doctor about all the patient’s medical conditions, but especially if the patient has:
- heart disease or high blood pressure
- increased pressure in their eye (glaucoma)
- high levels of calcium in their blood
- low levels of potassium in their blood
- a tumour in their adrenal gland or prostate
- diabetes
Par Twinject 0.15mg/0.15ml and 0.30mg/0.30ml Solution for Injection

- an overactive thyroid
- asthma
- severe kidney problems
- Parkinson's disease

Or if the patient is pregnant or elderly.

Tell your doctor if the patient or caregiver has any condition that makes it difficult to give the medicine properly, such as severe arthritis.

There is often a long period between supply of Twinject and an allergic reaction requiring adrenaline. Therefore, you should regularly check Twinject and ensure it is replaced within the expiry period. Please see section 5 for further information.

Using other medicines
Please tell your doctor or pharmacist if the patient is taking or has recently taken any other medicines, including medicines obtained without a prescription.

Certain medicines may affect the way the patient reacts to Twinject. Be sure to tell your doctor about all the medicines the patient takes including:

Drugs used to treat
- asthma, for example theophylline
- allergies (antihistamines), such as diphenhydramine or chlorpheniramine
- depression, such as venlafaxine, selegiline or amitriptyline
- thyroid problems, such as thyroid
- Parkinson's disease, such as levodopa or entacapone
- high blood pressure, such as propranolol or atenolol
- abnormal heart beat, such as digoxin or digoxin
- diabetes, such as insulin or metformin. Diabetic patients may need to adjust the dose of their diabetes medicines or insulin after using Twinject.

Also tell your doctor if the patient is taking oxytocin or alcohol.

Driving and using machines
After using Twinject the patient should avoid activities that could be dangerous, for example driving, working machinery or bike riding.

Pregnancy or Breastfeeding
Twinject should only be used in pregnancy if the benefits outweigh the risks to the unborn baby. If the allergic reaction is life threatening Twinject should be used.

If you are pregnant, breast feeding or planning to breast feed talk to your doctor before taking any medicine.

Important information about some of the ingredients of Twinject
Twinject contains sodium bisulphite (E223) which may rarely cause severe hypersensitivity (allergic) reactions and bronchospasm (tightening of the airways).
Twinject can be used even if the patient is allergic to sulphites if the allergic reaction is life-threatening.
Twinject contains less than 1 mmol sodium per dose i.e. it is essentially 'sodium free'.
5. **HOW TO USE TWINJECT**

Your doctor or pharmacist may show you how to use Twinject. Always use Twinject exactly as they have shown or told you. You should check with your doctor or pharmacist if you are not sure.

**Dosage**

*Children weighing between 15 and 30 kg.*

The usual dose is 0.15 mg adrenaline per injection into the outer side of the thigh muscle (intramuscular use).

This product is not normally used in children weighing less than 15 kg, but your doctor may have considered it appropriate to prescribe the product for a smaller child.

For children weighing more than 30 kg, the higher dose product (0.3 mg/0.3 ml) may be more appropriate.

Use of Twinject must always be followed by emergency medical care. As Twinject is designed as emergency treatment only, you should always seek medical help immediately after using Twinject, by reporting to the patient's doctor, the nearest hospital or by calling an ambulance. Make sure that you tell the healthcare professional that the patient has been given an injection of adrenaline and hand over the used Twinject for safe disposal.

**How and when should you use Twinject?**

Each Twinject can give 2 injections of adrenaline. How they should be given is described in the Step by Step instructions below.

Twinject should be injected into the outer thigh. Do not inject into blood vessels, hands, feet or the buttock. Accidental injection into the hands or fingers may result in reduced blood supply to these areas. If there is an accidental injection into these areas, you should immediately to the nearest hospital emergency department for treatment.

**FIRST DOSE**

**STEP A**

Remove the Twinject from the green carrying case.

- Pull off first GREEN end cap [*labelled 1*] to see a RED tip. *Never* put thumb, finger, or hand over the RED tip.

![Pull off first](image)

- Pull off second GREEN end cap [*labelled 2*].

![Pull off second](image)
STEP B
• Put the RED tip against the middle of the outer side of the thigh (upper leg) as shown. Twinject can be used through clothes, even thick ones such as jeans.
• Press down hard until the needle enters the thigh (upper leg) through the skin. Hold it in place while slowly counting to 10.

• Remove the Twinject from the thigh.
• Check the RED tip. If the needle is sticking out the dose was received. If needle is not sticking out repeat step B. Make sure both green caps labelled 1 and 2 have been removed prior to repeating step B.

Get emergency medical help now.

While you wait you should get ready to give the second dose of Twinject. Instructions are given on the Twinject label.

SECOND DOSE
STEP A
• Unscrew and remove the RED tip. Do not touch, bend or break the exposed needle.

STEP B
• Hold the BLUE plastic and pull the syringe out of the barrel (do not touch the needle).
STEP C

• Pull the YELLOW collar off the plunger. Be careful not to pull up on the plunger while removing the YELLOW collar.

Place the syringe in a safe place nearby where the exposed needle is protected:
• It is very important that you handle the syringe very carefully and try to keep the needle clean.
• You should also warn other people nearby about the presence of an exposed needle. This will reduce the risk of accidental injection.

If symptoms have not improved within about 5 minutes of giving the first dose, the second dose should be injected (Step D).

STEP D

• Put the needle into the middle of the outer side of the thigh (upper leg), through the skin, as shown.
• Push the plunger down all the way until it cannot go any further.

• Remove the Twinject syringe from the skin.

AFTER USE

You may notice that a small amount of liquid is in the oth doses have been given. This
is normal.

After Twinject has been used (whether or not the second dose was given) do not attempt to replace the needle cover because you may prick yourself.
Put the syringe, needle first into the carrying case.
Put the other half of the carrying case on and close it.
Make sure you get a new Twinject to replace the one that has been used.

If you use more Twinject than you should

If you think you have received too much Twinject get medical treatment right away. Too much adrenaline (Twinject) can cause dangerously high blood pressure, stroke, bleeding in the brain, irregular heart beat, abnormal kidney function, narrowing of the blood vessels and fluid in the lungs or death.

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

Like all medicines, Twinject can cause side effects, although not everybody gets them.

Twinject (adrenaline) can cause the following reactions:

- Sweating
- Anxiety
- Nervousness
- Tremor
- Headache
- Unusual or fast heartbeat
- Dizziness
- Coldness of skin and the extremities
- Breathing difficulty or chest pain
- Fluid in the lungs
- Nausea
- Vomiting
- Weakness
- Palor (paleness of the skin)
- Hallucinations
- Abnormal size of pupil
- Fainting
- High blood pressure
- Kidney problems
- Inability to urinate

It can also cause a high level of sugar or acid in the blood or a low level of potassium in blood.

Occasionally, at high doses, in susceptible patients, a sudden increase in blood pressure that may cause bleeding in the brain, irregular heartbeat and heart attack and reduced blood flow to the skin, mucous tissues and kidneys may occur.

Twinject contains bisulphite that may cause allergic-type reactions including severe ones or life-threatening or less severe asthmatic episodes in certain susceptible patients.

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.

5. HOW TO STORE TWINJECT

Keep out of the reach and sight of children.

Do not use Twinject after the expiry date that is stated on the carton after (abbreviation used for expiry date). The expiry date refers to the last day of that month.

Do not store above 25°C.

Do not refrigerate, or freeze

Store in the original container in order to protect from light.

Check Twinject regularly to be sure:

- If has not expired
- The medicine in Twinject is not cloudy or discoloured

Ask your doctor for a new Twinject if it is cloudy, discoloured or out of date.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Twinject contains

The active substance is adrenaline. One dose contains 0.15 mg (0.15 ml) of adrenaline. The prefilled syringe may deliver two doses of 0.15 ml of adrenaline.

The other ingredients are sodium chloride, chlorobutanol hemihydrate, sodium bisulphite (E222), hydrochloric acid, sodium hydroside, water for injections.
What Twinject looks like and contents of the pack

Twinject is a solution for injection in pre-filled syringe.
The solution is clear and colorless and is practically free from particles.

Twinject is provided as:
- One prefilled syringe per carton or
- Two prefilled syringes in a carton with a needle-free syringe for demonstration purposes.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Shionogi Ireland
Airsite Business Park
County Dublin
Ireland

This medicinal product is authorised in the Member States of the EEA under the following names:

Austria <(Name of the medicinal product)>
Belgium <(Name of the medicinal product)>
Bulgaria <(Name of the medicinal product)>
Czech Republic <(Name of the medicinal product)>
Cyprus <(Name of the medicinal product)>
Denmark <(Name of the medicinal product)>
Finland <(Name of the medicinal product)>
France <(Name of the medicinal product)>
Germany <(Name of the medicinal product)>
Greece <(Name of the medicinal product)>
Italy <(Name of the medicinal product)>
Luxembourg <(Name of the medicinal product)>
Malta <(Name of the medicinal product)>
Netherlands <(Name of the medicinal product)>
Norway <(Name of the medicinal product)>
Poland <(Name of the medicinal product)>
Portugal <(Name of the medicinal product)>
Romania <(Name of the medicinal product)>
Slovak Republic <(Name of the medicinal product)>
Slovenia <(Name of the medicinal product)>
Spain <(Name of the medicinal product)>
United Kingdom <(Name of the medicinal product)>

This leaflet was last approved in (MM/YYYY).

[To be completed nationally]
PAR Twinject 0.15mg/0.15ml and 0.30mg/0.30ml Solution for Injection UK/H/1231/001-2/DC

PACKAGE LEAFLET: INFORMATION FOR THE USER

Twinject 0.3 mg/0.3 ml solution for injection in pre-filled syringe
Adrenaline (epinephrine)

Read all of this leaflet carefully before you start using this medicine.

- 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. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- 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.

In this leaflet:
1. What Twinject is and what it is used for
2. Before you use Twinject
3. How to use Twinject
4. Possible side effects
5. How to store Twinject
6. Further information

1. WHAT TWINJECT IS AND WHAT IT IS USED FOR

Twinject contains adrenaline. Adrenaline helps treat life-threatening allergic reactions, by reducing swelling, relaxing muscles in the lungs to help breathing and by making the blood vessels smaller, to increase blood pressure.

Allergic reactions can be caused by stinging and biting insects or other animals, food, medicines, exercise, or sometimes the cause is not known.

Life-threatening allergic reactions may make it difficult to breathe and can cause wheezing, sneezing, hoarseness, hives, itching, swelling, skin redness, fast heartbeat, weak pulse, feeling very anxious, confusion, stomach pain, losing control of urine or bowel movements (incontinence), faintness, or "passing out" (unconsciousness).

2. BEFORE YOU USE TWINJECT

Do not use Twinject
- if you are allergic (hypersensitive) to adrenaline, sodium bisulphite or to any of the other ingredients of Twinject (see Section 6 'What Twinject contains').
However if the allergic reaction being treated is life-threatening Twinject can still be used.

Take special care with Twinject
Tell your doctor about all your medical conditions, but especially if you have:
- heart disease or high blood pressure
- increased pressure in their eye (glaucoma)
- high levels of calcium in their blood
- low levels of potassium in their blood
- a tumour in their adrenal gland or prostate
- diabetes
- an overactive thyroid
- asthma
- severe kidney problems
- Parkinson’s disease

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Or if you are pregnant or elderly.

Tell your doctor if you have any condition that makes it difficult to give the medicine properly, such as severe arthritis.

There is often a long period between supply of Twinject and an allergic reaction requiring adrenaline. Therefore, you should regularly check Twinject and ensure it is replaced within the expiry period. Please see section 5 for further information.

Using other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Certain medicines may affect the way you react to Twinject. Be sure to tell your doctor about all the medicines you take including:

Drugs used to treat
- asthma, for example theophylline
- allergies (antihistamines), such as diphenhydramine or chlorpheniramine
- depression, such as venlafaxine, selegiline or amitriptylline -
- thyroid problems, such as thyroxin
- Parkinson’s disease, such as levodopa or entacapone
- high blood pressure, such propranolol or atenolol
- abnormal heart beat, such as digitalis or digoxin
- diabetes, such as insulin or metformin. Diabetic patients may need to adjust the dose of their diabetes medicines or insulin after using Twinject.

Also tell your doctor if you are taking oxytocin or alcohol.

Driving and using machines
After using Twinject you should avoid activities that could be dangerous, for example driving, working machinery or bike riding.

Pregnancy or Breastfeeding
Twinject should only be used in pregnancy if the benefits outweigh the risks to the unborn baby. If the allergic reaction is life threatening Twinject should be used.

If you are pregnant, breast feeding or planning to breast feed talk to your doctor before taking any medicine.

Important information about some of the ingredients of Twinject
Twinject contains sodium bisulphite (E222) which may rarely cause severe hypersensitivity (allergic) reactions and bronchospasm (tightening of the airways).
Twinject can be used even if the patient is allergic to sulphites if the allergic reaction is life-threatening.
Twinject contains less than 1 mmol sodium per dose i.e. it is essentially ‘sodium free’.

3. HOW TO USE TWINJECT

Your doctor or pharmacist may show you how to use Twinject. Always use Twinject exactly as they have shown or told you. You should check with your doctor or pharmacist if you are not sure.
Dosage

Adults, adolescents and children weighing more than 30 kg:
The usual dose is 0.3 mg adrenaline per injection into the outer side of the thigh muscle (intramuscular use).

For children weighing between 15 and 30 kg, the lower dose product (0.15 mg/0.15 ml) may be more appropriate.

Use of Twinject must always be followed by emergency medical care. As Twinject is designed as emergency treatment only, you should always seek medical help immediately after using Twinject, by reporting to your doctor, the nearest hospital or by calling an ambulance. Make sure that you tell the healthcare professional that you have given yourself an injection of adrenaline and hand over the used Twinject for safe disposal.

How and when should you use Twinject?
Each Twinject can give 2 injections of adrenaline. How they should be given is described in the Step by Step instructions below.

Twinject should be injected into the outer thigh. Do not inject into blood vessels, hands, feet or the buttock. Accidental injection into the hands or fingers may result in reduced blood supply to these areas. If there is an accidental injection into these areas, you should go immediately to the nearest hospital emergency department for treatment.

FIRST DOSE

STEP A
Remove the Twinject from the blue carrying case.
• Pull off first GREEN end cap [labelled 1] to see a RED tip.
  • Never put thumb, finger, or hand over the RED tip.

• Pull off second GREEN end cap [labelled 2].
STEP B
• Put the RED tip against the middle of the outer side of the thigh (upper leg) as shown. Twinject can be used through clothes, even thick ones such as jeans.
• Press down hard until the needle enters the thigh (upper leg) through the skin. Hold it in place while slowly counting to 10.

• Remove the Twinject from the thigh.
• Check the RED tip. If the needle is sticking out the dose was received. If needle is not sticking out Repeat step B.Making sure both green caps labelled 1 and 2 have been removed prior to repeating step B.

Get emergency medical help now.

While you wait you should get ready to give the second dose of Twinject. Instructions are given on the Twinject label.

SECOND DOSE
STEP A
• Unscrew and remove the RED tip. Do not touch, bend or break the exposed needle.

STEP B
• Hold the BLUE plastic and pull the syringe out of the barrel (do not touch the needle).
STEP C
- Pull the YELLOW collar off the plunger. Be careful not to pull up on the plunger while removing the YELLOW collar.

Place the syringe in a safe place nearby where the exposed needle is protected:
- It is very important that you handle the syringe very carefully and try to keep the needle clean.
- You should also warn other people nearby about the presence of an exposed needle. This will reduce the risk of accidental injection.

If symptoms have not improved within about 5 minutes of giving the first dose, the second dose should be injected (Step D).

STEP D
- Put the needle into the middle of the outer side of the thigh (upper leg), through the skin, as shown.
- Push the plunger down all the way until it cannot go any further.

- Remove the Twinject syringe from the skin.

AFTER USE
You may notice that a small amount of liquid is in the syringe after both doses have been given. This is normal.

After Twinject has been used (whether or not the second dose was given) do not attempt to replace the needle cover because you may prick yourself.
Put the syringe, needle first into the carrying case.
Put the other half of the carrying case on and close it.
Make sure you get a new Twinject to replace the one that has been used.
If you use more Twinject than you should

If you think you have received too much Twinject get medical treatment right away. Too much adrenaline (Twinject) can cause dangerously high blood pressure, stroke, bleeding in the brain, irregular heart beat, abnormal kidney function, narrowing of the blood vessels and fluid in the lungs or death.

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, Twinject can cause side effects, although not everybody gets them.

Twinject (adrenaline) can cause the following reactions.

Sweating, anxiety, nervousness, tremor, headache, unusual, slow or fast heart beat, dizziness, coldness of skin and the extremities, breathing difficulty or chest pain, fluid in the lungs, nausea, vomiting, weakness, pallor (paleness of the skin), hallucinations, abnormal size of pupil, fainting, high blood pressure, kidney problems or inability to urinate.

It can also cause a high level of sugar or acid in the blood or a low level of potassium in blood.

Occasionally, at high doses, or in susceptible patients, a sudden increase in blood pressure that may cause bleeding in the brain, irregular heartbeat and heart attack and reduced blood flow to the skin, mucous tissues and kidneys may occur.

Twinject contains bisulphite that may cause allergic-type reactions that could be severe or life-threatening. It may also cause tightening of the airways in some patients.

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.

5. HOW TO STORE TWINJECT

Keep out of the reach and sight of children.
Do not use Twinject after the expiry date that is stated on the carton after (abbreviation used for expiry date). The expiry date refers to the last day of that month.

Do not store above 25°C.
Do not refrigerate, or freeze.
Store in the original container in order to protect from light.

Check Twinject regularly to be sure:

• it has not expired
• the medicine in Twinject is not cloudy or discoloured

Ask your doctor for a new Twinject if it is cloudy, discoloured or out of date.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.
6. FURTHER INFORMATION

What Twinject contains

The active substance is adrenaline. One dose contains 0.3 mg (0.3 ml) of adrenaline. The prefilled syringe may deliver two doses of 0.3 ml of adrenaline.

The other ingredients are sodium chloride, chlorobutanol hemihydrate, sodium bisulphite (E222), hydrochloric acid, sodium hydroxide, water for injections.

What Twinject looks like and contents of the pack

Twinject is a solution for injection in pre-filled syringe. The solution is clear and colorless and is practically free from particles.

Twinject is provided as:
- One prefilled syringe per carton or
- Two prefilled syringes in a carton with a needle-free syringe for demonstration purposes.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Shionogi Ireland
Airside Business Park
County Dublin
Ireland

This medicinal product is authorised in the Member States of the EEA under the following names:

Austria  <[Name of the medicinal product]>
Belgium  <[Name of the medicinal product]>
Bulgaria <[Name of the medicinal product]>
Czech Republic <[Name of the medicinal product]>
Cyprus  <[Name of the medicinal product]>
Denmark <[Name of the medicinal product]>
Finland <[Name of the medicinal product]>
France <[Name of the medicinal product]>
Germany <[Name of the medicinal product]>
Greece <[Name of the medicinal product]>
Italy <[Name of the medicinal product]>
Luxembourg <[Name of the medicinal product]>
Malta <[Name of the medicinal product]>
Netherlands <[Name of the medicinal product]>
Norway <[Name of the medicinal product]>
Poland <[Name of the medicinal product]>
Portugal <[Name of the medicinal product]>
Romania <[Name of the medicinal product]>
Slovak Republic <[Name of the medicinal product]>
Slovenia <[Name of the medicinal product]>
Spain <[Name of the medicinal product]>
United Kingdom <[Name of the medicinal product]>

This leaflet was last approved in {MM/YYYY}.

[To be completed nationally]
Module 4
Labelling

1. NAME OF THE MEDICINAL PRODUCT

Twinject 0.15 mg/0.15 ml solution for injection in pre-filled syringe
Adrenaline (epinephrine)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml of solution contains 1 mg of adrenaline
One dose contains 0.15 mg (0.15 ml) of adrenaline
The pre-filled syringe may deliver two doses of 0.15 mg (0.15 ml) adrenaline

3. LIST OF EXCIPIENTS

Sodium chloride, chlorobutanol hemihydrate, sodium bisulphite (E222), water for injection,
hydrochloric acid, sodium hydroxide (see leaflet for further information)

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled syringe
1 pre-filled syringe

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
9. **SPECIAL STORAGE CONDITIONS**

Do not store above 25°C, do not refrigerate or freeze, store in the original container to protect from light.

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Shionogi Ireland Ltd
Aiside Business Park
County Dublin, Ireland

12. **MARKETING AUTHORISATION NUMBER(S)**

[To be completed nationally]

13. **BATCH NUMBER**

Lot

14. **GENERAL CLASSIFICATION FOR SUPPLY**

[To be completed nationally]

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

Twinject 0.15 mg
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARRY CASE

1. NAME OF THE MEDICINAL PRODUCT

Twinject 0.15 mg/0.15 ml injection in pre-filled syringe
Adrenaline (epinephrine)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml of solution contains 1 mg of adrenaline
One dose contains 0.15 mg (0.15 ml) of adrenaline
The pre-filled syringe may deliver two doses of 0.15 mg (0.15 ml) adrenaline

3. LIST OF EXCIPIENTS

Sodium chloride, chlorobutanol hemihydrate, sodium bisulphite (E222), water for injection,
hydrochloric acid, sodium hydroxide (see leaflet for further information)

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled syringe
1 pre-filled syringe

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Twist and pull to open
Contains glass. Handle with care.
8. **EXPIRY DATE**

EXP

9. **SPECIAL STORAGE CONDITIONS**

Do not store above 25°C.
Do not refrigerate or freeze.
Store in the original container to protect from light.

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORITYHOLDER**

Shionogi Ireland Ltd
Airside Business Park
County Dublin, Ireland

12. **MARKETING AUTHORIZATION NUMBER(S)**

[To be completed nationally]

13. **BATCH NUMBER**

Lot

14. **GENERAL CLASSIFICATION FOR SUPPLY**

[To be completed nationally]

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**
**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING**

**WRAP LABEL**

<table>
<thead>
<tr>
<th>1. <strong>NAME OF THE MEDICINAL PRODUCT</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Twinject 0.15 mg/0.15 ml injection in pre-filled syringe</td>
</tr>
<tr>
<td>Adrenaline</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. <strong>STATEMENT OF ACTIVE SUBSTANCE(S)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Two doses of 0.15 mg/0.15 ml adrenaline</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. <strong>LIST OF EXCIPIENTS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium chloride, chlorobutanol hemihydrate, sodium bisulphite (E222), water for injection, hydrochloric acid, sodium hydroxide (see leaflet for further information)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. <strong>PHARMACEUTICAL FORM AND CONTENTS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Solution for injection: 1 pre-filled syringe</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. <strong>METHOD AND ROUTE(S) OF ADMINISTRATION</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Intramuscular use</td>
</tr>
<tr>
<td>Read the package leaflet before use</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. <strong>SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Keep out of the reach and sight of children.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>7. <strong>OTHER SPECIAL WARNING(S), IF NECESSARY</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Liquid will remain in syringe after use</td>
</tr>
<tr>
<td>Replace if cloudy or discoloured</td>
</tr>
</tbody>
</table>
A Remove green caps. Do not touch red tip.

B Press hard into thigh. Hold in place for 10 sec.

Call for Emergency Medical Help.

Prepare for second dose: Peel Here

Inject second dose if symptoms don't improve within about 5 min.

A Unscrew red tip. Do not let anything touch needle.

B Pull out.

C Remove yellow collar

D Push needle into thigh. Push plunger all the way.
8. **EXPIRY DATE**

EXP

9. **SPECIAL STORAGE CONDITIONS**

Do not store above 25°C, do not refrigerate or freeze, store in the original container to protect from light.

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Shionogi Ireland Ltd
Airside Business Park
County Dublin, Ireland

12. **MARKETING AUTHORISATION NUMBER(S)**

[To be completed nationally]

13. **BATCH NUMBER**

Lot

14. **GENERAL CLASSIFICATION FOR SUPPLY**

[To be completed nationally]

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**
PAR Twinject 0.15mg/0.15ml and 0.30mg/0.30ml Solution for Injection UK/H/1231/001-2/DC

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
CARTRIDGE (Small container)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Twinject 1mg/1ml Injection
Adrenaline

2. METHOD OF ADMINISTRATION

IM

3. EXPIRY DATE

EXP.

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1.1 ml (2 doses)

6. OTHER
PARTICULARS TO APPEAR ON THE OUTER PACKAGING CARTON BOX

1. NAME OF THE MEDICINAL PRODUCT

Twinject 0.3 mg/0.3 ml solution for injection in pre-filled syringe
Adrenaline (epinephrine)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml of solution contains 1 mg of adrenaline
One dose contains 0.3 mg (0.3 ml) of adrenaline
The pre-filled syringe may deliver two doses of 0.3 mg (0.3 ml) adrenaline

3. LIST OF EXCIPIENTS

Sodium chloride, chlorobutanol hemihydrate, sodium bisulphite (E222), water for injection,
hydrochloric acid, sodium hydroxide (see leaflet for further information)

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled syringe
1 pre-filled syringe

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT
OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
9. **SPECIAL STORAGE CONDITIONS**

Do not store above 25°C, do not refrigerate or freeze, store in the original container to protect from light.

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Shionogi Ireland Ltd  
Airside Business Park  
County Dublin, Ireland

12. **MARKETING AUTHORISATION NUMBER(S)**

[To be completed nationally]

13. **BATCH NUMBER**

Lot

14. **GENERAL CLASSIFICATION FOR SUPPLY**

[To be completed nationally]

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

Twinject 0.3 mg
**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARRY CASE**

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Twinject 0.3 mg/0.3 ml injection in pre-filled syringe</td>
</tr>
<tr>
<td>Adrenaline (epinephrine)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. STATEMENT OF ACTIVE SUBSTANCE(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 ml of solution contains 1 mg of adrenaline</td>
</tr>
<tr>
<td>One dose contains 0.3 mg (0.3 ml) of adrenaline</td>
</tr>
<tr>
<td>The pre-filled syringe may deliver two doses of 0.3 mg (0.3 ml) adrenaline</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. LIST OF EXCIPIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium chloride, chlorobutanol hemihydrate, sodium bisulphite (E222), water for injection, hydrochloric acid, sodium hydroxide (see leaflet for further information)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>4. PHARMACEUTICAL FORM AND CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solution for injection in pre-filled syringe</td>
</tr>
<tr>
<td>1 pre-filled syringe</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. METHOD AND ROUTE(S) OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intramuscular use</td>
</tr>
<tr>
<td>Read the package leaflet before use</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN</th>
</tr>
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<tbody>
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<td>Keep out of the reach and sight of children.</td>
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<table>
<thead>
<tr>
<th>7. OTHER SPECIAL WARNING(S), IF NECESSARY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Twist and pull to open</td>
</tr>
<tr>
<td>Contains glass. Handle with care.</td>
</tr>
</tbody>
</table>
8. **EXPIRY DATE**

EXP

9. **SPECIAL STORAGE CONDITIONS**

Do not store above 25°C.
Do not refrigerate or freeze.
Store in the original container to protect from light

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Shionogi Ireland Ltd
Aiside Business Park
County Dublin, Ireland

12. **MARKETING AUTHORISATION NUMBER(S)**

[To be completed nationally]

13. **BATCH NUMBER**

Lot

14. **GENERAL CLASSIFICATION FOR SUPPLY**

[To be completed nationally]

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**
## PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

### WRAP LABEL

### 1. NAME OF THE MEDICINAL PRODUCT

Twinject 0.3 mg/0.3 ml injection in pre-filled syringe
Adrenaline

### 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Two doses of 0.3 mg/0.3 ml adrenaline

### 3. LIST OF EXCIPIENTS

Sodium chloride, chlorobutanol hemihydrate, sodium bisulphite (E222), water for injection, hydrochloric acid, sodium hydroxide (see leaflet for further information)

### 4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection: 1 pre-filled syringe

### 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use
Read the package leaflet before use

### 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

### 7. OTHER SPECIAL WARNING(S), IF NECESSARY

Liquid will remain in syringe after use
Replace if cloudy or discoloured
A. Remove green caps. Do not touch red tip.

B. Press hard into thigh. Hold in place for 10 sec.

Call for Emergency Medical Help.

Prepare for second dose: Peel Here

Inject second dose if symptoms don’t improve within about 5 min.
A. Unscrew red tip. Do not let anything touch needle.

B. Pull out.

C. Remove yellow collar

D. Push needle into thigh. Push plunger all the way.
8. **EXPIRY DATE**

EXP

9. **SPECIAL STORAGE CONDITIONS**

Do not store above 25°C, do not refrigerate or freeze. Store in the original container to protect from light.

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Shionogi Ireland Ltd  
Airside Business Park  
County Dublin, Ireland

12. **MARKETING AUTHORISATION NUMBER(S)**

[To be completed nationally]

13. **BATCH NUMBER**

Lot

14. **GENERAL CLASSIFICATION FOR SUPPLY**

[To be completed nationally]

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**
MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

CARTRIDGE (Small container)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION
   
   Twinject 1mg/1ml Injection
   Adrenaline

2. METHOD OF ADMINISTRATION
   
   IM

3. EXPIRY DATE
   
   EXP:

4. BATCH NUMBER
   
   Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT
   
   1.1 ml (2 doses)

6. OTHER
Module 5
Scientific discussion during initial procedure

I INTRODUCTION

On 26th August 2010, Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Germany, Greece, Finland, France, Italy, Luxembourg, Malta, the Netherlands, Norway, Poland, Portugal, Romania, Spain, Slovenia, the Slovak Republic and the UK agreed to grant marketing authorisations to Shionogi Ireland for the medicinal products Twinject 0.15mg/0.15ml and 0.30mg/0.30ml Solution for Injection (PL 00039/0733-4; UK/H/1231/001-2/DC). The licences were granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After the national phase, licences were granted in the UK on 17th September 2010.

These applications were made under Article 10a of Directive 2001/83 EC, so called well-established use applications. These products are indicated for the emergency treatment for acute allergic reactions (anaphylaxis) caused by foods, drugs, latex, insect bites or stings, and other allergens, as well as exercise-induced or idiopathic anaphylaxis.

Twinject 0.15mg/0.15ml and 0.30mg/0.30ml Solution for Injection are dual-dose autoinjector devices, containing a solution of 0.1% adrenaline. They have been designed in order to allow for a possible second manual injection of adrenaline, should the patient need one. The first dose is to be immediately used when the first symptoms of anaphylactic shock appear. A second dose is available from the device and is to be administered approximately 5 minutes after the first administration, if the symptoms persist or worsen.

Adrenaline is a naturally occurring catecholamine secreted by the adrenal medulla in response to exertion or stress. Adrenaline is a sympathicomimetic α and β-adrenergic agonist with cyclic adenosine monophosphate-mediated, complex, bidirectional pharmacological effects on target organs. In anaphylaxis, its α1-adrenergic effects (vasoconstriction, increased peripheral vascular resistance and decrease mucosal edema) and some of its β2-adrenergic effects (bronchodilatation and decreased mediator release from mast cells and basophils) are of primary importance.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.
## II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Twinject 0.15mg/0.15ml Solution for Injection  
| Twinject 0.30mg/0.30ml Solution for Injection |
| Name(s) of the active substance(s) (USAN)         | Epinephrine (adrenaline) |
| Pharmacotherapeutic classification (ATC code)    | Adrenergic and dopaminergic agents, adrenaline (C01 CA24) |
| Pharmaceutical form and strength(s)             | Solution for injection, 0.15mg/0.15ml and 0.30mg/0.30ml |
| Reference numbers for the Decentralised Procedure | UK/H/1231/001-2/DC |
| Reference Member State                           | United Kingdom |
| Member States concerned                          | Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Germany, Greece, Finland, France, Italy, Luxembourg, Malta, the Netherlands, Norway, Poland, Portugal, Romania, Spain, Slovenia, the Slovak Republic |
| Marketing Authorisation Number(s)                | PL 00039/0733 and 0734 |
| Name and address of the authorisation holder     | Shionogi Ireland, 145 Lakeview Drive, Airside Business Park, Swords, County Dublin, Ireland |
III  SCIENTIFIC OVERVIEW AND DISCUSSION
III.1  QUALITY ASPECTS

DRUG SUBSTANCE
INN: Adrenaline (epinephrine)
Chemical Names: \((R)-4-(1-hydroxy-2-(methylamino)ethyl)benzene-1,2-diol\)
Structure:

\[
\begin{align*}
\text{Molecular formula: } & \text{ C}_9\text{H}_{13}\text{NO}_3 \\
\text{Molecular weight: } & 183.204 \\
\text{Physical form: } & \text{ A white to lightish brown crystalline powder}
\end{align*}
\]

Epinephrine is the subject of a European Pharmacopoeia monograph.

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis. No materials of animal or human origin are used in the production of the active substance.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. All impurities have been appropriately characterised and certificates of analysis have been provided for any working standards used. Batch analysis data are provided that comply with the proposed specification.

Suitable specifications for all materials used in the active substance packaging have been provided. The primary packaging meets the requirements for materials in contact with food.

Appropriate stability data have been generated, from studies carried out in accordance with ICH conditions. A suitable retest period has been set, based on the stability data provided.

DRUG PRODUCT

Other ingredients
Other ingredients consist of pharmaceutical excipients sodium chloride, chlorobutanol hemihydrate, sodium bisulphite, sodium hydroxide and hydrochloric acid. With the exception of sodium bisulphite, all excipients are controlled to their respective European Pharmacopoeia monograph. Sodium bisulphite is controlled to a suitable Japanese Pharmacopoeia monograph. Satisfactory certificates of analysis have been provided for all excipients. None of the excipients used are sourced from materials of animal or human origin.

Pharmaceutical Development
The objective of the pharmaceutical development programme was to develop a dual-dose auto-injector device, containing a solution of 0.1% adrenaline, which could be used in the emergency treatment of acute allergic reactions (anaphylaxis). Suitable pharmaceutical development data have been provided for these applications.
**Manufacture**
A description and flow-chart of the manufacturing method have been provided. In-process controls are satisfactory based on process validation data and controls on the finished products. Process validation has been carried out on batches of each product. The results appear satisfactory.

**Finished product specifications**
The finished product specifications are satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for any working standards used.

**Container Closure System**
The finished products are supplied in pre-filled syringes (containing 1.1 ml adrenaline), consisting of a Type I borosilicate glass cartridge, closed with an aluminium cap (containing a chlorobutyl rubber cap) and a chlorobutyl rubber insert plunger. The drug product and primary packaging configuration are fitted with a polypropylene needle hub, stainless steel needle and a clear polyethylene needle shield, in a measuring device (auto injector) dual-dose product. The pre-filled syringe is assembled into a plexi-glass assembly, then placed in a polypropylene carrying case in a carton.

The products are packed into either single or two-pack cartons.

Specifications and Certificates of Analysis for the primary packaging material have been provided. These are satisfactory. All primary packaging is controlled to European Pharmacopoeia standards and complies with guidelines concerning materials in contact with parenteral products.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 18 months has been set, with the storage conditions “Store below 25°C. Do not refrigerate or freeze. Store in the original package to protect from light.”

**Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL) and Labelling**
The SPC, PIL and labelling are pharmaceutically satisfactory.

The applicant has submitted results of PIL user testing. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

The marketing authorisation holder has stated that they may not intend to market all pack sizes of the finished product at the current time. However, they have committed to submitting mock-ups of any pack sizes to the relevant regulatory authorities before marketing.

**MAA Forms**
The MAA forms are pharmaceutically satisfactory.
**Expert Report**
The pharmaceutical expert report is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

**Conclusion**
It is recommended that Marketing Authorisations are granted for these applications.

### III.2 PRE-CLINICAL ASPECTS

#### PHARMACODYNAMICS, PHARMACOKINETICS, TOXICOLOGY

No new pre-clinical studies have been conducted in support of these applications, which is acceptable as the pharmacology, pharmacokinetics and toxicology of adrenaline is well-known. The non-clinical overview comprises a satisfactory review of the relevant literature.

#### ENVIRONMENTAL RISK ASSESSMENT

An acceptable environmental risk assessment, in-line with the Committee for Medicinal Products for Human Use (CHMP) *Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use* (EMEA/CHMP/SWP/4447/00), has been submitted. Phase II and Persistent Bio-accumulative and Toxic (PBT) compounds assessments are not required.

#### SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

The SPC is satisfactory from a preclinical viewpoint. The toxic effects to reproduction following adrenaline administration are well-known and are reflected adequately in Section 4.6 of the SPC. Minor amendments have been made to section 5.3 of the SPC during the decentralised procedure to attribute the teratogenic effects and fetal hypoxia to the relevant species.

#### PRE-CLINICAL EXPERT REPORT

The pre-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the pre-clinical aspects of the dossier.

#### OVERALL CONCLUSION ON THE PRE-CLINICAL PART

The applicant has provided an adequate review of the available pre-clinical data. There are no new pre-clinical data identified in the literature review that would change the benefit/risk analysis for epinephrine.

There are no objections to the grant of marketing authorisations from a pre-clinical point of view.

### III.3 CLINICAL ASPECTS

**Pharmacokinetics and pharmacodynamics**

No new data have been submitted and none are required for applications of this type. The pharmacology of adrenaline is well-described in the literature.

**Clinical efficacy**

The applicant reviewed studies discussing patients requiring more than one dose. 16% to 50% required greater than one adrenaline injection, and the relative number of patients requiring multiple adrenaline injection was linearly related to the severity classification and was found to increase significantly with increased symptoms severity. This relationship indicates that a greater amount of adrenaline for a longer period is required to reverse reactions of a greater severity.
In order to justify the product intended for marketing that includes two doses in one device, the clinical expert discusses the classification of the time-course of anaphylaxis, uniphasic, protracted or biphasic. Biphasic refers to a recurrence after the initial symptoms had completely subsided and in the absence of further exposure to the triggering agent.

An observation period is recommended for all patients because the reaction might fail to improve or worsen as the effect of adrenaline wears off (protracted anaphylaxis) and because of the risks of a biphasic reaction. Patients should always seek medical help, as reported intervals from initial treatment to recurrence range from 1 to 72 hours. Retrospective studies report biphasic reaction rates of 4% to 20%.

The recommended interval between the two doses is also discussed, with the suggestion that 5-10 to 15-20 minutes is the average interval.

The efficacy of intramuscular adrenaline in the treatment of acute anaphylaxis is well-recognised. Patients with known allergies are taught on self-administration of adrenaline intramuscular preparations in cases of emergencies in the community. Current resuscitation guidelines recommend that a second dose should be administered after 5 minutes, if no improvement or symptoms worsen.

Clinical safety
Administered systemically by any route, adrenaline commonly causes pharmacological adverse effects, such as anxiety, fear, restlessness, headache, pallor, tremor, dizziness or palpitations. Individuals who are particularly prone to adrenaline adverse events include patients with pre-existing cardiovascular disease, cocaine users, and patients with untreated hyperthyroidism. Adrenaline can precipitate hypertension and cardiac dysrhythmias, but such adverse events are more likely to be observed in adults with cardiovascular disease. However, in life-threatening situations, administration of adrenaline without any delay is critical and failure to use adrenaline promptly is more dangerous than its improper use.

After first-aid treatment with adrenaline injection, patients should be transported to the nearest hospital. Additional doses of adrenaline, as well as oxygen, H1-antihistamines, glucocorticoids and other interventions may be required.

The advantages of having two doses of adrenaline readily available in one device are quite clear. Allergic patients at risk of anaphylactic reactions, who have been prescribed adrenaline auto-injection devices, are always advised to have two doses available at all times. With the proposed formulation, the patients only need to carry one syringe with them, eliminating the need to have two separate devices.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL) and labelling
The SPC, PIL and labelling are medically satisfactory.
Clinical Expert Report
The clinical expert report is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

MAA Forms
The MAA Forms are medically satisfactory.

Pharmacovigilance System and Risk Management Plan
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Adrenaline is the treatment of choice for anaphylaxis. Twinject is a novel adrenaline autoinjector for the emergency treatment of anaphylaxis which contains two autoinjectable doses of adrenaline. The risk management plan mainly deals with the safety issues arising from the autoinjector as the safety profile of adrenaline is well-characterised.

Clinical Conclusion
The grant of Marketing Authorisations is recommended.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Twinject 0.15mg/0.15ml and 0.30mg/0.30ml Solution for Injection are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRE-CLINICAL
No new pre-clinical studies have been conducted in support of these applications, which is acceptable as the pharmacology, pharmacokinetics and toxicology of adrenaline is well-known. The non-clinical overview comprises a satisfactory review of the relevant literature.

EFFICACY
No new efficacy data have been submitted and none are required for applications of this type.

No new safety data have been submitted or required for this well-established use application. Adrenaline has a well-established side-effect profile and has been used extensively in the treatment of acute allergic reactions. The benefits of the availability of two doses of adrenaline in one device have been clearly discussed.

The SPC, PIL and labelling are satisfactory.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable, and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with adrenaline is considered to have demonstrated the therapeutic value of the compound and a clear argument has been presented for a two-dose device. The benefit-risk is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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