SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

SOMAVERT 30 mg powder and solvent for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 30 mg of pegvisomant.

After reconstitution, 1 ml of solution contains 30 mg of pegvisomant.*

Excipient with known effect

The 30 mg strength of the medicinal product contains 0.6 mg of sodium per vial of powder.

*produced in *Escherichia coli* cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for solution for injection (powder for injection).

The powder is white to slightly off-white.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of adult patients with acromegaly who have had an inadequate response to surgery and/or radiation therapy and in whom an appropriate medical treatment with somatostatin analogues did not normalise IGF-I concentrations or was not tolerated.

4.2 Posology and method of administration

Treatment should be initiated under the supervision of a physician experienced in the treatment of acromegaly.

Posology

A loading dose of 80 mg pegvisomant should be administered subcutaneously under medical supervision. Following this, SOMAVERT 10 mg reconstituted in 1 ml of solvent should be administered once daily as a subcutaneous injection.

Dose adjustments should be based on serum IGF-I levels. Serum IGF-I concentrations should be measured every four to six weeks and appropriate dose adjustments made in increments of 5 mg/day in order to maintain the serum IGF-I concentration within the age-adjusted normal range and to maintain an optimal therapeutic response.

Assessment of baseline levels of liver enzymes prior to initiation of SOMAVERT

Prior to the start of SOMAVERT, patients should have an assessment of baseline levels of liver tests (LTs) [serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum total bilirubin (TBIL), and alkaline phosphatase (ALP)]. For recommendations regarding initiation of SOMAVERT based on baseline LTs and recommendations for monitoring of LTs while on SOMAVERT, refer to Table A in *Special warnings and precautions for use (4.4).*

The maximum dose should not exceed 30 mg/day.

For the different dose regimens, the following strengths are available: SOMAVERT 10 mg, SOMAVERT 15 mg, SOMAVERT 20 mg, SOMAVERT 25 mg and SOMAVERT 30 mg.

Paediatric population

The safety and efficacy of SOMAVERT in children aged 0 to 17 years have not been established. No data are available.

Elderly

No dose adjustment is required.

Hepatic or renal impairment

The safety and efficacy of SOMAVERT in patients with renal or hepatic insufficiency has not been established.

Method of administration

Pegvisomant should be administered by subcutaneous injection.

The site of injection should be rotated daily to help prevent lipohypertrophy.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Growth hormone-secreting tumours

As growth hormone-secreting pituitary tumours may sometimes expand, causing serious complications (e.g. visual field defects), it is essential that all patients be carefully monitored. If evidence of tumour expansion appears, alternative procedures may be advisable.

Serum IGF-1 monitoring

Pegvisomant is a potent antagonist of growth hormone action. A growth hormone deficient state may result from administration of this medicinal product, despite the presence of elevated serum growth hormone levels. Serum IGF-I concentrations should be monitored and maintained within the age-adjusted normal range by adjustment of the pegvisomant dose.

ALT or AST elevations

Prior to the start of SOMAVERT, patients should have an assessment of baseline levels of liver tests [serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum total bilirubin (TBIL), and alkaline phosphatase (ALP)].
Evidence of obstructive biliary tract disease should be ruled out in patients with elevations of ALT and AST or in patients with a prior history of treatment with any somatostatin analogue. Administration of pegvisomant should be discontinued if signs of liver disease persist.
For recommendations regarding initiation of SOMAVERT, based on baseline liver tests (LTs) and recommendations for monitoring of liver tests while on SOMAVERT, refer to Table A.

Table A: Recommendations for initiation of SOMAVERT treatment based on baseline LTs and for periodic monitoring of LTs during SOMAVERT treatment

Baseline LT Levels	Recommendations
Normal	• May treat with SOMAVERT. • Serum concentrations of ALT and AST should be monitored at 4- to 6-week intervals for the first 6 months of treatment with SOMAVERT, or at any time in patients exhibiting symptoms suggestive of hepatitis.
Elevated, but less than or equal to 3 times ULN	• May treat with SOMAVERT; however, monitor LTs monthly for at least 1 year after initiation of therapy and then bi-annually for the next year.
Greater than 3 times ULN	• Do not treat with SOMAVERT until a comprehensive workup establishes the cause of the patient's liver dysfunction. • Determine if cholelithiasis or choledocholithiasis is present, particularly in patients with a history of prior therapy with somatostatin analogs. • Based on the workup, consider initiation of therapy with SOMAVERT. • If the decision is to treat, LTs and clinical symptoms should be monitored very closely.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate transaminase; LT = liver test; ULN = upper limit of normal.

If a patient develops LT elevations, or any other signs or symptoms of liver dysfunction while receiving SOMAVERT, the following patient management is recommended (Table B).

Table B. Clinical recommendations based on abnormal liver test results while on SOMAVERT

LT Levels and Clinical Signs/Symptoms	Recommendations
Elevated, but less than or equal to 3 times ULN	• May continue therapy with SOMAVERT. However, monitor LTs monthly to determine if further increases occur.
Greater than 3 but less than 5 times ULN (without signs/symptoms of hepatitis or other liver injury, or increase in serum TBIL)	• May continue therapy with SOMAVERT. However, monitor LTs weekly to determine if further increases occur (see below). • Perform a comprehensive hepatic workup to discern if an alternative cause of liver dysfunction is present.
At least 5 times ULN, or transaminase elevations at least 3 times ULN associated with any increase in serum TBIL (with or without signs/symptoms of hepatitis or other liver injury)	• Discontinue SOMAVERT immediately. • Perform a comprehensive hepatic workup, including serial LTs, to determine if and when serum levels return to normal. • If LTs normalise (regardless of whether an alternative cause of the liver dysfunction is discovered), consider cautious reinitiation of therapy with SOMAVERT, with frequent LT monitoring.
Signs or symptoms suggestive of hepatitis or other liver injury (e.g., jaundice, bilirubinuria, fatigue, nausea, vomiting, right upper quadrant pain, ascites, unexplained oedema, easy bruisability)	• Immediately perform a comprehensive hepatic workup. • If liver injury is confirmed, the drug should be discontinued.

Hypoglycaemia

The study conducted with pegvisomant in diabetic patients treated either by insulin or by oral hypoglycaemic medicinal products revealed the risk of hypoglycaemia in this population. Therefore, in acromegalic patients with diabetes mellitus, doses of insulin or hypoglycaemic medicinal products may need to be decreased (see section 4.5).

Improved fertility

The therapeutic benefits of a reduction in IGF-I concentration which results in improvement of the patient's clinical condition could potentially also improve fertility in female patients (see section 4.6).

Pregnancy

Acromegaly control may improve during pregnancy. Pegvisomant is not recommended during pregnancy (see section 4.6). If pegvisomant is used during pregnancy, IGF-I levels should be closely monitored and pegvisomant doses may need to be adjusted (see section 4.2) based on IGF-I values.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per dose. Patients on low sodium diets can be informed that this medicinal product is essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. It should be considered whether to continue treatment with somatostatin analogues. The use of this medicine in combination with other medicinal products for the treatment of acromegaly has not been extensively investigated.

Patients receiving insulin or oral hypoglycaemic medicinal products may require dose reduction of these active substances due to the effect of pegvisomant on insulin sensitivity (see section 4.4).

Pegvisomant has significant structural similarity to growth hormone which causes it to cross-react in commercially available growth hormone assays. Since serum concentrations of therapeutically-effective doses of this medicine are generally 100 to 1000 times higher than the actual serum growth hormone concentrations seen in acromegalics, measurements of serum growth hormone concentrations will be spuriously reported in commercially available growth hormone assays. Pegvisomant treatment should therefore not be monitored or adjusted based on serum growth hormone concentrations reported from these assays.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited amount of data from the use of pegvisomant in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).

SOMAVERT is not recommended during pregnancy and in women of childbearing potential not using contraception.

If pegvisomant is used during pregnancy, IGF-I levels should be closely monitored, especially during the first trimester. It may be necessary to adjust the dose of pegvisomant during pregnancy (see section 4.4).

Breast-feeding

The excretion of pegvisomant in breast milk has not been studied in animals. Clinical data are too limited (one reported case) to draw any conclusion on the excretion of pegvisomant in human breast milk. Therefore, pegvisomant should not be used in breast-feeding women. However, breast-feeding may be continued if this medicine is discontinued: this decision should take into account the benefit of pegvisomant therapy to the mother and the benefit of breast-feeding to the child.

Fertility

For pegvisomant no data on fertility are available.

The therapeutic benefits of a reduction in IGF-I concentration which results in improvement of the patient's clinical condition could potentially also improve fertility in female patients.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Summary of the safety profile

The list below contains adverse reactions seen in clinical trials with SOMAVERT.

In clinical studies, for patients treated with pegvisomant (n=550), the majority of adverse reactions to pegvisomant were of mild to moderate intensity, of limited duration and did not require discontinuation of treatment.

The most commonly reported adverse reactions occurring in ≥ 10% of patients with acromegaly treated with pegvisomant during the clinical trials were headache 25%, arthralgia 16% and diarrhoea 13%.

Tabulated list of adverse reactions

The list below contains adverse reactions seen in clinical trials or that were spontaneously reported, classified by system organ class and frequency.

Adverse reactions are listed according to the following categories:
Very common: ≥1/10
Common: ≥1/100 to <1/10
Uncommon: ≥1/1,000 to <1/100
Not known (cannot be estimated from the available data)

System Organ Class	**Very Common (≥1/10)**	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1,000 to < 1/100)**	**Frequency Not Known (Cannot Be Estimated From Available Data)**
Blood and lymphatic system disorders			thrombocytopenia, leukopenia, leukocytosis, haemorrhagic diathesis	
Immune system disorders			hypersensitivity reactions[b]	anaphylactic reaction[b], anaphylactoid reaction[b]
Metabolism and nutrition disorders		hypercholesterolaemia, hyperglycaemia, hypoglycaemia, weight increased	hypertriglyceridemia	
Psychiatric disorders		abnormal dreams	panic attack, short term memory loss, apathy, confusion, sleep disorder, libido increased	anger
Nervous system disorders	headache	somnolence, tremor, dizziness, hypoaesthesia	narcolepsy, migraine, dysgeusia	
Eye disorders		eye pain	asthenopia	
Ear and labyrinth disorders			Meniere's disease	
Cardiac disorders		oedema peripheral		
Vascular disorders		hypertension		
Respiratory, thoracic and mediastinal disorders		dyspnoea		laryngospasm[b]
Gastrointestinal disorders	diarrhoea	vomiting, constipation, nausea, abdominal distension, dyspepsia, flatulence	haemorrhoids, salivary hypersecretion, dry mouth, tooth disorder	
Hepatobiliary disorders		abnormal liver function tests (e.g.		

System Organ Class	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to < 1/100)	Frequency Not Known (Cannot Be Estimated From Available Data)
		transaminase elevation) (see section 4.4)		
Skin and subcutaneous tissue disorders		hyperhidrosis, contusion, pruritus[b], rash[b]	face oedema, dry skin, increased tendency to bruise, night sweats, erythema[b], urticaria[b]	angioedema[b]
Musculoskeletal and connective tissue disorders	arthralgia	myalgia, arthritis		
Renal and urinary disorders		haematuria	proteinuria, polyuria, renal impairment	
General disorders and administration site conditions		injection site reaction (including injection site hypersensitivity), injection site bruising or bleeding, injection site hypertrophy (e.g. lipohypertrophy)[a], influenza-like illness, fatigue, asthenia, pyrexia	feeling abnormal, impaired healing, hunger	

[a] see Description of selected adverse reactions below

[b] ADR related to hypersensitivity reaction

Description of selected adverse reactions

Most injection site reactions characterised as localised erythemas and soreness, spontaneously resolved with local symptomatic treatment, while pegvisomant therapy continued. Occurrence of injection site hypertrophy has been observed, including lipohypertrophy.

The development of isolated low-titre anti-growth hormone antibodies was observed in 16.9% of patients treated with pegvisomant. The clinical significance of these antibodies is unknown.

Systemic hypersensitivity reactions including anaphylactic/anaphylactoid reactions, laryngospasm, angioedema, generalized skin reactions (rash, erythema, pruritus, urticaria) have been reported in post marketing use. Some patients required hospitalization. Upon re-administration, symptoms did not re-occur in all patients.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple
App Store.

4.9 Overdose

There is limited experience of overdose with pegvisomant. In the one reported incident of acute overdose, where 80 mg/day was administered for 7 days, the patient experienced a slight increase in fatigue and dry mouth. In the week following discontinuation of treatment the adverse reactions noted were: insomnia, increased fatigue, oedema peripheral, tremor, and weight gain. Two weeks after stopping treatment, leukocytosis and moderate bleeding from injection and vein puncture sites was observed which were considered possibly related to pegvisomant.

In cases of overdose, administration of this medicine should be discontinued and not resumed until IGF-I levels return to within or above the normal range.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other anterior pituitary lobe hormones and analogues, ATC code: H01AX01.

Mechanism of action

Pegvisomant is an analogue of human growth hormone that has been genetically modified to be a growth hormone receptor antagonist. Pegvisomant binds to growth hormone receptors on cell surfaces, where it blocks growth hormone binding, and thus interferes with intracellular growth hormone signal transduction. Pegvisomant is highly selective for the GH receptor, and does not cross-react with other cytokine receptors, including prolactin.

Pharmacodynamic effects

Inhibition of growth hormone action with pegvisomant leads to decreased serum concentrations of insulin-like growth factor-I (IGF-I), as well as other growth

hormone-responsive serum proteins such as free IGF-I, the acid-labile subunit of IGF-I (ALS), and insulin-like growth factor binding protein-3 (IGFBP-3).

Clinical efficacy and safety

Acromegalic patients (n=112) have been treated in a 12-week, randomised, double-blind, multicentre study comparing placebo and pegvisomant. Dose-dependent, statistically significant reductions in mean IGF-I ($p<0.0001$), free IGF-I ($p<0.05$), IGFBP-3 ($p<0.05$) and ALS ($p<0.05$) were observed at all post-baseline visits in the pegvisomant treatment groups. The serum IGF-1 was normalised at the end of the study (week 12) in 9.7%, 38.5%, 75% and 82% of subjects treated with placebo, 10 mg/day, 15 mg/day or 20 mg/day pegvisomant respectively.

Statistically significant differences from placebo ($p<0.05$) were observed for improvements in the total signs and symptoms score for all dose groups compared to placebo.

A cohort of 38 acromegalic subjects has been followed in a long-term, open-label, dose-titration study for at least 12 consecutive months of daily dosing with pegvisomant (mean = 55 weeks). The mean IGF-I concentration in this cohort fell from 917 ng/ml to 299 ng/ml on pegvisomant, with 92% achieving a normal (age-adjusted) IGF-I concentration.

In different studies and also in Acrostudy, pegvisomant normalised IGF-1 levels in a high percentage of patients (>70%) and significantly decreased fasting plasma glucose (FPG) and fasting plasma insulin (FPI) levels.

Pegvisomant also improves insulin sensitivity, this is likely due to a blockade of the GH receptors on tissues, mainly the liver and also adipose tissue, kidneys, and skeletal muscles, thereby removing the detrimental effect of GH on insulin signaling, lipolysis, and gluconeogenesis. However, the mechanism of action of all these effects is not known with certainty. A decrease in doses of insulin or hypoglycaemic medicinal products may be needed in acromegalic patients with diabetes mellitus (see sections 4.4 and 4.5).

5.2 Pharmacokinetic properties

Absorption

Absorption of pegvisomant following subcutaneous administration is slow and prolonged, and peak serum pegvisomant concentrations are not generally attained until 33-77 hours after administration. The mean extent of absorption of a subcutaneous dose was 57% relative to an intravenous dose.

Distribution

The apparent volume of distribution of pegvisomant is relatively small (7-12 L).

Biotransformation

The metabolism of pegvisomant has not been studied.

Elimination

The mean total body systemic clearance of pegvisomant following multiple doses is estimated to be 28 ml/h for subcutaneous doses ranging from 10 to 20 mg/day. Renal clearance of pegvisomant is negligible and accounts for less than 1% of total body clearance. Pegvisomant is slowly eliminated from serum, with mean estimates of half-life generally ranging from 74 to 172 hours following either single or multiple-doses.

Linearity/non-linearity

After single subcutaneous pegvisomant administration no linearity is observed with rising doses of 10, 15 or 20 mg. Approximately linear pharmacokinetics is observed at steady state in the population pharmacokinetic studies. The data from 145 patients in two long-term studies who received daily doses of 10, 15, or 20 mg, demonstrate pegvisomant mean serum concentrations (± SD) of approximately 8800 ± 6300, 13200 ± 8000 and 15600 ± 10300 ng/ml, respectively.

The pharmacokinetics of pegvisomant are similar in normal healthy volunteers and acromegaly patients, although heavier individuals tend to have a higher total body clearance of pegvisomant than lighter individuals, and may thus require greater doses of pegvisomant.

5.3 Preclinical safety data

Non-clinical data revealed no special hazard for humans based on studies of repeated dose toxicity in rat and monkey. However, due to the marked pharmacological response in monkey, systemic exposures higher than those achieved in patients at therapeutic doses have not been studied.

Malignant fibrous histiocytomas associated with fibrosis and histiocytic inflammation were observed at injection sites in males in the rat carcinogenicity study at exposure levels equivalent to three times the human exposure based on mean plasma concentrations in two long-term studies at a daily dose of 30 mg. The relevance of this response for humans is currently unknown. The increased incidence of injection site tumours was most probably caused by irritation and the high sensitivity of the rat to repeated subcutaneous injections.

Early embryonic development and embryo-foetal development studies were conducted in pregnant rabbits with pegvisomant at subcutaneous doses of 1, 3, and 10 mg/kg/day. There was no evidence of teratogenic effects associated with pegvisomant administration during organogenesis. At 10 mg/kg/day (6 times the maximum human therapeutic dose based on body surface area), an increase in post-implantation loss was observed in both studies. No fertility study has been conducted.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:

Glycine

Mannitol (E421)

Disodium phosphate anhydrous

Sodium dihydrogen phosphate monohydrate

Solvent:

Water for Injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years.

After reconstitution, the product should be used immediately.

6.4 Special precautions for storage

Store the powder vial(s) in a refrigerator (2°C – 8°C). Do not freeze. Keep the vial(s) in their carton(s) in order to protect from light.

The carton(s) containing the SOMAVERT powder vial(s) may be stored at room temperature up to a maximum of 25°C for a single period of up to 30 days. The Use by date should be written on the carton (up to 30 days from the date removed from the refrigerator). The vial(s) must be protected from light and should not be placed back into the refrigerator. The SOMAVERT powder vial(s) must be discarded if not used within the 30 days of room temperature storage or the expiry date printed on the carton, whichever is earlier.

Store the pre-filled syringe(s) below 30°C or store in a refrigerator (2ºC - 8°C). Do not freeze.

After reconstitution:

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

30 mg of pegvisomant in powder in a vial (type I flint glass) with a stopper (chlorobutyl rubber) and 1 ml solvent (water for injections) in a pre-filled syringe (typeI borosilicate glass) with a plunger stopper (bromobutyl rubber) and a tip cap (bromobutyl rubber). The colour of the protective plastic cap is specific to the strength of the product.

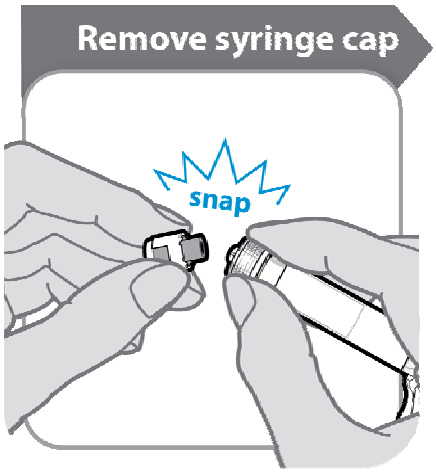
Pack sizes of 1 and 30 vial(s), pre-filled syringe(s) and safety needle(s).

Not all pack sizes may be marketed.

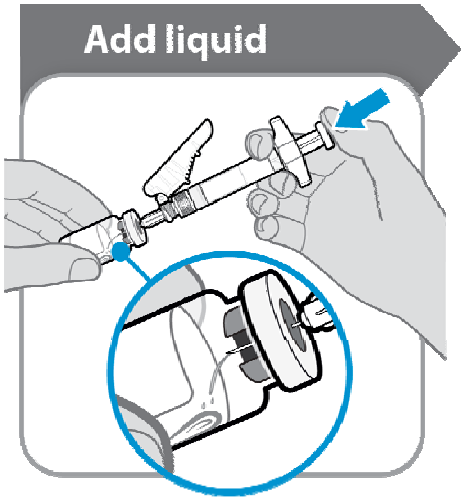
6.6 Special precautions for disposal

The syringe and safety needle used to administer the injection are provided with the medicinal product.

Before attaching the supplied safety needle the syringe cap will need to be removed from the pre-filled syringe. This is achieved by snapping it off. The syringe should be kept upright to avoid leakage and the end of the syringe should not be allowed to contact anything.



The powder should be reconstituted with 1 ml solvent. When adding the solvent from the syringe the vial and syringe should be held at an angle as shown in the diagram below.

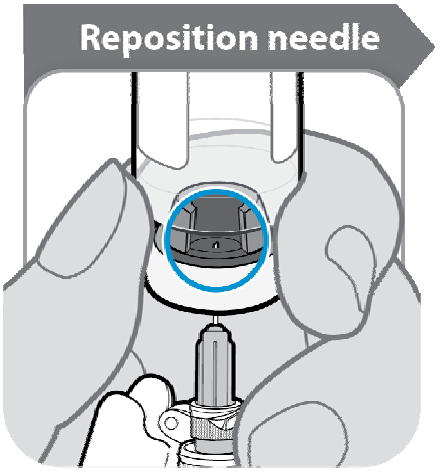


Add the solvent to the vial of powder. The solvent should be emptied into the vial slowly to avoid the possibility of a foam forming. This would make the medicine unusable. Gently dissolve the powder with a slow, swirling motion. Do not shake vigorously, as this might cause denaturation of the active substance.

After reconstitution, the reconstituted solution should be inspected visually for extraneous (or for any foreign) particulate matter or any variation in physical

appearance prior to administration. In the event of either being observed, discard the medicinal product.

Before withdrawing the dissolved SOMAVERT invert the vial with the syringe still inserted into it and ensure the gap in the stopper can be seen as shown in the diagram below:



Pull the needle down so that the needle tip is at its lowest point in the liquid. Slowly withdraw the plunger in the syringe to withdraw the medicine from the vial. If air is seen in the syringe, tap the barrel to float the bubbles to the top, and then gently push the bubbles out into the vial.

Before disposing of the syringe and needle fold the needle guard over the needle and ensure it clicks into place. The syringe and needle should never be reused.

For single use only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Pfizer Limited
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CT13 9NJ
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8 MARKETING AUTHORISATION NUMBER(S)

PLGB 00057/1639

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/01/2021

10 DATE OF REVISION OF THE TEXT

21/09/2022