ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Oczyesa 20 mg prolonged-release solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled pen of 1 mL contains octreotide hydrochloride equivalent to 20 mg octreotide.

Excipients with known effect

Oczyesa contains 63 mg of alcohol (ethanol) in each dose unit, which is equivalent to 63 mg/1 mL (6.5% w/w), and 408 mg soybean phosphatidylcholine.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release solution for injection.
Yellowish to yellow clear liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Oczyesa is indicated for maintenance treatment in adult patients with acromegaly who have responded to and tolerated treatment with somatostatin analogues.

4.2 Posology and method of administration

Posology

The recommended dose is 20 mg octreotide every 4 weeks administered by a single subcutaneous injection.

For patients transitioning from octreotide or lanreotide, patients should be instructed to take their first dose of Oczyesa at the end of the daily or monthly dosing interval of the previous treatment.

Oczyesa may be administered up to 1 week before or 1 week after the scheduled 4-week dose in exceptional circumstances (e.g. missed dose, non-adherence to treatment, etc.).

Monitoring of insulin-like growth factor-1 (IGF-1) levels and assessment of symptoms should be made periodically as per the clinician's discretion. Discontinuation of Oczyesa and switching patients to another somatostatin analogue should be considered if IGF-1 levels are not maintained after treatment with dose of 20 mg monthly or the patient cannot tolerate treatment with Oczyesa.

Missed dose
If a dose is missed, the next dose of Oczyesa should be administered as soon as possible.

Special populations

Elderly
No dose adjustment is required for elderly patients.

Hepatic impairment
In patients with liver cirrhosis, the half-life of the medicinal product may be increased. Monitoring of liver function in these patients is recommended (see section 5.2).

Renal impairment
Oczyesa can be used in patients with mild, moderate, or severe renal impairment. Clinical response and tolerability should be monitored (see section 5.2).

Paediatric population

The safety and efficacy of octreotide in children below 18 years of age have not been established. No data are available.

Method of administration

Subcutaneous use.

Prior to initiation of Oczyesa, patients should be trained on proper injection technique. For complete administration instructions with illustrations, see the instructions for use at the end of the package leaflet.

Oczyesa should be injected subcutaneously in the abdomen, thigh or buttock.

Patients should be instructed to rotate the injection site within or between injection areas.

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

Tumour expansion

As growth hormone (GH)-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.

Women of childbearing potential

The therapeutic benefits of a reduction in GH levels and normalisation of IGF-1 concentration in female acromegalic patients could potentially restore fertility. Female patients of childbearing potential should be advised to use adequate contraception if necessary during treatment with octreotide (see section 4.6).

Thyroid function

Thyroid function should be monitored in patients receiving prolonged treatment with octreotide.

Hepatic function

Hepatic function should be monitored during octreotide therapy.

Cardiovascular-related events

Common cases of bradycardia have been reported (see section 4.8). Dose adjustment of medicinal products such as beta blockers, calcium channel blockers, or agents to control fluid and electrolyte balance, may be necessary (see section 4.5).

Gallbladder-related events

Cholelithiasis has been reported during treatment with octreotide and may be associated with cholecystitis and biliary duct dilatation (see section 4.8). Additionally, cases of cholangitis have been reported as a complication of cholelithiasis in patients receiving octreotide injections in the post-marketing setting.

Ultrasonic examination of the gallbladder before, and at about 6- to 12-month intervals during octreotide therapy is recommended.

Glucose metabolism

Because of its inhibitory action on GH, glucagon, and insulin, octreotide may affect glucose regulation. Post-prandial glucose tolerance may be impaired. As reported for patients treated with subcutaneous octreotide, in some instances, the state of persistent hyperglycaemia may be induced as a result of chronic administration (see section 4.8). Hypoglycaemia has also been reported (see section 4.8).

Insulin requirements of patients with Type 1 diabetes mellitus therapy may be reduced by administration of octreotide. In non-diabetics and Type 2 diabetics with partially intact insulin reserves, octreotide administration can result in postprandial increases in glycaemia. It is therefore recommended to monitor glucose tolerance and antidiabetic treatment (see section 4.8).

Nutrition

Octreotide may alter absorption of dietary fats in some patients.
Depressed vitamin B12 levels and abnormal Schilling's tests have been observed in some patients receiving octreotide therapy. Monitoring of vitamin B12 levels is recommended during therapy with Oczyesa in patients who have a history of vitamin B12 deprivation.

4.5 Interaction with other medicinal products and other forms of interaction

Cardiovascular medicinal products

Dose adjustment of medicinal products that have bradycardic effects, such as beta blockers, calcium channel blockers, or agents to control fluid and electrolyte balance, may be necessary when Oczyesa is administered concomitantly (see section 4.4).

Insulin and antidiabetic medicinal products

Dose adjustments of insulin and antidiabetic medicinal products may be required when octreotide is administered concomitantly (see section 4.4).

Bromocriptine

Concomitant administration of octreotide and bromocriptine increases the bioavailability of bromocriptine.

Ciclosporin and cimetidine

Octreotide injections have been found to reduce the intestinal absorption of ciclosporin and to delay that of cimetidine.

Thyroid hormones replacement therapy

Octreotide may affect thyroid function (see sections 4.4 and 4.5). Therefore, regular monitoring of thyroid function and clinical monitoring is recommended during concomitant treatment with thyroid hormone replacement therapy as this may lead to thyroid imbalance.

Effects on metabolism of other medicinal products

Limited published data indicate that somatostatin analogues might decrease the metabolic clearance of compounds known to be metabolised by cytochrome P450 enzymes, which may be due to the suppression of GH. Since it cannot be excluded that octreotide may have this effect, other medicinal products mainly metabolised by CYP3A4 and which have a low therapeutic index should therefore be used with caution (e.g. quinidine, terfenadine).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Female patients of childbearing potential should be advised to use adequate contraception, if necessary, during treatment with octreotide (see section 4.4).

Pregnancy

There are limited amount of data (less than 300 pregnancy outcomes) from the use of octreotide in pregnant women, and in approximately one third of the cases the pregnancy outcomes are unknown. The majority of reports were received after post-marketing use of octreotide and more than 50% of exposed pregnancies were reported in patients with acromegaly. Most women were exposed to octreotide during the first trimester of pregnancy at doses ranging from 100-1 200 micrograms/day of subcutaneous short-acting octreotide or 10-40 mg/month of intramuscular long-acting octreotide. Congenital anomalies were reported in about 4% of pregnancy cases for which the outcome is known. No causal relationship to octreotide is suspected for these cases.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of Oczyesa during pregnancy (see section 4.4).

Breast-feeding

It is unknown whether octreotide is excreted in human milk. Animal studies have shown excretion of octreotide in breast milk. Patients should not breast-feed during Oczyesa treatment.

Fertility

It is not known whether octreotide has an effect on human fertility. Late descent of the testes was found for male offsprings of dams treated during pregnancy and lactation. Octreotide, however, did not impair fertility in male and female rats at doses of up to 1 mg/kg body weight per day (see section 5.3).

4.7 Effects on ability to drive and use machines

Octreotide has no or negligible influence on the ability to drive and use machines. Patients should be advised to be cautious when driving or using machines if they experience dizziness, asthenia/fatigue, or headache during treatment with Oczyesa (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The most frequent adverse reactions reported during octreotide therapy include gastrointestinal disorders, nervous system disorders, hepatobiliary disorders, and metabolism and nutritional disorders.

The most commonly reported adverse reactions in clinical studies with other formulations of octreotide were diarrhoea, abdominal pain, nausea, flatulence, headache, cholelithiasis, hyperglycaemia and constipation. Other commonly reported adverse reactions were dizziness, localised pain, biliary sludge, thyroid dysfunction (e.g. decreased thyroid stimulating hormone [TSH], decreased total T4, and decreased free T4), loose stools, impaired glucose tolerance, vomiting, asthenia, and hypoglycaemia.

Tabulated list of adverse reactions

The following adverse reactions, listed in Table 1, have been accumulated from clinical studies and post-marketing safety experience with octreotide.

Adverse reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000) very rare (< 1/10 000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Table 1: Tabulated list of adverse reactions

System organ class	Very common	Common	Uncommon	Frequency not known
Neoplasms benign, malignant and unspecified (including cysts and polyps)			Haemangioma of liver	
Blood and lymphatic system disorders				Thrombocytopenia[a]
Immune system disorders				Anaphylaxis[a], Hypersensitivity[a]
Endocrine disorders		Hypothyroidism[a] Thyroid disorder (e.g. decreased TSH, decreased total T4, and decreased free T4) [a]		
Metabolism and nutrition disorders	Hyperglycaemia[a]	Hypoglycaemia[a] Glucose tolerance impaired[a] Anorexia[a]	Dehydration[a]	
Nervous system disorders	Headache[a]	Dizziness[a]		
Cardiac disorders		Bradycardia[a]	Tachycardia[a]	
Respiratory, thoracic and		Dyspnoea[a]		

System organ class	Very common	Common	Uncommon	Frequency not known
mediastinal disorders				
Gastrointestinal disorders	Abdominal pain[a] Constipation[a] Flatulence[a] Nausea[a] Diarrhoea[a]	Abdominal distension[a] Dyspepsia[a] Vomiting[a] Steatorrhoea[a] Faeces discoloured[a]		
Hepatobiliary disorders	Cholelithiasis[a]	Cholecystitis Hyperbilirubinaemia[a]		Pancreatitis acute[a] Hepatitis acute[a] Cholestatic hepatitis[a], Cholestasis[a] Jaundice[a]
Skin and subcutaneous tissue disorders		Alopecia[a] Pruritus Rash[a]		Urticaria[a]
Musculoskeletal and connective tissue disorders		Arthralgia		
General disorders and administration site conditions	Injection site reactions[b]	Asthenia		
Investigations		Transaminases increased[a]		Increased alkaline phosphatase levels[a], Gamma-glutamyl transferase increased [a]

a The adverse reactions and frequencies were established based on data from other octreotide products.

b Injection site erythema, swelling, mass, pruritus, induration, pain, nodule, bruising, discomfort, rash, haematoma, oedema, paresthesia, dermatitis, haemorrhage, inflammation, extravasation and hypertrophy.

Description of selected adverse reactions

Gallbladder-related adverse reactions

Octreotide has been shown to inhibit gallbladder contractility and decrease bile secretion, which may lead to gallbladder abnormalities, and may result in complications. If gallstones do occur, they are usually asymptomatic. Symptomatic gallstones should be treated either by dissolution therapy with bile acids or by surgery.

In ACROINNOVA 1 (Study 1), chronic cholecystitis was reported by 1 patient (2.1%).
In ACROINNOVA 2 (Study 2), cholelithiasis was reported by 6 patients (4.4%), cholecystitis acute and cholecystitis were reported by 1 patient (0.7%) each.

Gastrointestinal disorders

In rare instances, gastrointestinal side effects may resemble acute intestinal obstruction, with progressive abdominal distension, severe epigastric pain, abdominal tenderness and guarding. The frequency of gastrointestinal adverse reactions is known to decrease over time with continued treatment with octreotide.

Hypersensitivity and anaphylactic reactions
Hypersensitivity and allergic reactions have been reported during post-marketing experience with octreotide. When these occur, they mostly affect the skin, rarely the mouth and airways. Isolated cases of anaphylactic shock have been reported.

Injection site reactions
Most injection site reactions were transient, and mild or moderate. None of these were severe. The most common injection site reactions were injection site erythema, injection site swelling, injection site pruritus, injection site induration, injection site pain, injection site nodule and injection site mass.

Metabolism and nutrition disorders
Although measured faecal fat excretion may increase, there is no evidence to date that long-term treatment with octreotide has led to nutritional deficiency due to malabsorption.

Cardiac disorders
Bradycardia is a common adverse reaction with somatostatin analogues. ECG changes such as QT prolongation, axis shifts, early repolarisation, low voltage, R/S transition, early R wave progression, and non-specific ST-T wave changes have been observed with octreotide. The relationship of these events to octreotide is not established because many of these patients have underlying cardiac diseases (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 national reporting system listed in Appendix V.

4.9 Overdose

A limited number of accidental overdoses of octreotide injections in adults and children have been reported. In adults, the doses ranged from 2 400-6 000 micrograms/day administered by continuous infusion (100-250 micrograms/hour) or subcutaneously (1 000 micrograms three times a day). The adverse events reported were arrhythmia, hypotension, cardiac arrest, brain hypoxia, pancreatitis, hepatic steatosis, diarrhoea, weakness, lethargy, weight loss, hepatomegaly, and lactic acidosis.

No unexpected adverse events have been reported in cancer patients receiving subcutaneous octreotide at doses of 3 000-30 000 micrograms/day in divided doses.

Paediatric population

In children, the doses ranged from 50-3 000 micrograms/day administered by continuous infusion (2.1-500 micrograms/hour) or subcutaneously (50-100 micrograms). The only adverse event reported was mild hyperglycaemia.

The management of overdose is symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Pituitary and hypothalamic hormones and analogues, somatostatin and analogues, ATC code: H01CB02

Mechanism of action

Octreotide is a synthetic octapeptide derivative of naturally occurring somatostatin with similar pharmacological effects, but with a considerably prolonged duration of action. It inhibits pathologically increased secretion of GH and of peptides and serotonin produced within the gastro-entero-pancreatic (GEP) endocrine system.

In animals, octreotide is a more potent inhibitor of GH, glucagon and insulin release than somatostatin is, with greater selectivity for GH and glucagon suppression.

In healthy subjects, octreotide has been shown to inhibit:
- release of GH stimulated by arginine, exercise- and insulin-induced hypoglycaemia,
- post-prandial release of insulin, glucagon, gastrin, other peptides of the GEP endocrine system, and arginine-stimulated release of insulin and glucagon,
- thyrotropin-releasing hormone (TRH)-stimulated release of thyroid-stimulating hormone (TSH).

Unlike somatostatin, octreotide inhibits GH secretion preferentially over insulin and its administration is not followed by rebound hypersecretion of hormones (i.e. GH in patients with acromegaly).

Pharmacodynamic effects

Octreotide substantially reduces and, in many cases, normalizes IGF-1 and GH levels in patients with acromegaly.

Single doses of octreotide given subcutaneously have been shown to inhibit gallbladder contractility and to decrease bile secretion in healthy volunteers. In clinical studies, the incidence of gallstone or biliary sludge formation was markedly increased (see sections 4.4 and 4.8).

Octreotide may cause clinically significant suppression of TSH (see sections 4.4 and 4.8).

Clinical efficacy and safety

The efficacy and safety of octreotide were established in two phase 3 studies in patients with acromegaly: a 24-week, randomised, double-blind, placebo-controlled, multi-centre study (study 1) and a 52-week, open-label, multi-centre study (study 2). Patients completing study 1 could roll over to study 2. Patients in both studies were on stable treatment with standard of care with injectable long-acting octreotide or lanreotide at time of enrolment.

Study 1
The study enrolled biochemically controlled patients who had IGF-1 levels below or equal to the upper limit of normal (ULN; mean of two measurements, adjusted for age and sex) at screening. Patients were randomised 2:1 to receive either octreotide or placebo for 24 weeks. At baseline, the mean age of patients was 55 years, 56% were women, and 96% were White.

The primary endpoint was the proportion of responders, i.e. patients with IGF-1 levels below or equal to the ULN at the end of the randomised, double-blind period (mean of the measurements at week 22 and week 24). Patients who discontinued treatment or were switched to rescue medication were regarded as non-responders in the analysis.

Study 1 met the primary endpoint of statistical superiority for octreotide over placebo (Table 2). Key secondary endpoints were also met, including the proportion of patients that were responders for both IGF-1 below or equal to ULN and GH below 2.5 mcg/L.

Table 2: Primary and key secondary efficacy endpoint outcomes

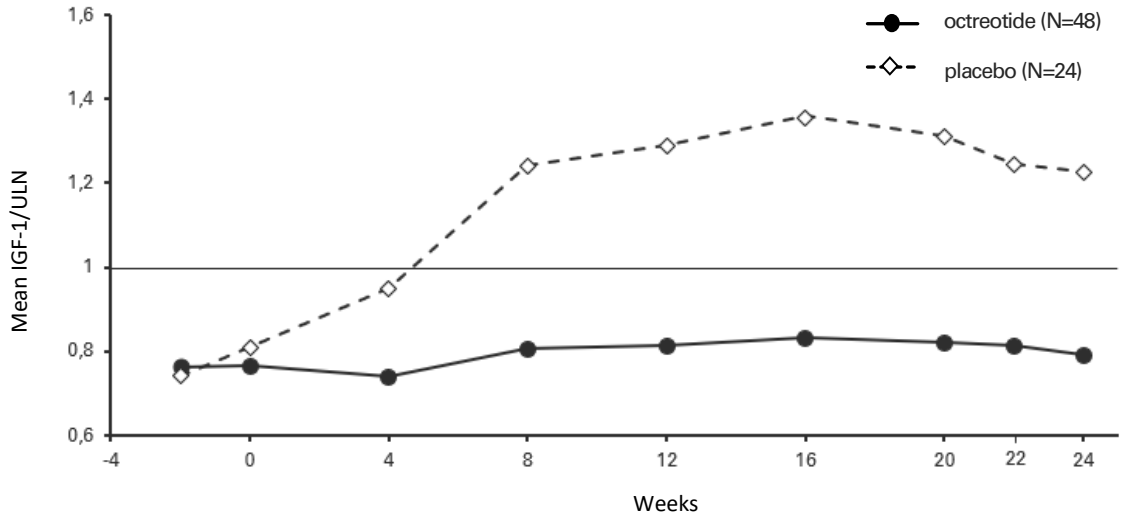
	octreotide responders (N= 48)	**placebo responders (N=24)**	**Difference in response rate for octreotide – placebo (95% CI)[a]**	**p-value**
Primary efficacy endpoint Proportion of patients with mean IGF-1 ≤ 1×ULN at week 22/24	72.2%	37.5%	34.6% (11.3-57.9)	0.0018
First key secondary efficacy endpoint Proportion of patients with mean IGF-1 ≤ 1×ULN at week 22/24, including patients with dose reduction[b]	72.2%	37.5%	34.6% (11.3-57.9)	0.0018
Second key secondary efficacy endpoint Proportion of patients with mean IGF-1 ≤ 1×ULN at week 22/24 and mean GH < 2.5 mcg/L at week 24	70.0%	37.5%	32.3% (8.8-55.7)	0.0035

a Mantel-Haenszel estimate of the common risk difference accounting previous treatment (long-acting octreotide or lanreotide) with 95% confidence intervals (CI) and upper-tail p-values.

b No patients required dose reduction in the study.

Mean IGF-1 levels were stable below the ULN in patients receiving octreotide and increased above ULN in the placebo arm (Figure 1).

Figure 1: Mean IGF-1/1×ULN over time



In an ANCOVA analysis of the change from baseline to the mean of week 22/24 in IGF-1/ULN, the LS Mean change from baseline was 0.04 in the octreotide arm and 0.52 in the placebo arm. The mean difference between the treatment arms (placebo) was -0.48 (95% CI: -0.75, -0.22). The p-value was 0.0003.

The median time to loss of IGF-1 response was not reached for patients receiving octreotide and was 8.4 weeks for patients in the placebo arm.

The proportions of patients with GH levels < 1.0 mcg/L at week 24 were assessed as secondary endpoint in study 1. The proportion of patients with mean GH < 1.0 mcg/L at Week 24 was 59.9% in

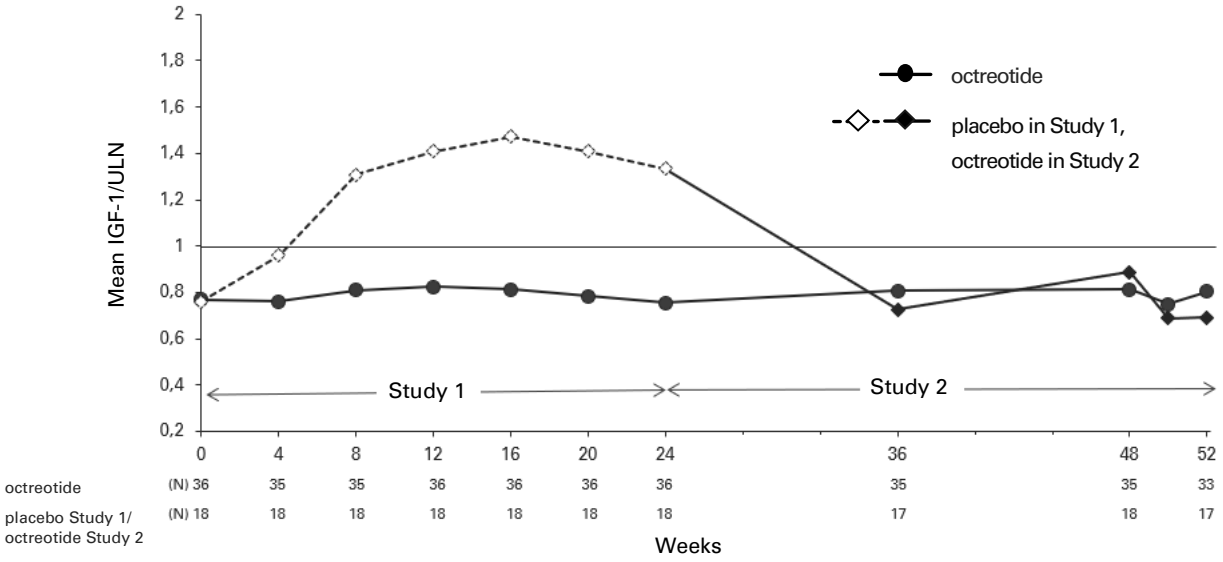
the octreotide arm and 37.5% in the placebo arm. The difference between the treatment arms (-placebo) was 21.3% (95% CI: -2.6%, 45.1%). The p-value was 0.0404.

Study 1 included several patient-reported outcomes, including the acromegaly quality of life questionnaire (AcroQoL) and treatment satisfaction questionnaire for medication (TSQM). The AcroQoL Total Score and TSQM convenience score increased from baseline (i.e. during treatment with long-acting octreotide or lanreotide) to week 24 in both treatment arms, with a larger increase in the octreotide arm than in the placebo arm; the differences between octreotide and placebo were not significant.

Study 2
Long-term safety and efficacy of octreotide were assessed in 135 patients with acromegaly enrolled in study 2. Fifty-four (54) patients were roll-over patients from Study 1 (36 randomized to octreotide and 18 to placebo) and 81 patients (both biochemically controlled and uncontrolled) were directly enrolled in Study 2.

For roll-over- patients who received octreotide in study 1, the mean IGF-1 values remained stable and below 1×ULN during 52 weeks of octreotide treatment. For roll-over patients who received placebo in study 1, IGF-1 values returned to normal after switching to treatment with octreotide in study 2 (Figure 2).

Figure 2: Mean IGF-1/ULN during long-term treatment for roll-over patients



N=number of patients with evaluable data at the certain visit.

Population analyses of efficacy data in Study 1 and Study 2
A population PKPD model describing the impact of octreotide on IGF-1 was developed. The structural model used model-based exposure of octreotide and was an indirect response model with medicinal product effects on the zero-order production rate constant. Medicinal product effects of octreotide were described as an inhibitory E_{max} function.

Simulations of the effect of octreotide on IGF-1 using the model showed a similar IGF-1 response for Oczyesa 20 mg given every 4 weeks compared to subcutaneous short-acting octreotide 0.25 mg given three times per day. Furthermore, comparable effects on IGF-1 concentrations over time were observed for dosing intervals ranging from 3 to 5 weeks.

5.2 Pharmacokinetic properties

Absorption

Bioavailability of octreotide for Oczyesa was 92-98% of that for subcutaneous short-acting octreotide, and 4-5 times higher than for intramuscular long-acting octreotide, without any initial lag-phase.

Maximum concentration of octreotide was reached in approximately 4 hours post dose. Thereafter, the octreotide concentration slowly decreased with a half-life of 9 to 12 days.

Comparable exposure was achieved with Oczyesa injected subcutaneously in the abdomen, thigh, or buttock.

Steady-state pharmacokinetics were achieved by the third injection of Oczyesa given every 4 weeks. Based on population pharmacokinetic modelling, the average octreotide concentration at steady state was 3.1 ng/mL, similar to subcutaneous short-acting octreotide given at a 0.25 mg dose injected 3-times daily (3.2 ng/mL), but with less daily variation.

Distribution

According to data obtained with subcutaneous short-acting octreotide injection, the volume of distribution is 0.27 L/kg. Plasma protein binding amounts to 65%. The amount of octreotide bound to blood cells is negligible.

Elimination

According to data obtained with subcutaneous short-acting octreotide injection, most of the peptide is eliminated via faeces, while approximately 32% of the dose is excreted unchanged in the urine.

The total body clearance is 160 mL/min.

Oczyesa exhibits absorption rate limited elimination of octreotide with an apparent terminal half-life of 217 to 279 hours (9 to 12 days).

Special populations

Elderly
No significant effect of age (ranging from 18-83 years) on octreotide pharmacokinetics was found with octreotide.

Renal impairment
No significant effect of creatinine clearance (CLCR) on clearance of octreotide was found analysing 191 study participants with normal renal function (CLCR ≥ 90 mL/min), 24 with mild renal impairment (CLCR 60-89 mL/min), and 1 subject with moderate renal impairment (CLCR 30-59 mL/min).

Impaired renal function did not affect the total exposure (AUC) with subcutaneous short-acting octreotide.

Hepatic impairment
The elimination capacity may be reduced in patients with liver cirrhosis, but not in patients with fatty liver disease.

5.3 Preclinical safety data

Acute and repeated dose toxicology, genotoxicity, carcinogenicity and reproductive toxicology studies of octreotide acetate in animals revealed no specific safety concerns for humans.

Reproduction studies of octreotide in animals revealed no evidence of teratogenic, embryo/foetal or other reproduction effects due to octreotide at parental doses of up to 1 mg/kg/day. Some retardation of the physiological growth was noted in the offspring of rats which was transient and attributable to GH inhibition brought about by excessive pharmacodynamic activity (see section 4.6).

No specific studies were conducted in juvenile rats. In the pre- and post-natal developmental studies, reduced growth and maturation was observed in the first filial generation (F1) offspring of dams given octreotide during the entire pregnancy and lactation period. Delayed descent of the testes was observed for male F1 offspring, but fertility of the affected F1 male pups remained normal. Thus, the above-mentioned observations were transient and considered to be the consequence of GH inhibition.

Carcinogenicity/chronic toxicity

No carcinogenicity studies have been conducted with octreotide hydrochloride. In rats receiving octreotide acetate at daily subcutaneous doses up to 1.25 mg/kg body weight, fibrosarcomas were observed, predominantly in a number of male animals, at the subcutaneous injection site after 52, 104 and 113/116 weeks. Local tumours also occurred in rats in the control group, however development of these tumours was attributed to disordered fibroplasia produced by sustained irritant effects at the injection sites, enhanced by the acidic lactic acid/mannitol vehicle. This non-specific tissue reaction appeared to be particular to rats. Neoplastic lesions were not observed either in mice receiving daily subcutaneous injections of octreotide at doses up to 2 mg/kg for 98 weeks, or in dogs treated with daily subcutaneous doses of octreotide for 52 weeks.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol dioleate
Soybean phosphatidylcholine
Ethanol anhydrous
Propylene glycol (E 1520)
Edetic acid
Ethanolamine

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

30 months

6.4 Special precautions for storage

Do not refrigerate.
Store in the original package in order to protect from oxygen and light.

6.5 Nature and contents of container

1 mL pre-filled pen supplied as single-dose, sterile, ready-to-use syringe (glass, Type I) with plunger stopper (fluoropolymer-coated bromobutyl rubber), a non-visible needle (22 gauge) and a protective cap with needle shield (synthetic rubber), fitted in an autoinjector.

The pre-filled pen is contained in a sealed aluminium pouch. The package contains a small white cylinder, included for storage purposes only.

Pack size of 1 single-dose pre-filled pen.

6.6 Special precautions for disposal and other handling

Instructions for use

For single use only (do not reuse the Oczyesa pre-filled pen).

Do not use if the Oczyesa pre-filled pen appears damaged.
Do not use if the packaging (carton and pouch) or the seal is damaged.
Do not use this medicine if you notice visible particles or if it is cloudy.

For full instructions for use please refer to the package leaflet.

Disposal

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

7. MARKETING AUTHORISATION HOLDER

Camurus AB
Rydbergs torg 4
SE-224 84 Lund
Sweden
medicalinfo@camurus.com

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1938/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Rechon Life Science AB
Soldattorpsvägen 5
SE- 216 13 Limhamn
Sweden

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR THE PRE-FILLED PEN

1. NAME OF THE MEDICINAL PRODUCT

Oczyesa 20 mg prolonged-release solution for injection in pre-filled pen
octreotide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen of 1 mL contains octreotide hydrochloride equivalent to 20 mg octreotide.

3. LIST OF EXCIPIENTS

Excipients: glycerol dioleate, soybean phosphatidylcholine, ethanol anhydrous, E1520, edetic acid, ethanolamine. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Prolonged-release solution for injection

1 pre-filled pen

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use
For single use only

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not refrigerate.
Store in the original package in order to protect from oxygen and 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

Camurus AB
Rydbergs torg 4
SE- 224 84 Lund
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1938/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Oczyesa 20 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

POUCH AND PRE-FILLED PEN

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

Oczyesa 20 mg prolonged-release solution for injection in pre-filled pen
octreotide
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

20 mg/1 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Oczyesa 20 mg prolonged-release solution for injection in pre-filled pen
octreotide

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

What is in this leaflet

1. What Oczyesa is and what it is used for

Oczyesa contains the active substance octreotide. Octreotide is a synthetic form of somatostatin, a natural substance found in the human body that controls the release of human growth hormone. Octreotide works in the same way as somatostatin, but its action lasts longer so it does not need to be taken so often.

Oczyesa is used for maintenance treatment in adults with acromegaly, a condition wherein the body produces too much growth hormone. It is used in patients in whom medicines like somatostatin have already been shown to be of benefit.

Normally, growth hormone regulates the growth of tissues, organs and bones. In people with acromegaly, increased production of growth hormone (usually from a non-cancerous tumour in the pituitary gland) leads to enlargement of bones and certain tissues, and symptoms such as headache, excessive sweating, numbness in the hands and feet, tiredness and joint pain. Treatment with Oczyesa can help relieve the symptoms.

2. What you need to know before you use Oczyesa

Do not use Oczyesa

- if you are allergic to octreotide or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor or pharmacist before using Oczyesa or during treatment if you have:
- **heart problems** since the medicine can affect the rate and regularity of your heartbeat.
- **gallbladder problems**, since prolonged use of Oczyesa can cause gallstones to form.
- **diabetes**, since Oczyesa may affect your blood sugar. Persistently increased blood sugar levels may occur during long-term use. Low blood sugar levels have also been reported. Therefore, your doctor may recommend monitoring your blood sugar levels and treatment of diabetes.

If you have Type 1 diabetes and you are being treated with insulin, your doses may need to be reduced during treatment with Oczyesa.
- ever had **lack of vitamin B12**. Since this medicine can decrease vitamin B12 levels in the blood, your doctor may wish to check your vitamin B12 level periodically during treatment with Oczyesa.

Monitoring during treatment

Tumours of the pituitary gland that produce excess growth hormone and lead to acromegaly sometimes expand, causing serious complications such as visual problems. It is essential that you are monitored for tumour growth while taking Oczyesa. If evidence of tumour expansion appears, your doctor may prescribe a different treatment.

Your doctor will regularly check your liver function during treatment and will also check your thyroid function if you are treated with Oczyesa over a long period of time.

Children and adolescents
Oczyesa is not recommended in children and adolescents below the age of 18. The safety and benefits of this medicine are not known in this age group.

Other medicines and Oczyesa
Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines.

Tell your doctor if you are taking any of the following medicines, since their activity or side effects may change when used together with Oczyesa. If you take these medicines, your doctor may need to adjust the doses of these medicines:
- medicines called beta blockers (e.g. atenolol, metoprolol) and calcium channel blockers (e.g. amlodipine, verapamil), used to treat high blood pressure or heart diseases;
- medicines to control your fluid and electrolyte balance;
- insulin or other medicines to treat diabetes;
- quinidine: a medicine to treat irregular heart rhythm;
- terfenadine: a medicine to treat allergic conditions;
- ciclosporin: a medicine to suppress transplant rejection, treat severe skin diseases, severe eye and joint inflammation.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

If you are pregnant, the use of Oczyesa should be avoided.

It is not known whether Oczyesa passes into breast milk. Do not breast-feed while using Oczyesa.

Women who can get pregnant should use effective contraception during treatment.

Driving and using machines
Oczyesa has no or negligible influence on the ability to drive and use machines. Avoid driving or using machines if your ability to react is reduced due to side effects such as dizziness, asthenia or headache.

Oczyesa contains alcohol
This medicine contains 63 mg of alcohol (ethanol) in each dose unit which is equivalent to 63 mg/1 mL (6.5% w/w). The amount in 1 dose of this medicine is equivalent to less than 2 mL beer or 1 mL wine.
The small amount of alcohol in this medicine will not have any noticeable effects.

3. How to use Oczyesa

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is 20 mg every 4 weeks. Oczyesa may be given up to 1 week before or 1 week after the scheduled 4-week dose in exceptional circumstances (e.g., missed dose, non-adherence to treatment, etc.).

If you are switching from another treatment with octreotide or lanreotide, the first dose of Oczyesa should be given at the end of the daily or monthly dosing interval of the previous treatment.

Your doctor will assess how the treatment works for you in terms of IGF-I and symptom control on a regular basis. Should control not be maintained or the medicine not be tolerated, you may be switched to another somatostatin analogue.

Oczyesa is given as a single injection under the skin (subcutaneously (SC)) of the belly, thigh or buttock. The injection should not be given in any other area. When receiving monthly injections, it is important to change the site where the injection is given each time. You may receive multiple injections in the same area, but each injection must be given in a different spot.

You should receive training on the right way to inject Oczyesa. Read the 'Instructions for use' for the pre-filled pen carefully before using Oczyesa.

Detailed instructions on how to use Oczyesa are provided at the end of this leaflet.

If you use more Oczyesa than you should
If you have used more Oczyesa than you should, you need to contact your doctor immediately.
The symptoms of an overdose are: abnormal or irregular heartbeat, low blood pressure, cardiac arrest (heart stops beating), reduced supply of oxygen to the brain, severe upper stomach pain, yellow skin and eyes, nausea (feeling sick), loss of appetite, diarrhoea, weakness, tiredness, lack of energy, weight loss, enlarged liver, discomfort, and high level of lactic acid in the blood.

If you forget to use Oczyesa
Do not take a double dose to make up for a forgotten dose. Administer the next dose as soon as you remember.

If you stop using Oczyesa
Do not stop taking this medicine without discussing with your doctor first. If you stop taking Oczyesa, your acromegaly symptoms may come back.

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

4. Possible side effects

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

Some side effects could be serious. Tell your doctor immediately if you get any of the following:

Very common (may affect more than 1 in 10 people)
- Gallstones (cholelithiasis), leading to sudden back pain
- High blood glucose levels (hyperglycaemia)

Common (may affect up to 1 in 10 people)
- Underactive thyroid gland (hypothyroidism) with tiredness, weight gain, and skin and hair changes
- Changes in thyroid function (thyroid disorder), as measured by blood tests
- Inflammation of the gallbladder (cholecystitis); symptoms may include pain in the upper right abdomen (belly), fever, nausea
- Low blood glucose levels (hypoglycaemia)
- Condition where the body has difficulty maintaining normal glucose levels (impaired glucose tolerance)
- Slow heartbeat (bradychardia)

Uncommon (may affect up to 1 in 100 people)
- Non-aggressive tumour of liver blood vessels
- Dehydration; symptoms may include thirst, low urine output, dark urine, dry flushed skin
- Fast heartbeat (tachycardia)

Not known (frequency cannot be estimated from the available data)
- Hypersensitivity (allergic) reactions, including skin rash
- A sudden, severe allergic reaction (anaphylaxis) which can cause difficulty in swallowing or breathing, swelling and tingling, possibly with a drop in blood pressure with dizziness or loss of consciousness.
- An inflammation of the pancreas gland (pancreatitis); symptoms may include sudden pain in the upper abdomen, nausea, vomiting, diarrhoea
- Reduced flow of bile from the liver because of a blockage (cholestasis)
- Liver inflammation (hepatitis, cholestatic hepatitis); symptoms may include nausea, vomiting, loss of appetite, generally feeling unwell, itching, light-coloured urine
- Yellowing of the skin and eyes (jaundice)
- Low blood levels of platelets, components that help the blood to clot (thrombocytopenia), which can lead to bleeding and bruising.

Other side effects
Tell your doctor or pharmacist if you notice any of the side effects listed below. They are usually mild and tend to disappear as treatment progresses.

Very common (may affect more than 1 in 10 people)
- Abdominal pain
- Constipation
- Nausea
- Diarrhoea
- Flatulence (wind)
- Headache
- Local reactions at the injection site

Common (may affect up to 1 in 10 people)
- Dizziness
- Weakness
- Difficulty breathing (dyspnoea)
- Indigestion (dyspepsia)
- Discomfort or bloating or swelling of your belly (abdominal distension)
- Vomiting
- Excess fat in stool (steatorrhoea)
- Discoloured stool
- Loss of appetite (anorexia)
- Increased blood level of bilirubin (hyperbilirubinaemia), a waste product from breakdown of red blood cells
- Increased levels of liver enzymes (transaminases increased)
- Hair loss (alopecia)
- Itching (pruritus)
- Rash
- Joint pain (arthralgia)

Not known (frequency cannot be estimated from the available data)
- Itchy rash (urticaria)
- Increased liver enzyme levels (alkaline phosphatase, gamma-glutamyl transferase) in the blood

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Oczyesa

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton, pouch and pre-filled pen label after 'EXP'. The expiry date refers to the last day of that month.

Do not refrigerate.

Store in the original package in order to protect from oxygen and light.

Do not use this medicine if you notice visible particles or if it is cloudy.

Oczyesa is for single use only. Any used pre-filled pen should be discarded.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Oczyesa contains
- The active substance is octreotide hydrochloride equivalent to 20 mg octreotide. The volume of each pre-filled pen is 1 ml containing 20 mg octreotide.
- The other ingredients are glycerol dioleate, soybean phosphatidylcholine, ethanol anhydrous (see also section 2, 'Oczyesa contains alcohol'), propylene glycol (E 1520), edetic acid, ethanolamine.

What Oczyesa looks like and contents of the pack
Oczyesa is a prolonged-release solution for injection. Each pre-filled pen contains a yellowish to yellow clear liquid.

Each pack contains 1 pre-filled pen with stopper, a non-visible needle with a protective cap and a needle shield, fitted in an autoinjector.
The pre-filled pen is contained in a sealed aluminium pouch. The package contains a small white cylinder, included for storage purposes only.

Marketing Authorisation Holder
Camurus AB
Rydbergs torg 4
SE- 224 84 Lund
Sweden
medicalinfo@camurus.com

Manufacturer
Rechon Life Science AB
Soldattorpsvägen 5
SE-216 13 Limhamn
Sweden

This leaflet was last revised in.

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu/en. There are also links to other websites about rare diseases and treatments.

INSTRUCTIONS FOR USE

Oczyesa 20 mg prolonged-release solution for injection in pre-filled pen
octreotide

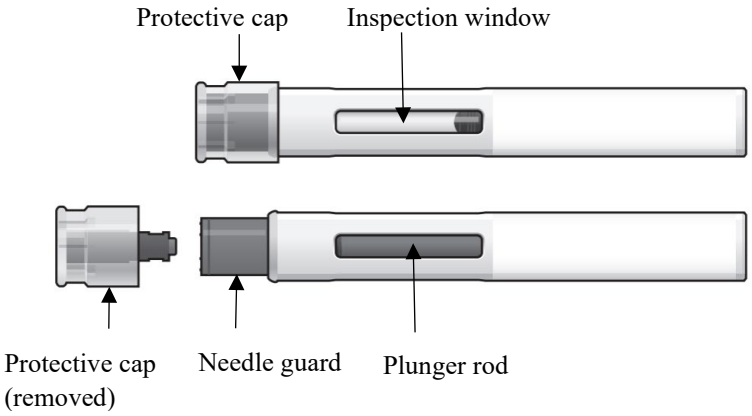
Single use
Pre-filled pen
Subcutaneous use

The instructions for use contain information on how to use Oczyesa.

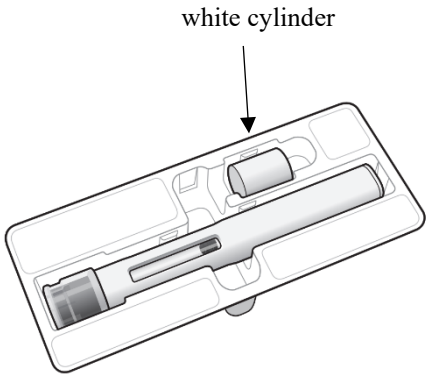
Read the instructions for use **all the way through** before using the Oczyesa pre-filled pen. Keep the instructions for use as you may need to read them again.

Do not inject yourself or someone else until you have been shown how to use the Oczyesa pre-filled pen. Your healthcare provider will show you or your caregiver how to prepare and inject a dose of this medicine before you try to do it for the first time. Call your healthcare provider if you have any questions.

The parts of the Oczyesa pre-filled pen before and after use



Note: Packaging contains a small white cylinder, included for storage purposes only. **Do not remove!**



Important information you need to know before injecting this medicine

- **For single use only** (do not reuse Oczyesa pre-filled pen).
- **For subcutaneous injection only** (inject directly into fatty layer under the skin).
- **Do not inject** intravascular (into the blood), intradermal (into the skin layer) or intramuscular (into the muscle).
- **Do not** use this medicine after the **expiry date** shown on the carton, pouch or on the pen label.
- **Do not** use if the pre-filled pen appears damaged.
- **Do not** use if the packaging (carton and pouch) or the seal is damaged.
- **Do not** remove the protective cap until you are ready to inject.

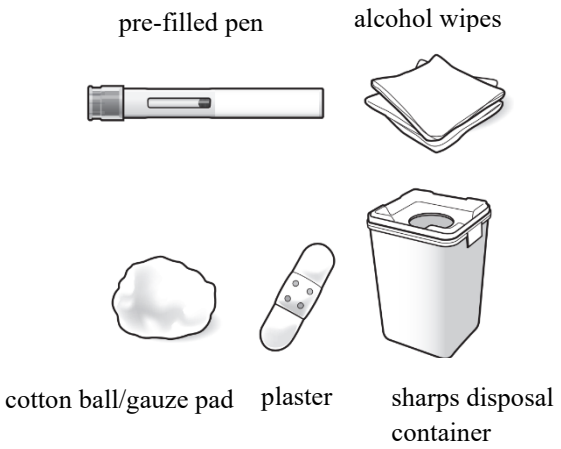
Storing the Oczyesa pre-filled pen

- Store the pre-filled pen in the original package in order to protect from oxygen and light.
- **Do not** refrigerate the pre-filled pen.
- **Keep Oczyesa out of the sight and reach of children.**

Preparing to inject Oczyesa

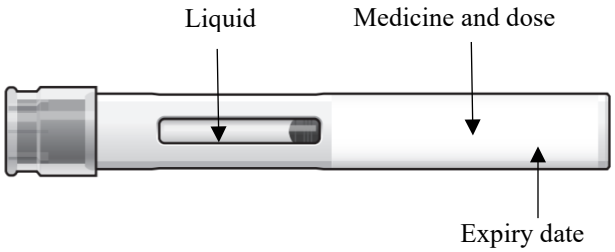
Step 1. Gather equipment
Place all the equipment needed for the injection on a clean flat surface:

- Oczyesa pre-filled pen
- alcohol wipe (not included)
- cotton ball or gauze pad (not included)
- plaster (not included)
- a sharps disposal container (not included) (see Step 10)



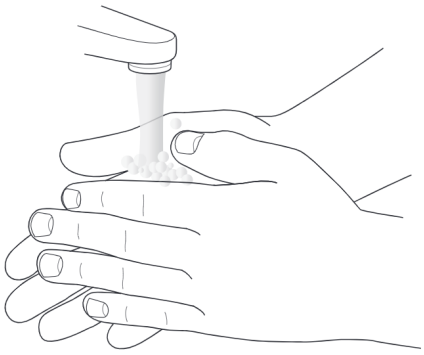
Step 2. Inspect the Oczyesa pre-filled pen

- Remove the pouch from the cardboard box. Open the pouch and remove the pre-filled pen.
- Check the label to be sure that you have the correct medicine.
- Check the **expiry date** shown on the cardboard box, the pouch or on the pre-filled pen label. Do not use the Oczyesa pre-filled pen if the expiry date has passed.
- Check that the **liquid is yellowish to yellow and clear**. You may see an air bubble. This is normal.
- **Do not use this medicine if you notice visible particles or if it is cloudy.**



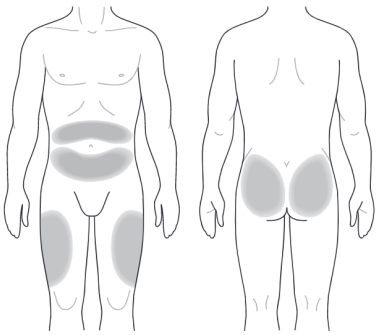
Step 3. Wash your hands

- Wash your hands well with soap and water. Dry your hands completely.



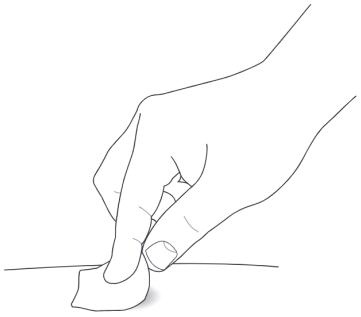
Step 4. Choose the injection site

- Choose an injection area (belly, thigh, or buttock). Choose an injection site in the injection area where there is enough fatty (subcutaneous) tissue. Each injection area can have multiple injection sites.
- You may need help from someone who has been instructed in how to give your injection if you cannot reach certain injection areas.
- **Do not** inject into skin that is tender, damaged, bruised or scarred.
- **Do not** inject in a recently used injection site in the chosen injection area.
- **Do not** inject within 5 cm of the navel.



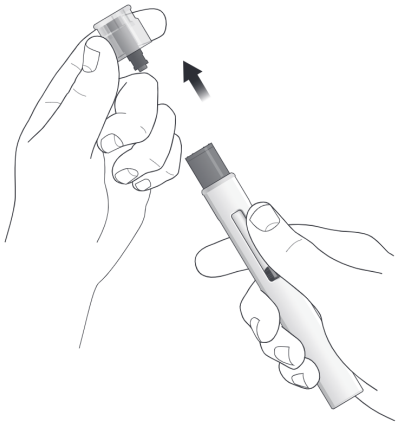
Step 5. Clean the injection site

- Clean the injection site with an alcohol wipe.
- Let the injection site air dry before injecting.
- **Do not** touch the cleaned area again before the injection.



Step 6. Remove and throw away the protective cap

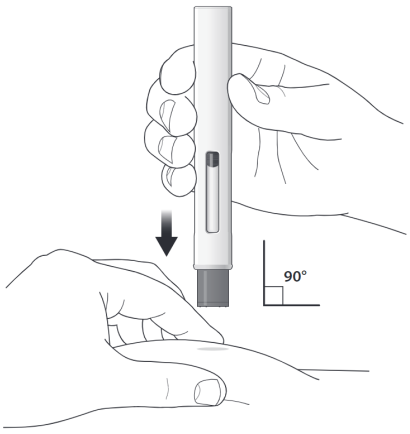
- Hold the Oczyesa pre-filled pen pointed up with one hand. With the other hand pull the protective cap straight off. It may take some force to remove. Do not wiggle or twist the cap.
- **Do not recap**. Throw away the protective cap right away.
- You may see a drop of liquid at the end of the needle. This is normal.
- **Do not** touch or press the needle guard. This could activate the pre-filled pen.



<u>Injecting Oczyesa</u>

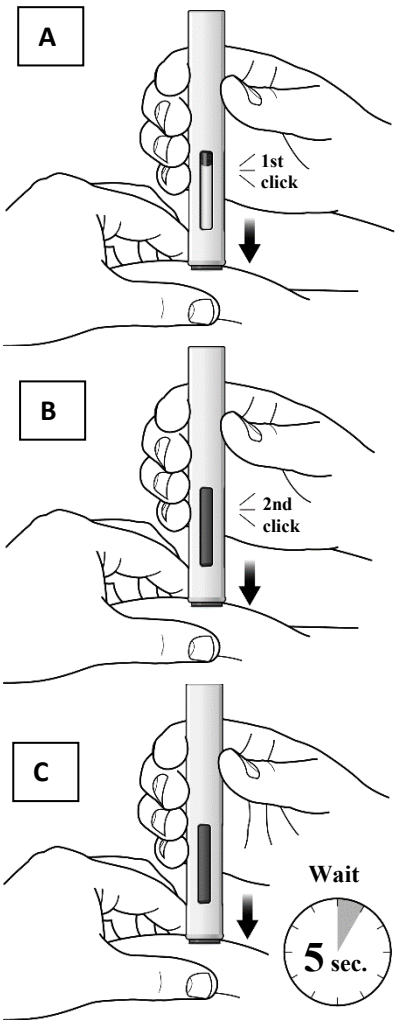
Step 7. Prepare to start the injection

- Pinch and hold the skin at the injection site between your thumb and fingers. **Hold the pinch until the injection is complete.**
- With your other hand hold the pre-filled pen so that you can see the inspection window.
- Place the pre-filled pen straight (at a 90 ° angle) and flat against the pinched skin.



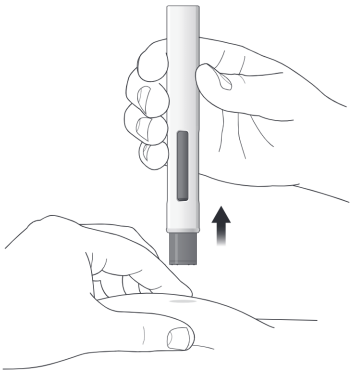
Step 8. Give the injection
Inject Oczyesa by following the steps in figures **A**, **B** and **C**.

- Push the pre-filled pen all the way down and hold the pre-filled pen against the skin. This will make the needle guard slide up into the pre-filled pen.
- You will hear a **first click** to let you know the injection has started.
- The plunger rod will move down through the inspection window.
- Continue to **hold** the pre-filled pen down.
- When you hear the **second click,** continue to keep the pre-filled pen down for an additional **5 seconds.**
- Check that the plunger rod is completely seen in the inspection window.



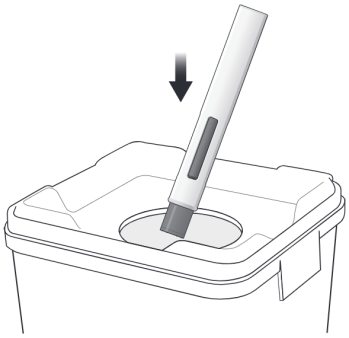
Step 9. Remove the Oczyesa pre-filled pen

- Remove the pre-filled pen from the skin. The injection is now completed, and the pinched skin can be released.
- The needle remains hidden by the needle guard to protect against needle-stick injury.
- You may have a small amount of blood or liquid at the injection site. This is normal. Use a cotton ball or gauze pad on the area and apply a plaster if needed.
- **Do not** rub the injection site.



<u>Dispose of Oczyesa pre-filled pen</u>

Step 10. Dispose of the Oczyesa pre-filled pen
Throw away (dispose of) the used Oczyesa pre-filled pen in a puncture resistant sharps disposal container right after use.
Do not throw away (dispose of) Oczyesa pre-filled pens in your household waste.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.



Annex IV

Conclusions on similarity and derogation presented by the European Medicines Agency

Conclusions presented by the European Medicines Agency on:

- **Similarity**

The CHMP is of the opinion that Oczyesa is similar to an authorised orphan medicinal product within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000 as further explained in the European Public Assessment Report.

- **Derogation**

CHMP is of the opinion that pursuant to Article 8 of Regulation (EC) No. 141/2000 the following derogation laid down in Article 8.3 of the same Regulation applies as further explained in European Public Assessment Report:
the holder of the marketing authorisation for Mycapssa is unable to supply sufficient quantities of the medicinal product.