EU Risk Management Plan for Oczyesa (octreotide)

RMP version to be assessed as part of this application: Not applicable

RMP Version number: 2.0

Data lock point for this RMP: 01-Dec-2025

Date of final sign-off: 25-Feb-2026

Rationale for submitting an updated RMP: Inclusion of long-term safety results from HS-19-647. Removing long-term safety as missing information.

Summary of significant changes in this RMP: Inclusion of long-term safety results from HS-19-647. Removing long-term safety as missing information.

Details of the currently approved RMP:

Version number: 2.0

Approved with procedure: EMA/VR/0000333073

Date of approval (EMA Opinion date): 07-May-2026

QPPV name: Johanna Strandell, MSc, PhD

QPPV signature: 

Table of content

Part I: Product(s) Overview

Table Part I.1 – Product(s) Overview

Active substance(s) **(INN or common name)**	Octreotide
Pharmacotherapeutic group(s) (ATC Code)	Somatostatin and analogues (H01CB02)
Marketing Authorisation Applicant	Camurus AB
Medicinal products to which this RMP refers	Oczyesa 20 mg prolonged-release solution for injection in pre-filled pen MA number: EU/1/25/1938/001
Invented name(s) in the European Economic Area (EEA)	Oczyesa
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Octreotide is a synthetic octapeptide derivative of naturally occurring somatostatin.
	Summary of mode 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 growth hormone and of peptides and serotonin produced within the gastroenteropancreatic endocrine system. In healthy subjects, octreotide has been shown to inhibit: • release of growth hormone stimulated by arginine, exercise- and insulin-induced hypoglycaemia • post-prandial release of insulin, glucagon, gastrin, other peptides of the gastroenteropancreatic endocrine system, and arginine-stimulated release of insulin and glucagon • thyrotropin-releasing hormone-stimulated release of thyroid-stimulating hormone. Unlike somatostatin, octreotide inhibits growth hormone secretion preferentially over insulin and its administration is not followed by rebound hypersecretion of hormones (i.e. growth hormone in patients with acromegaly).
	Important information about its composition: Each pre-filled pen contains Glycerol dioleate, Soybean phosphatidylcholine, Ethanol anhydrous, Propylene glycol (E 1520),

	Edetic acid, and Ethanolamine Excipient(s) 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.
Hyperlink to the Product Information	[Module 1.3.1]
Indication(s) in the EEA	Oczyesa is indicated for maintenance treatment in adult patients with acromegaly who have responded to and tolerated treatment with somatostatin analogues.
Dosage in the EEA	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 IGF-1 levels and assessment of symptoms should be made periodically as per 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. If a dose is missed, the next dose of Oczyesa should be administered as soon as possible. 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.
Pharmaceutical form(s) and strengths	Prolonged-release solution for injection. Yellowish to yellow-clear liquid. Each pre-filled pen of 1 mL contains octreotide hydrochloride equivalent to 20 mg octreotide.

Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

Oczyesa – 20 mg prolonged-release solution for injection is submitted under Article 10(3) of Directive 2001/83/EC as a hybrid medicine, with Sandostatin®, solution for injection/infusion as the reference medicinal product (Sandostatin).

In accordance with section V.C.1.1 of Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (EMA/838713/2011, Rev. 2), modules SI and SII have a reduced content, and modules SIV and SVI of this Risk Management Plan (RMP) are left empty.

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Although Oczyesa has a different pharmaceutical form and strength as the reference product, the route of administration, indication and target population of Oczyesa are the same as those of the reference product Sandostatin. The differences to the reference product are permissible and consistent with the requirements laid down in Article 10(3).

Part II: Module SII - Non-clinical part of the safety specification

The market authorisation application for Oczyesa is submitted as hybrid application with Sandostatin as the reference medicinal product. The non-clinical safety of Oczyesa, referred to as CAM2029 during the clinical trial programme, was evaluated because of the new formulation (lipid-based FluidCrystal technology) and strength. The non-clinical development program included pharmacokinetic (PK) studies, single- and repeated-dose toxicity studies (including local tolerance) and in vitro genotoxicity studies. The information summarised here describes the key safety findings from non-clinical studies and relevance to human usage.

Systemic Toxicity

The PK of CAM2029 in dogs was compared to Sandostatin LAR, which also has a duration of 4 weeks. CAM2029 showed higher maximum observed plasma concentration (Cmax) compared to an equivalent dose of Sandostatin LAR. There was no apparent difference in systemic toxicity. All in-life findings (liquid faeces, difficulty in standing, quiet behaviour, thin appearance, transient body weight loss and reduced food consumption) were considered to be related to the pharmacological effects of octreotide and evidence of recovery from these findings was clear after each dosing occasion.

The systemic safety of CAM2029 is also supported by the available extensive body of literature on octreotide.

Local tolerance

Subcutaneous injection

The main effects observed with CAM2029 in the toxicology studies were reversible injection site reactions, and similar reactions were also noted with the CAM2029 vehicle (placebo) formulation. The injection site reaction findings encompassed the anticipated physiological response to the presence of a biodegradable foreign material, a foreign body reaction, which is well described in the literature. Across species, the findings were similar. Swellings were observed at the SC injection sites, considered to represent the physical presence of the depot matrix in the SC tissue, all of which reduced in size with time. Substantial evidence was gathered in the non-clinical studies showing that this local response is local i.e., no indication of spread of the inflammatory response to adjacent tissues and that the injection

site reactions were self-limiting and reversible. Clear signs of depot elimination/biodegradation and reduction of the local reactions over time were recorded.

Intramuscular injection
Local responses observed with intramuscular injection were equivalent or milder in local toxicity compared to the SC injections. Therefore, inadvertent intramuscular injection of CAM2029 is not anticipated to result in any additional adverse reactions.

Based on the demonstrated reversibility of the injection site reactions, the non-clinical data do not indicate any concerns for chronic administration of CAM2029 in humans.

For further details on the non-clinical safety findings of injection site reactions, see [Module 2.6.6].

Genotoxicity and carcinogenicity

Assessment of carcinogenic potential of Sandostatin (octreotide acetate) demonstrated no carcinogenic potential relevant for the use of the drug in humans.

Octreotide hydrochloride was not genotoxic and is not expected to have a carcinogenic potential different from octreotide acetate as the systemic concentration of octreotide itself is the relevant parameter.

Reproductive and developmental toxicity

No reproductive toxicity studies have been conducted for CAM2029. Within the scope of the hybrid application, octreotide hydrochloride is expected to behave the same as octreotide acetate regarding reproductive toxicity as the systemic concentration of octreotide itself is the relevant parameter.

Studies with Sandostatin have shown that fertility was not impaired in rats treated with doses of up to 1 mg/kg/day (Sandostatin). This dose represents 13 times the clinical dose of CAM2029 20 mg every 4 weeks (based on body surface area).

Reproduction studies 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 physiological growth was noted in the offspring of rats which was transient and attributable to GH inhibition brought about by excessive pharmacodynamic activity.

In a pre-and post-natal developmental study, reduced growth and maturation was observed in the F1 offspring of dams given octreotide during the entire pregnancy and during 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.

For further details on the non-clinical safety findings of Reproductive and developmental toxicity see Module 2.6.6.

Part II: Module SIII - Clinical trial exposure

The clinical development program for CAM2029 in acromegaly includes seven clinical trials. Four of the clinical trials were Phase 1 trials in healthy volunteers, which featured single- and repeated-dose investigations of the pharmacokinetic (PK) and pharmacodynamic (PD) profiles, as well as safety and tolerability of CAM2029 [HS-05-194, HS-07-291, HS-11-411 and HS-19-664]. There was one Phase 2 clinical trial [HS-12-455] in patients with acromegaly or functioning neuroendocrine tumors (NET), and two Phase 3 trials in patients with acromegaly [HS-18-633 and HS-19-647 Main Part, HS-19-647 Final].

A high-level summary of the trials is presented in Table SIII.1, Table SIII.2, Table SIII.3 and Table SIII.4 includes cumulative exposure data, age group and sex distribution for patients with acromegaly that have been exposed to CAM2029.

In total, 420 subjects have been exposed to CAM2029 within the clinical development program, 280 subjects in the healthy volunteer trials, 153 patients with acromegaly and 5 patients with NET.

Table SIII.1: Clinical trials with CAM2029 for the treatment of acromegaly

Trial/ EudraCT number/ Module	Trial Objectives/ Population	Trial Design	Test products/ Dosage Regimen/ Route of Administration	Duration of Treatment	No. of Subjects/Patients	Trial Status/Type of Report
Trials in the early clinical development of CAM2029						
[HS-05-194] 2005-005845-20 Module 5.3.3.1	PK, PD, safety Healthy male volunteers	Phase 1, randomised, double-blind, parallel-group, placebo-controlled, single-dose trial assessing the PK and relative bioavailability of CAM2029. Subjects first received an injection (right buttock) of either placebo (7 subjects in each group) or saline (1 subject in each group) and then an injection (left buttock) of CAM2029 (6 subjects in each group), placebo (1 subject in each group), or saline (1 subject in each group).	**CAM2029** CAM2029-P (octreotide acetate) Group 1: 2.85 mg (0.1 mL), SC, buttock Group 2: 8.55 mg (0.3 mL), SC, buttock Group 3: 28.5 mg (1.0 mL), SC, buttock Group 4: 8.55 mg (0.3 mL), IM, buttock **Placebo** (FluidCrystal vehicle) Single SC or IM injection of the same volume as for the active formulation (0.1, 0.3, or 1.0 mL) **Saline** Two SC or IM doses of the same volume as for the active formulation (0.1, 0.3, or 1.0 mL)	Single dose, 11 weeks participation (9 weeks follow-up)	**CAM2029**: 24 subjects Group 1: 6 Group 2: 6 Group 3: 6 Group 4: 6 **Placebo** (vehicle/saline): 8 subjects	Completed/ Full CTR
[HS-07-291] 2009-012217-21 Module 5.3.4.1	PK, PD, safety Healthy volunteers	Phase 1, randomised, open-label, parallel-group, repeated-dose trial assessing the PK, PD, safety, and tolerability of CAM2029.	**CAM2029** CAM2029-BG (octreotide hydrochloride) Group A: 3 doses of 10 mg (0.33 mL), q4w, SC, buttock Group B: 3 doses of 20 mg (0.67 mL), q4w, SC, buttock Group C: 3 doses of 30 mg (1.0 mL), q4w, SC, buttock Group D: 3 doses of 10 mg (0.33 mL) q4w, SC, abdomen **Octreotide LAR** Group E: 3 doses of 20 mg (2.5 mL), q4w, IM, gluteal muscle	3 months	**CAM2029**: 77 subjects Group A: 21 Group B: 17 Group C: 19 Group D: 20 **Octreotide LAR:** 18 subjects	Completed/ Full CTR

Trial/ EudraCT number/ Module	Trial Objectives/ Population	Trial Design	Test products/ Dosage Regimen/ Route of Administration	Duration of Treatment	No. of Subjects/Patients	Trial Status/Type of Report
[HS-11-411] 2011-001548-31 Module 5.3.4.1	PK, PD, safety Healthy volunteers	Phase 1, randomised, open-label, parallel group, repeated-dose, active controlled trial assessing the PK, PD, safety, and tolerability of 3 formulations of CAM2029 compared to octreotide LAR in healthy volunteers. Subjects first received octreotide IR as run-in treatment.	**CAM2029** CAM2029-BP (octreotide hydrochloride) Group A: 3 doses of 10 mg (0.5 mL), q4w, SC, buttock Group B: 3 doses of 20 mg (1.0 mL), q4w, SC, buttock Group C: 3 doses of 30 mg (1.5 mL), q4w, SC, buttock CAM2029-BR (octreotide hydrochloride) Group D: 3 doses of 30 mg (1.5 mL), q4w, SC, buttock CAM2029-BV (octreotide hydrochloride) Group E: 3 doses of 10 mg (0.5 mL), q4w, SC, buttock Group F: 3 doses of 20 mg (1.0 mL), q4w, SC, buttock Group G: 3 doses of 30 mg (1.5 mL), q4w, SC, buttock **Octreotide LAR** Group H: 3 doses of 30 mg (2.5 mL), q4w, IM, gluteal muscle **Octreotide IR** 1 dose of 0.2 mg (2 mL), SC, buttock	3 months	**CAM2029**: 108 subjects Group A: 17 Group B: 16 Group C: 17 Group D: 14 Group E: 15 Group F: 14 Group G: 15 **Octreotide LAR:** Group H: 14 subjects **Octreotide IR**: 123 subjects	Completed/ Full CTR
[HS-12-455] 2013-000533-12 Module 5.3.4.2	PK, PD, efficacy, safety Patients with acromegaly or NET	Phase 2, randomised, open-label, multi-centre trial assessing the PK, PD, efficacy, and safety of CAM2029 in patients previously treated with octreotide LAR.	**CAM2029** CAM2029-BR 6 injections of 10 mg (0.5 mL), q2w, SC, upper thigh, or 3 injections of 20 mg (1.0 mL), q4w, SC, upper thigh **Octreotide LAR** Two single injections of 10, 20, or 30 mg (1 as run-in and 1 as run-out), IM, gluteal muscle	3 months	**CAM2029** Patients with acromegaly: 7 Patients with symptomatic NET: 5	Completed/ Full CTR

Trial/ EudraCT number/ Module	Trial Objectives/ Population	Trial Design	Test products/ Dosage Regimen/ Route of Administration	Duration of Treatment	No. of Subjects/Patients	Trial Status/Type of Report
Trials in the clinical development of the final market CAM2029 formulation						
[HS-19-664] 2020-002643-35 Module 5.3.4.1	PK, PD, safety Healthy volunteers	Phase 1, randomised, open-label, single- and repeated-dose trial, assessing the PK, PD, safety, and tolerability of different doses, dosing configurations and manufacturers of CAM2029. Subjects first received octreotide IR as run-in treatment.	**CAM29029** CAM2029-CY Part A, Cohort A1 Single injection 10 mg (0.5 mL) with a pre-filled pen (manufactured by FKA), SC, abdomen Part A, Cohort A2 Single injection 20 mg (1.0 mL) with a pre-filled pen (manufactured by FKA), SC, abdomen Part A, Cohort A3 Single injection 20 mg (1.0 mL) with a pre-filled syringe (manufactured by FKA), SC, abdomen Part B Single injection 20 mg (1.0 mL) with a pre-filled pen (manufactured by Rechon Life Sciences), SC, abdomen Part C 7 injections of 10 mg (0.5 mL) q1w with a pre-filled pen (manufactured by Rechon Life Sciences), SC, abdomen (alternating sides) **Octreotide IR** 4 doses of 0.25 mg every 8 hours, SC, abdomen	Parts A and B: single dose Part C: 7 weeks	**CAM2029**: 71 subjects in total[a] Part A and B (single dose of CAM2029): Part A Cohort A1: 16 Part A Cohort A2: 17 Part A Cohort A3: 15 Part B: 16 Part C (repeated doses of CAM2029): 7 **Octreotide IR:** 80 subjects in total	Completed/ Full CTR
[HS-18-633] 2019-001191-11 Module 5.3.5.1	Efficacy, safety Patients with acromegaly	Phase 3, randomised, double-blind, placebo-controlled, multi-centre trial assessing the efficacy and safety of CAM2029 in patients with acromegaly treated with octreotide LAR or lanreotide ATG at enrolment.	**CAM2029** CAM2029-CY 6 injections of 20 mg (1.0 mL) with a pre-filled syringe, q4w, SC, abdomen or thigh **Placebo** 6 injections of 1.0 mL placebo with a pre-filled syringe, q4w, SC, abdomen or thigh	24 weeks	**CAM2029**: 48 patients[b] **Placebo:** 24 patients	Completed/ Full CTR

Trial/ EudraCT number/ Module	Trial Objectives/ Population	Trial Design	Test products/ Dosage Regimen/ Route of Administration	Duration of Treatment	No. of Subjects/Patients	Trial Status/Type of Report
[HS-19-647 Main Part], [HS-19-647 Final] 2019-002190-66 Module 5.3.5.2	Long-term safety, efficacy Patients with acromegaly	Phase 3, open-label, single-arm, multi-centre trial assessing the long-term safety and efficacy of CAM2029 in patients with acromegaly treated with octreotide LAR or lanreotide ATG at enrolment. No control.	**CAM2029** CAM2029-CY **New patients** Main part: 13 injections of 20 mg (1.0 mL) (or 10 mg [0.5 mL] in case of down-titration) with a pre-filled syringe or a pre-filled pen, q4w, SC, abdomen, thigh, or buttock Extension part: q4w, SC, abdomen, thigh, or buttock, pre-filled pen **Roll-over patients from HS-18-633** Main part: 7 injections of 20 mg (1.0 mL) (or 10 mg [0.5 mL] in case of down-titration) with a pre-filled syringe or a pre-filled pen, q4w, SC, abdomen, thigh, or buttock (starting at Week 24) Extension part: q4w, SC, abdomen, thigh, or buttock, pre-filled pen	New patients: 52 weeks (main part) + 52 weeks (extension part) Roll-over patients: 28 weeks (main part) + 52 weeks (extension part)	**CAM2029**: 135 patients	Completed/ Main part CTR (interim) and Final CTR

ATG: autogel; CTR: clinical trial report; FKA: Fresenius-Kabi (drug product manufacturer); IM: intramuscular; IMP: investigational medicinal product; IR: immediate release; LAR: long-acting repeatable; NET: neuroendocrine tumours; PD: pharmacodynamic(s); PK: pharmacokinetic(s); qxw: every x weeks (x=1, 2 or 4); SC: subcutaneous

a. 71 subjects correspond to 66 unique individuals since 4 subjects were enrolled in both Cohort A2 and Cohort B (received 2 SC injections of 20 mg CAM2029 each) and 1 subject was enrolled in both Cohort A2 and Cohort C (received 2 SC injections of 10 mg CAM2029)
b. One patient was randomised but not exposed to IMP.

Source: [Module 5.2]

Table SIII.2: Duration of exposure of CAM2029 in patients with acromegaly during the clinical trial program

Cumulative for acromegaly indication			
Duration of exposure	HS-12-455 n(%)	HS-18-633 n(%)	HS-19-647[a] n(%)
≥4 weeks	5	47 (100)	135 (100)
≥24 weeks	NA	42 (89.4)	131 (97.0)
≥52 weeks	NA	NA	117 (86.7)
≥76 weeks	NA	NA	42 (31.1)
≥104 weeks	NA	NA	33 (24.4)
Total	5	47	135

a. 6 rollover subjects with exposure in HS-18-633 were also counted in HS-19-647
Reference: [Module 2.7.4, Table 9] (HS-18-633); [HS-19-647 Final, Table 12] (HS-19-647); [HS-12-455]

Table SIII.3: Age group distribution in target population during CAM2029 exposure in the clinical trial program

Cumulative for acromegaly indication			
Age group	HS-12-455 n(%)	HS-18-633 n(%)	HS-19-647[a] n(%)
Adults (e.g. 18 to 64 years)	3 (60.0)	34 (72.3)	114 (84.4)
Elderly people >=65 years	2 (40.0)	13 (27.7)	21 (15.6)
Total no of patients/indication	5	47	135

a. For 36 rollover subjects with exposure in HS-18-633 were also counted in HS-19-647
References: [Module 2.7.4, Table 16 and Table 18] (HS-18-633, HS-19-647); [HS-12-455]

Table SIII.4: Sex distribution in target population during CAM2029 exposure in the clinical trial program

Cumulative for acromegaly indication			
Sex	HS-12-455 n(%)	HS-18-633 n(%)	HS-19-647[a] n(%)
Female	2 (40.0)	28 (59.6)	76 (56.3)
Male	3 (60.0)	19 (40.4)	59 (43.7)
Total no of patients/indication	5	47	135

a. For 36 rollover subjects with exposure in HS-18-633 were also counted in HS-19-647
References: [Module 2.7.4, Table 16 and Table 18] (HS-18-633, HS-19-647); [HS-12-455]

Part II: Module SIV - Populations not studied in clinical trials

According to the Guideline on Good Pharmacovigilance Practices: Module V – Risk management systems, for new Marketing Authorization applications under Article 10(3) (hybrid application) of Directive 2001/83/EC, RMP module SIV is omitted.

SIV.1 Exclusion criteria in pivotal clinical trials within the development programme

Not applicable

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

Not applicable

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Not applicable

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

The WHO DDD lists the DDD for octreotide as 0.7 mg. However, this method for estimating patient exposure is not suitable due to being a long-acting product with the active substance being released over a period of 4 weeks (28 days).
One dose contains 20 mg of octreotide and is intended for once monthly use. The cumulative and interval patient exposure to Oczyesa from marketing experience was therefore estimated from the internal sale data of the MAH using the following methodology:

Number of patient - years = (number of doses sold x 28 [Days])/365 [Days]

SV.1.2 Exposure

Oczyesa was launched in Germany in October 2025. Post-marketing exposure of Oczyesa is very limited at the time of this report. Thus, the above calculation is not applied.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Not applicable.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

The safety data from the phase 3 trials shows that CAM2029 is well tolerated in patients with acromegaly with a long-term safety profile consistent with the well-established profile of approved, first-generation injectable somatostatin receptor analogues (SRLs), octreotide and lanreotide.

Summary of risks not considered important for inclusion in the list of safety concerns in the RMP

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):	• *Injection site reactions*
Known risks that require no further characterisation and are followed up via routine pharmacovigilance, namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered to by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised):	• *Gastrointestinal adverse reactions* • *Glucose metabolism abnormalities* • *Thyroid Function Abnormalities* • *Vitamin B12 Deficiency*
Known risks that do not impact the risk-benefit profile*:*	• *Gallbladder-related adverse reactions* • *Pancreatitis* • *Liver related adverse reactions* • *Bradycardia*
Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:	• *QT Prolongation related adverse reactions*
Other reasons for considering the risks not important or as missing information:	• *Use in pregnancy* • *Device use errors*

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

Injection site reactions

During the phase 3 trials with CAM2029, injection site adverse reactions were the most common group of adverse reactions reported. The most commonly reported injection site reactions were injection site pain, injection site erythema and injection site swelling. No serious injection site reactions were reported. Injection site reactions were generally mild and transient. In the phase 3 open-label, long-term safety and efficacy study (HS-19-647), the observed incidence of new injection site adverse

reactions decreased with treatment time in the trial from about 15% after the first injection to no or single cases after the last injections in the trial.

Injection site reactions are expected based on the SC administration route of CAM2029 and due to the physical presence of the depot matrix in the tissue. Furthermore, post-marketing data for the marketed medicinal product approved under brand name Buvidal which has the same delivery system, FluidCrystal, as CAM2029, show that injection site reactions are primarily non-serious and mild to moderate in their nature. With exposure of 1,8 million packages corresponding to 89,400 patient-years (data up to 21-Jan-2024), <10 reversible serious injection site reactions (consisting of injection site necrosis, injection site ulceration and injection site abcess) have been reported post-marketing with Buvidal.

Injection site reactions are not considered to impact the benefit-risk balance of CAM2029, as adverse reactions are mostly mild to moderate, and transient.

Known risks that require no further characterisation and are followed up via routine pharmacovigilance, namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered to by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised):

Gastrointestinal Adverse Reactions

Non-serious adverse reactions e.g. abdominal pain, nausea, flatulence, diarrhoea, constipation and fat malabsorption have been reported for octreotide (Sandostatin). These reactions start within hours after octreotide injection, and their severity have been reported to be dose dependent. The events usually resolve spontaneously within 7 to 14 days despite continuous treatment (Sandostatin). Due to the spontaneous resolution of GI events, a low proportion of patients (2.6%) discontinue therapy due to these symptoms. These adverse reactions are well understood from the physiological actions of somatostatin in the GI tract and exocrine pancreas and the spontaneous resolution of these symptoms is suggestive of rapid adaptation to the effect of octreotide on the GI tract and pancreas.

In the CAM2029 healthy volunteer trials, gastrointestinal adverse reactions such as diarrhea and abdominal pain were among the the most common adverse reactions. However, in the Phase 3 trials HS-18-633 and HS-19-647 including patients being on stable SRL doses at enrolment, the frequencies of GI reactions were lower.

According to octreotide post-marketing data the vast majority of GI events are non-serious. In rare instances, GI adverse reactions may resemble acute intestinal obstruction, with progressive abdominal distension, severe epigastric pain and abdominal tenderness.

GI adverse reactions are not considered to impact the benefit-risk balance of CAM2029, as they are mostly mild to moderate, and transient.

Glucose metabolism abnormalities

Octreotide has an inhibitory action on growth hormone (GH), glucagon secretion, and insulin, and may affect glucose regulation (Sandostatin). In patients with acromegaly, octreotide alters glucose tolerance with a decrease in the insulinogenic index (insulin/glucose) response to a glucose challenge (Koop). Post-prandial glucose tolerance may be impaired and, in some instances, the state of persistent hyperglycaemia may be induced as a result of chronic administration (Sandostatin). Hypoglycaemia has also been reported.

Hypoglycemia or hyperglycemia which occurs during octreotide therapy is usually mild, but may result in overt diabetes mellitus or necessitate dose changes in insulin or other hypoglycemic agents. Hyperglycaemia has been reported as very common (≥1/10), and hypoglycaemia and impaired glucose tolerance as common (≥1/100, <1/10) with the reference product (Sandostatin).

In the blinded phase 3 trial HS-18-633 there were no CAM2029 adverse reactions of glucose metabolism. In the open label trial HS-19-647, 4 patients (3.0%) experienced CAM2029 adverse reactions (inadequate control of diabetes mellitus [grade 2], diabetes mellitus, impaired glucose tolerance, and increased glycosylated hemoglobin [all grade 1]).

Monitoring of glucose is therefore recommended and anti-diabetic treatment should be adjusted or started accordingly.

Based on the current available information of octreotide and glucose metabolism, the information is not considered to impact the benefit-risk balance for CAM2029. The risk for altered glucose metabolism during treatment of CAM2029 is assessed as comparable to the reference product.

Thyroid Function Abnormalities

The prevalence of nodular thyroid disease is 59.1% and the prevalence of thyroid cancer is 4.3% in patients with acromegaly (Wolinski). IGF-1 is a thyroid growth factor, and there is a correlation between IGF-1 levels and thyroid volume in patients with acromegaly (Kan). In a retrospective study, treatment with SRL decreased the thyroid nodule volume in patients with active acromegaly. Octreotide suppresses secretion of thyroid-stimulating hormone (TSH), which may result in hypothyroidism. Hypothyroidism and thyroid disorder (e.g. decreased TSH, decreased total T4, and decreased free T4) have been reported as common (≥1/100, <1/10) in clinical trials with the reference product (Sandostatin).

In trial HS-18-633, 1 patient (2.1%) receiving CAM2029 was reported to have 'decreased free thyroxine'. In trial HS-19-647, 1 patient (0.7%) was reported to experience primary hypothyroidism. All thyroid function abnormalities in the phase 3 trials were assessed as not related to CAM2029 by the investigator.

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

Based on the currently available information on octreotide and thyroid function abnormalities, no impact on the benefit-risk balance for CAM2029 is considered. The risk for thyroid function abnormalities during treatment of CAM2029 is assessed as comparable to the reference product.

Vitamin B12 Deficiency

Decreased vitamin B12 levels have been observed in some patients receiving octreotide therapy (Sandostatin, PubChem Octreotide; Plöckinger). Deficiency of vitamin B12 can lead to an elevated circulating level of total homocysteine, which has been associated with the development of cardiovascular disease (Yuan).

There were no CAM2029 adverse reactions of vitamin B12 in the phase 3 trials HS-18-633 and HS-19-647.

Monitoring of vitamin B12 levels is recommended during therapy with octreotide in patients who have a history of vitamin B12 deprivation. (Sandostatin).

Based on the current available information, vitamin B12 deficiency is not considered to impact the benefit-risk balance for CAM2029. The risk for vitamin B12 deficiency during treatment of CAM2029 is assessed as comparable to the reference product.

Known risks that do not impact the risk-benefit profile*:*

Gallbladder-related adverse reactions

Cholelithiasis has been reported as very common (≥1/10), and cholecystitis, biliary sludge and hyperbilirubinaemia as common (≥1/100, <1/10) with the reference product (Sandostatin). It has been reported that up to one-third of octreotide-treated patients with acromegaly develop biliary sludge or gallstones, but symptomatic gallbladder disease only occurs in 1% of patients per treatment year (Koop, Lamberts).

The incidence of gallbladder abnormalities did not appear to be related to age, sex, or dose but was related to duration of exposure. Acute cholecystitis, ascending cholangitis, biliary obstruction, cholestatic hepatitis, or pancreatitis have been reported during octreotide therapy or following its withdrawal. There have been post-marketing reports of cholelithiasis resulting in complications requiring cholecystectomy. Treatment should be discontinued if complications of cholelithiasis are suspected. Even after cholecystectomy, cholesterol stones may form in the common bile duct and intrahepatic ducts (Koop, Lamberts, LiverTox).

In total, 14 subjects in the healthy volunteer trial HS-19-664 were reported with cholelithiasis. All events of cholelithiasis were asymptomatic. Most adverse reactions of cholelithiasis were reported as gallbladder sludge or sediment. All events of gallbladder sludge/gallstones were identified by ultrasound imaging (performed at trial entry and during the CAM2029 treatment period) and assessed as clinically significant findings, mild in severity, and assessed as related to CAM2029. One subject with gallbladder sludge experienced concurrent adverse events of elevated liver enzymes, discolored urine, and pale feces. In the phase 3 open-label, long-term safety and efficacy study (HS-19-647), the observed incidence of gallbladder-related adverse reactions was 6,7% (9 patients). In the same trial, cholelithiasis (Grade 2) and acute cholecystitis (Grade 1) were the only SAEs assessed as related to CAM2029. In the blinded phase 3 trial, HS-18-633, a related SAE of cholecystitis was reported in a patient receiving placebo.

Cholelithiasis and other gallbladder-related adverse reactions such as cholecystitis, biliary sludge, hyperbilirubinaemia are not considered to impact the benefit-risk balance of CAM2029 since the events are usually asymptomatic. Furthermore, the risk for cholelithiasis during treatment of CAM2029 is assessed as comparable to the reference product.

Pancreatitis

Octreotide has been associated with acute pancreatitis, which may be due to its inhibitory effect on GI hormone release, or may occur as a secondary effect to passage of gallbladder stones in the pancreatic duct leading to obstruction (LiverTox). In rare instances, acute pancreatitis has been reported within the first hours or days of octreotide treatment and resolved on withdrawal of the drug (Sandostatin). Furthermore, cholelithiasis induced pancreatitis has been reported for patients on long-term octreotide treatment.

In HS-18-633, pancreatitis-related adverse reactions occurred in 1 patient (2.1%), who experienced acute pancreatitis receiving CAM2029 (assessed as not related by the investigator) and 1 patient (4.2%) receiving placebo experienced increased lipase (assessed as related by the investigator). In HS-19-647 no pancreatitis-related adverse reactions were reported.

It is known that pancreatitis may occur in relation to octreotide treatment: however, during the clinical trial programme with CAM2029 there were no IMP-related pancreatitis events. Based on the currently available information pancreatitis is not considered to impact the benefit-risk balance for CAM2029. The risk for pancreatitis during treatment of CAM2029 is assessed as comparable to the reference product.

Liver-related adverse reactions

Elevated transaminase levels is a common adverse reaction with SRLs (Sandostatin). There are post-marketing reports of acute hepatitis without cholestasis, cholestatic hepatitis, jaundice, cholestatic jaundice, increased alkaline phosphatase levels and increased gamma glutamyl transferase levels (Sandostatin).

In HS-18-633, 1 patient (2.1%) receiving CAM2029 experienced a Liver transaminase adverse event, hepatomegaly, which was assessed as not related by the investigator. In HS-19-647 2 patients (1.5%) experienced increased gamma-glutamyl transferase, increased liver function test, and abnormal liver ultrasound (all assessed as not related by the investigator).

The hepatic function should be monitored during octreotide therapy (Sandostatin).

Based on the currently available information on octreotide and increased transaminase levels, no impact on the benefit-risk balance for CAM2029 is considered. The risk for increased transaminase levels during treatment of CAM2029 is assessed as comparable to the reference product.

Bradycardia

Bradycardia is a common adverse reaction with SRLs (Sandostatin).

No bradycardia-related adverse reactions have been reported during the phase 3 trials with CAM2029.

Based on the currently available information on octreotide and bradycardia, no impact on the benefit-risk balance for CAM2029 is considered. The risk for bradycardia during treatment of CAM2029 is assessed as comparable to the reference product.

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

QT Prolongation-related adverse reactions

In patients with acromegaly, 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 during treatment with octreotide (Sandostatin). The relationship of these events to octreotide acetate is not established because many of these patients have underlying cardiac diseases. In a very small trial, in 3 out of 6 acromegaly patients with abnormally long QTc interval, the interval was normalised after treatment with octreotide (Fatti). According to consensus recommendations for diagnosis and treatment of acromegaly comorbidities (Giustina), echocardiography and electrocardiogram (ECG) assessments should be performed annually if abnormal.

There were no CAM2029-related tachycardia-related adverse reactions (including no patients with QT prolongation) in HS-18-633. In HS-19-647 Grade 1 tachycardia occurred in 2 patients (1.5%) and one case of tachycardia was assessed as related to CAM2029.

Based on the currently available information for octreotide and tachyarrhythmias including torsade de pointes and QT prolongation, the information is not considered to impact the benefit-risk balance for CAM2029. The risk for tachyarrhythmias including torsade de pointes and QT prolongation during treatment of CAM2029 is assessed as comparable to the reference product.

Other reasons for considering the risks not important or as missing information:

Use in pregnancy

Data from pregnant women are limited (Sandostatin, EudraVigilance). Reproduction studies have been performed in rats and rabbits at doses up to 16 times the highest recommended human dose based on body surface area and revealed no evidence of harm to the fetus due to octreotide.

Despite octreotide being available on the market for more than 30 years, post-marketing data reveal a very limited number of pregnancy outcomes in patients with acromegaly (Sandostatin). Most women were exposed to octreotide during the first trimester of pregnancy at doses ranging from 100-1200 micrograms/day of octreotide s.c. or 10-40 mg/month of long-acting octreotide. Congenital anomalies were reported in about 4% of pregnancy cases for which the outcome is known. Referencing global figures where it is estimated that 6% of babies worldwide are born with a congenital disorder (World Health Organization), no causal relationship to octreotide is suspected for these cases.

Even if pregnant and lactating women are not studied in the clinical trials, the post-marketing information indicates that exposure is limited and the currently known risks are acceptable.

Device use errors

CAM2029 is being developed for convenient self-administration and home use. It is provided as a pre-filled pen (autoinjector) with a non-visible needle. CAM2029 is ready-to-use and can be stored at room temperature, i.e., does not require reconstitution or temperature conditioning before administration. The dose of CAM2029 for treatment of acromegaly is 20 mg every 4 weeks, administered SC in the abdomen, thigh, and buttock. For these reasons there is limited risk for device use errors.

There have been no adverse reactions related to device use error in any of the phase 3 trials.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Missing information: Long-term safety data

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

During assessment of the marketing authorisation application of Oczyesa, CHMP considered 'long-term safety' as missing information. The Applicant agreed to submit the final report of HS-19-647 to the EMA including up to two years of treatment of CAM2029.

The final CTR is provided as requested. Long-term data from treatment with CAM2029 (up to 2 years) showed consistent efficacy and safety over time with no new or unexpected safety findings. The safety profile of CAM2029 showed to be consistent with the one known for octreotide. The MEA is therefore considered to be fulfilled.

Long-term safety as missing information is removed from the list of safety concerns together with the related additional pharmacovigilance activities.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Not applicable

SVII.3.2. Presentation of the missing information

Not applicable

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities will be carried out as described in the Pharmacovigilance System Master File. No activities beyond adverse reactions reporting and signal detection are planned.

III.2 Additional pharmacovigilance activities

Not applicable, no additional activities are planned.

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable, no additional activities are planned.

Part IV: Plans for post-authorisation efficacy studies

Not applicable, no post-authorisation efficacy study is planned.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

No risks are considered important for inclusion in the list of safety concerns in the RMP

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of risk minimisation measures

Not applicable

Part VI: Summary of the risk management plan

Summary of risk management plan for Oczyesa (octreotide)

This is a summary of the risk management plan (RMP) for Oczyesa. The RMP details important risks of Oczyesa, how these risks can be minimised, and how more information will be obtained about risks and uncertainties related to Oczyesa (missing information).

The summary of product characteristics (SmPC) for Oczyesa and its package leaflet give essential information to healthcare professionals and patients on how Oczyesa should be used.

This summary of the RMP for Oczyesa should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the currently listed will be included in updates of the RMP.

I. The medicine and what it is used for

Oczyesa is authorised for maintenance treatment in adult patients with acromegaly who have responded to and tolerated treatment with somatostatin analogues (see SmPC for the full indication). It contains octreotide as the active substance, and it is administered via subcutaneous injection. Further information about the evaluation of the benefits of Oczyesa can be found in the EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: Oczyesa | European Medicines Agency (EMA)

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Oczyesa, together with measures to minimise such risks and the proposed studies for learning more about the risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

In summary, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities.*

II.A List of important risks and missing information

Important risks of Oczyesa are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Oczyesa. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	None

II.B Summary of important risks

No important identified or potential risks are included in the list of safety concerns for Oczyesa.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Oczyesa.

II.C.2 Other studies in post-authorisation development plan

There are no studies planned for Oczyesa.

Part VII: Annexes

In accordance with the Guideline on good pharmacovigilance practices (GVP), Module V – Risk management systems, Rev 2, Annex 1 is left empty.

Annex 4 - Specific adverse drug reaction follow-up forms

Not applicable.

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Not applicable.

Annex 7 - Other supporting data (including referenced material)

The following referenced material is included in [Module 5]:

EudraVigilance. European Medicines Agency. European Medicines Agency; Period up to 31/Oct/2024 [cited 03-Dec-2024]. European Medicines Agency - Login (europa.eu)

Fatti LM, Scacchi M, Lavezzi E, Pecori Giraldi F, De Martin M, Toja P, et al. Effects of treatment with somatostatin analogues on QT interval duration in acromegalic patients. Clin Endocrinol (Oxf). 2006;65(5):626-30.

Giustina A, Barkan A, Beckers A, Biermasz N, Biller BMK, Boguszewski C, et al. A consensus on the diagnosis and treatment of acromegaly comorbidities: An update. J Clin Endocrinol Metab. 2020;105(4):e937–46.

Kan S, Kizilgul M, Celik B, Beysel S, Caliskan M, Apaydin M, et al. The effect of disease activity on thyroid nodules in patients with acromegaly. Endocr J. 2019;66(4):301-7.

Koop BL, Harris AG, Ezzat S. Effect of octreotide on glucose tolerance in acromegaly. Eur J Endocrinol. 1994;130(6):581-6.

Lamberts SWJ, Hofland LJ. Anniversary review: Octreotide, 40 years later. Eur J Endocrinol. 2019;181(5):R173-83.

LiverTox: Clinical and Research Information on Drug-Induced Liver Injury. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Octreotide. [Updated 2016 Mar 30]. Available at: https://www.ncbi.nlm.nih.gov/books/NBK547947/. Accessed on 03-Dec-2024

Plöckinger U, Dienemann D, Quabbe HJ. Gastrointestinal side-effects of octreotide during long-term treatment of acromegaly. J Clin Endocrinol Metab. 1990;71(6):1658-62.

PubChem Octreotide. Bethesda (MD): National Library of Medicine (US), National Center for Biotechnology Information; 2004-. PubChem Compound Summary for CID 448601, Octreotide; [cited 2024 Dec 03]. Available at:.pubchem.ncbi.nlm.nih.gov/compound/Octreotide. Accessed on 03-Dec-2024

Sandostatin® Irish Summary of Product Characteristics, Jan 2024. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA0896-028-002_03012024152200.pdf. Accessed on 01-Nov-2024.

Wolinski K, Czarnywojtek A, Ruchala M. Risk of thyroid nodular disease and thyroid cancer in patients with acromegaly - meta-analysis and systematic review. PLoS One. 2014;9(2):e88787.

World Health Organization. Congenital disorders (who.int). Geneva: World Health Organization; 2024. [cited 2024 Dec 03] Available at:https://www.who.int/health-topics/congenital-anomalies#tab=tab_1. Accessed on: 03-Dec-2024

Yuan S, Mason AM, Carter P, Burgess S, Larsson SC. Homocysteine, B vitamins, and cardiovascular disease: a Mendelian randomization study. BMC Med. 2021;19(1):97.