ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Mycapssa 20 mg gastro-resistant hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gastro-resistant hard capsule contains octreotide acetate equivalent to 20 mg octreotide.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gastro-resistant hard capsule (gastro-resistant capsule)

White, size 0 enteric-coated hard gelatine capsules

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Mycapssa 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

Treatment may be initiated anytime following the last somatostatin analog injection and before the next injection would have been administered. The injectable somatostatin analogue should be discontinued. Treatment should be initiated at 40 mg daily, administered as 20 mg twice daily. During dose titration, insulin-like growth factor 1 (IGF-1) levels and the patient's signs and symptoms should be monitored every 2 weeks or as per clinician discretion, based on which dose adjustments should be considered. The dose should be increased in increments of 20 mg daily to obtain adequate control. Doses of 60 mg daily should be administered as 40 mg in the morning and 20 mg in the evening. Doses of 80 mg daily should be administered as 40 mg in the morning and 40 mg in the evening. The maximum recommended dose is 80 mg daily.

For patients receiving a stable dose of Mycapssa, monitoring of IGF-1 and assessment of symptoms should be made periodically per clinician discretion.

Discontinuation of Mycapssa and switching patients to another somatostatin analogue should be considered if IGF-1 levels are not maintained after treatment with the maximum recommended dose of 80 mg daily or the patient cannot tolerate treatment with Mycapssa.

Missed dose
If a dose of Mycapssa is missed the dose should be taken as soon as possible and at least 6 hours prior to the next scheduled dose, otherwise the missed dose should not be taken.

Special populations

Elderly
There is no evidence of reduced tolerability or altered dose requirements in elderly patients treated with octreotide.

Hepatic impairment
No dose adjustment is necessary in patients with Child Pugh A or B. Patients with Child Pugh C have not been studied; careful monitoring of these patients when initiating treatment with Mycapssa is recommended.

In patients with liver cirrhosis, the half-life of the medicinal product may be increased, necessitating adjustment of the maintenance dose.

Renal impairment
No dose adjustment is necessary in patients with mild, moderate, or severe renal impairment.
There is a significant increase in octreotide exposure in patients with end stage renal disease (ESRD). Patients with ESRD should start taking Mycapssa 20 mg daily. The maintenance dose should be adjusted based on IGF-1 levels, patient's signs and symptoms, and tolerability.

Paediatric population
The safety and efficacy of Mycapssa in children aged below 18 years have not been established. No data are available.

Method of administration

Oral use.

Mycapssa capsules should be swallowed whole with a glass of water, at least 1 hour before or at least 2 hours after eating any food. To minimise variability in the individual patient it is recommended to have a routine intake of Mycapssa capsules in relation to food every day (for example, Mycapssa should be routinely taken at least 1 hour before breakfast and at least 2 hours after dinner) (see section 5.2).

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

General

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.

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 should be monitored in patients receiving prolonged treatment with octreotide.

Hepatic function should be monitored during octreotide therapy.

Cardiovascular related events

Bradycardia and nodal arrhythmia 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 and related events

Cholelithiasis has been reported during treatment with octreotide and may be associated with cholecystitis (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 at about 6- to 12-month intervals during Mycapssa 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. Hypoglycaemia has also been reported.

Insulin requirements of patients with type I diabetes mellitus therapy may be reduced by administration of octreotide. In non-diabetics and type II 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.

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 Mycapssa in patients who have a history of vitamin B12 deprivation.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially sodium-free.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on Mycapssa

Concomitant administration of Mycapssa with esomeprazole has been found to decrease the bioavailability of Mycapssa. Medicinal products that alter the pH of the upper gastrointestinal tract (e.g. other proton pump inhibitors, H2-receptor antagonists, and antacids) may alter the absorption of Mycapssa and lead to a reduction in bioavailability. Concomitant administration of Mycapssa with proton pump inhibitors, H2-receptor antagonists, or antacids may require increased doses of Mycapssa.

Concomitant administration of Mycapssa with metoclopramide reduced the C_{max} and AUC of octreotide by an average of approximately 5% and 11%, respectively. Mycapssa should be titrated as indicated to clinical/biochemical effect.

Concomitant administration of Mycapssa with loperamide reduced the C_{max} and AUC of octreotide by an average of approximately 9% and 3%, respectively. Mycapssa should be titrated as indicated to clinical/biochemical effect.

Effects of Mycapssa on other medicinal products

Multiple mechanisms such as cytochrome P450 enzymes inhibition due to suppression of growth hormone, delayed gastric emptying or possibly enhanced permeability in some cases, are involved which may result in drug-drug interactions. Therefore, drug-drug interactions may vary between medicinal products. As a consequence, other medicinal products which have a narrow therapeutic index should therefore be used with caution and doses adjusted as necessary.

In a clinical study, it was shown that transient permeability enhancer (TPE®) excipients in the formulation increase the intestinal absorption of octreotide via paracellular transport, using the lactulose to mannitol ratio test (see section 5.1). No interaction studies with other drugs that are transported via the paracellular route (e.g. alendronate or desmopressin) were conducted.

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

Concomitant administration of hydrochlorothiazide (HCTZ) and Mycapssa resulted in a 9% decrease in C_{max} and 19% decrease in $AUC_{(0-5)}$ of HCTZ. Dose adjustment of HCTZ may be necessary.

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

Concomitant administration of metformin and Mycapssa resulted in no significant changes in the early exposure to metformin.

Octreotide has been found to reduce the intestinal absorption of ciclosporin (71% decrease in C_{max} and 63% decrease in $AUC_{(inf)}$) Dose adjustment of ciclosporin may be necessary.

Octreotide injections have been found to delay the intestinal absorption of cimetidine. Dose adjustment of cimetidine may be necessary.

Concomitant administration of octreotide injections and bromocriptine increases the bioavailability of bromocriptine. Dose adjustments of bromocriptine may be necessary.

Concomitant administration of lisinopril and Mycapssa increases the bioavailability of lisinopril (50% increase in C_{max} and 40% increase in $AUC_{(0-12)}$). Dose adjustment of lisinopril may be necessary when Mycapssa is administered concomitantly.

Concomitant administration of digoxin and Mycapssa has been found to decrease the rate of digoxin absorption.

Concomitant administration of levonorgestrel and Mycapssa decreases the bioavailability of levonorgestrel (38% decrease in C_{max} and 24% decrease in $AUC_{(0-5)}$), which may diminish the effectiveness of oral contraceptives containing progestogens (see section 4.6).

Concomitant administration of warfarin and Mycapssa resulted in no significant changes in the early exposure to warfarin.

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).

Concomitant administration of Mycapssa with levonorgestrel decreases levonorgestrel bioavailability (see section 4.5). Decreased bioavailability may potentially diminish the effectiveness of oral contraceptives containing progestogens. Women should be counselled to use an alternative non-hormonal method of contraception or a back-up method when Mycapssa is used with oral contraceptives.

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 100-1200 micrograms/day of subcutaneous octreotide or 10-40 mg/month of long-acting release 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 Mycapssa during pregnancy (see section 4.4).

Breast-feeding

It is unknown whether octreotide is excreted in human breast milk. Animal studies have shown excretion of octreotide in breast milk. A risk to the newborns cannot be excluded. Mycapssa should not be used during breast-feeding.

Fertility

It is not known whether octreotide has an effect on human fertility. Late descent of the testes was found for male offspring 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

Mycapssa 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 Mycapssa.

4.8 Undesirable effects

Summary of the safety profile

The most frequent adverse reactions reported during treatment with Mycapssa are mostly mild to moderate gastrointestinal disorders, with abdominal pain, diarrhoea, and nausea reported most frequently. The overall frequency of gastrointestinal adverse reactions is known to decrease over time with continued treatment.

Tabulated list of adverse reactions

The adverse drug reactions (ADRs) listed below have been accumulated from clinical studies and post-marketing safety experience with octreotide.

Adverse drug reactions are listed by System Organ Class according to the following classification: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); and not known (cannot be estimated from the available data).

Table 1: Tabulated list of adverse reactions

System organ class	**Very common**	**Common**	**Uncommon**	**Post-marketing safety experience (frequency not known)**
Infections and infestations			Diverticulitis, gastroenteritis, gastroenteritis viral, oral herpes	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			Haemangioma of liver	
Blood and lymphatic system disorders			Leukopenia	Thrombo-cytopenia*
Immune system disorders				Anaphylaxis*, allergy/hyper-sensitivity reactions*
Endocrine disorders		Hypo-thyroidism*, thyroid disorder (e.g. decreased thyroid stimulating hormone, decreased total T4, and decreased free T4)*		
Metabolism and nutrition disorders	Hyper-glycaemia**	Hypo-glycaemia**, impaired fasting glucose**, anorexia*	Decreased appetite, diabetes mellitus, hypertriglyceridaemia, dehydration*	
Psychiatric disorders			Agitation, anxiety, depression, disorientation, auditory hallucination, visual hallucination, insomnia, mood altered, mood swings	

System organ class	Very common	Common	Uncommon	Post-marketing safety experience (frequency not known)
Nervous system disorders	Headache**	Dizziness	Burning sensation, carpal tunnel syndrome, disturbance in attention, dysgeusia, hypoaesthesia, memory impairment, paraesthesia, presyncope, sinus headache, somnolence, tremor	
Eye disorders			Lacrimation increased	
Ear and labyrinth disorders			Vertigo	
Cardiac disorders		Bradycardia**	Nodal arrhythmia, tachycardia*	Cardiac disorder, arrhythmias*
Vascular disorders			Flushing, hypotension	
Respiratory, thoracic and mediastinal disorders		Dyspnoea*	Nasal mucosal disorder, throat irritation	
Gastrointestinal disorders	Abdominal pain, diarrhoea nausea, constipation**, flatulence**	Dyspepsia, vomiting, abdominal bloating*, steatorrhoea*, faeces soft**, faeces discoloured**, abdominal discomfort, abdominal distension, gastritis, gastro-oesophageal reflux disease	Acute pancreatitis, change of bowel habit, dry mouth, faecal incontinence, faecal volume increased, frequent bowel movements, gastrointestinal disorder, gastrointestinal motility disorder, haemorrhoidal haemorrhage, odynophagia, oesophageal achalasia, parotid gland enlargement, rectal tenesmus	
Hepatobiliary disorders	Chole-lithiasis**	Cholecystitis**, biliary sludge*, hyperbili-rubinaemia*	Bile duct obstruction, jaundice, post cholecystectomy syndrome, biliary colic, gallbladder disorder, hepatic steatosis	Acute hepatitis without cholestasis*, cholestatic hepatitis*, cholestasis*, cholestatic jaundice*
Skin and subcutaneous tissue disorders		Pruritus**, rash**, alopecia*	Allergic dermatitis, hyperhidrosis, hypertrichosis	Urticaria*

System organ class	Very common	Common	Uncommon	Post-marketing safety experience (frequency not known)
Musculoskeletal and connective tissue disorders		Arthralgia	Back pain, bone pain, flank pain, groin pain, joint swelling, muscle spasms, musculoskeletal discomfort, musculoskeletal pain, myalgia, pain in extremity, soft tissue swelling	
General disorders and administration site conditions [1]		Asthenia, fatigue, peripheral swelling	Feeling abnormal, feeling of body temperature change, malaise, pain, tenderness, thirst	
Investigations		Elevated liver function tests[2]	Blood creatine phosphokinase increased, blood creatinine increased, blood lactate dehydrogenase increased, blood urea increased, cardiac murmur, heart rate irregular, insulin-like growth factor increased, lipase increased, thyroxine increased, weight decreased, weight increased	Blood growth hormone increased

* These adverse reactions were not observed with Mycapssa. Their frequencies were established based on data from injectable octreotide

** Very common or common adverse reactions reported more frequently for injectable octreotide versus Mycapssa

[1] Injection site reactions were reported as very common ADR for injectable octreotide. Since Mycapssa is for oral administration only, this ADR is not included in the table

[2] For injectable octreotide, elevated transaminase levels were reported as common ADR, and increased alkaline phosphatase levels and gamma glutamyl transferase levels were reported post-marketing (frequency not known)

Description of selected adverse reactions

Gallbladder and related reactions

Somatostatin analogues have been shown to inhibit gallbladder contractility and decrease bile secretion, which may lead to gallbladder abnormalities or sludge. If gallstones do occur, they are usually asymptomatic; symptomatic stones should be treated either by dissolution therapy with bile acids or by surgery.

Cardiac disorders

Bradycardia is an adverse reaction with somatostatin analogues. ECG changes observed with octreotide include QT prolongation, axis shifts, early repolarisation, low voltage, R/S transition, early R wave progression, and non-specific ST-T wave changes. 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 (1,500 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.

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.

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.

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

In a single-dose study conducted in healthy volunteers, inhibition of GH was observed in all subjects receiving Mycapssa, as compared to their GH levels prior to Mycapssa.

In a study designed to assess the duration of Mycapssa-induced increased intestinal permeability, an increase in paracellular permeability was observed 2 hours after Mycapssa administration and returned to baseline by 5.5 hours after Mycapssa administration. Mycapssa-induced permeability is completely reversible within this timeframe.

Clinical efficacy and safety

The efficacy and safety of Mycapssa in patients with acromegaly were established in 3 phase 3 clinical studies: a 9-month, randomised, open-label, active-controlled study, preceded by a 6-month run-in phase (OOC-ACM-302); a 9-month, randomised, double-blind, placebo-controlled study (OOC-ACM-303); and a 7-month, open-label, baseline-controlled study (CH-ACM-01). All 3 studies were switch studies in patients with acromegaly who had responded to treatment with injectable somatostatin analogues. All 3 studies comprised optional open-label extension phases. In all 3 studies, the Mycapssa starting dose was 40 mg (20 mg in the morning and 20 mg in the evening). Dose increase of Mycapssa was allowed during dose titration to 60 mg (40 mg in the morning and 20 mg in the evening) and to a maximal dose of 80 mg daily (40 mg in the morning and 40 mg in the evening) until patients were deemed adequately controlled based on biochemical results and/or clinical judgement. Patients then maintained their target dose until end of treatment.

Study OOC-ACM-302
In the active-controlled study (OOC-ACM-302), 146 patients initiated Mycapssa run-in treatment within the routine dosing interval from their last somatostatin analogue injection. Mean baseline IGF-1 was 0.9 times the upper limit of normal (ULN). 116 patients (79.5%) completed the 6-month run-in phase; 30 patients (20.5%) discontinued. Most frequent reasons for discontinuation during the run-in phase were treatment failure (5.5%) and adverse events (9.6%; mostly mild to moderate gastrointestinal events).

Of the 146 patients enrolled, 92 patients (63.0%) completed the run-in phase and were biochemically controlled (defined as IGF-1 ≤ 1.3 times ULN and GH < 2.5 ng/mL). These patients were randomised to either continue treatment with Mycapssa or revert to their previous treatment with injectable somatostatin analogues.

The primary efficacy endpoint of study OOC-ACM-302 was the proportion of patients who were biochemically controlled throughout the 9-month randomised controlled treatment (RCT) phase. A patient was considered biochemically controlled if the IGF-1 time-weighted average of all IGF-1 assessments during the RCT phase was < 1.3 times ULN.

90.9% of patients treated with Mycapssa versus 100% of patients treated with injectable somatostatin analogues were biochemically controlled throughout the RCT phase. The primary endpoint met the prespecified non-inferiority criterion of -20% (see Table 2).

Table 2: Primary endpoint results of study OOC-ACM-302

	Mycapssa (N = 55)	**Injectable somatostatin analogues** (N = 37)
Primary analysis		
Biochemically controlled [1], n (%)	50 (90.9)	37 (100)
Difference in adjusted proportions [2]	-9.1	
95% CI	(-19.9, 0.5)	

[1] Defined as IGF-1 time-weighted average of all IGF-1 assessments during the RCT phase < 1.3 times ULN
[2] The adjusted difference and CI were obtained using the stratified M&N method
CI = confidence interval; IGF-1 = insulin-like growth factor 1; M&N = Miettinen & Nurminen; RCT = randomised controlled treatment; ULN = upper limit of normal

Table 3 includes data on active acromegaly symptoms reported during the run-in and RCT phases of OOC-ACM-302 study.

Table 3: Proportion of patients with active acromegaly symptoms in patients that enrolled to the randomised controlled treatment phase of study OOC-ACM-302

	Run-in phase		RCT phase	
Symptom	Baseline Run-in Injectable somatostatin analogues % (N = 92)	End of Run-in Mycapssa % (N = 92)	End of RCT Injectable somatostatin analogues % (N = 37)	End of RCT Mycapssa % (N = 55)
Joint pain	71	62	70	60
Swelling of extremities	47	33	41	42
Perspiration	50	42	54	38
Fatigue	75	64	65	64
Headache	50	48	43	53

RCT = randomised controlled treatment

Study OOC-ACM-303

The placebo-controlled study OOC-ACM-303 enrolled 56 patients. Mean baseline IGF-1 was 0.8 times ULN. The primary efficacy endpoint was the somatostatin dose-adjusted proportion of patients who maintained their biochemical response, defined similarly to the inclusion criteria, as an IGF-1 level less than or equal to the ULN at the end of 9 months of treatment. 58.2% of patients treated with Mycapssa versus 19.4% of patients treated with placebo maintained their biochemical response ($p = 0.0079$; see Table 4).

Table 4: Primary endpoint results of study OOC-ACM-303

	Mycapssa (N = 28)	**Placebo** (N = 28)
Maintained biochemical response [1], adjusted proportions [2]	58.16	19.42
Difference in adjusted proportions [2]	38.74	
95% CI	(10.68, 59.90)	
p-value	0.0079	

[1] Defined as average IGF-1 ≤ 1 x ULN after 9 months of treatment. Early discontinuation was regarded as non-response.

[2] Adjusted for treatment group, baseline SRL dose and baseline IGF-1 level

CI = confidence interval; IGF-1 = insulin-like growth factor 1; SRL = somatostatin receptor ligand; ULN = upper limit of normal

Study CH-ACM-01

The baseline-controlled study CH-ACM-01 enrolled 151 patients. Mean baseline IGF-1 was 0.9 times ULN. The primary efficacy endpoint was the proportion of responders at the end of the 7-month core treatment phase. Response was defined similarly to the inclusion criteria, as IGF-1 levels less than 1.3 times ULN and GH levels less than 2.5 ng/mL. Overall, 64.9% of patients were responders at the end of the core treatment phase (see Table 5).

Table 5: Primary endpoint results of study CH-ACM-01

	Mycapssa (N = 151)
Responders [1], n (%)	98 (64.9)
Exact 95% CI for % [2]	(58.4, 74.2)

[1] Defined as IGF-1 < 1.3 times ULN (adjusted for age and sex) and 2-hour integrated GH < 2.5 ng/mL after 7 months of treatment (LOCF analysis)

[2] Obtained using Clopper-Pearson (Exact) method

CI = confidence interval; GH = growth hormone; IGF-1 = insulin-like growth factor 1; LOCF = last observation carried forward; ULN = upper limit of normal

The individual symptom scores for swelling of extremities and joint pain showed a statistically significant improvement at the end of core treatment period, while treated with Mycapssa, compared to baseline, while treated with injectable somatostatin analogues (p = 0.0165 and p = 0.0382, respectively).

Paediatric population

See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Absorption

Orally administered octreotide is absorbed in the intestines via the paracellular route. Transient permeability enhancer (TPE®) excipients in the formulation facilitate the absorption of octreotide. In a clinical study it was shown that TPE excipients increase intestinal absorption via the paracellular route, using the lactulose to mannitol ratio test (see section 4.5). Increased permeability was shown to be transient and reversible (see section 5.1).

In healthy subjects, systemic exposure, as measured by AUC, of a single oral dose of Mycapssa (20 mg octreotide acetate) was 95% to 100% of that of a single dose of subcutaneous octreotide acetate (0.1 mg octreotide acetate), demonstrating comparable exposure. Peak octreotide levels (C_{max}) were 22%-33% lower following oral administration compared to the subcutaneous route. Absorption time was longer after oral administration than after subcutaneous administration; peak concentrations were reached at a median of 1.67-2.5 hours after oral administration and after 0.5 hours after subcutaneous administration.

After single-dose administration of Mycapssa, the systemic exposure of octreotide in healthy subjects increased dose-proportionally for doses between 3 and 40 mg. In patients with acromegaly, there was a dose-related increase in mean plasma octreotide concentrations after chronic administration of Mycapssa 40 mg (20 mg twice daily), 60 mg (40 mg morning/20 mg evening), and 80 mg (40 mg twice daily).

Effect of food on oral absorption
In healthy volunteer studies, administration of Mycapssa 20 mg with food led to an approximate 90% decrease in the extent of absorption. Full size high fat meals provided 1 hour prior or 2 hours post dose significantly decreased the absorption of Mycapssa (see section 4.2).

In all phase 3 studies Mycapssa capsules were taken at least 1 hour prior or at least 2 hours after eating any food.

Distribution

After subcutaneous injection, the volume of distribution is 0.27 L/kg, and the total body clearance 160 mL/min. Plasma protein binding amounts to 65%. The amount of octreotide bound to blood cells is negligible.

Elimination

The elimination half-life after subcutaneous administration is 100 minutes. Most of the peptide is eliminated via the faeces, while approximately 32% is excreted unchanged into the urine.

Half-life after single oral administration of Mycapssa was similar to the subcutaneous route (2.66 hours and 2.27 hours respectively).

In patients with acromegaly, elimination after chronic dosing was slightly slower than that seen in healthy volunteers, with mean apparent half-life values at steady state ranging from 3.2–4.5 hours across doses (20 mg, 40 mg, 60 mg, and 80 mg). Elimination is complete approximately 48 hours after the last dose in patients who have achieved steady-state plasma levels.

Special patient population

Patients with renal impairment
Exposure in subjects with severe renal impairment (estimated glomerular filtration rate [eGFR] 15–29 mL/min/1.73 m^2) was not substantially different from that of matched healthy controls. Subjects with end-stage renal disease (ESRD) requiring dialysis had higher mean plasma concentrations than those with severe renal impairment with higher mean values for peak plasma concentration, exposure (AUC), and half-life, consistent with an effect of renal impairment on octreotide exposure (see section 4.2).

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

Pharmacokinetics of octreotide after administration of 10 mg or 20 mg Mycapssa in subjects with stable cirrhosis and portal hypertension (Child Pugh A or B) were comparable to the pharmacokinetics in healthy volunteers (see section 4.2). No dose adjustment is necessary in patients with Child Pugh A or B.

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 acetate 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

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 the control rats, 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, or in cynomolgus monkeys treated orally with 20 mg/day octreotide (as octreotide capsules) for 9 months.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone
Sodium caprylate
Magnesium chloride
Polysorbate 80
Glyceryl monocaprylate
Glyceryl tricaprylate
Gelatine
Titanium dioxide (E171)
Methacrylic acid - ethyl acrylate copolymer (1:1)
Talc
Triethyl citrate
Silica, colloidal anhydrous
Sodium hydrogen carbonate
Sodium laurilsulfate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C). Do not freeze.

Mycapssa may be kept out of refrigeration for up to 1 month, at a temperature not above 25°C, after which the medicinal product must be discarded.

6.5 Nature and contents of container

Polychlorotrifluoroethylene [PCTFE]/polyethylene [PE]/polyvinylchloride [PVC]-aluminium blisters.

Pack size of 28 gastro-resistant hard capsules.

6.6 Special precautions for disposal and other handling

Patients should be instructed to gently remove capsules from the blister. Patients should press gently on top or bottom of a capsule; not press in the middle of a capsule as this could damage it. If a capsule is cracked or broken, patients should be advised to throw it away and remove a new capsule.

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

7. MARKETING AUTHORISATION HOLDER

Amryt Pharmaceuticals DAC
45 Mespil Road
Dublin 4
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1690/001

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 http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) 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(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Pharbil Pharma GmbH
Reichenberger Strasse 43
33605 Bielefeld
Germany

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.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

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

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Mycapssa 20 mg gastro-resistant hard capsules
octreotide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains octreotide acetate equivalent to 20 mg octreotide.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

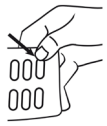
gastro-resistant hard capsules
28 gastro-resistant hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.

How to remove the capsule:



Press GENTLY on top or bottom of capsule.

DO NOT press the middle of the capsule.

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

Store in a refrigerator. Do not freeze.
During use, Mycapssa may be stored at no more than 25 °C for up to 1 month.

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

Amryt Pharmaceuticals DAC
45 Mespil Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1690/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Mycapssa

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 BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Mycapssa 20 mg gastro-resistant capsules
octreotide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Amryt Pharmaceuticals DAC

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Mycapssa 20 mg gastro-resistant hard capsules
octreotide

Read all of this leaflet carefully before you start taking 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 Mycapssa is and what it is used for

Mycapssa contains the active substance octreotide. Octreotide is a synthetic form of somatostatin, a natural substance 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.

Mycapssa 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 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 Mycapssa can help relieve the symptoms.

2. What you need to know before you take Mycapssa

Do not take Mycapssa
- 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 taking Mycapssa or during treatment if you have:
- **heart or blood circulation problems**, since the medicine can affect the rate and regularity of your heartbeat.
- **gallbladder problems.** Octreotide can cause gallstones to form, and your doctor will recommend ultrasound scans to check for this, usually every 6 to 12 months while you are being treated with this medicine.
- **diabetes**, since Mycapssa may affect your blood sugar. Persistent increased blood sugar levels may occur during long-term use. Low blood sugar levels have also been reported. Therefore, your doctor may recommend monitoring blood sugar levels and treatment of diabetes.

If you have type I diabetes and you are being treated with insulin, your doses may need to be reduced during treatment with Mycapssa.
- ever had **lack of vitamin B12**. If you have a history of lacking vitamin B12, your doctor may wish to check your vitamin B12 level periodically during treatment with Mycapssa since this medicine can decrease vitamin B12 levels in the blood.

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 Mycapssa. 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 when treatment with Mycapssa is prolonged.

Children and adolescents
Mycapssa is not recommended in children and adolescents under 18 years because it is not known if it is safe or effective in this age group.

Other medicines and Mycapssa
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Tell your doctor if you are taking the following medicines as they may change how Mycapssa works:

- medicines which control or reduce stomach acid
- metoclopramide: a medicine to treat nausea and vomiting
- loperamide: a medicine to treat diarrhoea

Also, tell your doctor if you are taking any of the following medicines, which may be affected when used with Mycapssa. If you take these medicines, your doctor may need to adjust the doses of these medicines:

- medicines called beta blockers, used to treat high blood pressure, heart disease or other illnesses
- medicines called calcium channel blockers, used to treat high blood pressure or heart diseases
- hydrochlorothiazide: a medicine to treat high blood pressure and tissue swelling caused by excess fluid
- quinidine: a medicine to treat irregular heart rhythm
- lisinopril: a medicine to treat high blood pressure and other heart and specific kidney diseases
- digoxin: a medicine to treat heart weakness and irregular heartbeat
- medicines to treat fluid and electrolyte balance
- insulin or other medicines to treat diabetes
- ciclosporin: a medicine to suppress transplant rejection, treat severe skin diseases, severe eye and joint inflammation
- bromocriptine: a medicine to treat Parkinson’s and other diseases (e.g. pituitary tumours) and to aid weaning
- oral contraceptives, such as birth control pills: a medicine to prevent pregnancy or to treat intensive menstrual bleeding
  Mycapssa may reduce the effectiveness of oral hormonal contraceptives containing progestogens.

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.

Avoid taking Mycapssa during pregnancy and breast-feeding. This is a precaution, as there is limited information on the use of Mycapssa during pregnancy and breast-feeding.

Women who can get pregnant should use effective contraception during treatment with Mycapssa. Discuss appropriate methods with your doctor as Mycapssa may reduce the effectiveness of oral contraceptives containing progestogens. If you are using such contraceptives, you are therefore advised to use other non-hormonal methods of contraception or add a back-up method while taking Mycapssa.

Driving and using machines
Mycapssa has no or negligible influence on the ability to drive and use machines. However, avoid driving or using machines if your ability to react is reduced due to side effects such as dizziness, weakness/fatigue or headache.

Mycapssa contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'.

3. How to take Mycapssa

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

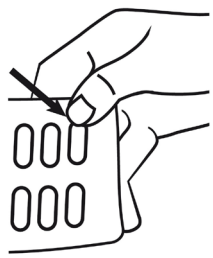
The recommended **starting dose is 1 capsule twice daily**.

The doctor will gradually increase the dose in steps of 1 capsule daily to adequately control your disease, up to a **maximum** recommended daily dose of **4 capsules**. Your doctor will check your symptoms and the levels of a substance called insulin-like growth factor every 2 weeks or so after each increase, to check how your body is responding to the new dose and find the right dose for you.

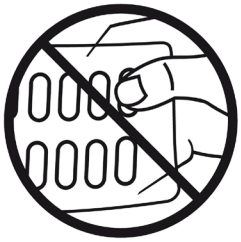
Your doctor will check your symptoms less frequently once you are on a regular daily dose. During these checks your doctor will make sure that the medicine is still working well for you.

Method of use
Always take this medicine as instructed by your doctor. Swallow the capsules whole with a glass of water, at least 1 hour before or 2 hours after eating any food. It is recommended to have a routine schedule for taking Mycapssa in relation to food every day (for example, take Mycapssa routinely at least 1 hour before breakfast and at least 2 hours after dinner).

How to remove a capsule from blister:
Press GENTLY on top or bottom of capsule.



DO NOT press the middle of the capsule. This could damage it.
If a capsule is cracked or broken, throw it away (discard it) and remove another capsule.



If you take more Mycapssa than you should
If you have accidentally taken more Mycapssa than you should, stop taking this medicine and tell your doctor straight away.

If you forget to take Mycapssa
Do not take a double dose to make up for a forgotten dose. Administer one dose as soon as you remember, as long as it is taken at least 6 hours before the next scheduled dose. Otherwise, skip the missed dose and take your next dose at the usual time.

If you stop taking Mycapssa
Do not stop taking this medicine without discussing with your doctor first. If you stop taking Mycapssa, 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.

Side effects can occur with the following frequencies:
Very common (may affect more than 1 in 10 people)
- abdominal (belly) pain
- diarrhoea
- nausea
- increased blood sugar level
- headache
- constipation
- wind
- gallstones

Common (may affect up to 1 in 10 people)
- dizziness
- discomfort or bloating or swelling of your abdomen (belly)
- indigestion
- inflammation of stomach lining
- disease caused by reflux of stomach juices
- vomiting
- joint pain
- weakness, fatigue
- swelling of arms and/or legs
- increased levels of liver enzymes
- low blood sugar level
- discoloured stool, soft stool
- loss of appetite
- slow heartbeat

- difficulty breathing
- excess fat in stool
- acute inflammation of the gallbladder
- thickening of bile
- increased blood level of bilirubin, a waste product from breakdown of red blood cells
- itching, rash
- hair loss
- thyroid problems

Uncommon (may affect up to 1 in 100 people)
- inflammation of abnormal pouches in the wall of the large intestine
- inflammation of the stomach and bowel lining
- herpes (sores) of the mouth lining
- non-aggressive tumour of liver blood vessels
- reduced number of white blood cells
- decreased appetite
- diabetes mellitus
- dehydration
- high blood fat values of triglycerides
- restlessness
- anxiety
- depression, disorientation, altered mood, mood swings
- hallucination in hearing, visual hallucination
- sleeping difficulties
- pain, numbness and tingling in the wrist or hand
- disturbed attention
- taste disturbance
- reduced memory
- abnormal sensation such as reduced sense of touch, burning, prickling, tingling and itchiness
- feeling faint
- headache due to blocked sinuses
- drowsiness
- shaking
- increased flow of tears
- irregular heartbeat, fast heartbeat
- sudden skin reddening and feeling very hot
- low blood pressure
- disorder of the inner lining in the nose, throat irritation
- acute pancreas inflammation
- change of bowel habit
- dry mouth
- stool incontinence, increased stool volume
- frequent bowel movements
- stomach and bowel disorder, such as motility disorder
- bleeding haemorrhoids (piles)
- pain when swallowing
- a disorder called achalasia which can cause the lower gullet sphincter to remain closed, causing difficulty in swallowing
- parotid (jaw) gland enlargement
- feeling of incomplete bowel emptying
- bile duct obstruction
- yellowing of the skin, internal organs and/or whites of the eyes
- complaints after surgical removal of the gallbladder called post cholecystectomy syndrome
- gallbladder attack, gallbladder disorder
- fatty liver
- allergic skin inflammation
- increased sweating

- condition of excessive body hair
- pain, such as back pain, bone pain, flank pain, groin pain
- joint swelling
- muscle spasms
- discomfort or pain of muscles and skeleton
- pain in arms and legs
- soft tissue swelling
- feeling abnormal or unwell
- feeling of body temperature change
- tenderness
- thirst
- heart murmur
- increased or decreased weight
- increased blood levels of:
    - creatine phosphokinase
    - creatinine
    - lactate dehydrogenase
    - urea
    - insulin-like growth factor
    - lipase
    - thyroxine

Not known (frequency cannot be estimated from the available data)
- heart disorder
- increased growth hormone levels in the blood
- low platelet counts, potentially leading to bruising or bleeding
- severe allergic reactions or other allergic reactions
- abnormal heart rhythms
- liver inflammation
- reduced bile flow
- jaundice
- nettle-rash

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 Mycapssa

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 and blister after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C – 8 °C). Do not freeze.

Mycapssa can be kept out of refrigeration for up to 1 month, but may not be stored above 25 °C, after which the medicine must 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 Mycapssa contains
- The active substance is octreotide. One capsule contains octreotide acetate equivalent to 20 mg octreotide.
- The other ingredients are povidone, sodium caprylate, magnesium chloride, polysorbate 80, glyceryl monocaprylate, glyceryl tricaprylate, gelatine, titanium dioxide (E171), methacrylic acid - ethyl acrylate copolymer (1:1), talc, triethyl citrate, silica, colloidal anhydrous, sodium hydrogen carbonate, sodium laurilsulfate (see section 2 “Mycapssa contains sodium”).

What Mycapssa looks like and contents of the pack
Mycapssa are white gastro-resistant hard capsules (gastro-resistant capsule). They are packed in plastic/aluminium blisters in a carton.

Pack size: 28 gastro-resistant hard capsules

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
Amryt Pharmaceuticals DAC
45 Mespil Road
Dublin 4
Ireland

Manufacturer
Pharbil Pharma GmbH
Reichenberger Strasse 43
33605 Bielefeld
Germany

This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.