ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Palsonify 20 mg film-coated tablets
Palsonify 30 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Palsonify 20 mg film-coated tablets

Each film-coated tablet contains 20 mg of paltusotine (as paltusotine hydrochloride).

Palsonify 30 mg film-coated tablets

Each film-coated tablet contains 30 mg of paltusotine (as paltusotine hydrochloride).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Palsonify 20 mg film-coated tablets

Pink, biconvex oval film-coated tablets, 16 mm length and 8 mm width, debossed with “PAL” on one side and “20” on the other side.

Palsonify 30 mg film-coated tablets

Yellow, biconvex oval film-coated tablets, 18 mm length and 9 mm width, debossed with “PAL” on one side and “30” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Palsonify is indicated for the medical treatment of adult patients with acromegaly.

4.2 Posology and method of administration

Posology

For medically naïve patients, the recommended initial dose is 20 mg Palsonify by oral route once daily for 2 weeks and if well tolerated, the dose should be increased to 40 mg once daily. After 2 to 4 weeks on Palsonify 40 mg once daily, if 40 mg is well tolerated, the dose can be increased to 60 mg based on insulin-like growth factor-1 (IGF-1) levels or clinical signs and symptoms.

For non-medically naïve patients, the recommended initial dose is 40 mg Palsonify by oral route once a day. After 2 to 4 weeks on Palsonify 40 mg once daily, based on IGF-1 levels or clinical signs and symptoms, the dose can be increased to 60 mg once daily.

Based on tolerability (see section 4.8), the dose may be temporarily reduced by 20 mg. Once adverse reactions have resolved, paltusotine can be resumed at the previous dose.

Monitoring of IGF-1 levels and assessment of symptoms should be made periodically as per the clinician's discretion. Normalisation of IGF-1 levels may require a longer treatment duration in patients with high IGF-1 levels at baseline. In patients with elevated baseline IGF-1 levels (e.g. ≥ 2.5×upper limit of normal [ULN]), especially in medically naïve patients, a more regular re-evaluation of the benefit risk of the treatment in monotherapy should be considered.

Missed dose
If the daily dose of Palsonify is missed, the patient should be told not to take the missed dose and continue with the next scheduled dose.

Drug-drug interactions

Strong inducer of CYP3A4/5, UGT1A1, and P-gp
In case of co-administration with strong inducers (e.g. carbamazepine), based on IGF-1 levels and patient's safety, paltusotine dose should be increased up to three-fold the therapeutic dose without exceeding 120 mg daily (see section 4.5).

Moderate or weak inducer of CYP3A4/P-gp
In case of co-administration with moderate (e.g. efavirenz) or weak (e.g. prednisone) inducers, based on IGF-1 levels and patient's safety, paltusotine dose may be increased without exceeding 120 mg daily (see section 4.5).

Proton pump inhibitor (PPI)
In case of co-administration with PPIs (e.g. lansoprazole, omeprazole), dose of paltusotine may be increased up to two-fold the therapeutic dose based on IGF-1 levels and patient's safety (see section 4.5).

Special populations

Elderly (≥ 65 years old)
No dose adjustment is required based on age (see section 5.2).

Hepatic impairment
No dose adjustment is required in patients with mild, moderate or severe hepatic impairment (see section 5.2).

Renal impairment
No dose adjustment is required in patients with mild, moderate or severe renal impairment (see section 5.2).

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

Method of administration

Oral use.
This medicinal product should be swallowed whole with a glass of water, on an empty stomach, at least 6 hours after a meal (e.g. after overnight fast), and at least 1 hour prior to a meal.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Tumour expansion

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

Women of childbearing potential

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

Cardiovascular abnormalities

Cardiac conduction abnormalities and other ECG changes such as PR interval prolongation and bradycardia have occurred during treatment with paltusotine in clinical studies (see section 4.8). These ECG changes may occur in patients with acromegaly. Dose adjustments of concomitantly used medicinal products that have bradycardia effects (e.g. beta blockers) may be necessary (see section 4.5).

Gallbladder-related events

Palsonify may inhibit gallbladder contractility and decrease bile secretion, which may lead to gallbladder stones or sludge. Cholelithiasis and its complications have been reported with the use of paltusotine (see section 4.8). If complications of cholelithiasis are suspected, evaluation and appropriate treatment should be initiated, and benefit-risk should be considered in determining whether or not to continue treatment with paltusotine.

Glucose metabolism

Because of its effect on GH, glucagon, and insulin, paltusotine may affect glucose regulation. Hyperglycaemia was reported in patients treated with Palsonify in clinical studies (see section 4.8). Blood glucose levels should be monitored when Palsonify treatment is initiated or the dose is altered, and antidiabetic treatment should be adjusted accordingly (see section 4.5).

Thyroid function abnormalities

Somatostatin analogues may suppress the secretion of thyroid-stimulating hormone (TSH), which may result in hypothyroidism. Periodic assessment of thyroid function (TSH and total and/or free T4) is recommended during treatment with paltusotine (see section 4.5).

Nutrition

Somatostatin analogues may alter absorption of dietary fats in some patients.

Vitamin B12 deficiency

Decreased vitamin B12 levels have been observed in patients treated with somatostatin analogues. Vitamin B12 levels during treatment with Palsonify should be monitored if clinically indicated.

4.5 Interaction with other medicinal products and other forms of interaction

Agents that may decrease paltusotine plasma concentration

Strong inducers of multiple enzymes and transporters (CYP3A4/5, UGT1A1, and P-gp)
A clinical study in healthy subjects showed following a 60 mg paltusotine administration, carbamazepine, a strong inducer of CYP3A4/5, UGT1A1, and P-gp, decreased paltusotine C_{max} and AUC by approximately 40% and 70%, respectively. Co-administration of paltusotine with strong inducers may thus decrease the therapeutic response.

In case of co-administration with strong inducers (e.g. carbamazepine), based on IGF-1 levels and patient's safety, paltusotine dose should be increased up to three-fold the therapeutic dose without exceeding 120 mg daily (see section 4.2).

Moderate or weak inducers of CYP3A4/P-gp
Based on the observed 70% decrease in paltusotine exposure following strong inducer (carbamazepine), a smaller decrease in exposure is expected following moderate or weak inducer. Co-administration of paltusotine with a moderate (e.g. efavirenz) or weak (e.g. prednisone) CYP3A4/P-gp inducer may thus decrease therapeutic response and dose adjustment may be necessary according to the clinical response.

In case of co-administration with moderate (e.g. efavirenz) or weak (e.g. prednisone) CYP3A4/P-gp inducers, based on IGF-1 levels and patient's safety, paltusotine dose may be increased without exceeding 120 mg daily (see section 4.2).

Proton pump inhibitors
A clinical study in healthy subjects showed PPIs caused a dose-dependent decreases in paltusotine AUC by approximately 20% and 40% following 20 mg and 60 mg paltusotine dose, respectively.

Co-administration of paltusotine with PPIs demonstrated a dose-dependent decrease in paltusotine exposure that may thus decrease therapeutic response and dose adjustment may be necessary according to the clinical response.

In case of co-administration with PPIs (e.g. lansoprazole, omeprazole), dose of paltusotine may be increased to two-fold the therapeutic dose based on IGF-1 levels and patient's safety (see section 4.2).

Cyclosporine
A clinical study conducted in healthy subjects showed, following 200 mg cyclosporine administration, paltusotine exposure was increased by ≤ two-fold. No paltusotine dose adjustment is necessary.

Effects of paltusotine on the pharmacokinetics of other medicinal products

Cyclosporine
A clinical study in healthy subjects, 40 mg paltusotine caused approximately 50% and 35% decreases in cyclosporine C_{max} and AUC in whole blood, respectively. Co-administration of paltusotine with cyclosporine resulted in a decrease in cyclosporine bioavailability.

Adjustment of cyclosporine dose to maintain therapeutic levels may be necessary. Recommended therapeutic medicinal product monitoring for cyclosporine should be followed.

CYP3A4 substrates
A clinical study in healthy subjects, 60 mg paltusotine caused approximately 30% increases in AUC of midazolam, a CYP3A4 substrate. Dose adjustments for CYP3A4 substrates without a narrow therapeutic index are not necessary. Caution and appropriate monitoring are recommended if paltusotine is co-administered with a CYP3A4 substrate with a narrow therapeutic index (e.g. tacrolimus).

CYP2D6 substrates
In vitro, paltusotine is an inhibitor of CYP2D6 (see section 5.2). Caution is advised if paltusotine is co-administered with a CYP2D6 substrate (e.g. carvedilol, nebivolol, metoprolol, fluoxetine, or dextromethorphan). No clinical drug-drug interaction study was performed. Dose adjustments for CYP2D6 substrates are not necessary.

P-gp substrates
In vitro, paltusotine is an inhibitor of P-gp (see section 5.2). Caution is advised if paltusotine is co-administered with a P-gp substrate with a narrow therapeutic index (e.g. digoxin). No clinical drug-drug interaction study was performed. Dose adjustments for P-gp substrates are not necessary.

Metformin
A clinical study in healthy volunteers, showed concomitant administration of metformin and paltusotine resulted in a decrease in metformin exposure by 22%, Cmax by 39%. The clinical result is considered relevant as this result is not expected based on in vitro finding of MATE inhibition by paltusotine. Nevertheless, the change in metformin exposure is not considered clinically significant. Therefore, no dose adjustment is necessary.

Pharmacodynamic interactions

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

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

Thyroid hormones replacement therapy
Somatostatin analogues may affect thyroid function (see sections 4.4). Therefore, monitoring of thyroid function and clinical monitoring is recommended during concomitant treatment thyroid hormone replacement therapy as this may lead to thyroid imbalance.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data from the use of paltusotine in pregnant women. Animal studies do not indicate direct or indirect harmful effects at human exposure with respect to reproductive toxicity (see section 5.3).
As a precautionary measure, it is preferable to avoid the use of Palsonify during pregnancy.

Breast-feeding

It is unknown whether paltusotine/metabolites are excreted in human milk. Available toxicological data in animals have shown excretion of paltusotine/metabolites in milk (see section 5.3). A risk to the suckling newborns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with Palsonify.

Fertility

No human data on the effect of paltusotine on fertility are available. Although no effects on mating or fertility were identified in animal studies, changes in reproductive parameters were reported in female rats (see section 5.3).

4.7 Effects on ability to drive and use machines

Palsonify has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Gastrointestinal symptoms of diarrhoea (18%), abdominal pain (7%), nausea (5%) and abdominal discomfort (3%) were the most frequently reported adverse reactions with paltusotine.

Tabulated list of adverse reactions

The safety of paltusotine was evaluated in 169 adults with acromegaly in two randomised, double-blind, placebo-controlled studies.

A total of 233 patients were exposed to paltusotine in all phase 2 and 3 and open label extension (OLE) acromegaly studies. The median duration of treatment with paltusotine in patients with acromegaly was 65.4 weeks (range: 0.7 to 244.3 weeks).

Adverse reactions are listed by MedDRA system organ class (SOC) and frequency, using the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse reactions

System organ class	Adverse reaction	Frequency
Metabolism and nutrition disorders	Hyperglycaemia	Common
	Decreased appetite	Common
Nervous system disorders	Headache	Common
	Dizziness	Uncommon
Cardiac disorders	Sinus bradycardia[a]	Common
Gastrointestinal disorders	Diarrhoea	Very common
	Abdominal pain	Common
	Nausea	Common
	Abdominal discomfort	Common
	Abdominal distension	Common
	Vomiting	Common
Hepatobiliary disorders	Cholelithiasis	Common
	Bile duct stone	Uncommon
Skin and subcutaneous tissue disorders	Alopecia	Common
General disorders and administration site conditions	Fatigue	Common

[a] Sinus bradycardia includes preferred terms: sinus bradycardia and bradycardia.

Description of selected adverse reactions

Bradycardia
Events of bradycardia occurred in 6% of patients treated with paltusotine, were asymptomatic and did not lead to the discontinuation of the medicinal product. The events occurred in patients with and without a history of bradycardia, occurred in the first three months of treatment and there was no clear dose association. The mean reduction in heart rate was 6 beats per minute (bpm) (see section 4.4).

Gallbladder-related adverse reactions
In randomised studies, cholelithiasis occurred between 6 and 9 months after the start of paltusotine. In all patients exposed to paltusotine in the clinical development program, cholelithiasis occurred in 4.7% and bile duct stone in 0.4%. In patients who had not received previous treatment with somatostatin receptor ligand therapies, cholelithiasis was reported in 8.3% (2/24) of patients. No patients discontinued paltusotine due to cholelithiasis (see section 4.4).

Gastrointestinal disorders
Most gastrointestinal adverse reactions occurred within the first two months of paltusotine initiation, all were non serious and had a median duration ranging between 4 to 12 days. The majority of the adverse reaction were mild, none were severe and improved with continued treatment. There were no discontinuations due to gastrointestinal adverse reactions.

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

There are no clinical data available on the effects associated with overdose and no incidents of overdose have been observed with paltusotine. Animal studies indicate that bradycardia or hypertension may result from overdose. If overdose is suspected, supportive treatment should be employed in the management of overdose with a medicinal product with potential bradycardia.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Pituitary and hypothalamic hormones and analogues, ATC code: H01CB06

Mechanism of action

Similar to the natural hormone somatostatin (SST), paltusotine demonstrates potent suppression of GH and IGF-1 secretion. Paltusotine exerts its pharmacological activity via highly selective binding (> 4 000-fold) to somatostatin receptor 2 (SST2) and exhibits little or no affinity for other SST receptor subtypes. Paltusotine inhibits cyclic adenosine monophosphate (cAMP) accumulation via human SST2 activation with an average drug (agonist) concentration that results in half-maximal response (EC_{50}) of 0.25 nM.

Pharmacodynamic effects

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

Cardiac electrophysiology
At 4.6 times the exposure of the paltusotine 60 mg therapeutic dose, clinically significant QTc interval prolongation was not observed.

Clinical efficacy and safety

The efficacy and safety of paltusotine for the medical treatment of adults with acromegaly was established in two phase 3 randomised, double-blind, parallel group, placebo-controlled clinical studies (PATHFNDR-2 and PATHFNDR-1).

Study PATHFNDR-2
This 24-week study (PATHFNDR-2) enrolled 111 adult patients with acromegaly who were not receiving medical treatment and were biochemically uncontrolled at randomisation. Patients were either not previously medically treated or had no treatment within the previous 4 months prior to screening (not medically treated) or were receiving, and washed out of, somatostatin receptor ligand monotherapy with octreotide or lanreotide during screening (washout). IGF-1 levels were required to be ≥ 1.3×ULN for those not medically treated and ≥ 1.1×ULN with at least a 30% rise in IGF-1 during the screening period for the washout patients. Patients were randomised to receive either paltusotine (N=54) or placebo (N=57) for the 24-week treatment period. The starting dose was 20 mg/day during 2 weeks and the dose could be increased to 40 mg/day at the week 2 visit after confirming tolerability. At week 6, the dose could be increased to 60 mg once daily, if the 40 mg dose was acceptably tolerated and based on biochemical control and the week 4 IGF-1 was > 0.9×ULN. Dose down-titration was allowed at any time during the randomised control phase of the study if the dose was not tolerated. After week 12, the dose was maintained until the end of the randomised controlled period of the study (week 24).

Fifty-three per cent (53%) of patients were female; 52% were White, 31% Asian, 3% Black or African American, 9% Other and 5% Unknown race. The mean age at time of enrolment was 47 years (9% were ≥ 65 years). The mean duration since diagnosis of acromegaly was 87 months with 89% of patients receiving pituitary surgery within a mean duration of 75 months prior to study participation. The overall baseline mean IGF-1 was 2.3×ULN in the not medically treated patients and 1.5×ULN in the washout patients.

The primary endpoint was met, with 55.6% of paltusotine patients achieving biochemical control (IGF-1 level ≤ 1.0×ULN) at week 24 compared to 5.3% of placebo-treated patients (p-value < 0.0001).

In addition to achieving the primary endpoint, paltusotine produced statistically significant (p-value < 0.0001) reductions of IGF-1 to normal levels in both not medically treated (42.5%) and washout (92.9%) patients compared to placebo-treated patients regardless of prior treatment history (Table 2).

An analysis of change from baseline in IGF-1 to week 24 showed that, while baseline mean IGF-1×ULN levels was consistent between the paltusotine and placebo groups (2.0 and 2.2, respectively), paltusotine resulted in a statistically significant difference (p-value < 0.0001) compared to placebo-treated patients among all patients as well as in both the not medically treated and washout groups (Table 2).

Table 2: Study PATHFNDR-2 overall efficacy results based on IGF-1 levels

IGF-1 normalisation	**paltusotine (N=54)**	**placebo (N=57)**	**p-value**
Proportion of patients who achieved IGF-1 level ≤ 1.0×ULN at week 24, n (%)	30 (55.6%)	3 (5.3%)	< 0.0001
Not medically treated or previously treated, n/N (%)	17/40 (42.5%)	1/42 (2%)	< 0.0001
Medically naïve, n/N (%)	5/22 (22.7%)	1/24 (4.2%)	0.1509
Previously treated, n/N (%)	12/18 (66.7%)	0/18 (0)	< 0.0001
Washout, n/N (%)	13/14 (92.9%)	2/15 (13.3%)	< 0.0001

Change from baseline in IGF-1	paltusotine (N=54)	placebo (N=57)	p-value
Change from baseline in IGF-1 at week 24 (xULN), LS mean (SE)	-0.819 (0.0789)	0.087 (0.0751)	< 0.0001
Not medically treated or previously treated, LS mean (SE)	-0.887 (0.0903)	0.070 (0.0881)	< 0.0001
Medically naïve, LS mean (SE)	-0.829 (0.1357)	0.046 (0.1299)	< 0.0001
Previously treated, LS mean (SE)	-0.964 (0.1151)	0.108 (0.1151)	< 0.0001
Washout, LS mean (SE)	-0.600 (0.1044)	0.152 (0.1008)	< 0.0001

IGF-1 at week 24 is based on the average of the last 2 measurements of IGF-1 collected at weeks 22 and 24. When one of the two last IGF-1 measurements was missing a single value was used. Week 24 is the end of the randomised controlled portion of the study; if a patient received rescue therapy, the last assessment prior to rescue is used.
IGF-1=insulin-like growth factor-1, LS=least squares, SE=standard error, ULN=upper limit of normal.

Treatment with paltusotine resulted in an approximately 37% reduction in IGF-1 by 4 weeks following initiation of treatment and was sustained through the end of the treatment period (Figure 1).

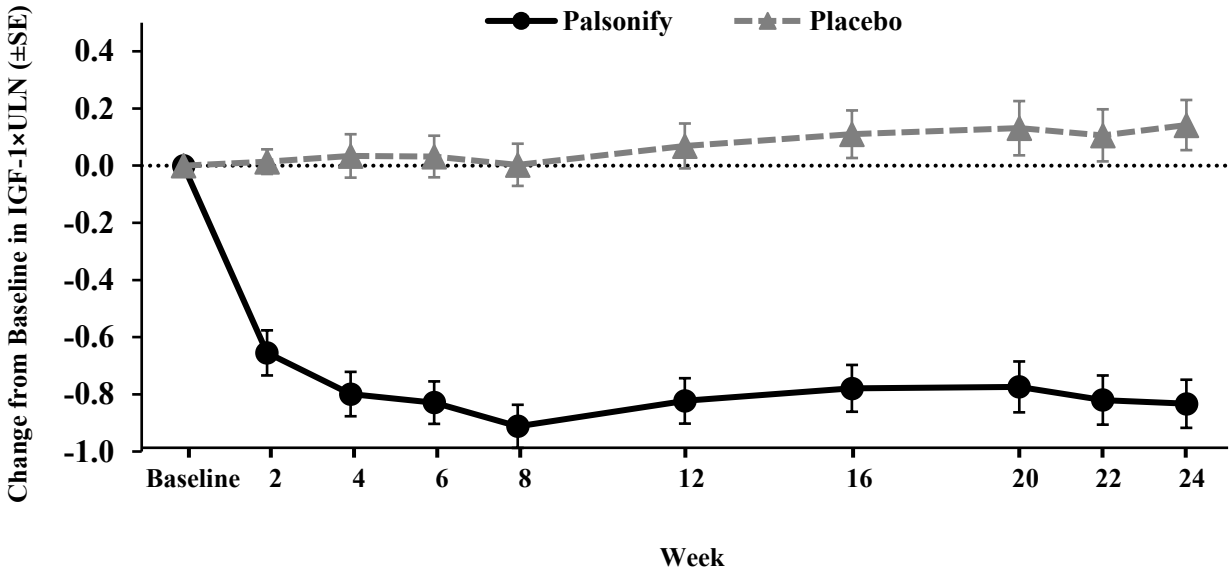

Figure 1: Study PATHFNDR-2 LS mean (±SE) IGF-1 (×ULN) change from baseline by visit for all patients
The population includes all randomised patients based on multiple imputation methods.
IGF-1=insulin-like growth factor-1, LS=least squares, SE=standard error, ULN=upper limit of normal.

An analysis of time to response from randomisation demonstrated 59% of paltusotine-treated patients achieved IGF-1 normalisation compared to 9% in the placebo-treated group during the study. The majority of IGF-1 normalisation events occurred during the first 4 weeks of treatment. These results are consistent with the primary endpoint analysis which demonstrated continued response in a majority of paltusotine-treated patients through the end of week 24.

Table 3: Study PATHFNDR-2 proportion of patients with IGF-1< 1.3×ULN

IGF-1 < 1.3×ULN	paltusotine (N=54)	placebo (N=57)	p-value
Proportion of patients who achieved IGF-1 level < 1.3×ULN at week 24, n (%)	36 (66.7%)	8 (14%)	< 0.0001
Not medically treated or previously treated, n/N (%)	22/40 (55%)	4/42 (9.5%)	< 0.0001
Medically naïve, n/N (%)	8/22 (36.4 %)	2/24 (8.3 %)	0.0495
Previously treated, n/N (%)	14/18 (77.8%)	2/18 (11.1%)	0.0001
Washout, n/N (%)	14/14 (100%)	4/15 (26.7%)	< 0.0001

IGF-1 at week 24 is based on the average of the last 2 measurements of IGF-1 collected at weeks 22 and 24. When one of the two last IGF-1 measurements was missing a single value was used. Week 24 is the end of the randomised controlled portion of the study; if a patient received rescue therapy, the last assessment prior to rescue is used.
IGF-1=insulin-like growth factor-1, ULN=upper limit of normal.

Consistent with the paltusotine mechanism of action, target GH levels of < 1.0 ng/mL were achieved in 57% in the paltusotine-treated patients compared with 17.5% in the placebo-treated patients (p-value < 0.0001) at week 24 (Table 4).

Table 4: Study PATHFNDR-2 proportion of patients with GH < 1.0×ULN

GH < 1.0×ULN	paltusotine (N=54)	placebo (N=57)	p-value
Proportion of patients who achieved GH < 1.0×ULN at week 22, n (%)	31 (57.4%)	10 (17.5%)	< 0.0001
Not medically treated or previously treated, n/N (%)	21/40 (52.5%)	3/42 (7.1%)	< 0.0001
Medically naïve, n/N (%)	8/22 (36.4%)	1/24 (4.2%)	0.0148
Previously treated, n/N (%)	13/18 (72.2%)	2/18 (11.1%)	0.0005
Washout, n/N (%)	10/14 (71.4%)	7/15 (46.7%)	0.3297

GH=growth hormone, ULN=upper limit of normal.

Study PATHFNDR-2 measured clinical symptom severity for 7 items associated with acromegaly (headache pain, joint pain, sweating, fatigue, weakness in legs, swelling, and numbness or tingling) using the acromegaly symptoms diary (ASD), with each item score ranging from 0 (no symptoms) to 10 (worst symptoms). A preliminary threshold range to characterise meaningful within patient change for the ASD total is a -4 to -6 point change for improvement or worsening out of a total score of 70. At baseline, patients presented with mild to moderate symptoms. The change from baseline to week 24 in total ASD score shows a statistically significant improvement of -2.669 for the paltusotine-treated patients compared to a worsening of 2.754 for placebo-treated patients (p-value=0.0039). In not medically treated or previously treated patients who received paltusotine, the ASD score showed an improvement of -4.187 compared to a worsening of 0.163 in placebo-treated patients. In washout patients, those receiving paltusotine exhibited an improvement of -1.610 compared to worsening of 5.777 in those receiving placebo (Table 5).

Table 5: Change from baseline to week 24 in total ASD score in study PATHFNDR-2

	paltusotine (N=54)	placebo (N=57)	Treatment difference (95% CI)	p-value
Change from baseline in total ASD score to week 24				
LS mean (SE)	-2.669 (±1.422)	2.754 (±1.364)	-5.423 (-9.070, -1.776)	0.0039
Not medically treated or previously treated	-4.187 (±1.605)	0.163 (±1.565)	-4.349 (-8.831, 0.132)	0.0570

	paltusotine (N=54)	placebo (N=57)	Treatment difference (95% CI)	p-value
Medically naïve	-3.189 (±1.976)	2.669 (± 1.848)	-5.868 (-11.336, -0.380)	0.0367
Previously treated	-5.344(±2.547)	-3.381 (±2.621)	-1.963 (-9.44, 5.518)	0.5967
Washout	-1.610 (±2.209)	5.777 (±2.054)	-7.387 (-13.638, -1.137)	0.0224

Week 24 is the end of the randomised controlled portion of the study; if a patient received rescue therapy, the last assessment prior to rescue is used. Baseline total ASD is the sum of the weekly average on or prior to day 1, and post-baseline total ASD is the sum of the weekly average on or prior to the scheduled visit date, inclusive of the date of visit, for 7 items (headache, joint pain, sweating, fatigue, weakness in legs, swelling, and numbness or tingling).At baseline, mean total ASD score was 17.48 in the paltusotine group, and 15.54 in the placebo group.
ASD=Acromegaly symptoms diary, CI=confidence interval, LS=least squares, SE=standard error.

Results by ASD individual item score change from baseline to week 24 for all patients showed for all 7 items a trend in favour of paltusotine, 5 of which were statistically significant (headache pain, sweating, fatigue, weakness in legs, swelling; $p < 0.05$).

The LS means (±SE) change from baseline to end of treatment in most bothersome symptoms were -0.553 (±0.4219) in the paltusotine group and 0.357 (±0.3770) in the placebo group, with a treatment difference of -0.910 (95% CI: -1.976, 0.157) in favour of paltusotine (nominal p=0.0935).

The observed safety and tolerability profile remained unchanged (see section 4.8) and the durability of the clinical treatment benefits were retained in patients dosed for 120 weeks in the ongoing OLE study PATHFNDR-2.

Study PATHFNDR-1
This 36-week study (PATHFNDR-1) enrolled 58 patients who were biochemically controlled on injectable depot octreotide or lanreotide somatostatin receptor ligand therapy. All patients were required to be biochemically controlled (defined as IGF-1 levels ≤ 1.0×ULN) during screening and at randomisation. Patients were randomised to receive either paltusotine (N=30) or placebo (N=28) for the 36-week treatment period. The dose could be titrated from 40 mg to a maximum of 60 mg based on IGF-1 value or decreased based on tolerability. After week 24, the paltusotine dose was maintained until the end of the randomised controlled period (week 36).

Fifty-five per cent (55%) of patients were female, 72% were White, 3% Asian, 5% Black or African American, 12% Other, 7% Unknown race. The mean age at time of enrolment was 55 years (28% were ≥ 65 years). The mean duration since diagnosis of acromegaly was 155 months with 86% of patients receiving pituitary surgery within a mean duration of 138 months prior to study participation. The baseline mean IGF-1 was 0.83×ULN with a baseline mean GH level of 0.90 ng/mL. Of enrolled patients, 59% were previously treated with octreotide and 41% previously treated with lanreotide. The majority of patients enrolled were on the mid or high doses of approved somatostatin receptor ligand therapy prior to screening.

The primary endpoint was met, with 83.3% of paltusotine-treated patients maintained biochemical control (IGF-1 level ≤ 1.0×ULN) at week 36 compared to 3.6% of placebo-treated patients (Table 6).

Table 6: Study PATHFNDR-1 overall efficacy results based on IGF-1 levels

IGF-1 normalisation	**paltusotine (N=30)**	**placebo (N=28)**	**p-value**
Proportion of patients who maintained response in IGF-1 at week 36 (≤ 1.0×ULN), n (%)	25 (83.3%)	1 (3.6%)	< 0.0001
Change from baseline in IGF-1	**paltusotine (N=30)**	**placebo (N=28)**	**p-value**
Change from baseline in IGF-1 at week 36 (×ULN) LS mean (SE)	0.042 (±0.093)	0.833 (±0.096)	< 0.0001

Week 36 is the end of the randomised controlled portion of the study; if a patient received rescue therapy, the last assessment prior to rescue is used.
IGF-1=insulin-like growth factor 1, LS=least squares, SE=standard error, ULN=upper limit of normal.

Paltusotine demonstrated stable IGF-1 levels in patients who switched from prior somatostatin receptor ligand therapy, which was sustained through the end of the 36-week treatment period (IGF-1×ULN: 0.04±0.093). In contrast, patients randomised to placebo showed a rise in IGF levels (IGF-1×ULN: 0.83±0.096) at week 36 and the difference between groups at the end of the treatment period was statistically significant (p-value < 0.0001) (Figure 2).

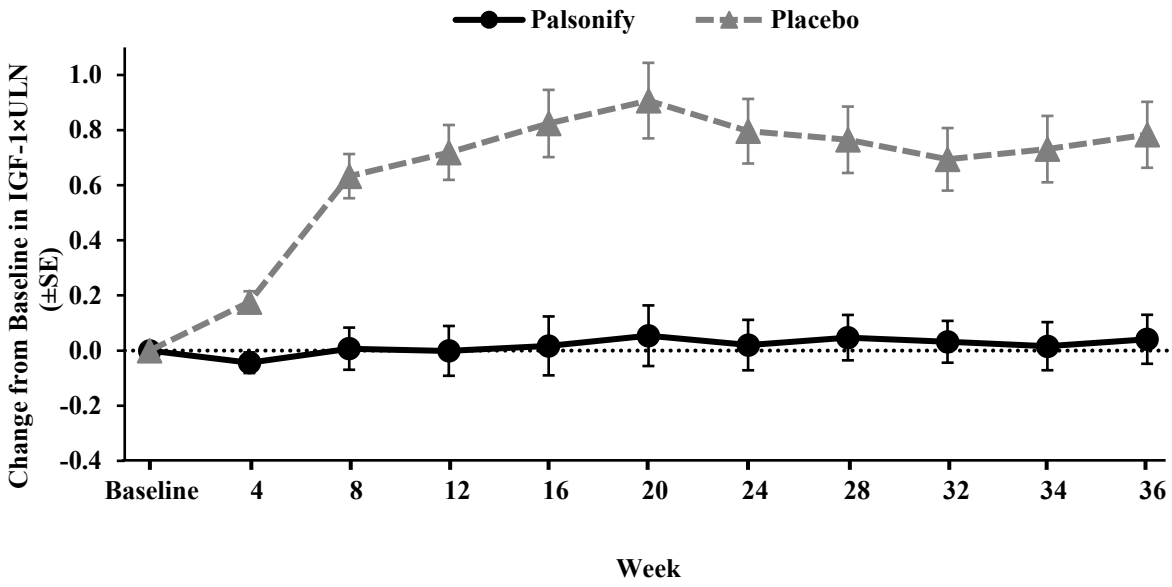

Figure 2: Study PATHFNDR-1 LS mean (±SE) IGF-1 (×ULN) change from baseline by visit for all patients

The population includes all randomised patients based on multiple imputation methods.
IGF-1=insulin-like growth factor-1, LS=least squares, SE=standard error, ULN=upper limit of normal.

Target GH levels of < 1.0 ng/mL were maintained in 87% of patients controlled at baseline in the paltusotine treated patients compared with 28% in the placebo-treated patients (p-value < 0.0003) at week 34.

Study PATHFNDR-1 measured acromegaly clinical symptom severity in 7 items (headache pain, joint pain, sweating, fatigue, weakness in legs, swelling, and numbness or tingling) using the ASD. A preliminary threshold range to characterise meaningful within patient change for the ASD total is a -4 to -6 point change for improvement or worsening out of a total score of 70. At baseline, patients

presented with mild to moderate symptoms. The change from baseline to week 36 in total ASD score showed an improvement of -0.606 for the paltusotine-treated patients compared to a worsening of 4.558 for the placebo-treated patients (p-value=0.0216) (Table 7).

Table 7: Change from baseline to week 36 in total ASD score in study PATHFNDR-1

	paltusotine (N=30)	**placebo (N=28)**	**Treatment difference (95% CI)**	**p-value**
Change from baseline to week 36 in ASD total score				
LS Mean (SE)	-0.606 (±1.504)	4.558 (±1.593)	-5.164 (-9.536, -0.792)	0.0216

Week 36 is the end of the randomised controlled portion of the study; if a patient received rescue therapy, the last assessment prior to rescue is used. Baseline total ASD is the sum of the weekly average on or prior to day 1, and post-baseline total ASD is the sum of the weekly average on or prior to the scheduled visit date, inclusive of the date of visit, for 7 items (headache, joint pain, sweating, fatigue, weakness in legs, swelling, and numbness or tingling).At baseline, mean total ASD score was 13.21 in the paltusotine group, and 10.86 in the placebo group.
ASD=Acromegaly symptoms diary, CI=confidence interval, LS=least squares, SE=standard error.

Results by ASD individual item score change from baseline to week 36 showed for all 7 items a trend in favour of paltusotine, 2 of which were statistically significant (joint pain and numbness or tingling; p-value< 0.05). No single ASD item predominantly affected the overall total ASD score, indicating there was improvement and stabilisation across acromegaly symptoms evaluated in the paltusotine treated patients compared with the placebo-treated patients.

The LS means (±SE) change from baseline to end of treatment in most bothersome symptoms were -0.530 (±0.360) in the paltusotine group and 0.617 (±0.381) in the placebo group, with a treatment difference of -1.147 (95% CI: -2.199, -0.094) in favour of paltusotine (nominal p=0.0335).

The observed safety and tolerability profile remained unchanged (see section 4.8) and the durability of the clinical treatment benefits were retained in patients dosed for 120 weeks in the ongoing OLE study PATHFNDR-1.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Palsonify in all subsets of the paediatric population in the treatment of acromegaly (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

In healthy volunteers, after a single oral dose the median T_{max} ranged from 1.4 to 2.0 h (Table 8). At steady state, following a 60 mg dose, the paltusotine geometric mean (geometric %CV) C_{max} was 290 (67.5) ng/mL and the geometric mean (geometric %CV) AUC_{0-24} was 2 890 (63.5) ng*h/mL. In the population pharmacokinetic (PK) analysis, accumulation ratios were 1.31 for C_{max} and 1.55 for AUC_{0-24}. Steady state is reached by 1 week. The PK in healthy volunteers is similar to patients with acromegaly.

Table 8: Exposure parameters of single dose of paltusotine when administered with a 1-hour postdose fast

	20 mg	40 mg	60 mg
C_{max} (ng/mL)	80.7 (54)	153 (36)	258 (51)
AUC_{0-24} (ng*h/mL)	651 (53)	1 310 (41)	2 370 (45)
T_{max} (h)	1.4 (0.8-4.0)	1.5 (1.5-4.0)	2.0 (1.0-4.0)

Data are shown as geometric means (geometric %CV) except for T_{max}, which is shown as median (range).
AUC_{0-24} = area under the plasma concentration-time curve from time 0 to 24 hours, C_{max} = maximum (peak) plasma drug concentration, T_{max} =time to reach maximum (peak) plasma concentration following drug administration

The absolute bioavailability of paltusotine film-coated tablets is 51%.

Effect of food on oral absorption
Relative to administration in the fasted state, administration of paltusotine with a high-fat meal reduced the AUC by 85% and the C_{max} by 81%. Administration of paltusotine with a low-fat meal reduced AUC by 72% and the C_{max} by 68% (see section 4.2).

Distribution

The apparent volume of distribution (Vz/F) of paltusotine film-coated tablets is 406 L. Paltusotine is highly plasma protein bound to both albumin (> 99%) and α-1-acid glycoprotein (> 98%). The blood to plasma ratio was near 1.

Metabolism

Paltusotine is metabolised primarily hepatically via glucuronidation and oxidation. *In vitro*, glucuronidation was the major pathway of metabolism and is primarily mediated by UGT1A1 and UGT1A9. Oxidation was a secondary pathway and was primarily catalysed by CYP3A4/5 with a minor contribution from CYP2D6. Paltusotine is a P-gp substrate. *In vitro* studies suggest inhibition of UGT1A1 is not expected to have clinical meaningful increase in paltusotine exposure.

Elimination

After maximal concentrations were attained, paltusotine concentration declined with apparent terminal half-life (t½) of 25.5 hours which supports once-daily dosing. The apparent clearance of paltusotine film-coated tablets is 11.0 L/h.

Following oral administration of radiolabelled paltusotine, faecal excretion was the predominant route of elimination with observed mean recovery of total administered radioactivity being 90% and 3.9% in faeces and urine, respectively. Unchanged paltusotine was a major component in excreta.

Linearity

Paltusotine exhibited dose-proportional increases in exposures for doses ranging from 20 mg to 120 mg in healthy participants. Apparent dose proportional increases were observed for mean steady-state trough concentrations up to 60 mg once daily dosing in patients with acromegaly.

Special populations

Age, body weight, gender, race, and UGT1A1 polymorphism
Gender, and UGT1A1 polymorphism do not have a clinically relevant effect on the pharmacokinetics of paltusotine. No dose adjustments of paltusotine based on these factors are required.

Based on population PK analysis, age (290 participants [92%] aged 18-65 years and 25 elderly participants [8%], including 20 aged 65-74 years, 5 aged 75-84 years, none aged 85 years or more) did not have a clinically relevant effect on the pharmacokinetics of paltusotine.

Based on population PK analysis, body weight (mean: 76 kg; median: 73 kg; interquartile range: 65-85 kg; min: 45 kg; max: 138 kg) did not have a clinically meaningful effect on exposure of paltusotine.

Based on population PK analysis (196 White participants, 12 Black or African American participants, 17 Chinese participants, 35 Japanese participants, 48 of another race, and 7 of unknown race), race did not have a clinically meaningful effect on exposure of paltusotine.

Hepatic impairment
In a study comparing participants with mild, moderate, or severe hepatic impairment to participants with normal hepatic function, paltusotine exposure was not altered. No dose adjustment is required (see section 4.2).

Renal impairment
As renal clearance has a minor contribution to the elimination of paltusotine in humans, no dedicated PK study was performed in patients with renal impairment. In a population PK analysis including 279 participants with normal renal function (eGFR ≥ 90 mL/min), 32 with mild renal impairment (eGFR 60 to < 90 mL/min), and 4 with moderate renal impairment (eGFR 30 to < 60 mL/min), renal function did not have a meaningful effect on paltusotine exposures. No data are available in patients with severe and end stage renal impairment (eGFR < 30 mL/min).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of acute and repeated dose toxicity, safety pharmacology, genotoxicity and carcinogenicity potential.

Reproductive and developmental toxicity

In fertility and early embryonic development studies of rats at doses of up to 500 mg/kg/day (18-times the clinical dose of 60 mg based on AUC), no paltusotine effect on mating or fertility were observed. However, females at this dose level presented decreased numbers of corpora lutea and implantation sites as well as increased preimplantation loss resulting in fewer numbers of live embryos; these findings were not reported at doses up to 75 mg/kg/day (5-times the clinical dose of 60 mg based on AUC).

Embryo-foetal development studies in rats and rabbits with doses up to 500 mg/kg/day (rat) and 75 mg/kg/day (rabbit) showed no evidence of teratogenic effects (up to 11 times and 5.2 times the clinical dose of 60 mg based on AUC in rat and in rabbit, respectively). In rabbits, the highest dose showed an increased incidence of abortions associated with maternal toxicity (decreased food intake and body weight loss) and a decrease in mean foetal body weights. This was not observed at the 25 mg/kg/day dose (2.9 times the clinical dose of 60 mg based on AUC).

In a pre- and postnatal development study in rat, decreased body weight was observed during the preweaning and postweaning development periods at 500 mg/kg/day, the highest dose tested. There were no treatment-related effects on sexual maturation, neurobehavioral or reproductive function of the first filial (F1) generation rats at any dose level. Excretion of paltusotine into maternal milk was demonstrated with milk-to-plasma concentration ratios at 4 hours postdosing on lactation day (LD) 20 ranging from 2.4- to 3.8-fold.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Copovidone
Cellulose, microcrystalline
Crospovidone
Silica, colloidal anhydrous
Magnesium stearate
Mannitol (E 421)

Film-coating

Palsonify 20 mg film-coated tablets
Hypromellose
Titanium dioxide (E 171)
Triacetin (E 1518)
Iron oxide, yellow (E 172)
Iron oxide, red (E 172)

Palsonify 30 mg film-coated tablets
Hypromellose
Titanium dioxide (E 171)
Triacetin (E 1518)
Iron oxide, yellow (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

A heat induction sealed, white high-density polyethylene (HDPE) bottle with a white child-resistant polypropylene (PP) closure.

Each bottle contains 60 film-coated tablets and a silica gel desiccant.
Each carton contains one bottle.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Crinetics Pharmaceuticals Europe GmbH

Barbara Strozzilaan 201
1083HN Amsterdam
Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/26/2021/001
EU/1/26/2021/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Crinetics Pharmaceuticals Europe GmbH
Barbara Strozzilaan 201
1083HN Amsterdam
Netherlands

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

OUTER CARTON – 20 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Palsonify 20 mg film-coated tablets
paltusotine

2. STATEMENT OF ACTIVE SUBSTANCE

Each film-coated tablet contains 20 mg paltusotine (as hydrochloride).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

60 film-coated tablets

5. METHOD AND ROUTE OF ADMINISTRATION

Oral use. Swallow the tablets whole.
Read the package leaflet before use.

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

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

Crinetics Pharmaceuticals Europe GmbH
Barbara Strozzilaan 201
1083HN Amsterdam
Netherlands

12. MARKETING AUTHORISATION NUMBER

EU/1/26/2021/001 60 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Palsonify 20 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL – 20 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Palsonify 20 mg tablets
paltusotine

2. STATEMENT OF ACTIVE SUBSTANCE

Each tablet contains 20 mg paltusotine (as hydrochloride).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Tablets
60 tablets

5. METHOD AND ROUTE OF ADMINISTRATION

Oral use
Read the package leaflet before use.

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

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

Crinetics Pharmaceuticals Europe GmbH

12. MARKETING AUTHORISATION NUMBER

EU/1/26/2021/001 60 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – 30 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Palsonify 30 mg film-coated tablets
paltusotine

2. STATEMENT OF ACTIVE SUBSTANCE

Each film-coated tablet contains 30 mg paltusotine (as hydrochloride).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets
60 film-coated tablets

5. METHOD AND ROUTE OF ADMINISTRATION

Oral use
Read the package leaflet before use.

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

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

Crinetics Pharmaceuticals Europe GmbH
Barbara Strozzilaan 201
1083HN Amsterdam
Netherlands

12. MARKETING AUTHORISATION NUMBER

EU/1/26/2021/002 60 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Palsonify 30 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL – 30 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Palsonify 30 mg tablets
paltusotine

2. STATEMENT OF ACTIVE SUBSTANCE

Each tablet contains 30 mg paltusotine, (as hydrochloride).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Tablets
60 tablets

5. METHOD AND ROUTE OF ADMINISTRATION

Oral use
Read the package leaflet before use.

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

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

Crinetics Pharmaceuticals Europe GmbH

12. MARKETING AUTHORISATION NUMBER

EU/1/26/2021/002 60 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Palsonify 20 mg film-coated tablets
Palsonify 30 mg film-coated tablets
paltusotine

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

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 or nurse.
- 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 or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Palsonify is and what it is used for
2. What you need to know before you take Palsonify
3. How to take Palsonify
4. Possible side effects
5. How to store Palsonify
6. Contents of the pack and other information

1. What Palsonify is and what it is used for

Palsonify contains the active substance paltusotine. It works by targeting a receptor for a natural hormone in your body called somatostatin, which acts by reducing the growth hormone production by the pituitary tumour.

Palsonify is used in adults for the treatment of acromegaly.

Acromegaly is a rare condition. Most often, it's caused by a noncancerous tumour in a small gland in the brain (called the pituitary gland). This tumour causes the gland to release too much growth hormone (GH). This extra GH leads to symptoms such as enlarged hands or feet, headache, excessive sweating, numbness in the hands and feet, tiredness and joint pain.

The active substance in Palsonify, paltusotine, blocks the release of growth hormone by the pituitary gland by attaching to somatostatin receptors (targets). This is expected to improve symptoms of acromegaly.

2. What you need to know before you take Palsonify

Do not take Palsonify
- if you are allergic to paltusotine or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking Palsonify, or during treatment if you have:

* Heart problems: Palsonify can affect the rate of your heartbeat (see section 2 Other medicines and Palsonify).
* Gallbladder problems: Palsonify can cause gallstones to form (with sudden pain in the upper right area of your belly (abdomen), sudden pain in your right shoulder or between your shoulder blades, yellowing of your skin or the whites of your eyes, or pale stools).
* Diabetes: Palsonify may affect your blood sugar. Increased blood sugar levels may occur. Therefore, your doctor may recommend monitoring blood sugar levels and treatment of diabetes (see section 2 Other medicines and Palsonify).
* Ever had lack of vitamin B12: Medicines that target somatostatin receptor can decrease vitamin B12 levels in the blood, your doctor may wish to check your vitamin B12 level periodically during treatment with Palsonify.

Monitoring during treatment

Tumours of the pituitary gland that produce excess growth hormone and lead to acromegaly sometimes expand, causing serious complications such as problems with eyesight. Your doctor will monitor you for signs and symptoms of tumour growth while you are receiving treatment with Palsonify. If evidence of tumour expansion appears, your doctor may prescribe a different treatment.

Your doctor will regularly check your thyroid function during treatment.

Children and adolescents
Do not give this medicine to children and adolescents under 18 years. It is not known if it is safe or effective in this age group.

Other medicines and Palsonify
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 any of the following medicines, since their activity or side effects may change when used together with Palsonify. If you take these medicines, your doctor may need to adjust the doses of these medicines:
* medicines called beta blockers (e.g. atenolol, metoprolol, carvedilol, nebivolol), and cardiac glycosides (e.g. digoxin) used to treat high blood pressure or heart diseases
* fluoxetine (an antidepressant)
* dextromethorphan (a cough suppressant)
* tacrolimus (a medicine to suppress transplant rejection)
* insulin or other medicines to treat diabetes

Tell your doctor if you are taking the following medicines as they may reduce the effectiveness of Palsonify by reducing the amount of Palsonify in the blood:
* carbamazepine and phenytoin (used to treat seizures and epilepsy)
* apalutamide (used to treat prostate cancer)
* efavirenz (used to treat HIV)
* prednisone (used to help suppress the body's immune system)
* lansoprazole and similar medicines (used to control or reduce stomach acid)

Tell your doctor if you are taking the following medicine as Palsonify may reduce the effectiveness of this medicine. If you take this medicine, your doctor may need to adjust the doses of this medicine:
* cyclosporine (a medicine to suppress transplant rejection, treat severe skin diseases, severe eye and joint inflammation)

If you are not sure if the above applies to you, ask your doctor or pharmacist.

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.

You should not use Palsonify if you are pregnant.

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

Women who can become pregnant should use effective contraception (birth control) during treatment with Palsonify.

Driving and using machines
Palsonify has no or negligible influence on the ability to drive and use machines.

3. How to take Palsonify

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

Palsonify is available as film-coated tablets taken by mouth. If it is the first time you are taking medicine for acromegaly, the recommended starting dose is 20 mg taken once daily. If it is not the first time that you take medicine for acromegaly, the recommended starting dose is 40 mg taken once daily. Your doctor will check your symptoms and the level of a substance called insulin-like growth factor after at least 2 to 4 weeks of treatment to check how you are responding. If necessary, your doctor may increase your dose up to 60 mg taken once daily.
Your doctor may temporarily reduce the dose by 20 mg based on how well you tolerate treatment.
Your doctor may temporarily increase the dose of paltusotine due to administration with other medicinal products (see section 2 Other medicines and Palsonify).

Swallow the tablets whole with a glass of water, on an empty stomach, at least 6 hours after a meal (e.g. after overnight fast), and at least 1 hour before your next meal.

If you take more Palsonify than you should
If you have taken more Palsonify than you should, stop taking the medicine and contact your doctor or pharmacist immediately.

If you forget to take Palsonify
Do not take a double dose to make up for a forgotten dose. Skip the missed dose and then take the next dose as usual on the next day.

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

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.
Contact your doctor if you experience any side effects. Your doctor may pause treatment with Palsonify until your symptoms improve and/or they may reduce the dose you receive.

Very common (may affect more than 1 in 10 people)
- Diarrhoea

Common (may affect up to 1 in 10 people)
- High blood glucose levels (hyperglycaemia)
- Decreased appetite
- Headache

- Slow heart rate (sinus bradycardia)
- Belly (abdominal) pain
- Feeling sick (nausea)
- Abdominal discomfort
- Swelling of your belly (abdominal distension)
- Vomiting
- Gallstones (cholelithiasis)
- Hair loss (alopecia)
- Fatigue

Uncommon (may affect up to 1 in 100 people)
- Gallstones in the bile duct (bile duct stone)
- Dizziness

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Palsonify

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 bottle after "EXP". The expiry date refers to the last day of that month.

No special storage conditions.

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 Palsonify contains
* The active substance is paltusotine (as paltusotine hydrochloride).

Palsonify 20 mg film-coated tablets contain 20 mg of paltusotine.
Palsonify 30 mg film-coated tablets contain 30 mg of paltusotine.

* The other ingredients are:
  Tablet core: copovidone, microcrystalline cellulose, crospovidone, anhydrous colloidal silica, magnesium stearate, mannitol (E 421).
  Film-coating:
  Palsonify 20 mg film-coated tablets: Hypromellose, titanium dioxide (E 171), triacetin (E 1518), yellow iron oxide (E 172), red iron oxide (E 172).
  Palsonify 30 mg film-coated tablets: Hypromellose, titanium dioxide (E 171), triacetin (E 1518), yellow iron oxide (E 172).

What Palsonify looks like and contents of the pack
Palsonify 20 mg film-coated tablets are pink, biconvex oval film-coated tablets, 16 mm length and 8 mm width, debossed with "PAL" on one side and "20" on the other side.

Palsonify 30 mg film-coated tablets are yellow, biconvex oval film-coated tablets, 18 mm length and 9 mm width, debossed with "PAL" on one side and "30" on the other side.

Palsonify 20 mg and 30 mg film-coated tablets are available in plastic bottles, secured with child-resistant closure and heat induction sealed.

Each bottle contains 60 film-coated tablets and a silica gel desiccant.
Each carton contains one bottle.

Marketing Authorisation Holder and Manufacturer
Crinetics Pharmaceuticals Europe GmbH
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Other sources of information

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

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.