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

Ogsiveo 50 mg film-coated tablets
Ogsiveo 100 mg film-coated tablets
Ogsiveo 150 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ogsiveo 50 mg film-coated tablets

Each film-coated tablet contains 50 mg of nirogacestat (as nirogacestat dihydrobromide).

Excipients with known effect
Each film-coated tablet contains 57.8 mg of lactose monohydrate.
Each film-coated tablet contains sunset yellow FCF (E 110).

Ogsiveo 100 mg film-coated tablets

Each film-coated tablet contains 100 mg of nirogacestat (as nirogacestat dihydrobromide).

Excipients with known effect
Each film-coated tablet contains 115.7 mg of lactose monohydrate.
Each film-coated tablet contains sunset yellow FCF (E 110).

Ogsiveo 150 mg film-coated tablets

Each film-coated tablet contains 150 mg of nirogacestat (as nirogacestat dihydrobromide).

Excipients with known effect
Each film-coated tablet contains 173.5 mg of lactose monohydrate.
Each film-coated tablet contains sunset yellow FCF (E 110).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Ogsiveo 50 mg film-coated tablets

Round, biconvex, orange film-coated tablets 8 mm diameter, debossed with “50” on one side.

Ogsiveo 100 mg film-coated tablets

Round, light orange film-coated tablets 10 mm diameter, debossed with “100” on one side.

Ogsiveo 150 mg film-coated tablets

Oval, yellow orange film-coated tablets 8.5 mm in width, 17.5 mm in length, debossed with “150” on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ogsiveo as monotherapy is indicated for the treatment of adult patients with progressing desmoid tumours who require systemic treatment.

4.2 Posology and method of administration

Ogsiveo should be initiated and monitored by a physician experienced in the use of anticancer therapies.

Posology

The recommended dose is 150 mg Ogsiveo twice daily, one dose in the morning and one dose in the evening. This dose should not be exceeded.

Duration of treatment
Ogsiveo should be continued until disease progression or unacceptable toxicity.

Missed dose
If a dose of Ogsiveo is missed, patients should not take an additional dose. Patients should take the next prescribed dose.

Dose adjustments for adverse reactions
The recommended dose modifications for selected adverse reactions are provided in Table 1.

For other severe adverse reactions, or in the event of life-threatening adverse reactions, Ogsiveo should be withheld until the reaction is resolved to Grade ≤ 1 or baseline. Ogsiveo should only be restarted at a dose of 100 mg twice daily and only after carefully considering the potential benefit and likelihood of recurrence of the adverse reaction. Ogsiveo should be permanently discontinued for recurrence of severe or life-threatening adverse reaction upon rechallenge at the reduced dose.

Dose modifications should be made if patients experience the following adverse reactions (grades refer to Common Terminology Criteria for Adverse Events):

Table 1: Recommended dose modifications for adverse reactions in patients treated with Ogsiveo

Adverse reaction	**Recommended action**
Diarrhoea	
Grade 3 diarrhoea persisting for ≥ 3 days despite maximal medical therapy	Ogsiveo should be withheld until reaction is resolved to Grade ≤ 1 or baseline, then it should be restarted at a dose of 100 mg twice daily.
Skin reactions	
Grade 3 folliculitis	Ogsiveo should be withheld until reaction is resolved to Grade ≤ 1 or baseline, then it should be restarted at a dose of 100 mg twice daily.
Grade 3 maculopapular rash	Ogsiveo should be withheld until reaction is resolved to Grade ≤ 1 or baseline, then it should be restarted at a dose of 100 mg twice daily.
Grade 3 hidradenitis	Ogsiveo should be withheld until reaction is resolved to Grade ≤ 1 or baseline, then it should be restarted at a dose of 100 mg twice daily.

Adverse reaction	Recommended action
Electrolyte abnormalities	
Grade 3 hypophosphataemia persisting for ≥ 7 days despite maximal replacement therapy	Ogsiveo should be withheld until reaction is resolved to Grade ≤ 1 or baseline, then it should be restarted at a dose of 100 mg twice daily.
Grade 3 hypokalaemia despite maximal replacement therapy	Ogsiveo should be withheld until reaction is resolved to Grade ≤ 1 or baseline, then it should be restarted at a dose of 100 mg twice daily.
Hepatic abnormalities	
Alanine transaminase (ALT) or Aspartate transaminase (AST) ≥ 3 to 5 x ULN	Ogsiveo should be withheld until ALT, AST, or both are resolved to < 3 x ULN or baseline, then it should be restarted at a dose of 100 mg twice daily.
ALT or AST > 5 x ULN	Ogsiveo should be permanently discontinued.
Other adverse reactions	
Anaphylaxis or other severe hypersensitivity reaction	Ogsiveo should be permanently discontinued.

Special populations

Elderly population
No dose adjustment is recommended for patients who are aged 65 years or over.
Clinical data in patients aged 65 years or over is limited.

Renal impairment
No dose adjustment is recommended in patients with mild or moderate renal impairment.
Administration is not recommended in patients with severe renal impairment (see section 5.2).

Hepatic impairment
No dose adjustment is recommended in patients with mild or moderate hepatic impairment.
Administration is not recommended in patients with severe hepatic impairment (see section 5.2).

Paediatric population
The safety and efficacy of Ogsiveo in children from 2 to 18 years of age have not been established. Ogsiveo should not be used in children from birth to less than 2 years of age because of potential safety concerns related to structural and functional growth. Currently available data are described in sections 4.8 and 5.1, but no recommendation on a posology can be made.

Method of administration

Ogsiveo is for oral use.

The tablets may be taken with or without food. Tablets should not be broken, chewed or crushed because there are no data currently available to support other methods of administration.

Patients should avoid consuming grapefruit and grapefruit juice while taking Ogsiveo (see section 4.5).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Pregnancy (see sections 4.4 and 4.6)
- Women of childbearing potential not using highly effective contraception (see sections 4.4 and 4.6)
- Breast-feeding (see section 4.6)

4.4 Special warnings and precautions for use

Diarrhoea

Diarrhoea was reported in patients receiving nirogacestat (see section 4.8). Patients who experience diarrhoea during treatment with nirogacestat should be monitored and managed using anti-diarrhoeal medicinal products. For Grade 3 diarrhoea that persists for ≥ 3 days despite maximal medical therapy, nirogacestat should be withheld until diarrhoea is resolved to Grade ≤ 1 or baseline, then it should be restarted at 100 mg twice daily (see section 4.2).

Skin and subcutaneous tissue disorders

Dermatologic reactions, including maculopapular rash, folliculitis, and hidradenitis, were reported in patients receiving nirogacestat (see section 4.8). Patients should be monitored for dermatologic reactions throughout the course of treatment and managed as clinically indicated. For Grade 3 dermatologic reactions, nirogacestat should be withheld until resolved to Grade ≤ 1 or baseline, then it should be restarted at a dose of 100 mg twice daily (see section 4.2).

Ovarian toxicity

Ovarian toxicity was reported in female patients of childbearing potential receiving nirogacestat (see section 4.8). Ovarian toxicity, identified based on abnormal reproductive hormone levels or peri-menopausal symptoms, was reported in 75% of women of childbearing potential receiving nirogacestat in the DeFi study. Ovarian toxicity has been reported to resolve in 79% of women of childbearing potential during treatment. Follow up information is available for all but two out of 27 patients; after stopping treatment, ovarian toxicity was reported to resolve in all women of childbearing potential for whom data are available (see section 4.8). Effects of nirogacestat on human fertility are unknown. Based on findings from animal studies, female fertility may be impaired. Women of childbearing potential should be advised about the risk of ovarian toxicity before initiating treatment with nirogacestat. Patients should be monitored for changes in menstrual cycle regularity or the development of symptoms of oestrogen deficiency, including hot flashes, night sweats, and vaginal dryness.

Electrolyte abnormalities

Electrolyte abnormalities, including hypophosphataemia and hypokalaemia, were reported in patients receiving nirogacestat (see section 4.8). Phosphate and potassium levels should be monitored regularly and supplemented as necessary. For Grade 3 hypophosphataemia persisting for ≥ 7 days despite maximal replacement therapy, nirogacestat should be withheld until resolved to Grade ≤ 1 or baseline, then it should be restarted at a dose of 100 mg twice daily (see section 4.2). For Grade 3 hypokalaemia of any duration, despite maximal replacement therapy, nirogacestat should be withheld until resolved to Grade ≤ 1 or baseline, then it should be restarted at a dose of 100 mg twice daily (see section 4.2).

Hepatic abnormalities

ALT or AST elevations were reported in patients who received nirogacestat (see section 4.8). Liver function tests should be monitored regularly. For ALT or AST ≥ 3 to 5 x ULN, nirogacestat should be withheld until ALT, AST, or both are resolved to < 3 x ULN or baseline, then it should be restarted at a dose of 100 mg twice daily. For ALT or AST > 5 x ULN, nirogacestat should be permanently discontinued (see section 4.2).

Non-melanoma skin cancers

Non-melanoma skin cancers (basal cell carcinoma and squamous cell carcinoma) were reported in patients receiving nirogacestat (see section 4.8). Skin examinations should be performed prior to initiation of nirogacestat and routinely during treatment with nirogacestat. Cases should be managed

according to clinical practices and patients may continue with nirogacestat treatment without dose adjustment.

Embryo-foetal toxicity – Contraception in males and females

Nirogacestat may cause foetal harm when administered to a pregnant woman (see sections 4.6 and 5.3). Patients should be advised of the potential risk to a foetus. Women of childbearing potential must have a negative pregnancy test prior to initiating nirogacestat treatment. Pregnancy testing during treatment with nirogacestat should be considered for women of childbearing potential experiencing amenorrhoea. Women of childbearing potential receiving nirogacestat must use highly effective contraceptive methods during treatment with nirogacestat and for 1 week after the last dose of nirogacestat (see section 4.6). Women of childbearing potential should be advised to inform their healthcare provider immediately of a known or suspected pregnancy, and they must stop taking nirogacestat if they become pregnant.

Male patients with female partners of childbearing potential should be advised to use highly effective contraceptive methods during treatment with nirogacestat and for 1 week after the last dose of nirogacestat (see section 4.6).

Excipients

This medicinal product contains lactose (see sections 2 and 6.1). Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

This medicinal product contains sunset yellow FCF (E110) (see sections 2 and 6.1), which may cause allergic reactions.

Each film-coated tablet contains less than 1 mmol sodium (23 mg), that is to say essentially sodium-free (see section 6.1).

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Nirogacestat is primarily metabolized by CYP3A4 and is a substrate of P-glycoprotein (P-gp).

Agents that may increase nirogacestat serum concentrations

Effect of moderate and strong CYP3A4 inhibitors
In a clinical study, co-administration of itraconazole (a strong CYP3A4 inhibitor and P-gp inhibitor) increased nirogacestat C_{max} by 2.5-fold and AUC by 8.2-fold. Co-administration with moderate CYP3A4 inhibitors is also expected to result in clinically relevant increases in exposure.

Concomitant use with strong inhibitors of CYP3A4 (e.g., clarithromycin, oral ketoconazole, itraconazole) and moderate inhibitors of CYP3A4 (e.g., erythromycin and fluconazole) should therefore be avoided.

Alternative concomitant medicinal products with no or minimal CYP3A4 inhibition should be considered. If therapeutic alternatives are not available, Ogsiveo should be immediately interrupted for the period of time in which a strong or moderate CYP3A4 inhibitor is given.

Patients should avoid consuming grapefruit and grapefruit juice when taking Ogsiveo since they include inhibitors of CYP3A4 (see section 4.2).

Agents that may decrease nirogacestat serum concentrations

Effect of strong and moderate CYP3A4 inducers
The effects of CYP3A4 inducers on nirogacestat exposure have not been evaluated in a clinical study. Moderate and strong inducers are expected to result in clinically relevant decreases in exposure of nirogacestat that could lead to reduced efficacy. Concomitant treatment with strong inducers of CYP3A4 (e.g., carbamazepine, phenytoin, rifampicin, phenobarbital and St. John's wort) and moderate CYP3A inducers (e.g., efavirenz and etravirine) should therefore be avoided. In patients for whom CYP3A4 inducers are indicated, alternative agents with less enzyme induction potential should be selected.

Effect of acid-reducing agents
Nirogacestat has pH-dependent solubility, with substantially reduced solubility at pH greater than 6.0. The effects of acid reducing agents (i.e., H2-receptor antagonists, proton pump inhibitors and antacids) on nirogacestat exposure have not been evaluated in a clinical study, however, co-administration of these medicinal products may reduce the bioavailability of nirogacestat. Concomitant use of Ogsiveo with proton pump inhibitors and H2 blockers is not recommended. However, if concomitant use with acid reducing agents cannot be avoided, Ogsiveo can be staggered with antacids by administering Ogsiveo 2 hours before or 2 hours after antacid use.

Effects of nirogacestat on the pharmacokinetics of other medicinal products

CYP substrates
A drug-drug interaction study in healthy volunteers investigating the effects of multiple doses of nirogacestat at a dose of 95 mg once daily on the exposure of midazolam, a sensitive CYP3A4 substrate, resulted in a 1.3-fold increase in midazolam C_{max} and a 1.6-fold increase in midazolam AUC. The effect of the clinical dose of nirogacestat (150 mg twice daily) on midazolam exposure has not been studied and may be different. Ogsiveo should not be used with concomitant administration of CYP3A4 substrates that have narrow therapeutic indices (e.g., cyclosporine, tacrolimus, digitoxin, warfarin, carbamazepine).

Since no study has been performed investigating the effect of nirogacestat on systemic contraceptive steroid exposure, it is unknown whether nirogacestat reduces the effectiveness of systemically acting hormonal contraceptives. Women of childbearing potential must use highly effective contraceptive methods (see section 4.6).

In vitro studies showed that nirogacestat may induce CYP2C8, CYP2C9, CYP2C19, and CYP2B6 and thus there is a risk that nirogacestat can cause decreased exposure of substrates of these enzymes. When substrates of CYP2C8, CYP2C9, CYP2C19, and CYP2B6 are administered with Ogsiveo, evaluation for reduced efficacy of the substrate should be performed and dose adjustment of the substrate may be required to maintain optimal plasma concentrations.

Drug transporter systems
A single-dose drug-drug interaction study demonstrated that nirogacestat did not affect the exposure of dabigatran, a P-gp substrate, which supports the absence of clinically meaningful P-gp inhibition by nirogacestat.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Women of childbearing potential and men with female partners of childbearing potential should be advised to avoid pregnancy while on Ogsiveo (see section 4.4).

Women of childbearing potential must use highly effective contraceptive methods during treatment with Ogsiveo and for 1 week after the last dose of Ogsiveo (see section 4.4). It is unknown whether nirogacestat reduces the effectiveness of systemically acting hormonal contraceptives. Patients should be advised to use at least one highly effective method of contraception (such as an intrauterine device) or two complementary forms of contraception including a barrier method during treatment with Ogsiveo and for 1 week after the last dose of Ogsiveo. Women of childbearing potential should be advised to inform their healthcare provider immediately of a known or suspected pregnancy, and they must stop taking Ogsiveo if they become pregnant. Women of childbearing potential should not donate eggs (oocytes) during treatment with Ogsiveo and for 1 week after the last dose of Ogsiveo.

Male patients with female partners of childbearing potential must use highly effective contraceptive methods during treatment with Ogsiveo and for 1 week after the last dose of Ogsiveo (see section 4.4). Male patients should not donate sperm during treatment with Ogsiveo and for 1 week after the last dose of Ogsiveo.

Pregnancy

Based on findings from animal studies and its mechanism of action, Ogsiveo may cause foetal harm when administered to a pregnant woman. Ogsiveo is contraindicated in pregnant women (see sections 4.3 and 5.3). Women of childbearing potential must have a negative pregnancy test prior to initiating Ogsiveo treatment. Pregnancy testing during treatment with Ogsiveo should be considered for women of childbearing potential experiencing amenorrhoea. Patients should be advised of the potential risk to a foetus. If a patient becomes pregnant while taking Ogsiveo, treatment must be discontinued. A spontaneous abortion was reported by a woman in the DeFi study who conceived while receiving nirogacestat.

Breast-feeding

There are no data regarding the presence of nirogacestat or its metabolites in either human or animal milk or its effects on a breastfed child or on milk production. Because of the potential for serious adverse reactions in a breastfed child, women must not breastfeed during treatment with Ogsiveo and for 1 week after the last dose of Ogsiveo (see section 4.3).

Fertility

Fertility studies were not conducted in humans. The effect of Ogsiveo on fertility in humans is not known. Based on findings from animal studies, male and female fertility may be impaired (see section 5.3).

4.7 Effects on ability to drive and use machines

Ogsiveo has no or negligible influence on the ability to drive and use machines. Since fatigue and dizziness may occur in patients taking nirogacestat (see section 4.8), caution should be observed by patients who experience those adverse reactions when driving or operating machinery.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions are: diarrhoea (85%), rash (65%), ovarian toxicity in women of childbearing potential (60%), nausea (59%), fatigue (50%), hypophosphataemia (50%), headache (40%), and stomatitis (40%).

The most frequently reported serious adverse reaction was ovarian toxicity (premature menopause, 3%). The most common severe adverse reactions were diarrhoea (16%) and hypophosphataemia (13%).

Permanent discontinuation of nirogacestat due to an adverse event occurred in 19% of patients. The most common adverse reactions leading to discontinuation were diarrhoea (5%), ovarian toxicity (5%), and increased ALT (3%).

The frequency of dose interruption of nirogacestat due to adverse reactions was 59%. The most common adverse reactions leading to dose interruption were diarrhoea (11%), rash maculo-papular (10%), hypophosphatemia (6%) and nausea (5%).

The frequency of dose reduction of nirogacestat due to adverse reactions was 44%. The most common adverse reactions leading to dose reduction were diarrhoea (9%), rash maculo-papular (6%), stomatitis (3%), and hypophosphatemia (3%).

Tabulated list of adverse reactions

Unless otherwise stated, the frequencies of adverse reactions are based on all-cause adverse event frequencies identified in 88 patients exposed to nirogacestat 150 mg twice daily during a median duration of 21.5 months in clinical studies.

The adverse reactions are ranked under heading of 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) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2: Adverse reactions reported

System organ class	Adverse reaction	All grades	Grades 3-4
Gastrointestinal disorders	Diarrhoea	Very common	Very common
	Nausea	Very common	Common
	Stomatitis[a]	Very common	Common
	Dry mouth	Very common	--
Skin and subcutaneous disorders	Rash[b]	Very common	Common
	Alopecia	Very common	--
	Folliculitis	Very common	Common
	Hidradenitis	Common	Common
	Dry skin	Very common	--
	Pruritis	Very common	--
Neoplasms benign, malignant and unspecified	Basal cell carcinoma	Common	--
	Squamous cell[c] carcinoma	Common	--
Metabolism and nutrition disorders	Hypophosphataemia	Very common	Very common
	Hypokalaemia	Very common	Common
Nervous system disorders	Headache	Very common	--
	Dizziness	Very common	--
Investigation	Proteinuria	Very common	--
	Glycosuria	Very common	--
Blood and lymphatic system disorders	Eosinophilia	Very common	--
Renal and urinary disorders	Renal tubular disorder	Common	--
Injury, poisoning and procedural complications	Bone fracture[d]	Common	--
Hepatobiliary disorders	ALT increased	Very common	Common
	AST increased	Very common	Common

System organ class	Adverse reaction	All grades	Grades 3-4
Reproductive system and breast disorders	Ovarian toxicity[e]	Very common	--
Respiratory, thoracic and mediastinal disorders	Cough	Very common	--
	Upper respiratory tract infection[f]	Very common	--
	Dyspnoea	Very common	--
	Epistaxis	Very common	--
General disorders and administration site conditions	Fatigue	Very common	Common
	Influenza-like illness	Very common	--

[a] Stomatitis includes stomatitis, mouth ulceration, oral pain, and oropharyngeal pain.
[b] Rash includes rash maculo-papular, dermatitis acneiform, rash, rash erythematous, rash pruritic, and rash papular.
[c] Squamous cell carcinoma included squamous cell carcinoma of skin and squamous cell carcinoma.
[d] Bone fracture includes fracture, foot fracture, hand fracture, radius fracture, hip fracture and rib fracture.
[e] Ovarian toxicity includes ovarian failure, premature menopause, amenorrhoea, oligomenorrhoea, menstruation irregular, dysmenorrhoea, heavy menstrual bleeding, vulvovaginal dryness, hot flush, decreased anti-Müllerian hormone (AMH) and increased follicle-stimulating hormone (FSH).
[f] Upper respiratory tract infection (URTI) includes URTI, viral URTI, acute sinusitis, and sinusitis.
-- Represents no cases were reported.

Description of selected adverse reactions

The data described below reflect results of the randomised, double-blind, Phase 3 DeFi study in patients with desmoid tumours treated with 150 mg BID nirogacestat (N=69) or placebo (N=72) twice daily.

Diarrhoea
In the double-blind phase of the DeFi study, diarrhoea was reported in 84% of patients receiving nirogacestat compared to 35% in patients receiving placebo. Grade 3 events occurred in 16% and 1% of patients, respectively (see section 4.4). Grade ≤ 2 diarrhoea resolved in 74% of patients who continued on nirogacestat treatment. The median time to first onset of diarrhoea in patients receiving nirogacestat was 9 days (range 2 to 234 days). Diarrhoea led to dose reduction in 10% of patients and treatment discontinuation in 7% receiving nirogacestat.

Skin and subcutaneous tissue disorders
In the double-blind phase of the DeFi study, dermatologic reactions were reported at a higher incidence in patients receiving nirogacestat than in those receiving placebo; they included maculo-papular rash (32% vs 6%), hidradenitis (9% vs 0), and folliculitis (13% vs 0) (see section 4.4). The median time to rash events was 22 days (range 2 to 603 days). Skin and subcutaneous disorders led to dose reduction in 9% of patients receiving nirogacestat, including maculo-papular rash in 4% and hidradenitis in 3%. Maculo-papular rash led to treatment discontinuation in 1%.

Ovarian toxicity
In the double-blind phase of the DeFi study, 75% of women of childbearing potential receiving nirogacestat reported ovarian toxicity (defined as ovarian failure, premature menopause, amenorrhea, oligomenorrhea, and menopause) compared to no patients receiving placebo. There were three serious adverse reactions of ovarian toxicity, all premature menopause, representing 11% of all participants reporting ovarian toxicity. The median time to first onset of ovarian toxicity was 8.9 weeks (range 1 day to 54 weeks), and the overall median duration was 18.9 weeks (range 11 days to 215 weeks). Ovarian toxicity has been reported to resolve in 79% of women of childbearing potential during treatment. Follow up information is available for all but two out of 27 patients; after stopping treatment, ovarian toxicity was reported to resolve in all women of childbearing potential for whom data are available. The median time to resolution after discontinuing nirogacestat was 10.9 weeks (range 4 to 18 weeks). Effects of nirogacestat on fertility are unknown (see section 4.4). An exposure-

response relationship was identified between nirogacestat and serum follicular stimulating hormone (FSH) levels, with FSH increasing linearly with increasing serum concentrations of nirogacestat.

Electrolyte abnormalities
Electrolyte abnormalities were reported in patients receiving nirogacestat in the double-blind phase of the DeFi study, including hypophosphataemia (43%) and hypokalaemia (12%), compared to 7% and 1%, respectively, in patients receiving placebo. Median time to first onset of hypophosphataemia and hypokalaemia was 15 days (range 1 to 833 days) and 15 days (range 1 to 57 days), respectively. Grade 3 events of hypophosphataemia and hypokalaemia occurred in 3% of patients receiving nirogacestat compared to no patients receiving placebo (see section 4.4). Hypophosphataemia and hypokalaemia led to dose reduction in 4% and 1% of patients receiving nirogacestat, respectively. Hypophosphataemia led to dose discontinuation in 1% of patients receiving nirogacestat.

Hepatic abnormalities
ALT and AST elevations were reported in 19% and 17%, respectively, of patients receiving nirogacestat in the double-blind phase of the DeFi study compared to 8% and 11%, respectively, in patients receiving placebo. Median time to first onset of ALT and AST elevations was 22 days (ALT range 8 to 924 days; AST range 1 to 1023 days). Grade 3 ALT and AST elevations (> 5 x ULN) occurred in 3% of patients treated with nirogacestat compared to 1% in the placebo arm (see section 4.4). ALT and AST elevations each led to dose reduction in 1% of patients receiving nirogacestat. ALT and AST elevations led to dose discontinuation in 4% and 3% of patients receiving nirogacestat, respectively.

Non-melanoma skin cancers
Non-melanoma skin cancers were reported at a higher incidence in patients receiving nirogacestat than in those receiving placebo in the double-blind phase of the DeFi study, including squamous cell carcinoma (3% vs 0) and basal cell carcinoma (1% vs 0), with one patient reporting both types of non-melanoma skin cancer (see section 4.4). An additional two cases of non-melanoma skin cancer were reported outside of the double-blind phase of the DeFi study.

Proximal renal tubule effect
Glycosuria and proteinuria were observed in 52% and 46%, respectively, of patients receiving nirogacestat in the double-blind phase of the DeFi study, compared with 1% and 39%, respectively, in patients receiving placebo. Median time to onset of glycosuria and proteinuria was 85 days (range 55 to 600 days) and 72 days (range 38 to 937 days), respectively. One patient in the DeFi study reported renal tubular disorder with increased urinary excretion of uric acid, glucose and phosphate, but no excess excretion of low molecular weight proteins (beta2-microglobulin) or any change in renal function. The event was managed with dose reduction.

Bone fracture
In the double-blind phase of the DeFi study, bone fractures were reported in 6% of patients receiving nirogacestat compared with no patients receiving placebo. All reports of bone fracture were non-serious and Grade 1 or 2. The median time to first onset of bone fracture events in patients receiving nirogacestat was 125 days (range 1 to 739 days). Bone fracture events did not lead to dose reduction or treatment discontinuation in any patient receiving nirogacestat.

Paediatric population

Epiphyseal disorder, manifesting as a widening of the epiphyseal growth plate, was reported in 4 of 26 (15%) paediatric patients with open growth plates treated with nirogacestat outside of the DeFi study. The events included epiphysiolysis, hip fracture, epiphyseal disorder, and osteonecrosis. All 4 paediatric patients were between the ages of 11 and 12 years. See section 4.2 for information on paediatric use.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Signs and symptoms

The symptoms of Ogsiveo overdose are expected to be an extension of its pharmacological actions and may include diarrhoea, nausea, vomiting, hypophosphataemia, elevated transaminases, and epistaxis.

Management of overdose

Due to the high level of protein binding, Ogsiveo is not expected to be dialyzable in patients with normal serum protein levels. In the event of an overdosage, treatment with Ogsiveo should be stopped and general supportive measures should be initiated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, other antineoplastic agents; ATC Code: L01XX81

Mechanism of action

Nirogacestat is a reversible and non-competitive inhibitor of gamma secretase that blocks proteolytic activation of the Notch receptor.

Cardiac electrophysiology

The effects of nirogacestat concentration on QTc interval prolongation were predicted using a model-based analysis. The 90% confidence intervals for the predicted mean change in QTcF were below 10 msec at the expected C_{max} at supratherapeutic doses. Therefore, no clinically significant prolongation in QTcF interval is associated with therapeutic dosing of Ogsiveo.

Clinical efficacy and safety

The DeFi study was an international, multicentre, randomised (1:1), double-blind, placebo-controlled Phase 3 study in adult patients with progressing desmoid tumours. Patients with histologically confirmed desmoid tumours that had progressed by ≥ 20% as measured by RECIST v1.1 within 12 months of screening and where continued progressive disease did not result in immediate significant risk to the patient were eligible. Randomisation was stratified by target tumour location(s) (intra-abdominal or extra-abdominal). Patients with multiple target tumours located both in the intra-and extra-abdominal location were classified as intra-abdominal. Patients received 150 mg nirogacestat or placebo orally twice daily in 28-day cycles until disease progression, death, or unacceptable toxicity. The primary efficacy measure was progression-free survival (PFS). Progression was determined radiographically using RECIST v1.1 by a blinded, independent central imaging review, or as clinically assessed by the investigator and qualified via blinded, independent, central review, or by death due to any cause. Additional efficacy measures included objective response rate (ORR), change from baseline in pain at Cycle 10, change from baseline in desmoid tumour-specific symptom severity at Cycle 10, change from baseline in role functioning and physical functioning at Cycle 10, and change from baseline in overall quality of life at Cycle 10. Pain was measured by the 7-day average of item #3 (i.e., worst pain) from the Brief Pain Inventory (BPI) Short Form. Desmoid tumour-specific symptom severity and physical functioning were measured using the GOunder/DTRF DEsmoid Symptom/Impact Scale (GODDESS).

A total of 142 patients were randomised: 70 to nirogacestat and 72 to placebo. Overall, the median age was 34 years (range: 18 to 76); 4% were 65 of age or older; 65% were female; race was 83% White, 6% Black, 3% Asian, and 8% other; 73% had an ECOG performance status (PS) of 0, 27% had an ECOG PS of 1, and < 1% had an ECOG PS of 2. Twenty-three percent of patients had intra-abdominal disease or both intra- and extra-abdominal disease, and 77% had only extra-abdominal disease. Forty-one percent of patients had multifocal disease and 59% had single focal disease. Of 105 patients with known somatic tumour mutation status, 81% had a *CTNNB1* mutation and 21% had an *APC* mutation. Seventeen percent of patients had a family history of familial adenomatous polyposis (FAP). Twenty-three percent of the patients had received no prior therapy and 44% had received ≥ 3 prior lines of therapy. Prior therapy included systemic therapy (61%), surgery (53%), and radiotherapy (23%). Thirty-six percent of patients were previously treated with chemotherapy and 33% were previously treated with a tyrosine kinase inhibitor. Fifty percent had a BPI-SF item 3 (worst pain) score of ≥ 2 at baseline.

Efficacy results from the ITT population, which included all randomised patients, are presented below. PFS and ORR improvements were in favour of nirogacestat regardless of baseline characteristics including tumour location and type of prior therapies.

Table 3: Efficacy results in patients with RECIST 1.1 progressing desmoid tumours

	Nirogacestat N = 70	**Placebo N = 72**
Progression-free survival		
Number (%) of patients with event	12 (17)	37 (51)
Radiographic progression [a]	11 (16)	30 (42)
Clinical progression [a]	1 (1)	6 (8)
Death	0	1 (1)
Median (months) (95% CI) [b]	NR (NR, NR)	15.1 (8.4, NR)
Hazard ratio (95% CI)	0.29 (0.15, 0.55)	
p-value [c]	< 0.001	
Objective response rate [a]		
ORR, n (%)	29 (41)	6 (8)

	Nirogacestat N = 70	**Placebo N = 72**
95% CI [d]	(29.8, 53.8)	(3.1, 17.3)
CR	5 (7)	0
PR	24 (34)	6 (8)
p-value [e]	< 0.001	

Abbreviations: CI: confidence interval; CR: complete response; ORR: objective response rate; PR: partial response; NR: Not Reached

[a] Assessed by blinded independent central review.

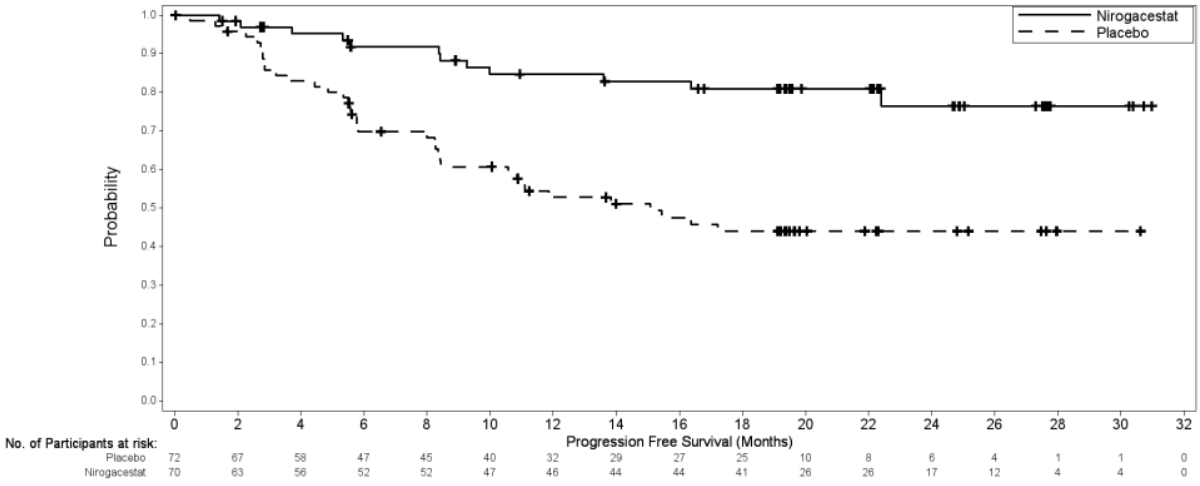
[b] Obtained using Kaplan-Meier Methodology.

[c] p-value was from a one-sided stratified log-rank test.

[d] Obtained using exact method based on binomial distribution.

[e] p-value was from a two-sided Cochran-Mantel-Haenszel test.

Figure 1: Kaplan-Meier curve of PFS



Note: Median and 95% confidence intervals were estimated from the Kaplan-Meier method. Due to the low number of events in the nirogacestat arm, the Kaplan-Meier estimate of median time to progression was unable to be estimated.

Patient-reported outcomes

PFS results were supported by change from baseline in patient-reported worst pain favouring the nirogacestat arm at Cycle 10 (-1.6 vs -0.2; LS mean difference: -1.3; 95% confidence interval: -2.1 to -0.6; $p < 0.001$).

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Ogsiveo in one or more subsets of the paediatric population in the treatment of soft tissue sarcoma. See Section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Absorption

Peak concentrations of nirogacestat are reached approximately 1.5 hours after oral administration. Nirogacestat absolute bioavailability following oral administration is approximately 19.2% (Range: 16.2%-24.3%).

Distribution

The blood-to-plasma ratio of nirogacestat is estimated to be approximately 0.5 in humans. The serum protein binding is approximately 99.6% *in vitro*. Nirogacestat is highly bound to both human serum albumin and to α-1 acid glycoprotein but with a greater affinity for α1 acid glycoprotein. Based on the population pharmacokinetic analysis, the apparent oral volume of distribution of nirogacestat in desmoid tumour patients was estimated to be 1430 L.

Biotransformation

Nirogacestat is extensively metabolized mainly by CYP3A4. There is incomplete knowledge of major or active metabolites *in vivo* due to limitations of detecting non-radiolabelled metabolites. Numerous minor metabolites have been detected in circulation and excreta.

Elimination

After a single oral dose of radiolabelled nirogacestat in healthy subjects, approximately 65% of the dose is recovered within 13 days following the administration; 38% is eliminated in faeces, 17% is eliminated in urine, and 10% of the recovered label is found in expired air. Unchanged nirogacestat in the urine accounts for less than 0.01% and in faeces for less than 0.5% of the administered dose.

The population pharmacokinetic analysis in the desmoid tumour population estimates an apparent terminal elimination half-life of about 23 hours. The apparent oral systemic clearance is approximately 45 L/hr.

Linearity/non-linearity

Nirogacestat exposure increases with escalating single and repeat doses, with proportional increases over the 50-150 mg dose range.

Steady-state conditions are achieved by approximately 7 days following repeat administration. The population pharmacokinetic analysis estimates an accumulation ratio of approximately 1.5 in desmoid tumour patients.

Special populations

Effects of hepatic impairment
The pharmacokinetics of nirogacestat were evaluated in patients with moderate hepatic impairment (HI) based on Child-Pugh classification. Total nirogacestat exposure (AUC) was not affected by moderate hepatic impairment, but peak exposure (C_{max}) was reduced by 28% with a higher volume of distribution and longer half-life.

Effects of renal impairment
The effects of renal impairment on nirogacestat pharmacokinetics have not been evaluated in a dedicated clinical study. In a PopPK model, no clinically meaningful relationship was observed between renal function tests and nirogacestat pharmacokinetics. There were two subjects with mild and moderate renal impairment, respectively, out of 335 subjects included in the PopPK analysis. No subjects with severe renal impairment were included in the PopPK analysis.

5.3 Preclinical safety data

In repeat dose toxicity studies in rats and dogs, most of the toxicities were associated with gamma secretase inhibition. The effects included ovarian atrophy, alterations in the estrous cycle, decreased cellularity in gut-associated lymphoid tissue, and decreased cellularity of mesenteric lymph nodes. In the rat study, growth plate thickening was observed. In addition, all dose levels evaluated in the rat study showed chronic progressive nephropathy, pulmonary phospholipidosis, and salivary gland

necrosis in a dose-dependent manner. In the dog study, treatment-related effects were present within the intestines, spleen, gall bladder, liver, kidney, testes, and ovary. The intestinal and liver findings were associated with generalized inflammation and associated clinical pathology changes in most of the dogs. A NOAEL was not identified in the 3-month oral toxicity studies in rats or dogs. The lowest dose in the rat study was 5 mg/kg/day (human equivalent dose 50 mg/day) and in the dog the lowest dose was 2 mg/kg/day (human equivalent dose of 70 mg/day). Systemic exposures were also below the human systemic exposures (AUC) administered 150 mg BID of nirogacestat.

Carcinogenicity

Notch signalling appears to have both an oncogenic and tumour suppressor function. The carcinogenic potential of nirogacestat was evaluated in a 6-month transgenic rasH2 mice study. At doses up to 100 mg/kg/day an increased incidence of hemangiosarcoma was observed. At 100 mg/kg/day, systemic exposures (AUC) were below (0.2-fold) those in humans administered 150 mg BID nirogacestat. The carcinogenic potential in rats has not been assessed.

Reproductive and developmental toxicity

Nirogacestat reduced fertility indices in both male and female rats, which correlated with ovarian atrophy, reduced testes weights, and decreased sperm motility and effects on sperm morphology. In addition, early embryonic loss occurred in fertility studies. In a preliminary embryo-foetal development study, nirogacestat induced significant and dose-related embryo loss, early resorptions and decreased foetal weights in surviving embryos. These effects occurred at 20 mg/kg/day resulting in systemic exposures below (approximately 0.45-fold) human exposures after administration of nirogacestat at 150 mg BID (see section 4.4).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Cellulose, microcrystalline
Lactose monohydrate
Sodium starch glycolate
Magnesium stearate

Tablet coating

Macrogol polyvinyl alcohol graft copolymer (E 1209)
Talc (E553b)
Titanium dioxide (E171)
Glycerol monocaprylocaprate type 1/mono/diglycerides (E471)
Polyvinyl alcohol - partially hydrolyzed (E1203)
FD&C yellow #6/sunset yellow FCF aluminium lake (E110)
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

Ogsiveo 50 mg film-coated tablets

HDPE bottle with child resistant closure and induction seal containing 120 or 180 tablets.

Ogsiveo 100 mg film-coated tablets
Ogsiveo 150 mg film-coated tablets

Clear PVC/PVDC blisters with aluminium lidding containing 14 tablets. One pack contains 56 tablets in 4 blisters.

Not all pack sizes may be marketed.

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

SpringWorks Therapeutics Ireland Limited
Hamilton House, 28 Fitzwilliam Place
Dublin 2, D02 P283
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1932/001
EU/1/25/1932/002
EU/1/25/1932/003
EU/1/25/1932/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorization: 14 August 2025

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 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

Patheon France S.A.S
40 Boulevard de Champaret
38300 Bourgoin Jallieu
France

Rottendorf Pharma GmbH
Ostenfelder Strasse 51-61
D-59320 Ennigerloh
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

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

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

- **Risk management plan (RMP)**

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

An updated RMP should be submitted:

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

- **Additional risk minimisation measures**

Prior to the launch of Ogsiveo (nirogacestat) in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at minimising in utero exposure to Ogsiveo (nirogacestat) and the subsequent potential risk of embryo-fetal toxicity.

The MAH shall ensure that in each Member State where Ogsiveo (nirogacestat) is marketed, all healthcare professionals who are expected to prescribe or patients who are expected to use Ogsiveo (nirogacestat) have access to/are provided with the following educational materials:

- Physician educational material
- Patient card

Physician educational material:

- The Summary of Product Characteristics
- Guide for healthcare professionals:

The healthcare professional guide should contain the following key elements:

- Nirogacestat may cause embryo-foetal harm, including foetal loss, when administered to a pregnant woman.
- Nirogacestat is contraindicated in pregnant women and in women of childbearing potential not using highly effective contraception.
- A pregnancy test must be performed and be negative before start of treatment with nirogacestat.
- Women of childbearing potential should be advised to use highly effective contraceptive methods during treatment with nirogacestat and for 1 week after the last dose of nirogacestat.
- Nirogacestat may reduce the efficacy of hormonal contraceptives.
- Patients should be advised to use at least one highly effective method of contraception (such as an intrauterine device) or two complementary forms of contraception including a barrier method.
- Female patients of childbearing potential should be informed about the potential risk of embryo-foetal harm and the use of appropriate contraceptive measures before start of treatment with nirogacestat.
- Pregnancy testing during treatment with nirogacestat should be considered for women of childbearing potential experiencing amenorrhea.
- Male patients with female partners of childbearing potential should be advised to use highly effective contraceptive methods during treatment with nirogacestat and for 1 week after the last dose of nirogacestat.
- Patients should be advised to tell their doctor immediately if they suspect that they are pregnant.
- Patients should be given the patient card.

The patient card:

The patient card should contain the following key elements:

- Nirogacestat may cause embryo-foetal harm, including foetal loss, when used during pregnancy.
- Patients who are women of childbearing potential, and male patients with female partners who are of childbearing potential, have to use highly effective contraceptive methods during treatment with nirogacestat and for 1 week after the last dose.
- If you are a woman who can become pregnant or a man with a partner who can become pregnant, you must use at least one highly effective method of contraception (such as an intrauterine device) or two complementary forms of contraception including a barrier method.

- If you suspect that you may be pregnant during treatment with nirogacestat, contact your treating oncologist immediately. If you are pregnant, you must not take nirogacestat.

- **Obligation to conduct post-authorisation measure**

The MAH shall complete, within the stated timeframe, the below measure:

Description	**Due date**
The applicant is required to develop effective measures (i.e. an optimized formulation, manufacturing process and/or control strategy) to ensure the sum of ASYM-136911 and ASYM-136912 impurities does not exceed the AI limit of 1.5 µg/day throughout shelf-life and submit the appropriate variation to implement the change(s) and tighten the release and shelf-life specification limit to NMT 1.5 µg/day in the finished product.	Q3 2027
A Progress report should be submitted.	Q3 2026

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Ogsiveo 50 mg film-coated tablets
nirogacestat

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 50 mg nirogacestat (as nirogacestat dihydrobromide).

3. LIST OF EXCIPIENTS

Contains lactose and sunset yellow FCF (E110). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet
120 film-coated tablets
180 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Swallow whole. Do not break, chew or crush.
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

Store below 25°C.

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

SpringWorks Therapeutics Ireland Limited
Hamilton House, 28 Fitzwilliam Place
Dublin 2, D02 P283
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1932/001 120 film-coated tablets
EU/1/25/1932/002 180 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ogsiveo 50 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

1. NAME OF THE MEDICINAL PRODUCT

Ogsiveo 50 mg tablets
nirogacestat

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 50 mg nirogacestat (as nirogacestat dihydrobromide).

3. LIST OF EXCIPIENTS

Contains lactose and E110, see leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

tablet
120 tablets
180 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Swallow whole.
Do not break, chew or crush.
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

Store below 25°.C

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

SpringWorks Therapeutics

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1932/001 120 film-coated tablets
EU/1/25/1932/002 180 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

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Ogsiveo 100 mg film-coated tablets
nirogacestat

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 100 mg nirogacestat (as nirogacestat dihydrobromide)

3. LIST OF EXCIPIENTS

Contains lactose and sunset yellow FCF (E110). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet
56 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Swallow whole. Do not break, chew or crush.

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

Store below 25°C.

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

SpringWorks Therapeutics Ireland Limited
Hamilton House, 28 Fitzwilliam Place
Dublin 2, D02 P283
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1932/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ogsiveo 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Ogsiveo 100 mg film-coated tablets
nirogacestat

2. NAME OF THE MARKETING AUTHORISATION HOLDER

SpringWorks Therapeutics Ireland Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Ogsiveo 150 mg film-coated tablets
nirogacestat

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 150 mg nirogacestat (as nirogacestat dihydrobromide)

3. LIST OF EXCIPIENTS

Contains lactose and sunset yellow FCF (E110). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet
56 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Swallow whole. Do not break, chew or crush.

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

Store below 25°C.

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

SpringWorks Therapeutics Ireland Limited
Hamilton House, 28 Fitzwilliam Place
Dublin 2, D02 P283
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1932/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ogsiveo 150 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Ogsiveo 150 mg film-coated tablets
nirogacestat

2. NAME OF THE MARKETING AUTHORISATION HOLDER

SpringWorks Therapeutics Ireland Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Ogsiveo 50 mg film-coated tablets
Ogsiveo 100 mg film-coated tablets
Ogsiveo 150 mg film-coated tablets
nirogacestat

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

What is in this leaflet

1. What Ogsiveo is and what it is used for

Ogsiveo is a medicine that contains the active substance nirogacestat which inhibits a protein called gamma-secretase. Gamma-secretase inhibitors treat cancer by stopping the activity of certain proteins that are involved in the growth of cancer cells.

Ogsiveo is used in adults to treat progressing desmoid tumours (soft tissue tumours that form in fibrous (connective) tissue, usually in the arms, legs or abdomen, that do not spread to other locations). It is used in adults who require treatment with a medicine given by mouth or injection (systemic therapy.

2. What you need to know before you take Ogsiveo

Do not take Ogsiveo:
- If you are are allergic to nirogacestat or any of the other ingredients of this medicine (listed in section 6).
- If you are pregnant (see Pregnancy section below)
- If you are able to become pregnant and are not using highly effective contraception (birth control) (see Contraception in men and women section below).
- If you are breast-feeding (see Breastfeeding section below).

Warnings and precautions

Talk to your doctor or nurse if any of the following happen to you while you are taking Ogsiveo (see also section 4: Possible side effects).

- **If you experience severe diarrhoea or diarrhoea that lasts longer than two days** and does not respond to treatment, stop taking the medicine and seek medical advice straight away. Your doctor may pause treatment with Ogsiveo until your symptoms improve, give you other medicines, lower the dose or tell you to drink more fluids.

- **If you experience a rash** tell your doctor or nurse as soon as possible. Your doctor may give you a medicine to treat these or may pause treatment with Ogsiveo or lower the dose.

- **Ovarian problems.** You may experience symptoms such as hot flashes, night sweats, vaginal dryness and menstrual cycle changes, including irregular periods or no periods. These side effects went away in the majority of women while they were still on treatment and in all women who stopped taking Ogsiveo.

Examinations:

- Your doctor will do blood tests to check your electrolytes (salts) and liver function during treatment.

- **Skin cancers.** Certain types of skin cancer, called basal cell carcinoma and squamous cell carcinoma, have been reported in patients taking Ogsiveo. Your doctor should perform regular examinations of your skin during treatment with Ogsiveo. Tell your doctor or nurse if you have any new or changing skin lesions such as a small white or flesh coloured bump, a scaly red patch, an open sore, or a wart that may crust or bleed easily.

Children and adolescents
Do not give Ogsiveo to children and adolescents aged under 18 years as the safety and efficacy have not been established in this population. Ogsiveo may be detrimental to bone growth in growing children.

Other medicines and Ogsiveo
Tell your doctor if you are taking, have recently taken or might take any other medicines, including herbal medicines, while receiving Ogsiveo.

Tell your doctor or pharmacist if you are taking any of the following medicines:

- Clarithromycin, erythromycin - used to treat bacterial infections
- Itraconazole, ketoconazole, fluconazole - used to treat serious fungal infections
- Cyclosporine, tacrolimus - used to prevent transplant rejection
- Fostamatinib - used to treat low blood platelet count
- Ritonavir, atazanavir, efavirenz and etravirine - used to treat HIV infections/AIDS
- Diltiazem - used to treat high blood pressure and chest pain
- Hormonal contraceptives agents (birth control medicines) (see Contraception in men and women section below)
- Rifampicin - used to treat tuberculosis (TB)
- Carbamazepine, phenytoin, phenobarbital - used to treat epilepsy
- St. John's wort (*Hypericum perforatum*) - a herbal medicine used for depression
- Midazolam used for anaesthesia, sedation or to decrease anxiety
- Digitoxin, dofetilide - used to treat heart conditions or correct irregular heartbeats
- Warfarin - used to thin your blood
- Antacids (short acting medicines containing minerals such as calcium, magnesium, aluminium or bicarbonate that neutralise the acid in your stomach) These medicines may interfere with

Ogsiveo absorption and reduce how well it works. Take Ogsiveo 2 hours before or 2 hours after taking the antacid.
- H2 blockers (such as famotidine and cimetidine), and proton pump inhibitors (such as omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole) - used to reduce acid in the stomach. These medicines may interfere with Ogsiveo absorption and reduce how well it works and you should not take these during treatment with Ogsiveo.

Ogsiveo with food and drink
Avoid consuming grapefruit and grapefruit juice when taking Ogsiveo as this may increase the likelihood and or severity of side effects.

Pregnancy
Do not take Ogsiveo if you are pregnant. If you can become pregnant, your doctor will check if you are pregnant before you start treatment with Ogsiveo. You will also have pregnancy tests during your treatment if you have stopped having periods or have unusual menstrual bleeding. If you suspect that you may be pregnant, tell your doctor or nurse straight away. If you are pregnant, you must stop taking Ogsiveo. Ogsiveo may cause harm to the unborn baby if taken during pregnancy.

Contraception in men and women

If you are a woman who can become pregnant or a man with a partner who can become pregnant, you must use at least one highly effective method of contraception (such as an intrauterine device) or two complementary forms of contraception including a barrier method (such as condoms in combination with spermicide) during treatment with Ogsiveo and for 1 week after the last dose. Talk to your healthcare provider about birth control methods that may be right for you.

Breast-feeding
It is not known if Ogsiveo passes into breast milk. Do not breast-feed during treatment with Ogsiveo and for 1 week after the last dose.

Fertility
Based on findings in animal studies, Ogsiveo may impair female and male fertility. There are no data concerning fertility in humans.

Women who can get pregnant should not donate eggs (oocytes) during treatment and for 1 week after the last dose of Ogsiveo.
Men should not donate sperm during treatment with Ogsiveo and for 1 week after the last dose.

Driving and using machines
Ogsiveo has no or negligible influence on the ability to drive or capacity to use machines, however, since fatigue and dizziness may occur in patients taking nirogacestat, exercise caution if you experience these side effects.

Ogsiveo contains lactose
Ogsiveo contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

Ogsiveo contains sodium
Each film-coated tablet contains less than 23 mg sodium (main component of cooking/table salt). This means Ogsiveo is essentially sodium-free.

Ogsiveo contains sunset yellow FCF (E 110)
Ogsiveo contains sunset yellow FCF (E 110) which may cause allergic reactions.

3. How to take Ogsiveo

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

How much to take
The recommended dose is 150 mg to be taken two times a day, one dose in the morning and one dose in the evening.

Taking Ogsiveo
- Swallow the tablet whole.
- Do not break, crush or chew the tablet. The tablet can be taken with or without food.
- Do not consume grapefruit or grapefruit juice while taking Ogsiveo.
- If your doctor has told you to take antacid medicine, take Ogsiveo 2 hours before or 2 hours after taking the antacid (see section 2 "Other medicines and Ogsiveo").

If you take more Ogsiveo than you should
If you have taken more tablets than you should, contact your doctor, pharmacist or nurse straight away. You may experience diarrhoea, nausea, vomiting, and nosebleeds.

If you forget to take Ogsiveo
Skip the missed dose and take your next dose at your regular time. Do not take a double dose to make up for a forgotten dose.

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.

- **If you experience severe diarrhoea or diarrhoea that lasts longer than two days and does not respond to treatment, stop taking the medicine and seek medical advice straight away.** Very common (may affect more than 1 in 10 people).

- **If you experience a rash, small painful lumps in your groin, armpits, buttocks or under your breasts, or pimples around the base of your hairs, tell your doctor or nurse as soon as possible.** Very common (may affect more than 1 in 10 people).

Other side effects
Talk to your doctor if you get any of the following side effects:

Very common (may affect more than 1 in 10 people):
- nausea
- mouth sores or pain (stomatitis)
- dry mouth
- dry skin
- itchiness (pruritus)
- hair loss (alopecia)
- inflammation of hair follicles (folliculitis)
- low levels of phosphate (hypophosphataemia) and potassium seen in blood tests (hypokalaemia)
- headache
- dizziness
- changes in protein (proteinuria) and sugar levels in your urine (glycosuria)
- increase in the number of a type of white blood cells (eosinophilia)

- abnormal laboratory values for liver function (alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased)
- ovarian problems such as hot flashes, night sweats, vaginal dryness and menstrual cycle changes, including irregular periods or no periods (ovarian toxicity).
- cough
- upper respiratory tract (nose and throat) infections (upper respiratory tract infections)
- difficulty breathing (dyspnoea)
- nosebleeds (epistaxis)
- tiredness (fatigue)
- flu-like symptoms (influenza-like illness)

Common (may affect up to 1 in 10 people):
- painful skin condition that causes lumps and abscesses in areas with sweat glands, such as the groin and armpits (hidradentitis)
- skin cancer (basal cell carcinoma, squamous cell carcinoma). Symptoms may be small white or flesh coloured bump, a scaly red patch, an open sore, or a wart that may crust or bleed easily.
- kidney problems (renal tubular disorder)
- bone fracture

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. 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 Ogsiveo

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 packaging. The expiry date refers to the last day of that month.

Store this medicine below 25°C.

Do not throw away your medicine 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 Ogsiveo contains

The active substance is nirogacestat (as nirogacestat dihydrobromide).

Ogsiveo 50 mg film-coated tablets
Each film-coated tablet contains 50 mg of nirogacestat (as nirogacestat dihydrobromide).

Ogsiveo 100 mg film-coated tablets
Each film-coated tablet contains 100 mg of nirogacestat (as nirogacestat dihydrobromide).

Ogsiveo 150 mg film-coated tablets
Each film-coated tablet contains 150 mg of nirogacestat, (as nirogacestat dihydrobromide).

The other ingredients are:

Core tablet: cellulose microcrystalline, lactose monohydrate, sodium starch glycolate, and magnesium stearate.
Coating: Macrogol polyvinyl alcohol graft copolymer (E 1209), talc (E553b), titanium dioxide (E171), glycerol monocaprylocaprate type 1/mono/diglycerides (E471), polyvinyl alcohol - partially hydrolysed (E1203), FD&C yellow #6/sunset yellow FCF aluminium lake (E110), iron oxide yellow (E172)
See section 2 “Ogsiveo contains lactose, sodium and sunset yellow”.

What Ogsiveo looks like and contents of the pack

Ogsiveo 50 mg film-coated tablets

Ogsiveo 50 mg film-coated tablets are round and orange, debossed with “50” on one side, and are 8 mm in diameter. The tablets are supplied in an HDPE bottle with child resistant closure and induction seal containing 120 or 180 tablets.

Ogsiveo 100 mg film-coated tablets / Ogsiveo 150 mg film-coated tablets

Ogsiveo 100 mg film-coated tablets are round and light orange, debossed with “100” on one side, and are 10 mm in diameter.
Ogsiveo 150 mg film-coated tablets are oval and yellow orange, debossed with “150” on one side, and are 8.5 x 17.5 mm in size.
The tablets are supplied in cartons containing 56 film-coated tablets in clear PVC/PVDC blisters containing 14 tablets per blister.

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Other sources of information

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