PDL DRUG REVIEW

Proprietary Name: Ogsiveo®
Common Name: nirogacestat
PDL Category: Antineoplastics

Pharmacology/Usage: Nirogacestat, the active ingredient of Ogsiveo®, is a gamma secretase inhibitor that blocks proteolytic activation of the Notch receptor. When dysregulated, Notch can activate pathways that contribute to tumor growth.

Indication: For adult patients with progressing desmoid tumors who require systemic treatment.

There is no pregnancy category for this medication; however, the risk summary indicates that based on findings from animal studies and its mechanism of action, Ogsiveo® can cause fetal harm or loss of pregnancy when administered to a pregnant woman. There are no available data on use in pregnant women. Advise pregnant women of the potential risk to a fetus. As Ogsiveo® can cause fetal harm when administered to a pregnant woman, verify pregnancy status in females of reproductive potential prior to starting Ogsiveo®. Advise females of reproductive potential to use effective contraception during treatment and for 1 week after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with Ogsiveo® and for 1 week after the last dose. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Film-Coated Tablets: 50mg, 100mg, and 150mg.

Swallow tablets whole and do not break, crush, or chew prior to swallowing.

Recommended Dosage: The recommended dosage is 150mg PO BID with or without food until disease progression or unacceptable toxicity. If a patient vomits or misses a dose, instruct the patient to take the next dose at its scheduled time.

There are recommended dose modifications for Ogsiveo® for selected severe adverse reactions. Refer to the prescribing information for additional information.

Drug Interactions: Nirogacestat is a CYP3A substrate. Avoid concomitant use of Ogsiveo® with strong or moderate CYP3A inhibitors, including grapefruit products, Seville oranges, and starfruit.

Avoid concomitant use of Ogsiveo® with strong or moderate CYP3A inducers.

Nirogacestat is poorly soluble at pH ≥6. Avoid concomitant use of Ogsiveo® with proton pump inhibitors and H2 blockers. If concomitant use cannot be avoided, Ogsiveo® can be staggered with antacids (e.g., administer Ogsiveo® 2 hours before or 2 hours after antacid use).

Nirogacestat increases exposure of CYP3A substrates. Avoid concomitant of Ogsiveo® use with CYP3A substrates where minimal concentration changes may lead to serious adverse reactions.

Nirogacestat decreases exposure of CYP2C19 substrates. Avoid concomitant use of certain CYP2C19 substrates with Ogsiveo® where decreased concentrations of CYP2C19 substrates may lead to significant decreases in efficacy of the CYP2C19 substrate unless otherwise recommended in the prescribing information for the CYP2C19 substrate.

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Ogsiveo®) minus reported % incidence for placebo for all grades. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included diarrhea (49%), nausea (15%), stomatitis (35%), abdominal pain (8%), ovarian toxicity (75%), rash (54%), alopecia (17.6%), fatigue (16%), headache (15%), cough (14%), dyspnea (10%), and upper respiratory tract infection (14.2%).

Listed % incidence for laboratory abnormalities= reported % incidence for drug (Ogsiveo®) minus reported % incidence for placebo for all grades. Please note that an incidence of 0% means the incidence was the same as or less than placebo. The most frequently laboratory abnormalities included decreased phosphate (54%), increased urine glucose (51%), increased urine protein (15%), increased aspartate aminotransferase (15%), increased alanine aminotransferase (9%), and decreased potassium (17.8%).

Diarrhea, sometimes severe, can occur in patients treated with Ogsiveo®. Median time to first diarrhea events for patients treated with Ogsiveo® in a clinical trial was 9 days (range 2 to 434 days). Monitor patients and manage using antidiarrheal medications. Modify the dose as recommended.

Female reproductive function and fertility may be impaired in patients treated with Ogsiveo®. Impact on fertility may depend on factors including the duration of therapy and the state of gonadal function at the time of treatment. The long-term effects of Ogsiveo® on fertility have not been established. Advise patients on the potential risks for ovarian toxicity before starting treatment. In addition, monitor patients for changes in menstrual cycle regularity or the development of symptoms of estrogen deficiency.

ALT or AST elevations occurred in 30% and 33% of patients who received Ogsiveo® in a clinical study, respectively. Monitor liver function tests regularly and modify dose as recommended.

New non-melanoma skin cancers can occur in patients treated with Ogsiveo®. Perform dermatologic evaluations prior to the start of Ogsiveo® and routinely during treatment.

Electrolyte abnormalities can occur in patients treated with Ogsiveo®. In a clinical trial, these included decreased phosphate (65%) and decreased potassium (22%). Monitor phosphate and potassium levels regularly and supplement as necessary. Modify dose as recommended.

Contraindications: There are no contraindications listed with this product.

Manufacturer: SpringWorks Therapeutics, Inc.

Analysis: The efficacy of Ogsiveo® was assessed in DeFi, an international, multicenter, randomized, double-blind, placebo-controlled trial that included adults (N=142) with progressing desmoid tumors not amenable to surgery. Patients were eligible if the desmoid tumor had progressed within 12 months of screening. In the study, patients were randomized to Ogsiveo® or placebo twice daily until disease progression or unacceptable toxicity. Tumor imaging occurred every 3 months. The median age of included patients was 34 years (range 18 to 76), while 65% were female, 83% were white, 73% had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 27% had an ECOG PS of 1, and 0.7% had an ECOG PS of 2. Furthermore, 23% had intra-abdominal disease or both intra- and extra-abdominal disease, 77% had only extra-abdominal disease, 23% had no prior therapy, 44% received ≥3 prior lines of therapy, 33% were previously treated with a tyrosine kinase inhibitor and 36% were previously treated with chemotherapy. In addition, prior therapy included surgery (53%), radiotherapy (23%) and systemic therapy (61%).

The major efficacy outcome was progression-free survival (PFS), based on RECIST v1.1 as assessed by blinded independent central review or on clinical progression by the investigator (and confirmed by independent review). Clinical progression required worsening of symptoms resulting in a global deterioration of health status causing the permanent discontinuation from trial treatment and the start of emergent treatment for desmoid tumors. Objective response rate (ORR) was an additional efficacy outcome measure. Worst pain (item 3) was assessed daily using Brief Pain Inventory-Short Form (BPI-SF), an 11-point numerical rating scale ranging from 0 (‘no pain’) to 10 (‘pain as bad as you can imagine’)

and averaged over 7 days prior to each visit. Results are presented in the table below, which was adapted from the prescribing information.

	Ogsiveo® (N=70)	Placebo (N=72)
PFS		
Number (%) of patients with event	12 (17%)	37 (51%)
Radiographic progression	11 (16%)	30 (42%)
Clinical progression	1 (1%)	6 (8%)
Death	0	1 (1%)
Median (months)	Not Reached	15.1
HR; p-value	0.29; p<0.001	
ORR		
ORR, n (%)	29 (41%)	6 (8%)
Complete Response (CR)	5 (7%)	0
Partial Response (PR)	24 (34%)	6 (8%)
p-value	<0.001	

PFS results were supported by the change from baseline in patient-reported worst pain favoring the Ogsiveo® arm.

An exploratory analysis of PFS based on only radiographic progression demonstrated a hazard ratio of 0.31.

Place in Therapy: Ogsiveo® is a gamma secretase inhibitor indicated for adult patients with progressing desmoid tumors who require systemic treatment. It is recommended to perform dermatologic evaluations prior to the start of treatment and routinely during treatment. In addition, monitor phosphate, potassium, and liver function tests regularly. The efficacy of Ogsiveo® was assessed in a multicenter, double-blind, placebo-controlled study that included adults with progressing desmoid tumors not amenable to surgery. The major efficacy outcome was PFS; compared with placebo, Ogsiveo® was significantly more effective regarding the primary outcome (HR 0.29), as well as objective response rate. Ogsiveo® is the first FDA approved targeted therapy with this indication.

Summary

It is recommended that Ogsiveo® should be non-recommended in order to confirm the appropriate diagnosis and clinical parameters for use.

PDL Placement: ☐ **Recommended**
☒ **Non-Recommended with Conditions**

References

[1] Ogsiveo [package insert]. Stamford, CT: SpringWorks Therapeutics, Inc; 2024.