# NEW DRUG APPROVAL

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| **Brand Name** | Tascenso ODT™ |
| **Generic Name** | fingolimod |
| **Drug Manufacturer** | Handa Neuroscience LLC |

## New Drug Approval

FDA approval date: December 23, 2021

Review designation: Standard

Type of review: Type 2 - New Active Ingredient; NDA 214962

Dispensing restriction: N/A

## Place in Therapy

### DISEASE DESCRIPTION & EPIDEMIOLOGY

Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system (CNS) characterized by inflammation, demyelination, gliosis, and neuronal loss. Pathologically, perivascular lymphocytic infiltrates, and macrophages produce degradation of myelin sheaths that surround neurons. Neurological symptoms vary and can include vision impairment, numbness and tingling, focal weakness, bladder and bowel incontinence, and cognitive dysfunction. Symptoms vary depending on lesion location. Clinical symptoms characterized by acute relapses typically first develop in young adults. A gradually progressive course then ensues with permanent disability in 10 to 15 years. MS groups into seven categories based on disease course:

- Relapsing-remitting (RR): 70 to 80% of MS patients demonstrate an initial onset characterized by a relapsing-remitting (RR) course, demonstrating the following neurologic presentation. New or recurrent neurological symptoms consistent with MS. Symptoms last 24 to 48 hours. They develop over days to weeks.
- Primary progressive (PP): 15 to 20% of patients present with a gradual deterioration from the onset, with an absence of relapses.
- Secondary progressive (SP): this is characterized by a more gradual neurologic deterioration after an initial RR course. Superimposed relapses can be a feature of this clinical course, as well, although this is not a mandatory feature.
- Progressive-relapsing (PR) MS: in 5% of patients, a gradual deterioration with superimposed relapses occurs.
- Clinically isolated syndrome (CIS): often classified as a single episode of inflammatory CNS demyelination.
- Fulminant: characterized by severe MS with multiple relapses and rapid progression towards disability.
- Benign: a clinical course characterized by an overall mild disability. Relapses are rare.

Approximately 400,000 individuals in the United States and 2.5 million individuals worldwide have multiple sclerosis. The disease is three-fold more common in females than in males. While the age of onset is usually between 20 to 40 years, the disease can present at any age. Almost 10% of the cases present before the age of 18. An overall prevalence of 1 in 1000 is cited for populations of European ancestry. Less is understood about the prevalence in non-European populations, and most data suggests lower prevalence in those of East Asian and African descent. Recent studies have noted a high prevalence in African American populations, similar to that of European ancestry. MS demonstrates a prevalence based on latitude gradient with increased prevalence in northern latitudes of Europe and North America.

## Efficacy

The efficacy of Tascenso ODT™ is based on the relative bioavailability of Tascenso ODT™ orally disintegrating tablets compared to fingolimod capsules in healthy adults. Tascenso ODT™ is not approved for use in adults. The clinical studies described below were conducted using fingolimod capsules.

**Adults-**

The efficacy of fingolimod was demonstrated in 2 studies that evaluated once-daily doses of fingolimod capsules 0.5 mg and 1.25 mg in patients with relapsing-remitting MS (RRMS). Both studies included patients who had experienced at least 2 clinical relapses during the 2 years prior to randomization or at least 1 clinical relapse during the 1 year prior to randomization and had an Expanded Disability Status Scale (EDSS) score from 0 to 5.5. Study 1 was a 2-year randomized, double-blind, placebo-controlled study in patients with RRMS who had not received any interferon-beta or glatiramer acetate for at least the previous 3 months and had not received any natalizumab for at least the previous 6 months. Neurological evaluations were performed at screening, every 3 months and at time of suspected relapse. MRI evaluations were performed at screening, Month 6, Month 12, and Month 24. The primary endpoint was the annualized relapse rate. Median age was 37 years, median disease duration was 6.7 years and median EDSS score at baseline was 2.0. Patients were randomized to receive fingolimod 0.5 mg (N = 425), 1.25 mg (N = 429), or placebo (N = 418) for up to 24 months. Median time on study drug was 717 days on 0.5 mg, 715 days on 1.25 mg, and 719 days on placebo.

The annualized relapse rate was significantly lower in patients treated with fingolimod than in patients who received placebo. The secondary endpoint was the time to 3-month confirmed disability progression as measured by at least a 1-point increase from baseline in EDSS (0.5-point increase for patients with baseline EDSS of 5.5) sustained for 3 months. Time to onset of 3-month confirmed disability progression was significantly delayed with fingolimod treatment compared to placebo. The 1.25 mg dose resulted in no additional benefit over the fingolimod 0.5 mg dose.

**Table 1: Clinical and MRI Results of Study 1**

| | Fingolimod Capsules 0.5 mg N = 425 | Placebo N = 4 | p-value |
|---|---|---|---|
| **Clinical Endpoints** Annualized relapse rate (primary endpoint) | 0.18 | 0.40 | < 0.001 |
| Percentage of patients without relapse | 70% | 46% | < 0.001 |
| Hazard ratio‡ of disability progression | 0.70 | | 0.02 |
| (95% CI) | (0.52, 0.96) | | |
| **MRI Endpoint** Mean (median) number of new or newly enlarging T2 lesions over 24 months | 2.5 (0) | 9.8 (5.0) | < 0.001 |
| Mean (median) number of T1 Gd enhancing lesions at Month 12 | 0.2 (0) | 1.1 (0) | < 0.001 |

All analyses of clinical endpoints were intent-to-treat. MRI analysis used evaluable dataset.
‡Hazard ratio is an estimate of the relative risk of having the event of disability progression on fingolimod as compared to placebo.

Study 2 was a 1-year randomized, double-blind, double-dummy, active-controlled study in patients with RRMS who had not received any natalizumab in the previous 6 months. Prior therapy with interferon-beta or glatiramer

acetate up to the time of randomization was permitted. Neurological evaluations were performed at screening, every 3 months, and at the time of suspected relapses. MRI evaluations were performed at screening and at Month 12. The primary endpoint was the annualized relapse rate. Median age was 36 years, median disease duration was 5.9 years, and median EDSS score at baseline was 2.0. Patients were randomized to receive fingolimod capsules 0.5 mg (N = 431), 1.25 mg (N = 426), or interferon beta-1a, 30 mcg via the intramuscular route (IM) once-weekly (N = 435) for up to 12 months. Median time on study drug was 365 days on fingolimod 0.5 mg, 354 days on 1.25 mg, and 361 days on interferon beta-1a IM.

The annualized relapse rate was significantly lower in patients treated with fingolimod 0.5 mg than in patients who received interferon beta-1a IM. The key secondary endpoints were number of new and newly enlarging T2 lesions and time to onset of 3- month confirmed disability progression as measured by at least a 1-point increase from baseline in EDSS (0.5-point increase for those with baseline EDSS of 5.5) sustained for 3 months. The number of new and newly enlarging T2 lesions was significantly lower in patients treated with fingolimod than in patients who received interferon beta-1a IM. There was no significant difference in the time to 3-month confirmed disability progression between fingolimod and interferon beta-1a-treated patients at 1 year. The 1.25 mg dose resulted in no additional benefit over the fingolimod 0.5 mg dose. The results for this study are shown in Table 3. Pooled results of study 1 and study 2 showed a consistent and statistically significant reduction of annualized relapse rate compared to comparator in subgroups defined by gender, age, prior MS therapy, and disease activity.

**Table 2: Clinical and MRI Results of Study 2**

| | Fingolimod Capsules 0.5 mg N = 429 | Interferon beta-1a IM 30 mcg N = 431 | p-value |
|---|---|---|---|
| **Clinical Endpoints** Annualized relapse rate (primary endpoint) | 0.16 | 0.33 | < 0.001 |
| Percentage of patients without relapse | 83% | 70% | < 0.001 |
| Hazard ratio‡ of disability progression | 0.71 | | 0.21 |
| (95% CI) | (0.42, 1.21) | | |
| **MRI Endpoint** Mean (median) number of new or newly enlarging T2 lesions over 12 months | 1.6 (0) | 2.6 (1.0) | 0.002 |
| Mean (median) number of T1 Gd enhancing lesions at Month 12 | 0.2 (0) | 0.5 (0) | < 0.001 |

All analyses of clinical endpoints were intent-to-treat. MRI analysis used evaluable dataset.
‡ Hazard ratio is an estimate of the relative risk of having the event of disability progression on fingolimod as compared to control.

**Pediatric Patients (10 to less than 18 Years of Age) –**

Study 4 (NCT01892722) evaluated the efficacy of once-daily oral doses of fingolimod capsules in pediatric patients 10 to less than 18 years of age with relapsing-remitting multiple sclerosis. Study 4 was a 215 patient, double-blind, randomized, clinical trial that included a comparison of the 0.25 mg fingolimod dose to intramuscular interferon beta-1a. Prior therapy with interferon-beta, dimethyl fumarate, or glatiramer acetate up to the time of randomization was permitted. The study included patients who had experienced at least 1 clinical relapse during the year prior or 2 relapses during the 2 years prior to screening, or evidence of 1 or more Gd-enhancing lesions on MRI within 6 months prior to randomization and had an EDSS score from 0 to 5.5. Neurological evaluations were

scheduled at screening, every 3 months, and at the time of suspected relapses. MRI evaluations were performed at screening and every 6 months throughout the study. The primary endpoint was the annualized relapse rate.
At baseline, the median age was 16 years, median disease duration since first symptom was 1.5 years, and median EDSS score was 1.5. One patient received no study drug and is excluded from the analysis of efficacy. Median duration of exposure to study drug was 634 days in the fingolimod group (n = 107) and 547 days in the interferon beta-1a group (n = 107). In the fingolimod group, 6.5% of patients did not complete the study, compared to 18.5% in the interferon beta-1a group. The primary endpoint, the annualized relapse rate (ARR), was significantly lower in patients treated with fingolimod (0.122) than in patients who received interferon beta-1a (0.675). Relative reduction in ARR was 81.9%. The annualized rate of the number of new or newly enlarged T2 lesions up to month 24 (key secondary endpoint) was significantly lower in patients treated with fingolimod, as was the number of Gd-enhancing T1 lesions per scan up to month 24.

**Table 3: Clinical and MRI Results of Study 4**

| | Fingolimod Capsules PO N = 107 | Interferon beta-1a mcg IM N = 107 | p-value | Relative Reduction |
|---|---|---|---|---|
| **Clinical endpoints** | | | | |
| Annualized relapse rate (primary endpoint) | 0.122 | 0.675 | < 0.001* | 81.9% |
| | | | | |
| Percent of patients remaining relapse-free at 24 months | 86.0% | 45.8% | | |
| **MRI endpoints** | | | | |
| Annualized rate of the number of new or newly enlarging T2 lesions | 4.393 | 9.269 | < 0.001* | 52.6% |
| Mean number of Gd-enhancing T1 | 0.436 | 0.436 | < 0.001* | 66.0% |

All analyses of clinical endpoints were on full analysis set. MRI analyses used the evaluable dataset.
*Indicates statistical significance vs. Interferon beta-1a IM at two-sided 0.05 level.

## Safety

### ADVERSE EVENTS

**Adults-**
In clinical trials (Studies 1, 2, and 3), a total of 1212 patients with relapsing forms of multiple sclerosis received fingolimod 0.5 mg capsules. This included 783 patients who received fingolimod 0.5 mg in the 2-year placebo-controlled trials (Studies 1 and 3) and 429 patients who received fingolimod 0.5 mg in the 1-year active-controlled trial (Study 2). The overall exposure in the controlled trials was equivalent to 1716 person-years. Approximately 1000 patients received at least 2 years of treatment with fingolimod 0.5 mg capsules. In all clinical studies, including uncontrolled extension studies, the exposure to fingolimod 0.5 mg capsules was approximately 4119 person-years. In placebo-controlled trials, the most frequent adverse reactions (incidence ≥ 10% and greater than placebo) for fingolimod 0.5 mg capsules were headache, liver transaminase elevation, diarrhea, cough, influenza, sinusitis, back pain, abdominal pain, and pain in extremity. Adverse events that led to treatment discontinuation and occurred in more than 1% of patients taking fingolimod 0.5 mg capsules, were serum transaminase elevations (4.7% compared to 1% on placebo) and basal cell carcinoma (1% compared to 0.5% on placebo). Table 4 lists

adverse reactions in clinical studies in adults that occurred in ≥ 1% of fingolimod-treated patients and ≥ 1% higher rate than for placebo.

**Table 4: Adverse Reactions Reported in Adult Studies 1 and 3 (Occurring in ≥ 1% of Patients and Reported for Fingolimod 0.5 mg Capsules at ≥ 1% Higher Rate than for Placebo)**

| Adverse Drug Reactions (%) | Fingolimod 0.5 mg Capsules N = 783 | | Placebo N = 773 |
|---|---|---|---|
| **Infections** | | | |
| Influenza | 11 | | 8 |
| Sinusitis | 11 | | 8 |
| Bronchitis | 8 | | 5 |
| Herpes zoster | 2 | | 1 |
| Tinea versicolor | 2 | | < 1 |
| **Cardiac disorders** Bradycardia | 3 | | 1 |
| **Nervous system disorders** | | | |
| Headache | 25 | | 24 |
| Migraine | 6 | | 4 |
| **Gastrointestinal disorders** | | | |
| Nausea | 13 | | 12 |
| Diarrhea | 13 | | 10 |
| Abdominal pain | 11 | | 10 |
| **General disorders and administration-site conditions** Asthenia | 2 | | 1 |
| **Musculoskeletal and connective tissue disorders** | | | |
| Back pain | 10 | | 9 |
| Pain in extremity | 10 | | 7 |
| **Skin and subcutaneous tissue disorders** | | | |
| Alopecia | 3 | | 2 |
| Actinic keratosis | 2 | | 1 |
| **Investigations** | | | |
| Liver transaminase elevations (ALT/GGT/AST) | 15 | | 4 |

| | | | |
|---|---|---|---|
| Blood triglycerides increased | 3 | | 1 |
| **Respiratory, thoracic, and mediastinal disorders** | | | |
| Cough | 12 | | 11 |
| Dyspnea | 9 | | 7 |
| **Eye disorders**<br>Vision blurred | 4 | | 2 |
| **Vascular disorders**<br>Hypertension | 8 | | 4 |
| **Blood and lymphatic system disorders** | | | |
| Lymphopenia | 7 | | < 1 |
| Leukopenia | 2 | | < 1 |
| **Neoplasms benign, malignant, and unspecified (including cysts and polyps)** | | | |
| Skin papilloma | 3 | | 2 |
| Basal cell carcinoma | 2 | | 1 |

**Vascular Events-**

Vascular events, including ischemic and hemorrhagic strokes, and peripheral arterial occlusive disease were reported in premarketing clinical trials in patients who received fingolimod doses (1.25-5 mg) higher than recommended for use in MS.

**Seizure-**

Cases of seizures, including status epilepticus, have been reported with the use of fingolimod capsules in clinical trials and in the postmarketing setting in adults.

**Pediatric Patients 10 Years of Age and Older-**

In the controlled pediatric trial (Study 4), the safety profile in pediatric patients receiving fingolimod capsules daily was similar to that seen in adult patients.

## WARNINGS & PRECAUTIONS

**Bradyarrhythmia and Atrioventricular Blocks-**

Tascenso ODT™ treatment results in decreased heart rate and may prolong the QT interval, patients with a prolonged QTc interval (> 450 msec pediatric males, or > 460 msec pediatric females) before dosing or during 6-hour observation, or at additional risk for QT prolongation (e.g., hypokalemia, hypomagnesemia, congenital long-QT syndrome), or on concurrent therapy with QT prolonging drugs with a known risk of torsades de pointes.

**Atrioventricular Blocks-**

Initiation of Tascenso ODT™ treatment has resulted in transient AV conduction delays.

**Infections-**

**Risk of Infections-**

Tascenso ODT™ causes a dose-dependent reduction in peripheral lymphocyte count to 20%-30% of baseline values because of reversible sequestration of lymphocytes in lymphoid tissues. Tascenso ODT™ may therefore increase the risk of infections, some serious in nature. Life-threatening and fatal infections have occurred in association with fingolimod, the active moiety in Tascenso ODT™.

**Herpes Viral Infections-**

In placebo-controlled trials in adult patients treated with fingolimod capsules, the rate of herpetic infections was 9% in patients receiving fingolimod 0.5 mg and 7% on placebo. Two patients died of herpetic infections during controlled trials. One death was due to disseminated primary herpes zoster and the other was to herpes simplex encephalitis. In both cases, the patients were taking a 1.25 mg dose of fingolimod (higher than the recommended 0.25 mg dose) and had received high-dose corticosteroid therapy to treat suspected MS relapses. Cases of Kaposi's sarcoma have been reported in patients treated with fingolimod in the postmarketing setting.

**Cryptococcal Infections-**

Cryptococcal infections, including cases of fatal cryptococcal meningitis and disseminated cryptococcal infections, have been reported with fingolimod in the postmarketing setting. Cryptococcal infections have generally occurred after approximately 2 years of fingolimod treatment but may occur earlier.

**Prior and Concomitant Treatment with Antineoplastic, Immunosuppressive, or Immune-Modulating Therapies-**

In clinical studies, patients who received fingolimod capsules did not receive concomitant treatment with antineoplastic, noncorticosteroid immunosuppressive, or immune-modulating therapies used for treatment of MS. Concomitant use of Tascenso ODT™ with any of these therapies, and also with corticosteroids, would be expected to increase the risk of immunosuppression.

**Varicella Zoster Virus Antibody Testing/Vaccination-**

Patients without a healthcare professional confirmed history of chickenpox or without documentation of a full course of vaccination against VZV should be tested for antibodies to VZV before initiating Tascenso ODT™. VZV vaccination of antibody-negative patients is recommended prior to commencing treatment with Tascenso ODT™, following which initiation of treatment with Tascenso ODT™ should be postponed for 1 month to allow the full effect of vaccination to occur.

**Human Papilloma Virus (HPV) Infection-**

Human papilloma virus (HPV) infections, including papilloma, dysplasia, warts, and HPV-related cancer, have been reported in patients treated with fingolimod in the postmarketing setting. Vaccination against HPV should be considered prior to treatment initiation with Tascenso ODT™, taking into account vaccination recommendations. Cancer screening, including Papanicolaou (Pap) test, is recommended as per standard of care for patients using an immunosuppressive therapy.

**Progressive Multifocal Leukoencephalopathy-**

Cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients with MS who received fingolimod, the active moiety in Tascenso ODT™, in the postmarketing setting.

**Macular Edema-**

Sphingosine 1-phosphate (S1P) receptor modulators, including Tascenso ODT™, have been associated with an increased risk of macular edema. Perform an examination of the fundus, including the macula, in all patients before starting treatment, again 3 to 4 months after starting treatment, and again at any time after a patient reports visual disturbances while on Tascenso ODT™ therapy.

**Liver Injury-**

Clinically significant liver injury has occurred in patients treated with fingolimod in the postmarketing setting. Signs of liver injury, including markedly elevated serum hepatic enzymes and elevated total bilirubin, have occurred as early as ten days after the first dose and have also been reported after prolonged use. Cases of acute liver failure requiring liver transplant have been reported.

**Posterior Reversible Encephalopathy Syndrome-**

There have been rare cases of posterior reversible encephalopathy syndrome (PRES) reported in adult patients receiving fingolimod. Symptoms reported included sudden onset of severe headache, altered mental status, visual disturbances, and seizure. Symptoms of PRES are usually reversible but may evolve into ischemic stroke or cerebral hemorrhage.

**Respiratory Effects-**

Dose-dependent reductions in forced expiratory volume over 1 second (FEV1) and diffusion lung capacity for carbon monoxide (DLCO) were observed in patients treated with fingolimod, the active moiety in Tascenso ODT™, as early as 1 month after treatment initiation.

**Fetal Risk-**

Based on findings from animal studies, Tascenso ODT™ may cause fetal harm when administered to a pregnant woman.

**Severe Increase in Disability After Stopping Tascenso ODT™-**

Severe increase in disability accompanied by multiple new lesions on MRI has been reported after discontinuation of fingolimod in the postmarketing setting. Patients in most of these reported cases did not return to the functional status they had before stopping fingolimod. The increase in disability generally occurred within 12 weeks after stopping fingolimod but was reported up to 24 weeks after fingolimod discontinuation.

**Tumefactive Multiple Sclerosis-**

MS relapses with tumefactive demyelinating lesions on imaging have been observed during fingolimod therapy and after fingolimod discontinuation in the postmarketing setting. Most reported cases of tumefactive MS in patients receiving fingolimod have occurred within the first 9 months after fingolimod initiation, but tumefactive MS may occur at any point during treatment. Cases of tumefactive MS have also been reported within the first 4 months after fingolimod discontinuation.

**Increased Blood Pressure-**

In adult MS controlled clinical trials, patients treated with fingolimod 0.5 mg capsules had an average increase over placebo of approximately 3 mmHg in systolic pressure, and approximately 2 mmHg in diastolic pressure, first detected after approximately 1 month of fingolimod treatment initiation and persisting with continued treatment. Hypertension was reported as an adverse reaction in 8% of patients on fingolimod 0.5 mg capsules and in 4% of patients on placebo.

**Malignancies-**

The risk of basal cell carcinoma (BCC) and melanoma is increased in patients treated with fingolimod, the active moiety in Tascenso ODT™. In two-year placebo-controlled trials in adult patients, the incidence of BCC was 2% in patients on fingolimod 0.5 mg capsules and 1% in patients on placebo. Melanoma, squamous cell carcinoma and Merkel cell carcinoma have been reported with fingolimod in the postmarketing setting. Cases of lymphoma, including both T-cell and B-cell types and CNS lymphoma, have occurred in patients receiving fingolimod, the active moiety in Tascenso ODT™. The reporting rate of non-Hodgkin lymphoma with fingolimod is greater than that expected in the general population adjusted by age, gender, and region. Cutaneous T-cell lymphoma (including mycosis fungoides) has also been reported with fingolimod in the postmarketing setting.

**Immune System Effects Following Tascenso ODT™ Discontinuation-**

Fingolimod remains in the blood and has pharmacodynamic effects, including decreased lymphocyte counts, for up to 2 months following the last dose of Tascenso ODT™. Lymphocyte counts generally return to the normal range within 1-2 months of stopping therapy. Because of the continuing pharmacodynamic effects of fingolimod, initiating other drugs during this period warrants the same considerations needed for concomitant administration.

**Hypersensitivity Reactions-**

Hypersensitivity reactions, including rash, urticaria, and angioedema have been reported with fingolimod in the postmarketing setting. Tascenso ODT™ is contraindicated in patients with history of hypersensitivity to fingolimod or any of its excipients.

## CONTRAINDICATIONS

Tascenso ODT™ is contraindicated in patients who have:

- in the last 6 months experienced myocardial infarction, unstable angina, stroke, TIA, decompensated heart failure requiring hospitalization or Class III/IV heart failure.
- a history or presence of Mobitz Type II second-degree or third-degree AV block or sick sinus syndrome, unless patient has a functioning pacemaker.

- a baseline QTc interval ≥ 500 msec.
- cardiac arrhythmias requiring anti-arrhythmic treatment with Class Ia or Class III anti-arrhythmic drugs.
- had a hypersensitivity reaction to fingolimod or any of the excipients in Tascenso ODT™. Observed reactions include rash, urticaria, and angioedema.
- Concomitant use with other products containing fingolimod.

## Clinical Pharmacology

### MECHANISMS OF ACTION

Fingolimod is metabolized by sphingosine kinase to the active metabolite, fingolimod-phosphate. Fingolimod phosphate is a sphingosine 1-phosphate receptor modulator and binds with high affinity to sphingosine 1-phosphate receptors 1, 3, 4, and 5. Fingolimod-phosphate blocks the capacity of lymphocytes to egress from lymph nodes, reducing the number of lymphocytes in peripheral blood. The mechanism by which fingolimod exerts therapeutic effects in multiple sclerosis is unknown but may involve reduction of lymphocyte migration into the central nervous system.

## Dose & Administration

### ADULTS

None

### PEDIATRICS

0.25 mg orally once daily

### GERIATRICS

None

### RENAL IMPAIRMENT

None

### HEPATIC IMPAIRMENT

None

## Product Availability

### DOSAGE FORM(S) & STRENGTH(S)

Orally disintegrating tablets: 0.25 mg.