CLINICAL UPDATE

Brand Name	Tascenso ODT™
Generic Name	fingolimod
Drug Manufacturer	Cycle Pharmaceuticals Ltd

Clinical Update

TYPE OF CLINICAL UPDATE

Updated indication and new strength

FDA APPROVAL DATE

December 09, 2022

LAUNCH DATE

N/A

REVIEW DESIGNATION

Standard

TYPE OF REVIEW

Type 2 - New Active Ingredient; New Drug Application (NDA): 214962

DISPENSING RESTRICTIONS

N/A

Overview

INDICATION(S) FOR USE

It is a sphingosine 1-phosphate receptor modulator indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in patients 10 years of age and older.

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.

DOSAGE FORM(S) AND STRENGTH(S)

Orally disintegrating tablets: 0.25 mg and 0.5 mg.

DOSE & ADMINISTRATION

In adults and pediatric patients 10 years of age and older weighing more than 40 kg, the recommended dose is 0.5 mg orally once daily.

In pediatric patients 10 years of age and older weighing less than or equal to 40 kg, the recommended dose 0.25 mg orally once daily.

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.

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 = 418	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 (95% CI)	0.70 (0.52, 0.96)		0.02
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 24	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 2. 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 intramuscularly 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 (95% CI)	0.71 (0.42, 1.21)		0.21
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 0.25 mg or fingolimod capsules 0.5 mg in pediatric patients 10 to less than 18 years of age with relapsing-remitting multiple sclerosis. Study 4 was a 215 patient, doubleblind, randomized, clinical trial that compared fingolimod 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 0.25 or 0.5 mg orally N = 107	Interferon beta-1a 30 mcg intramuscularly 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 lesions per scan up to Month 24	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.