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APPLICATION NUMBER:

214962Orig2s000

SUMMARY REVIEW

Summary Review

Date	December 23, 2021
From	Paul Lee, MD, PhD, Deputy Director, Division of Neurology 2 (DN2) Nick Kozauer, MD, Director, DN2
Subject	Summary Review
NDA#	NDA 214962 under 505(b)(2)[1]
Applicant	Handa Neuroscience, LLC
Date of Submission	October 27, 2021
PDUFA Goal Date	December 27, 2021
Proprietary Name	Tascenso
Established or Proper Name	Fingolimod lauryl sulfate orally disintegrating tablet
Dosage Form(s)	0.25 mg
Applicant Proposed Indication(s)/Population(s)	Tascenso 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, (b) (4)
Applicant Proposed Dosing Regimen(s)	0.25 mg (patients 10 years of age and older weighing less than or equal to 40 kg) (b) (4) orally once daily
Recommendations on Regulatory Actions	Approval of 0.25 mg dose for patients 10 years and older weighing less than or equal to 40 kg (b) (4)

[1]The referenced drug for this 505(b)(2) application is Gilenya (NDA 022527)

1. Summary Review

This Class 1 Resubmission after Tentative Approval of this 505(b)(2) application proposes approval of Tascenso (fingolimod lauryl sulfate orally disintegrating tablet or ODT) using the 505(b)(2) regulatory pathway, relying on the previous findings of safety and effectiveness for Gilenya (fingolimod) as the listed drug (LD). The applicant proposes the same disease indication, "relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease," as for the LD, Gilenya, but the applicant is only seeking an approval of the 0.25 mg dose which is indicated for the treatment of relapsing forms of MS in pediatric patients 10 years old and older weighing less than or equal to 40 kg.

Tascenso (fingolimod lauryl sulfate orally disintegrating tablet) was shown to be bioequivalent to the LD, Gilenya, in two pivotal bioequivalence studies (FGL-P01 and FGL-P02) that were reviewed in the original 505(b)(2) application submitted on December 18, 2020.

The Division sent the applicant a tentative approval (TA) letter on October 18, 2021, which stated: "[f]inal approval of your application is subject to expiration of period(s) of patent protection and/or exclusivity." At the time, the applicant proposed 0.25 mg and 0.5 mg products were blocked from final approval due to three-year exclusivities that have since expired on November 11, 2021.

On October 27, 2021, the applicant submitted a "Minor Amendment to request final approval of our NDA for the 0.25 mg strength of TASCENSO ODT." The applicant did not request a new action regarding the 0.5 mg dose in this submission.

CDER determined that it is appropriate to approve the applicant's fingolimod orally disintegrating tablets, 0.25 mg product because sponsor of the LD (Novartis) did not bring an action for patent infringement against the applicant's 0.25 mg product, and, therefore, the 0.25 mg product is not subject to any 30-month stay of approval or any other barriers to approval.

The 0.25 mg dose of Gilenya is only indicated for the treatment of relapsing forms of MS in patients ages 10 years and older who weigh less than or equal to 40 kg. Labeling for Tascenso reflects this indicated population, which would be children 10 years or older who weight 40 kg or less. Labeling negotiations with the applicant have been completed, and the applicant has accepted all recommended changes.

In the absence of legal barriers to the approval of the applicant's 0.25 mg ODT tablets, the Tascenso 0.25 mg dose will be approved. This decision will necessitate an administrative splitting of the application because the sponsor's original application, which received a tentative approval action, included both the 0.25 mg and 0.5 mg doses, but in the minor amendment submitted October 27, 2021, the applicant did not request a regulatory decision regarding the 0.5 mg dose of Tascenso; a 30-month stay of approval that remains in effect for the 0.5 mg dose because of patent infringements for the 0.5 mg dose. The splitting of this application is consistent with the Office of New Drugs' policy when a particular dose cannot be approved because of a patent, exclusivity, or a 30-month stay of approval.

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/s/

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Summary Memorandum for Regulatory Action

Date	October 18, 2021
From	Paul R. Lee, MD, PhD, Deputy Director, Division of Neurology 2
Subject	Summary Memorandum for Regulatory Action
NDA/BLA # and Supplement#	NDA 214962 under 505(b)(2)[1]
Applicant	Handa Pharma
Date of Submission	December 18, 2020
PDUFA Goal Date	October 18, 2021
Proprietary Name	Tascenso
Established or Proper Name	Fingolimod lauryl sulfate orally disintegrating tablet (ODT)
Dosage Form(s)	0.25 mg (b) (4)
Applicant Proposed Indication(s)/Population(s)	Fingolimod ODT 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, (b) (4)
Applicant Proposed Dosing Regimen(s)	0.25 mg (patients weighing ≤40kg) (b) (4) orally once daily
Recommendation on Regulatory Action	Tentative Approval
Recommended Indication(s)/Population(s) (if applicable)	Same as proposed

[1]The referenced drug for this 505(b)(2) application is Gilenya (NDA 022527)

Recommended Dosing Regimen(s) (if applicable)	Same as proposed

1. Benefit-Risk Assessment

The application provides an adequate bridge to Gilenya, the referenced product for this 505(b)(2) application. Therefore, the previous findings of safety and effectiveness for Gilenya also apply to Tascenso.

2. Background

The applicant seeks approval of Tascenso (fingolimod lauryl sulfate oral disintegrating tablet) using the 505(b)(2) regulatory pathway for Gilenya (fingolimod), relying on the previous findings of safety and effectiveness for Gilenya. Gilenya is approved for the treatment of relapsing forms of multiple sclerosis in patients 10 years and older.

Significant FDA communications with the applicant included a pre-IND written response (July 2016). The applicant submitted the NDA on December 18, 2020, without any meetings after the pre-IND meeting and without formally opening the IND. There was an agreement with an initial Pediatric Study Plan (September 2020) to waive studies in children younger than 10 (due to rarity of multiple sclerosis in this age group) and that the applicant would not conduct pediatric studies in ages 10 to < 18 years because the referenced product, Gilenya, is approved for ages 10 and up.

The applicant performed two Phase 1 studies in healthy volunteers to establish a bioequivalence bridge between Tascenso and Gilenya, as well as to characterize the pharmacokinetic (PK) properties of Tascenso. The applicant submitted the findings from these studies (FGL-P01 and FGL-P02) in this NDA.

3. Product Quality

The Product Quality [Chemistry, Manufacturing, and Controls (CMC)] review team recommends approval. Martha Heimann, Ph.D., is the CMC Team Lead. Please refer to Dr. Heimann's memorandum for a listing of the members of the Office of Product Quality team who reviewed this application.

There were concerns with content uniformity (b) (4) identified during review that were adequately addressed by the applicant. Otherwise, there were no significant issues identified with the drug product, drug substance, and manufacturing processes.

The applicant provided adequate data to support the proposed shelf-life of 24 months.

The manufacturing and testing sites were acceptable based on the Agency's most recent inspections which indicated no significant issues. Due to pandemic-related restrictions, no inspections were conducted for this application.

4. Nonclinical Pharmacology/Toxicology

There was no nonclinical review of this application because there were no nonclinical studies submitted with the application, and there were no changes in the nonclinical sections of the proposed labeling from the approved labeling of the referenced product. There are no novel excipients nor other components of the drug product that necessitated additional nonclinical investigations. Therefore, there was no need for nonclinical studies to evaluate this drug product which has the same drug substance, fingolimod, as the referenced product, Gilenya, because Gilenya has been evaluated extensively in pre- and post-marketing with respect to toxicology and the approved labeling language is adequately reflective of the established risks of fingolimod exposure to ensure safe and effective use.

5. Clinical Pharmacology

The clinical pharmacology team recommends approval because the applicant has established an adequate PK bridge to Gilenya, which is approved for the treatment of relapsing forms of MS.

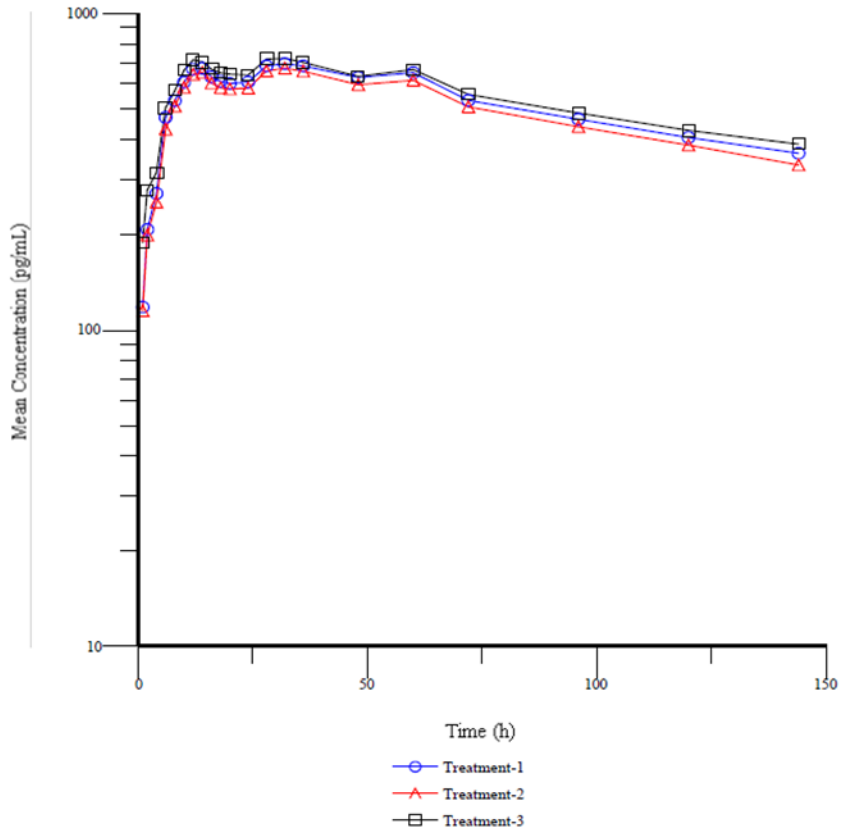
The office of Clinical Pharmacology review team consisted of Xiaohan Cai, Ph.D. and Gopichand Gottipati, Ph.D.

The applicant conducted two studies (FGL-P01 and FGL-P02) in support of this 505(b)(2) application, and both trials were considered pivotal bioequivalence trials because both studies provided findings in support of establishing an adequate pharmacokinetic (PK) bridge to the referenced drug, Gilenya.

Study FGL-P01 was a single-dose, parallel group, comparative bioavailability study of fingolimod 0.5 mg orally disintegrating tablets versus fingolimod 0.5 mg capsules following the administration of a 1 mg dose in healthy adult subjects under fasting conditions. The purpose of this trial was to establish the comparative bioavailability between fingolimod ODT and the referenced drug under fasted conditions. There were 75 healthy volunteers who enrolled and completed this trial, and data from all 75 individuals were analyzed in the primary PK population.

In Study PGL-P01, as demonstrated in Figure 1 and Table 1, fingolimod ODT met the criteria for bioequivalence to Gilenya with regard to the exposure of fingolimod (both C_{max} and AUC), when administered in the fasted state.

Figure 1: Applicant Figures, Fingolimod Plasma Concentration after Administration of Fingolimod ODT and Gilenya (Study FGL-P01)



Treatment 1: fingolimod ODT without water

Treatment 2: fingolimod ODT administered with 240 ml of water

Treatment 3: Gilenya administered with 240 ml of water

Table 1: Reviewer Table, Summary of Bioequivalence Parameters for Fasted State, Study FGL-P01

Parameter	Geometric Least Square Means		Ratio (%)	90% Confidence Limits (%)	
	Fingolimod ODT with water (n=25)	Gilenya with water (n=25)		Lower	Upper
C_{max}	682.5	753.8	90.54	84.54	96.98
AUC_{0-144}	70155.9	77014.8	91.09	84.66	98.01

Source: Clinical Pharmacology Review

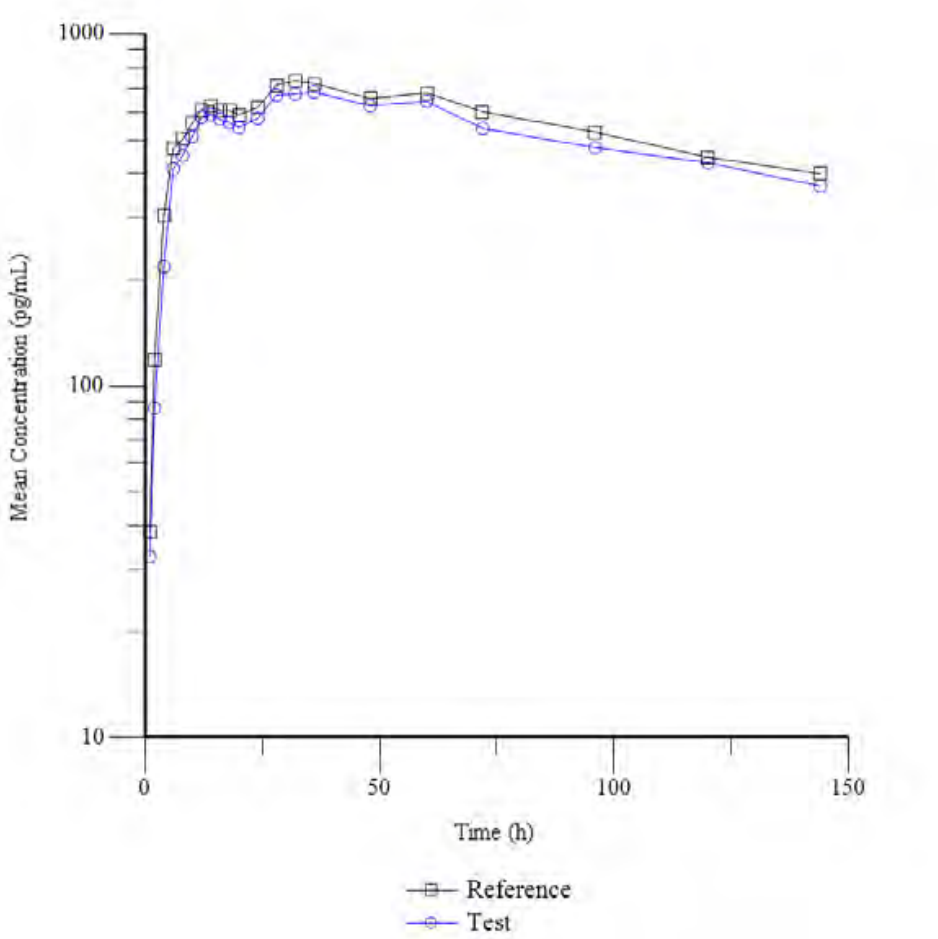
The clinical pharmacology review concluded that in Study FGL-P01, the comparative bioavailability of fingolimod PK between fingolimod ODT and Gilenya (both administered under fasting conditions) met the standard bioequivalence criteria, that is, the 90% confidence interval of the geometric mean ratio between fingolimod ODT and Gilenya for Cmax and AUC_{0-144h}, were within 80-125%. The clinical pharmacology review also compared the findings with and without water for fingolimod ODT and found that bioequivalence for fingolimod PK parameters was established in both of these fasted conditions and that co-administration of water had no impact on fingolimod ODT's PK parameters.

The clinical pharmacology reviewer noted that fingolimod-phosphate (fingolimod-P), which is the active metabolite of fingolimod, did not meet the standard bioequivalence criteria. The C_{max} value for fingolimod-P following administration of fingolimod ODT fell just below the 80% geometric mean ratio cutoff (90% Confidence Interval: 77.03-96.14). The Tmax for fingolimod-P after administration of fingolimod ODT was bioequivalent to Gilenya' s fingolimod-P T_{max}, as was the AUC_{0-144h}. The failure to achieve bioequivalence with respect to C_{max} for fingolimod-P in this trial is not likely to be clinically significant. While the mechanism of action of fingolimod is not completely understood, the expected clinical benefit of fingolimod occurs with chronic dosing and thus a small difference in the C_{max} of the active metabolite after a single dose is not expected to impact the longitudinal efficacy of fingolimod, a conclusion supported by the fact that the PK parameter that informs chronic exposure, AUC_{0-144h}, achieved bioequivalence with respect to fingolimod-P.

Study FGL-P02 was a single-dose, parallel, comparative bioavailability study of fingolimod 0.5 mg orally disintegrating tablets versus Gilenya 0.5 mg capsules following the administration of a 1 mg dose in healthy adult subjects under fed conditions. The purpose of this trial was to establish the comparative bioavailability between fingolimod ODT and the referenced drug under fed conditions. There were 38 healthy volunteers who enrolled and completed this trial, and data from all 38 individuals were analyzed in the primary PK population.

In Study PGL-P02, as demonstrated in Figure 2 and Table 2, fingolimod ODT met the criteria for bioequivalence to Gilenya with regard to the exposure of fingolimod (both Cmax and AUC), when administered in the fed state.

Figure 2: Applicant Figures, Fingolimod Plasma Concentration after Administration of Fingolimod ODT and Gilenya (Study FGL-P02)



Reference: Gilenya
Test: fingolimod ODT

Table 2: Reviewer Table, Summary of Bioequivalence Parameters for Fed State, Study FGL-P02

Parameter	Geometric Least Square Means		Ratio (%)	90% Confidence Limits (%)	
	Fingolimod ODT (n=25)	Gilenya (n=25)		Lower	Upper
C_{max}	718.0	752.3	95.44	88.07	103.44
AUC_{0-144}	72440.1	78202.0	92.63	84.35	101.73

The clinical pharmacology review concluded that in Study FGL-P02, the comparative bioavailability of fingolimod PK between fingolimod ODT and Gilenya (both administered under fasting conditions) met the standard bioequivalence criteria with the 90% confidence interval of the geometric mean ratio between fingolimod ODT and Gilenya for Cmax and AUC_{0-144h}, were within 80-125%. The fingolimod-P PK parameters also met bioequivalence criteria, and so unlike the fasted study, the fed trial achieved a finding of acceptable bioequivalence on both the serum levels of fingolimod and the active metabolite fingolimod-P which provides further confidence that the lack of finding of bioequivalence for Cmax of fingolimod-P in the Study FGL-P02 was not a consistent finding with fingolimod ODT and is very unlikely to be clinically significant.

The OCP review evaluated the analytical methods used to quantify fingolimod and fingolimod-P in serum and found the methods were validated and acceptable. There were no inspection of the clinical and analytical sites because recent inspections had revealed no significant issues at these sites.

The OCP review concluded that applicant has submitted adequate information to support approval, based upon an established pharmacokinetic bridge to the referenced drug, Gilenya, which is an approved product that, like fingolimod ODT, is a non-selective modulator of S1P receptors.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

The application contains no new efficacy information for review. Because of the adequately established PK bridge to Gilenya, substantial evidence of effectiveness is provided by reference to the previous clinical trial findings of substantial evidence of efficacy as described in the approved labeling for Gilenya.

8. Safety

Laura Baldassari, M.D., reviewed the safety data provided in this application. She recommends approval because the types of adverse events and the rates of these events in the development program for fingolimod ODT are similar to those described in the approved labeling for Gilenya. In addition, the applicant provided an adequate PK bridge to the Gilenya NDA obviating a need for efficacy data.

The safety population for this application includes 69 healthy adult volunteers exposed to fingolimod ODT who participated in the two Phase 1 trials undertaken by the applicant. All 69 patients received only a single exposure to fingolimod ODT; there were no volunteers who were exposed to more than one dose which is a limitation of the safety database and therefore the safety of fingolimod ODT will be reliant on the prior, extensive safety database of Gilenya.

Table 3 is adapted from Dr. Baldassari's review and summarizes the two Phase 1 trials and exposures for fingolimod ODT.

Table 3: Reviewer Table, Description of Clinical Studies of Fingolimod ODT

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Clinical Pharmacology Studies							
FGL-P01 (HND-P5-777)	Single center, randomized, single dose parallel comparative Bioavailability study, comparing fingolimod ODT to fingolimod capsule in healthy fasting adult volunteers	Treatment 1: 1 mg fingolimod ODT PO with water in AM Treatment 2: 1 mg fingolimod ODT PO without water in AM Treatment 3: 1 mg fingolimod with water in AM	PK, safety	Single dose	75	Healthy volunteers	1 site in Canada
FGL-P02 (HND-P1-318)	Single center, randomized, single dose, 2-treatment parallel comparative bioavailability study, comparing fingolimod ODT to fingolimod capsule in healthy fed adult volunteers	1 mg fingolimod ODT (test) or 1 mg fingolimod (reference) under fed conditions	PK, safety	Single dose	38	Healthy volunteers	1 site in Canada

Source: Clinical Review, Table 2

Deaths and Serious Adverse Events

There were no deaths and no serious adverse events in either of the two Phase 1 trials.

Dropouts/Discontinuations

There were no dropouts or discontinuations due to adverse events.

Treatment-Emergent Adverse Events

The reported frequency of adverse events in healthy volunteers in patients receiving either fingolimod ODT or Gilenya was low; no single event occurred in more than 10% of participants. The reported adverse events were mild and did not require treatment.

As shown in the following table, the most common events reported in these two trials were atrioventricular blocks. Interruption of cardiac conduction manifesting as heart block is a known, common, and significant safety cardiovascular issue established for fingolimod and is the reason that first dose administration of Gilenya must occur in a medically monitored setting. (b) (4)

warnings about dose interruption and the need for first dose monitoring after interruption, the final negotiated labeling for fingolimod ODT includes all labeling language on Gilenya' s labeling regarding cardiovascular risks and mitigation strategies and aligns with the labeling for the referenced product.

There were more first and second degree heart block adverse events reported in the fingolimod ODT as compared to those exposed to Gilenya. A theoretical concern of the ODT preparation would be a higher risk of heart block due to a potentially more rapid introduction of fingolimod to the heart afforded by the ODT. The Office of Cardiology and Renal Products provided a consultation regarding cardiovascular risks associated with fingolimod ODT and agreed that there

was a slight discrepancy in cardiovascular events but concluded that the difference was small and not likely to represent a true increase in risk between the fingolimod ODT formulation and Gilenya. Dr. Baldassari and the cardiology consultant both note that the fingolimod dose used in both of these studies, 1 mg, is double the highest strength (0.5 mg) approved to treat relapsing forms of multiple sclerosis, and so these safety findings are difficult to interpret given that they occurred in the setting of a supra-therapeutic dose of fingolimod. The consultation did agree that all labeling related to cardiovascular risks and first-dose monitoring should reflect the established risks of Gilenya.

Many of the remaining treatment-emergent adverse events are represented as adverse events on the existing labeling of Gilenya (bradycardia, chest discomfort, dizziness, headache, musculoskeletal pain, nausea). There were two isolated single events of unclear relationship to the study treatment (reflux, tongue discoloration). While herpetic infections occur more frequently in fingolimod-treated individuals, the oral herpes event reported in this development program, is highly unlikely to have been the result of a single exposure which would not suppress the immune system to an extent that herpetic recrudescence would be likely to occur.

Table 4: Reviewer Table, All Adverse Events, Studies FGL-P01 and FGL-P02

Adverse Event (Preferred Term)[1]	Fingolimod ODT 1 mg (n = 69)	Fingolimod (Gilenya) 1 mg (n = 44)
Atrioventricular Block 1st degree	6 (8.7%)	1 (2.%3)
Atrioventricular Block 2nd degree	4 (5.8%)	2 (4.5%)
Headache	3 (4.3%)	3 (6.8%)
Dizziness	3 (4.3%)	2 (4.5%)
Somnolence	0	3 (6.8%)
Back pain	0	2 (4.5%)
Nodal arrhythmia	2 (2.9%)	0
Abdominal distension	1 (1.4%)	0
Anxiety	1 (1.4%)	0
Bradycardia	1 (1.4%)	0
Chest discomfort	1 (1.4%)	0
Chills	1 (1.4%)	0
Duodenogastric reflux	1 (1.4%)	0
Hyperhydrosis	0	1 (2.3%)
Musculoskeletal pain	1 (1.4%)	0
Nausea	0	1 (2.3%)
Oral herpes	0	1 (2.3%)
Pain in extremity	0	1 (2.3%)
Procedural dizziness	0	1 (2.3%)
Throat irritation	1 (1.4%)	0
Tinnitus	1 (1.4%)	0
Tongue discoloration	0	1 (2.3%)
Vessel puncture site bruise	1 (1.4%)	0

Source: Clinical Review

[1] table indicates events but a single patient may have experienced more than one of the listed events

Safety Update
There was no long-term safety update to the application because the two studies featured single exposures, and it is unlikely that this update could provide any meaningful safety findings attributable to fingolimod.

Conclusion
The safety data submitted with this application for fingolimod ODT are consistent with the known safety profile of Gilenya and support approval with similar labeling to the referenced product.

9. Advisory Committee Meeting

There was no advisory committee for this 505(b)(2) application because efficacy has been established through bioequivalence with the listed drug, Gilenya, the clinical trials were acceptable, the safety findings were clear, and the safety profile was similar to the listed drug.

10. Pediatrics

No clinical pediatric data are provided. The listed product, Gilenya, is indicated to treat patients age 10 years and older and was approved for use in pediatric patients based on findings from an adequate and well-controlled efficacy trial conducted in children with relapsing forms of MS. An initial Pediatric Study Plan proposed by the applicant that proposes no further pediatric studies patients 10 years and older and a waiver for studies in patients less than 10 years old due to rarity of MS in this youngest age group was found to be acceptable.

11. Other Relevant Regulatory Issues

Exclusivity/Patent Issues
A tentative approval action will be taken for this application. The listed product upon which this application relies is subject to a period of pediatric exclusivity protection (which would apply to the 0.25 mg dose which is only approved for

pediatric use in patients weighing less than 40 kg) until November 11, 2021. (b) (4)

Therefore, a final approval of this application under section 505(c)(3) of the Act [21 U.S.C. 355(c)(3)] may not be made effective until the patent and/or exclusivity period has expired.

Controlled Substances Issues

The Controlled Substances Staff provided a review of the application and noted there was no evidence of a euphoria-related signal in the referenced product and none in the submission for Tascenso.

12. Labeling

The labeling for Tascenso will rely on the approved Gilenya labeling. (b) (4)

applicant agreed to labeling language regarding varicella virus testing that was consistent with the approved labeling for Gilenya. There are no outstanding labeling issues.

13. Postmarketing Recommendations

There are no postmarketing requirements or commitments.

14. Recommended Comments to the Applicant

None.

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