Generic Fingolimod Products Fail Assay Test

Whitepaper

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Introduction

In February 2023 Cycle Pharmaceuticals launched TASCENSO ODT®, an orally disintegrating tablet (ODT) formulation of fingolimod, approved for the treatment of Multiple Sclerosis, including clinically isolated syndrome (CIS), relapsing remitting multiple sclerosis (RRMS), and secondary progressing multiple sclerosis (SPMS). Cycle Pharmaceuticals offers TASCENSO ODT patient support services through Cycle Vita™, including those previously offered by the Gilenya GO Program®. As of January 2023, Novartis stopped accepting new patients onto the Gilenya GO Program and co-pay support will be withdrawn completely at the end of 2023.[1]

As at 29 November 2023, a total of 12 AB-rated generic versions of Novartis's 0.5 mg Gilenya® (fingolimod) capsules have been launched in the US for the treatment of CIS, RRMS, and SPMS.[2]

Following the availability of generic fingolimod capsules, concerns were raised by MS prescribers around the world with respect to the quality of generic fingolimod capsules, and specifically the accuracy of the actual fingolimod content.[3]

Cases of relapse following a switch from Gilenya® (fingolimod) capsules to a generic alternative have been reported by prescribers and patients to the clinical team at Cycle Vita™.[4] Relapse may be caused by lower than required fingolimod content in generic fingolimod capsules. Prescribers have also expressed concern that higher levels of fingolimod in generic products may pose a risk to patients through excess lowering of lymphocyte counts below safe levels.

In response to these concerns, Cycle Pharmaceuticals conducted assay analyses of the fingolimod content within select generic fingolimod capsules. Within the scope of these tests, Cycle Pharmaceuticals sourced and analyzed the fingolimod content of FDA-approved generic fingolimod capsules from four different applicant holders. The generic fingolimod capsules were analyzed in an FDA-inspected facility using a method that has been previously used to verify the fingolimod content of both TASCENSO ODT and Gilenya capsules. The results demonstrated large variability in fingolimod content between applicant holders. The FDA typically requires that drugs contain between 90.0% – 110.0% of the label claim of active ingredient. The analysis found that, on two separate testing instances, of two different bottles of the same batch, Zydus Pharmaceuticals USA Inc generic fingolimod product demonstrated only 76.8% and

[1] Gilenya, 2022. Frequently Asked Questions About Gilenya. Accessed August 25th, 2023. Available: https://www.gilenya.com/multiple-sclerosis/faqs

[2] National Library of Medicine, 2023. Daily Med search results for fingolimod. Accessed August 22nd, 2023. Available: https://dailymed.nlm.nih.gov/dailymed/search.cfm?labeltype=all&query=fingolimod&audience=professi

[3] Menendez L, Osherov M, Nitsan Z, Alkrenawi M, Gelfand A, Hovel N, Appel S, Milo R. The consequences of switching from Gilenya® to generics for fingolimod. Mult Scler Relat Disord. 2023 Jun;74:104692. doi: 10.1016/j.msard.2023.104692. Epub 2023 Mar 31. PMID: 37099833. https://multiplesclerosisnewstoday.com/news-posts/2016/07/21/low-quality-generic-ms-drugs-can-be-toxic-and-ineffective/

[4] Data on file: REF-00079

76.1% of the required fingolimod dosage, while Apotex Inc generic fingolimod registered at only 85.5%. The other two generic fingolimod products analyzed, HEC Pharm Co Ltd distributed by Rising Pharmaceuticals Inc and Mylan Pharmaceuticals Inc were found to have 92.4% and 102.1% fingolimod content respectively, demonstrating the large variability between generic products. The results of the analysis performed are shown below in Table 1.

As all generic fingolimod capsules are AB-rated to Gilenya, a prescription for Gilenya or generic fingolimod capsules may be filled by the pharmacy with any FDA-approved generic product, without prescriber approval.[5] There is also the possibility of receiving product from different applicant holders from month to month, and in some cases different applicant holders in a single dispense from a pharmacy.

TASCENSO ODT is NOT AB-rated to Gilenya (fingolimod) capsules. As a result, a prescription for TASCENSO ODT must be filled with TASCENSO ODT and cannot be filled with Gilenya or generic fingolimod capsules. The reverse is also true, that a prescription for Gilenya or generic fingolimod capsules cannot be filled with TASCENSO ODT. All commercial batches of 0.5 mg TASCENSO ODT manufactured to date have contained between 100.3% – 100.8% of label fingolimod dosage.

Results

Table 1. Assay results from different fingolimod applicant holders.

Applicant Holder	Assay Results (% of Labelled Content)	Proprietary Name	Country of Manufacture	FDA Acceptance Criteria
Novartis Pharmaceuticals Corp	97.1%	GILENYA®	Switzerland	90.0% – 110.0% of label claim
Cycle Pharmaceuticals Ltd	100.3% – 100.8%	TASCENSO ODT®	UK	
Zydus Pharmaceuticals USA Inc (Test 1)	76.8%	Fingolimod hydrochloride	India	
Zydus Pharmaceuticals USA Inc (Test 2)	76.1%	Fingolimod hydrochloride	India	
HEC Pharm Co Ltd, distributed by Rising Pharmaceuticals Inc	92.4%	Fingolimod hydrochloride	China	
Mylan Pharmaceuticals Inc	102.1%	Fingolimod hydrochloride	India	
Apotex Inc	85.5%	Fingolimod hydrochloride	India	

[5] FDA 2023. FDA Orange Book Preface. Accessed August 25th, 2023. Available: https://www.fda.gov/drugs/development-approval-process-drugs/orange-book-preface

Method

Summary of Drugs Tested

Generic fingolimod capsules and Gilenya were sourced in the US by an approved supplier and shipped under controlled temperature to the UK for analysis. All products were maintained as per the labelled storage conditions (20 to 25 °C) during transportation and storage.

Table 2. Dates of assay analyses with expiry dates of tested batches.

Applicant Holder	Proprietary Name	Date of Analysis	Expiry Date
Novartis Pharmaceuticals Corp	GILENYA®	MAR 2020	APR 2021
Cycle Pharmaceuticals Ltd	TASCENSO ODT®	JAN 2023	NOV 2025
Zydus Pharmaceuticals USA Inc (Test 1)	Fingolimod hydrochloride	AUG 2023	SEP 2024
Zydus Pharmaceuticals USA Inc (Test 2)	Fingolimod hydrochloride	NOV 2023	SEP 2024
HEC Pharm Co Ltd, distributed by Rising Pharmaceuticals Inc	Fingolimod hydrochloride	AUG 2023	JAN 2025
Mylan Pharmaceuticals Inc	Fingolimod hydrochloride	AUG 2023	NOV 2024
Apotex Inc	Fingolimod hydrochloride	NOV 2023	JUN 2025

Analysis

Analysis was conducted by an analytical laboratory at an FDA-inspected manufacturing site using an HPLC assay method validated for the analysis of TASCENSO ODT. Whilst the method is not validated for the analysis of fingolimod capsules, there was no indication that inactive ingredients interfered with the analysis. Analysis of Gilenya and two of the generic capsule products performed using the same method all generated results within the expected acceptance criteria. Generic fingolimod products tested from Zydus Pharmaceuticals USA Inc and Apotex Inc generated assay results well below the expected acceptance criteria.

Analysis is performed on 10 dosage units to generate an assay result overall for the combined 10 units. Analysis is performed in duplicate (assay result generated for each of two sets of 10 units), and the final assay result is reported as the mean of the duplicate results. Overall, good consistency was observed for duplicate preparations for each product.

Cycle Pharmaceuticals has informed the FDA of the findings from these analyses via MedWatch reports and remains available to support further investigation if needed.

Gilenya and the Gilenya GO Program are registered trademarks of Novartis AG. TASCENSO ODT is a registered trademark of Handa Neuroscience, LLC. Cycle Vita is a trademark of Cycle Pharmaceuticals Limited in the United States.

Indication and Important Safety Information

Indications

TASCENSO 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, in patients 10 years of age and older.

Contraindications

- Patients who in the last 6 months experienced myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure with hospitalization, or Class III/IV heart failure.
- Patients with a history or presence of Mobitz Type II 2nd degree or 3rd degree AV block or sick sinus syndrome, unless patient has a functioning pacemaker.
- Patients with a baseline QTc interval ≥ 500 msec.
- Patients with cardiac arrhythmias requiring anti-arrhythmic treatment with Class Ia or Class III anti-arrhythmic drugs.
- Patients who had a hypersensitivity to fingolimod or any excipients in TASCENSO ODT.
- Concomitant use with other products containing fingolimod.

Important Safety Information

Warnings and Precautions:

Due to a risk for bradyarrhythmia and AV blocks patients should be monitored during TASCENSO ODT treatment initiation. TASCENSO ODT may increase blood pressure, risk of infections and may cause fetal harm. Cases of Progressive Multifocal Leukoencephalopathy (PML) and of clinically significant liver injury have occurred in patients treated with fingolimod in the postmarketing setting. If PML is confirmed, treatment should be discontinued; Immune Reconstitution Inflammatory Syndrome (PML-IRIS) has been reported after discontinuation. TASCENSO ODT increases risk of macular edema. Rare cases of Posterior Reversible Encephalopathy Syndrome in adults have been reported with fingolimod. Fingolimod can have respiratory effects. Severe increase in disability accompanied by multiple new lesions on MRI has been reported following discontinuation of fingolimod. MS relapses with tumefactive demyelinating lesions on imaging have been observed during fingolimod therapy and after discontinuation. The risk of basal cell carcinoma and melanoma is increased in patients treated with fingolimod. Cases of lymphoma have been reported in patients receiving fingolimod. The reporting rate of non-Hodgkin lymphoma with fingolimod is greater than that expected in the general population. Fingolimod remains in the blood and has pharmacodynamic effects, including decreased lymphocyte counts for up to 2 months following the

last dose. Hypersensitivity reactions including rash, urticaria, and angioedema have been reported with fingolimod. Cases of seizures, including status epilepticus, have been reported with the use of fingolimod.

Adverse Reactions:

In clinical trials, the most common adverse reactions (incidence ≥ 10% and >placebo) are headache, liver transaminase elevation, diarrhea, cough, influenza, sinusitis, back pain, abdominal pain, and pain in extremity.

Drug Interactions:

Patients on QT prolonging drugs with a known risk of torsades de pointes should be monitored during initiation of treatment with TASCENSO ODT. Monitor patients during use of systemic ketoconazole. Use of live attenuated vaccines during, and for 2 months after stopping TASCENSO ODT, should be avoided.

For more detailed information, please refer to the full Prescribing Information at www.tascenso.com/PI.

To report SUSPECTED ADVERSE REACTIONS, contact Cycle Pharmaceuticals Ltd at 1-888-533-1625 or the FDA at: 1-800-FDA-1088 or www.fda.gov/medwatch.