Novartis Gilenya FDO Program
Clinical Protocol and Highlights from Prescribing Information (PI)

Highlights from Prescribing Information  - the link to the full text PI is as follows: [http://www.pharma.us.novartis.com/product/pi/pdf/gilenya.pdf](http://www.pharma.us.novartis.com/product/pi/pdf/gilenya.pdf)

“Bradyarrhythmia and Atrioventricular Block

GILENYA, in controlled studies, was shown to induce a dose-dependent reduction in heart rate and has been associated with atrioventricular (AV) conduction delays including 1st or 2nd degree AV block following administration of the initial dose.

After the first dose of GILENYA, the heart rate decrease starts within an hour and is maximal after approximately 6 hours. In clinical studies, the average decrease in heart rate was approximately 13 beats per minute (bpm). Heart rates below 40 bpm were rarely observed. Patients who experienced bradycardia were generally asymptomatic, but some patients experienced mild to moderate symptoms, including dizziness, fatigue, palpitations and chest pain, which resolved within the first 24 hours on treatment”

At initial FDO of Gilenya .5 mg, the frequency of first and second degree AV blocks was .1% for each. Frequency of all bradycardia was 3.5% with 1% in the placebo group. One case of complete AV block occurred in a patient taking 1.25mg FD (complete recovery within 24 hours) but none in the .5 mg groups. Mean decline was 8 bpm. One asymptomatic patient was inappropriately given Isoproterenol.

Summary of .5 mg FDO side effects in 1176 patients:
- Bradycardia with mean decrease of 8 bpm in 3.5% vs. 1% in placebo group
- Only 4 cases of symptomatic bradycardia were seen none of whom required treatment. Three of the four had mild dizziness and one had moderate somnolence later that evening. Symptoms in all 4 resolved in 24 hours. All were sent home.
- All bradycardia resolved in 30 days

CONTRAINDICATIONS

- Patients who in the last 6 months experienced myocardial infarction, unstable angina, stroke, TIA, decompensated heart failure requiring hospitalization or Class III/IV heart failure.
- Mobitz Type II second-degree or third-degree atrioventricular (AV) block or sick sinus syndrome, unless patient has a functioning pacemaker.
- Baseline QTc interval > 500 ms should not be dosed and should be referred back to Neurologist
- Baseline QTc interval ≥450 ms males and >470 ms females should not be dosed in a 6 hour observation and should be referred back to Neurologist to arrange 24 hour continuous monitoring.
- Treatment with Class Ia or Class III anti-arrhythmic drugs.
Precautions

Heart rate Lowering Medications:

Experience with GILENYA is limited in patients receiving concurrent therapy with drugs that slow heart rate (e.g., beta blockers, heart-rate lowering calcium channel blockers such as diltiazem or verapamil, or digoxin). Because the initiation of GILENYA treatment is also associated with slowing of the heart rate, concomitant use of these drugs during GILENYA initiation may be associated with severe bradycardia or heart block. The possibility to switch to non-heart-rate lowering drugs should be evaluated by the physician prescribing the heart-rate lowering drug before initiating GILENYA. In patients who cannot switch, overnight continuous ECG monitoring after the first dose is recommended. These patients should be referred back with call to the Neurologist.

QT prolonging drugs:

GILENYA has not been studied in patients treated with drugs that prolong the QT interval. Drugs that prolong the QT interval have been associated with cases of torsades de pointes in patients with bradycardia. Since initiation of GILENYA treatment results in decreased heart rate and may prolong the QT interval, patients on QT prolonging drugs with a known risk of torsades de pointes (e.g., citalopram, chlorpromazine, haloperidol, methadone, erythromycin) should be monitored overnight with continuous ECG in a medical facility [see Dosage and Administration (2) and Warnings and Precautions (5.1)].

Pre-Existing Conditions:

Patients with some preexisting conditions (e.g. ischemic heart disease, history of myocardial infarction, congestive heart failure, history of cardiac arrest, cerebrovascular disease, uncontrolled hypertension, history of symptomatic bradycardia, history of recurrent syncope, severe untreated sleep apnea, AV block, sinoatrial heart block) may poorly tolerate the Gilenya-induced bradycardia, or experience serious rhythm disturbances after the first dose of Gilenya.

Varicella zoster virus antibody testing/vaccination:

As for any immune modulating drug, before initiating GILENYA therapy, patients without a history of chickenpox or without vaccination against varicella zoster virus (VZV) should be tested for antibodies to VZV. VZV vaccination of antibody-negative patients should be considered prior to commencing treatment with GILENYA, following which initiation of treatment with GILENYA should be postponed for 1 month to allow the full effect of vaccination to occur.

Hepatic Effects:

Elevations of liver enzymes may occur in patients receiving GILENYA. Recent (i.e. within last 6 months) transaminase and bilirubin levels should be available before initiation of GILENYA therapy. During clinical trials, 3-fold the upper limit of normal (ULN) or greater elevation in liver transaminases occurred in 8% of patients treated with GILENYA 0.5 mg, as compared to 2% of patients on placebo. Elevations 5-fold the ULN occurred in 2% of patients on GILENYA
and 1% of patients on placebo. In clinical trials, GILENYA was discontinued if the elevation exceeded 5 times the ULN. Recurrence of liver transaminase elevations occurred with re-challenge in some patients, supporting a relationship to drug. The majority of elevations occurred within 6-9 months. Serum transaminase levels returned to normal within approximately 2 months after discontinuation of GILENYA. Liver enzymes should be monitored in patients who develop symptoms suggestive of hepatic dysfunction, such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine. GILENYA should be discontinued if significant liver injury is confirmed. Patients with pre-existing liver disease may be at increased risk of developing elevated liver enzymes when taking GILENYA. Because GILENYA exposure is doubled in patients with severe hepatic impairment, these patients should be closely monitored, as the risk of adverse reactions is greater.
FDO Provider Clinical Protocols

Initial Evaluation

1) Review any labs if provided. Call and review any abnormal results with treating Neurologist.

2) Perform pre FDO EKG (see EKG SOP), even if patient previously had baseline EKG performed. If pre-FDO EKG indicates prolonged QTc interval (>450 msec of males and >470 msec for females) at baseline, do not proceed with FDO. These patients will need to be referred back to the prescribing neurologist to arrange 24 hour observation with continuous monitoring if and when FDO is performed.

3) Perform brief orientation assessment and validate cardiac history, including cardiac medications (please include in nursing flow sheet)

4) Contraindications to beginning the FDO include the following and if present, do not start the FDO. Refer the patient back to their Neurologist for further evaluation with a cardiologist and contact the neurologist with findings. FDO monitoring of these patients will need to be inpatient with continuous EKG monitoring. Please note it is the Neurologists responsibility to evaluate the patient and make the decision to prescribe Gilenya. However, GAN providers should validate that there are no known contraindications or higher risks prior to beginning the FDO.

- Recent (within 6 months) occurrence of myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, or Class III/IV heart failure
- History or presence of Mobitz Type II 2nd degree or 3rd degree AV block or sick sinus syndrome, unless patient has a pacemaker
- Treatment with Class Ia or Class III anti-arrhythmic drugs
- Patient on any known heart rate lowering drug or drugs that can potentially prolong the QT interval with a known risk of Torsades-See attached list.

(Please notify the prescribing neurologist)

Always notify the referring Neurologist if the FDO cannot be initiated or the patient requires treatment or referral related to symptomatic bradycardia.
If there are questions post initial assessments please call Dr. Latha Brubaker at 281-725-7029.
If no contraindications exist, approve initiation of FDO.

Interval Checks

1) Review and sign off on all Vital Sign checks. Vital signs will be performed a minimum of every 30 minutes during the first hour of the FDO and then every hour throughout the rest of the 6 hours or as needed.

2) Sitting and standing vitals are to be performed on the baseline and final vital sign checks or as needed.

3) Customer service check at 3 hours or more if desired by Provider

4) Perform discharge evaluation and Post FDO EKG after 6 hours (See discharge criteria and discharge process below)
Bradycardia Management

1) Use clinical judgment remembering that a decreased pulse from baseline is not bradycardia
2) Only treat symptomatic bradycardia otherwise continue observation
3) For mild moderate decreasing pulse allowing the Patient to walk with assistance may improve the rate due to the positive chronotropic and inotropic effects of activity.
4) If symptomatic and P < 55
   - Assess ABC’s
   - EKG & O2 @ 2 liters at the discretion of provider
   - Monitor VS’s q 30 minutes with pulse oximetry
   - Atropine .5 to 1.0 mg IV or by simple butterfly per standard ACLS protocols if significant symptoms or altered mental status.
   (Note on Atropine usage: To the extent possible based on location and availability; follow AHA protocols for BLS and bradycardia and transfer patient ASAP.)
   - Run a rhythm strip before and after administration of Atropine
   - AED’s in most centers have a rhythm monitor function if clinically needed
   - A single dose should be sufficient but this is unknown since no patients required treatment to date
   - Should a patient require pharmacologic intervention for symptomatic Bradycardia, continuous 24 hour EKG monitoring in a medical facility is required (transfer to the emergency room), and the FDO should be repeated for the second dose of Gilenya
   - Fill out ER transfer form that will be sent with EMS along with copy of patient chart prior to transferring
   - Notify treating Neurologist and arrange for hospital transfer if continued symptoms

Discharge Criteria: After 6 hours of monitoring release home if all apply:

1) P > 50 or P > 80% of baseline value
2) Pulse rate at 6 hours not at lowest value measured during observation period. (may be hypothetically reflective of continuing decline in pulse)
3) Patients must have no symptoms associated with decreased pulse
4) EKG post dose does not show any new onset second degree or higher AV block
5) If discharge criteria are not met continue monitoring for another 2 hours or until the finding has resolved.
6) No prolonged QTc interval (≥450 msec males, ≥470 msec females). These patients will need to be transferred to the ER for 24 hour continuous monitoring.
   - Fill out ER transfer form that will be sent with EMS along with copy of patient chart prior to transferring
7) As a courtesy, notify the Neurologist if the patient has any challenges during FDO.

Discharge Process

1) Complete final Vital Signs Flow Sheet and Treating Physician report be reported to the Neurologist by Pharma Customer Support.. 
   NOTE: the Vital Signs Flow Sheet and Treating Physician report need to be completed even if the FDO cannot be performed. Indicate on these forms the clinical findings and rationale for not performing the FDO
2) Assist staff with filling out a AE form if indicated
3) Courtesy call to Neurologist office with patient status.
Please feel free to contact the National Medical Director for the Novartis Program, Dr. Latha Brubaker, at 281-725-7029 for any clinical questions or concerns during the FDO.