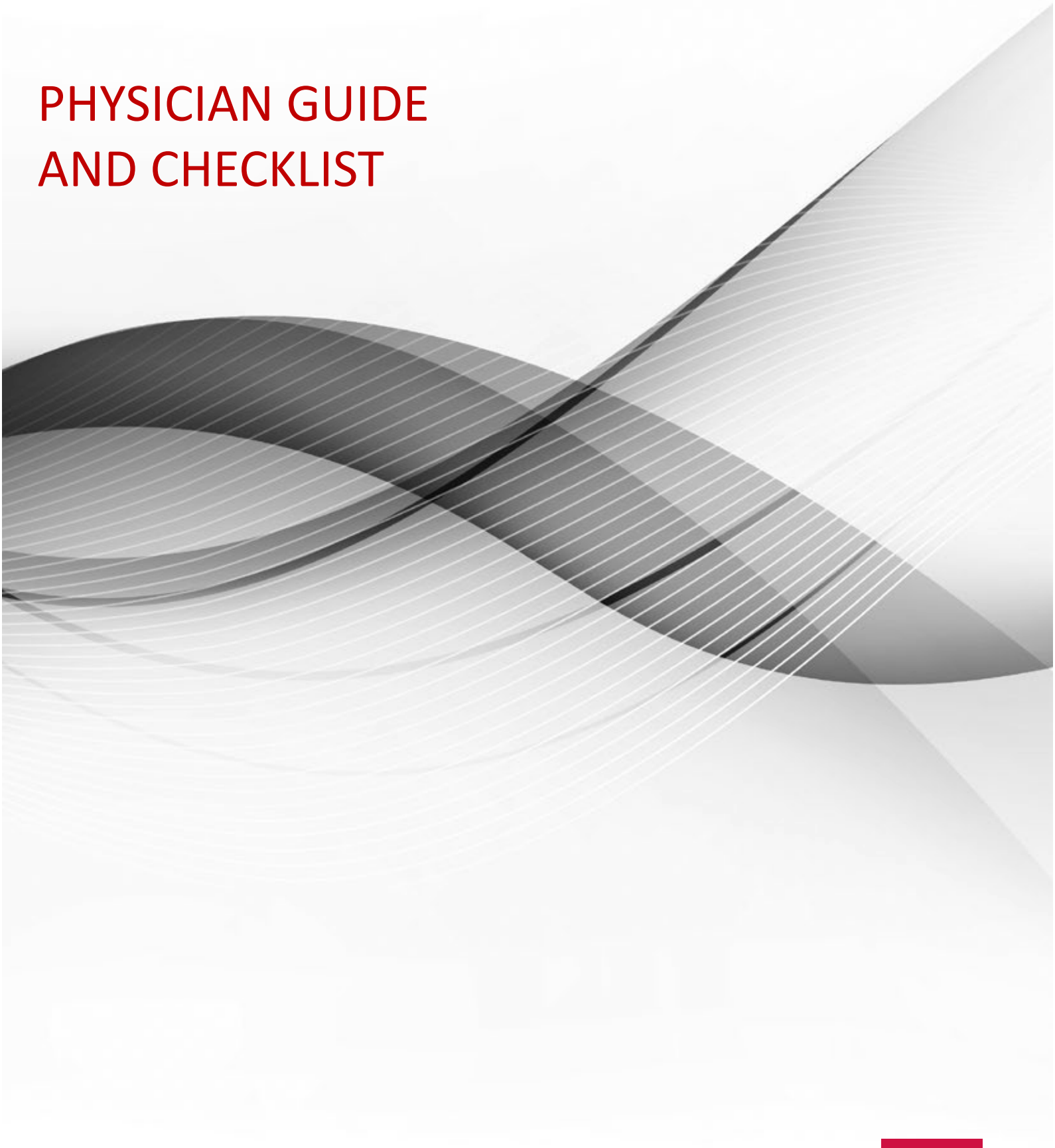
PHYSICIAN GUIDE AND CHECKLIST



TARO-Fingolimod

TARO

TARO-Fingolimod

As with the use of all medications, certain side effects associated with the use of Taro-Fingolimod are known. Specific testing and monitoring activities are required to ensure safety in the use of Taro-Fingolimod. The checklist included on page 8 of this booklet, completed with dates and values and added to the patient's chart, can ensure these activities are conducted in a timely manner and will serve as a record of completion.

Considerations for Patient Selection

Taro-Fingolimod is contraindicated in patients with the following conditions:

- Patients who are hypersensitive to fingolimod or to any ingredient in the formulation of Taro-Fingolimod or component of the container
- Patients with increased risk for opportunistic infections, including those who are immunocompromised due to treatment (e.g. antineoplastic, immunosuppressive or immunomodulating therapies, total lymphoid irradiation or bone marrow transplantation) or disease (e.g. immunodeficiency syndrome)
- Patients with severe active infections including active chronic bacterial, fungal or viral infections (e.g., hepatitis, tuberculosis)
- Patients with known active malignancies, except for patients with basal cell carcinoma
- Patients with severe hepatic impairment (Child-Pugh Class C)
- Patients who in the last 6 months had myocardial infarction, unstable angina pectoris, stroke/transient ischemic attack, decompensated heart failure (requiring inpatient treatment), or New York Heart Association Class III/IV heart failure
- Patients with severe cardiac arrhythmias requiring anti-arrhythmic treatment with Class Ia or Class III anti-arrhythmic drugs
- Patients with second-degree Mobitz type II atrioventricular (AV) block or third-degree AV block, or sick-sinus syndrome, if they do not have a pacemaker
- Patients with a baseline QTc interval ≥500 msec
- Women who are pregnant or of childbearing potential not using effective contraception. Pregnancy must be excluded before start of treatment as fingolimod may cause fetal harm.

TARO-Fingolimod

In addition, Taro-Fingolimod is NOT recommended in patients with the following conditions. If being considered in spite of this recommendation, a cardiology consultation is advised to determine benefit versus risk, and a monitoring plan. At least overnight monitoring is recommended in patients with:

- history or presence of sino-atrial heart block
- QTc prolongation > 470 msec (females) or > 450 msec (males)
  - or taking QTc-prolonging drugs, including those listed on page 29 of the Taro-Fingolimod product monograph
  - or with relevant risk factors for QTc prolongation (e.g., hypokalemia, hypomagnesemia, or congenital QTc prolongation)
- history of cardiac arrest
- history of severe untreated sleep apnea
- history of symptomatic bradycardia
- history of recurrent syncope
- history of uncontrolled hypertension
- on concurrent therapy with beta-blockers, with heart-rate lowering calcium channel blockers or with other substances that may decrease heart rate

Other considerations:

Taro-Fingolimod treatment results in increased levels of total cholesterol, LDL cholesterol, and triglycerides.

- Consider this when treating patients with pre-existing hyperlipidemia, atherosclerosis, or ischemic heart disease.

Use with caution in patients with severe respiratory disease, pulmonary fibrosis, moderate and severe asthma, or chronic obstructive pulmonary disease.

- Reduced forced expiratory volume in one second (FEV1) and diffusion lung capacity for carbon monoxide (DLCO) were observed in patients treated with fingolimod as early as one month after treatment initiation.

Renal impairment: use with caution

Hepatic impairment: contraindicated in severe impairment; use with caution in mild to moderate impairment

TARO-Fingolimod

Paediatric use: not indicated

Geriatric use: not sufficiently studied; use with caution

Patients with diabetes: use with caution

Prior to Initiating Treatment with Taro-Fingolimod

Taro-Fingolimod is contraindicated in patients at an increased risk of opportunistic infections and in patients with severe, active infections including active, chronic bacterial, fungal, or viral infections.

- Delay the start of Taro-Fingolimod in patients with severe, active infection until resolved. Taro-Fingolimod reduces circulating lymphocyte counts to 20-30% of baseline values via reversible retention in lymphoid organs
- Check complete blood count (CBC) before starting therapy if no recent result is available (i.e., within six months or after discontinuation of prior therapy)
- Consult product monograph if changing treatment to Taro-Fingolimod from another immunosuppressive therapy for relapsing-remitting MS (RRMS).

Taro-Fingolimod may reversibly increase liver transaminase levels.

- Check transaminase levels according to the schedule in the checklist on page 8.

Note: If liver transaminases rise more than five times above the upper limit of normal (ULN) during therapy, more frequent monitoring should be instituted, including serum bilirubin and alkaline phosphatase (ALP) measurements. With repeated confirmation of liver transaminases above five times the ULN, treatment with Taro-Fingolimod should be interrupted and only restarted once liver transaminase values have normalized. The benefits and risks of treatment should be reassessed prior to reinitiation of treatment.

Macular edema, with or without visual symptoms, has been reported in patients treated with fingolimod, usually in the first three to four months of therapy.

- Patients with diabetes or a previous history of uveitis are at greater risk and should have an eye exam before starting therapy.
- All patients should have an eye exam after three to four months of therapy (see checklist below) and at any time in any patient complaining of visual disturbances.

- In addition to an eye exam prior to initiating therapy and at three to four months after initiating treatment, regular follow-up evaluations are recommended for MS patients with diabetes mellitus or a history of uveitis while receiving Taro-Fingolimod therapy.

Taro-Fingolimod is contraindicated in patients with known active malignancies, except for patients with basal cell carcinoma. Basal cell carcinoma and other skin cancers have been reported in patients receiving fingolimod.

- Monitor for suspicious skin lesions before initiating treatment

There have been very rare fatal cases of varicella zoster virus (VZV) infections in patients taking fingolimod. Patients need to be assessed for their immunity to VZV prior to Taro-Fingolimod treatment.

- It is recommended that patients without a healthcare professional confirmed history of chickenpox or documentation of a full course of vaccination with varicella vaccine undergo antibody testing to VZV before initiating Taro-Fingolimod therapy.
- A full course of vaccination with varicella vaccine is recommended (if not contraindicated) for antibody-negative patients prior to commencing treatment with Taro-Fingolimod (see checklist on page 8).
- If vaccinated, treatment with Taro-Fingolimod should only be initiated one month after the patient has been vaccinated to allow full effect of vaccination to develop.

Taro-Fingolimod is contraindicated in patients who are hypersensitive to fingolimod or to any ingredient in the formulation of Taro-Fingolimod.

- Verify the patient does not have hypersensitivity to the drug or any ingredient in the formulation (non-drug ingredients are listed on page 39 of the Taro-Fingolimod product monograph).

TARO-Fingolimod

During Treatment with Taro-Fingolimod

Include the following in the differential diagnosis when evaluating a patient with an exacerbation:

- Disseminated varicella zoster virus infection
- Progressive multifocal leukoencephalopathy (PML)
  - Typically presents as diverse symptoms, progressing over days to weeks, and includes progressive unilateral weakness or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes.
  - Be vigilant for clinical symptoms or MRI findings that may be suggestive of PML. If PML is suspected, Taro-Fingolimod treatment should be suspended until PML has been excluded.
- Cryptococcal meningitis
  - Cases (sometimes fatal) have been reported, generally after two to three years of treatment, but may occur earlier.
- Posterior reversible encephalopathy syndrome (PRES)
  - Symptoms of PRES include sudden onset severe headache, nausea, vomiting, altered mental status, visual disturbances, and seizure.

Avoid use of live-attenuated vaccines during treatment.

- Other vaccines are still recommended, but response can be expected to be reduced.

Seizures, including status epilepticus, have been reported with the use of fingolimod

Patients should have an ophthalmic assessment 3 to 4 months after starting treatment with fingolimod and at any other time if the patient complains of visual changes

Instruct patients to immediately report symptoms and signs of infection during therapy and for two months following discontinuation.

Check complete blood count (CBC) during therapy with fingolimod

Do not co-administer with antineoplastic, immunosuppressive, or immune-modulating therapies.

Corticosteroids administered for up to five days in trials did not increase overall rate of infection. Exercise caution if using a longer course of therapy.

Instruct patients to report symptoms of hepatic dysfunction, such as unexplained vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine during treatment.

Monitor for suspicious skin lesions regularly during treatment. Evaluate any unusual lesions promptly.

Taro-Fingolimod was teratogenic in animal studies when given during the period of organogenesis.

- Advise female patients of the teratogenic risk of Taro-Fingolimod and the need for effective contraception during treatment with Taro-Fingolimod. Consider requesting a pregnancy test before starting treatment if the possibility of pregnancy exists.
- Provide a pregnancy warning card.
- If a patient becomes pregnant while taking Taro-Fingolimod, physicians should discontinue treatment and report this event by calling the Taro-Fingolimod Pregnancy Registry at 1.866.877.5180.

Provide all patients with a patient information booklet.

After Discontinuation of Treatment with Taro-Fingolimod

Avoid the use of live-attenuated vaccines for two months after discontinuation of Taro-Fingolimod.

Women should continue effective contraception for two months after stopping therapy with Taro-Fingolimod.

Advise male patients wishing to conceive a child that, while available data do not suggest that fingolimod would be associated with an increased risk of male-mediated fetal toxicity, some clinicians consider it prudent to stop the medication for at least 3 months before trying to conceive a child with their partner.

TARO-Fingolimod

CHECKLIST FOR STARTING THERAPY

Before Treatment:

- ❑ Assess contraindications
- ❑ CBC (verify lymphocytes in normal range) ___/___/___

Verify varicella zoster virus (VZV) immunity:

- ❑ Documented previous infection ___/___/___
- ❑ Full course of vaccine ___/___/___
- ❑ If none, VZV antibody testing ___pos ___ neg
  - * If negative, administer full course of VZV vaccine.
- ❑ Full course of vaccine ___/___/___
  - * Wait one month before starting therapy.

NOTE: Include disseminated herpetic infection in differential diagnosis if patient presents with atypical MS relapse or multiorgan failure. In cases of disseminated herpes infection, antiviral therapy and discontinuation of Taro-Fingolimod is recommended.

- ❑ Transaminase and bilirubin levels (unless tested within the last six months) ___/___/___

- ❑ Eye exam for patients with diabetes mellitus or a history of uveitis

In women of childbearing potential:

- ❑ consider a pregnancy test before starting treatment if any possibility of pregnancy exists
- ❑ provide pregnancy warning card and patient booklet to consider other risks
- ❑ discuss birth control options

Immediately Before First Dose:

- ❑ ECG
- ❑ BP ___/___
- ❑ HR _____

Hour 1:

- ❑ BP ___/___
- ❑ HR _____

...continues

TARO-Fingolimod

Hour 2:
- ❑ BP ___/___
- ❑ HR _____

Hour 3:
- ❑ BP ___/___
- ❑ HR _____

Hour 4:
- ❑ BP ___/___
- ❑ HR _____

Hour 5:
- ❑ BP ___/___
- ❑ HR _____

Hour 6:
- ❑ ECG
- ❑ BP ___/___
- ❑ HR _____

If HR has not started to rebound, monitor for an additional two hours:

Hour 7:
- ❑ BP ___/___
- ❑ HR _____

Hour 8:
- ❑ BP ___/___
- ❑ HR _____

During Treatment:

- ❑ Transaminase and bilirubin levels every 3 months in the first year of treatment and periodically thereafter
- ❑ Monitor for signs and symptoms of cryptococcal meningitis which can be fatal and can occur 2 to 3 years after treatment starts or earlier
- ❑ Monitor for clinical symptoms or MRI findings suggesting progressive multifocal encephalopathy (PML) which can occur 2 to 3 years after treatment starts. Stop therapy until PML has been excluded
- ❑ Stop treatment if pregnancy occurs and report the pregnancy

TARO-Fingolimod