Krintafel™ (tafenoquine) – New drug approval

- On July 20,2018, GlaxoSmithKline (GSK) and Medicines for Malaria Venture (MMV) announced the FDA approval of Krintafel (tafenoquine), for the radical cure (prevention of relapse) of *Plasmodium vivax* malaria in patients aged 16 years and older who are receiving appropriate antimalarial therapy for acute *P. vivax* infection.

- The *Plasmodium* parasite is a complex organism with a lifecycle spanning both humans and mosquitoes. After an infected mosquito bite, the *P. vivax* parasite infects the blood and causes an acute malaria episode.

    - *P. vivax* also has the ability to lie dormant in the liver (in a form known as hyponozoite) from where it can reactivate to cause relapses of malaria. Relapses can occur weeks, months or even years after the initial infection. The dormant liver forms of the parasite cannot be readily treated with most anti-malarial treatments active against the blood-stage parasite.
    - Primaquine which is 8-aminoquinoline and currently the only FDA-approved medicine that targets the dormant liver stage to prevent relapse. It must be taken for 14 days to be effective, a regimen that is associated with poor compliance.

- *P. vivax* malaria has a significant public health and economic impact, primarily in South-Asia, South-East Asia, Latin America and the horn of Africa. The disease is estimated to cause around 8.5 million clinical infections every year. The clinical features of *P. vivax* malaria include fever, chills, vomiting, malaise, headache and muscle pain, and in some cases, can lead to severe malaria and be fatal.

- Krintafel is an 8-aminoquinoline derivative with activity against all stages of the *P. vivax* lifecycle, including hypnozoites.

- The efficacy and safety of Krintafel were approved based two clinical trials: a placebo-controlled trial in 522 adults with *P. vivax* and a dose-ranging trial. All patients received chloroquine phosphate to treat the acute infection. The primary endpoint was the recurrence-free efficacy rate, defined by initial parasite clearance, no need for antimalarial medications, and confirmed parasite-free at 6 months.

    - In the placebo-controlled study, recurrence-free efficacy was 60% in the tafenoquine group vs. 26% in the placebo group. In addition, the odds ratio was 0.24 (95% CI: 0.15, 0.38, $p < 0.001$).
    - In the dose-ranging trial, the recurrence-free efficacy rate was 84% with Krintafel vs. 39% for placebo (difference = 45% [95% CI: 29%, 61%]).

- Krintafel is contraindicated in:
    - Patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency or unknown G6PD status.
    - Breastfeeding by a lactating woman when the infant is found to be G6PD deficient or if G6PD status is unknown.
    - Known hypersensitivity reactions to tafenoquine, other 8-aminoquinolines, or any component of Krintafel.

- Other warnings and precautions of Krintafel include hemolytic anemia, methemoglobinemia, psychiatric effects, and hypersensitivity reactions.

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- The most common adverse reactions (≥ 5%) with Krintafel use were dizziness, nausea, vomiting, headache, and decreased hemoglobin.

- The recommended dose of Krintafel in patients aged 16 years and older is a single dose of 300 mg (two 150-mg tablets) coadministered on the first or second day of the appropriate antimalarial therapy for acute *P. vivax* malaria.

    — All patients must be tested for G6PD deficiency prior to prescribing Krintafel.
    — Pregnancy testing is recommended for females of reproductive potential prior to initiating treatment with Krintafel.

- Approvals by the FDA and the Australian Therapeutics Good Administration will be informative to other regulatory agencies for their own approval process in malaria-endemic countries where tafenoquine will be provided as a not-for-profit medicine to maximize access to those who need it most.

- GSK's launch plans are pending. Krintafel will be supplied as 150 mg tablets