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US FDA approves Krintafel (tafenoquine) for the radical cure of *P. vivax* malaria

First single-dose medicine to prevent the relapse of *P. vivax* malaria marks a major contribution towards malaria eradication efforts

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GSK and Medicines for Malaria Venture (MMV) today announced that the United States Food and Drug Administration (FDA) has approved, under Priority Review, single-dose *Krintafel* (tafenoquine) for the radical cure (prevention of relapse) of *Plasmodium vivax* (*P. vivax*) malaria in patients aged 16 years and older who are receiving appropriate antimalarial therapy for acute *P. vivax* infection.

Dr. Hal Barron, Chief Scientific Officer and President of Research and Development, GSK, said: "Today's approval of *Krintafel*, the first new treatment for *Plasmodium vivax* malaria in over 60 years, is a significant milestone for people living with this type of relapsing malaria. Together with our partner, Medicines for Malaria Venture, we believe *Krintafel* will be an important medicine for patients with malaria and contribute to the ongoing effort to eradicate this disease."

Dr. David Reddy, Chief Executive Officer of MMV said: “The US FDA’s approval of *Krintafel* is a major milestone and a significant contribution towards global efforts to eradicate malaria. The world has waited decades for a new medicine to counter *P. vivax* malaria relapse. Today, we can say the wait is over. Moreover, as the first ever single-dose for this indication, *Krintafel* will help improve patient compliance. We are proud to have worked side-by-side with GSK for more than a decade to reach this point. Our focus is now on working to ensure the medicine reaches the vulnerable patients that need it most.”

The approval was based on efficacy and safety data from a comprehensive global clinical development *P. vivax* radical cure programme designed in agreement with the FDA. Thirteen studies in healthy volunteers and patients directly supported the programme. The primary evidence for the clinical efficacy and safety of the 300mg single-dose, to which more than 800 subjects were exposed, was provided by three randomised, double-blind studies: DETECTIVE Part 1 and Part 2 (TAF112582) and GATHER (TAF116564). The results of the two phase III studies were announced in June 2017. The submission included data analysed from a total of thirty-three studies involving more than 4,000 trial subjects exposed to the 300mg single-dose and other doses of tafenoquine.

With the approval of *Krintafel*, the FDA awarded GSK a tropical disease priority review voucher. The tropical disease priority review voucher programme is designed to encourage development of new drugs and biological products for prevention and treatment of certain neglected tropical diseases affecting millions of people throughout the world.

The new drug application (NDA) was submitted by GSK to the FDA in November 2017 and a regulatory submission was also made to the Australian Therapeutics Good Administration (TGA) in December 2017. A decision from the TGA is awaited. Approvals by FDA and TGA 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 maximise access to those who need it most.

About *Krintafel* (tafenoquine)

Krintafel is an 8-aminoquinoline derivative with activity against all stages of the *P. vivax* lifecycle, including hypnozoites. It was first synthesised by scientists at the Walter Reed Army Institute of Research in 1978. GSK's legacy in the research and development of tafenoquine as a potential medicine for malaria commenced over 20 years ago. In 2008, GSK entered into a collaboration with the not-for-profit drug research partnership, MMV, to develop tafenoquine as an anti-relapse medicine for patients infected with *P. vivax*. The tafenoquine clinical programme is part of GSK's global health programme aimed at improving healthcare for vulnerable populations.

About *Plasmodium vivax* malaria

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. It also has the ability to lie dormant in the liver (in a form known as hypnozoite) from where it periodically reactivates to cause relapses of *P. vivax* malaria. Hence, a single *P. vivax* infection can give rise to multiple episodes of malaria, in the absence of a new mosquito bite. These 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. The 8-aminoquinoline, primaquine, is 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.

The use of a medicine that targets the dormant liver forms of the parasite, co-administered with currently available anti-malarials such as chloroquine or artemisinin-based combination therapies (ACTs) is known as radical cure.

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.

GSK's commitment to malaria

Malaria remains one of the greatest global healthcare challenges. Whilst good progress has been made in the fight against malaria this progress is fragile. GSK supports the WHO target to cut malaria cases and deaths by 90% by 2030 and believes that with renewed global commitment from all stakeholders working together, this goal can be met. GSK is playing its part by building on its 40-year commitment to work with partners to fight malaria in the lab and on the ground.

Important safety information

CONTRAINDICATIONS

Krintafel should not be administered to:

- patients who have glucose-6-phosphate dehydrogenase (G6PD) deficiency or have not been tested for G6PD deficiency
- patients who are breastfeeding a child known to have G6PD deficiency or one that has not been tested for G6PD deficiency
- patients who are allergic to tafenoquine or any of the ingredients in *Krintafel* or who have had an allergic reaction to similar medicines containing 8-aminoquinolines.

WARNINGS AND PRECAUTIONS

Hemolytic Anemia

Breakdown of red blood cells (hemolytic anemia) may occur in a patient who has G6PD deficiency. G6PD testing must be performed before prescribing *Krintafel*. Treatment with *Krintafel* is contraindicated in patients with G6PD deficiency or unknown G6PD.

G6PD Deficiency in Pregnancy or Lactation

The use of *Krintafel* during pregnancy may cause hemolytic anemia in a G6PD-deficient fetus. *Krintafel* is not recommended during pregnancy. Females of reproductive potential should avoid pregnancy or use effective contraception for 3 months after the dose of *Krintafel*.

A G6PD-deficient infant may be at risk for hemolytic anemia from exposure to *Krintafel* through breast milk. Infant G6PD status should be checked before breastfeeding begins. *Krintafel* is contraindicated in breastfeeding women when the infant is found to be G6PD deficient or the G6PD status of the infant is unknown. A woman with a G6PD-deficient infant or if the G6PD status of the infant is not known should not breastfeed for 3 months after the dose of *Krintafel*.

Methemoglobinemia

Asymptomatic elevations in methemoglobin have been observed in the clinical trials of *Krintafel*. Physicians should carefully monitor individuals with nicotinamide adenine dinucleotide (NADH)-dependent methemoglobin reductase deficiency and advise patients to seek medical attention if signs of methemoglobinemia occur.

Psychiatric Effects

Serious psychiatric adverse reactions have been observed in patients with a previous history of psychiatric conditions at doses higher than the approved dose. The benefit of treatment with *Krintafel* must be weighed against the potential risk for psychiatric adverse reactions in patients with a history of psychiatric illness. Due to the long half-life of *Krintafel* (15 days), any signs or symptoms of psychiatric adverse reactions that may occur could be delayed in onset and/or duration.

Hypersensitivity Reactions

Serious hypersensitivity reactions (e.g., angioedema) have been observed with administration of *Krintafel*. Due to the long half-life of *Krintafel* (15 days), any signs or symptoms of hypersensitivity adverse reactions that may occur could be

delayed in onset and/or duration. Physicians should advise patients to seek medical attention if signs of hypersensitivity occur.

ADVERSE REACTIONS

The most common adverse reactions (³5%) observed for *Krintafel* in clinical trials were dizziness, nausea, vomiting, headache, and decreased hemoglobin.

DRUG INTERACTIONS

Physicians should avoid coadministration of *Krintafel* with drugs that are substrates of organic cation transporter-2 (OCT2) or multidrug and toxin extrusion (MATE) transporters (for example, dofetilide, metformin).

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch .

GSK - a science-led global healthcare company with a special purpose: to help people do more, feel better, live longer. For further information please visit www.gsk.com

Medicines for Malaria Venture (MMV) - MMV is a leading product development partnership (PDP) in the field of antimalarial drug research and development. Its mission is to reduce the burden of malaria in disease-endemic countries by discovering, developing and facilitating delivery of new, effective and affordable antimalarial drugs.

Since its foundation in 1999, MMV and partners have built the largest portfolio of antimalarial R&D and access projects ever assembled, and brought forward seven new medicines that are already saving lives. MMV's success is based on its extensive partnership network of around 160 active pharmaceutical, academic and endemic-country partners in more than 55 countries.

MMV's vision is a world in which innovative medicines will cure and protect the vulnerable and under-served populations at risk of malaria, and help to ultimately

eradicate this terrible disease.

Cautionary statement regarding forward-looking statements

GSK cautions investors that any forward-looking statements or projections made by GSK, including those made in this announcement, are subject to risks and uncertainties that may cause actual results to differ materially from those projected. Such factors include, but are not limited to, those described under Item 3.D 'Principal risks and uncertainties' in the company's Annual Report on Form 20-F for 2017.



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