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Kozenis (tafenoquine) approved by the Australian Therapeutic Goods Administration for the radical cure of *P. vivax* malaria

Approval marks a major step in global eradication efforts and will support registrations in malaria-endemic countries

GSK and Medicines for Malaria Venture (MMV) today announced that the Australian Therapeutic Goods Administration (TGA) has approved single-dose *Kozenis* (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 the acute *P. vivax* infection.

Anne Belcher, VP and General Manager GSK Australia, said: "We are delighted to have achieved approval for single-dose tafenoquine. In addition to providing a treatment option for *P. vivax* infected patients in Australia, the TGA approval of *Kozenis* will support regulatory submissions in *P. vivax*-endemic countries where there is significant unmet medical need for simple and effective therapies. Working with our partner, Medicines for Malaria Venture, our intent is to drive patient access in these countries by providing tafenoquine at an affordable price as part of global efforts to eradicate malaria."

David Reddy, Chief Executive Officer of MMV said: "MMV wholeheartedly welcomes TGA's approval of tafenoquine for the treatment of relapsing malaria. Together with the recent approval by the US FDA, Australia's endorsement serves to underscore the importance and benefit of this important medicine to people debilitated by *P. vivax* malaria. Having worked closely with our partner GSK to get tafenoquine this far, we will lose no time in working with the regulatory authorities and National Malaria Control Programs in *P. vivax*-endemic countries to jointly get this transformative new single-dose cure to patients in need."

The approval was based on efficacy and safety data from a comprehensive global clinical development programme for *P. vivax* radical cure which supported an overall positive benefit–risk profile for the proposed indication. 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.

The decision by the TGA follows approval of tafenoquine (*Krintafel*) by the US Food and Drug Administration (FDA) on 20 July 2018. Approvals by the FDA and TGA will be informative to regulatory agencies in malaria-endemic countries for their own reviews. In these countries, tafenoquine will be provided at an affordable price to maximise access to those who need it most. Following TGA approval, GSK is planning for supply to Australia in 2019.

About *Kozenis* (tafenoquine)

Kozenis 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

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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

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.¹ It is estimated that 38% of malaria cases in Australia are caused by *P. vivax*.² 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.³

The *Plasmodium* parasite is a complex organism with a lifecycle spanning both humans and mosquitoes.⁴ 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 antimalarial treatments active against the blood-stage parasite.

The use of a medicine that targets the dormant liver forms of the parasite, co-administered with currently available antimalarials such as chloroquine or artemisinin-based combination therapies (ACTs) is known as radical cure. Up to recently, the 8-aminoquinoline, primaquine, was the only approved medicine to target the dormant liver stage to prevent relapse.⁵ However, primaquine's 14-day treatment regimen is often associated with poor compliance.^{6,7,8}

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

Tafenoquine is contraindicated in the following:

- G6PD deficiency
- Pregnancy
- Breastfeeding an infant who is G6PD deficient or if the G6PD status of the infant is unknown
- Patients with known hypersensitivity to tafenoquine, other 8-aminoquinolines, or any component of the formulation

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Haemolytic anaemia and G6PD deficiency

Due to the risk of haemolytic anaemia in patients with G6PD deficiency, G6PD testing must be performed before prescribing tafenoquine. Withhold tafenoquine from patients with G6PD enzyme levels <70% of normal. Monitor patients for clinical signs or symptoms of haemolytic anaemia. Advise patients to seek medical attention if signs of haemolytic anaemia occur.

Methaemoglobinaemia

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Asymptomatic elevations in methaemoglobin were observed in clinical studies (see section 4.8 Adverse effects). If signs or symptoms of methaemoglobinaemia occur, appropriate therapy should be instituted. Caution is advised in patients with nicotinamide adenine dinucleotide (NADH)-dependent methaemoglobin reductase deficiency.

Psychiatric Effects

Mild to moderate, self-limiting psychiatric adverse reactions (e.g. anxiety, abnormal dreams) have been reported in clinical trials of tafenoquine. While there were no reports of serious psychiatric adverse reactions in clinical trials following a single 300 mg dose, cases of depression and psychosis have occurred following higher single doses (350 to 600 mg) of tafenoquine, mostly in subjects with a previous history of psychiatric disorders. Serious psychiatric disorders such as psychosis and depression have been associated with some quinoline anti-malarials. Caution is advised when administering tafenoquine to patients with a current or past history of serious psychiatric disorders. Individual patient risk-benefit should be assessed. Due to the long half-life of tafenoquine (15 days), psychiatric effects and hypersensitivity reactions may be delayed in onset and/or duration.

INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Tafenoquine is an inhibitor of human transporters organic cation transporter 2 (OCT2) and multidrug and toxin extrusion transporter (MATE) in vitro, potentially resulting in increased exposure to their substrates (e.g., dofetilide). There is a small risk of lactic acidosis due to increased metformin exposure secondary to blockade of these transporters. Therefore, use with caution with metformin. Drugs with a narrow therapeutic index that are substrates of the renal transporters OCT2 and MATE should not be co-administered (e.g. phenformin, buformin, dofetilide, procainamide, and pilsicainide).

ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Common adverse reactions (occurring in >1% of patients treated with tafenoquine) included blood creatinine increased, dizziness, elevated methaemoglobin, haemoglobin decreased, headache, insomnia, nausea, and vomiting

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at <https://www.tga.gov.au/reporting-problems>.

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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 underserved populations at risk of malaria, and help to ultimately eradicate this terrible disease.

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**PBS information - This product is not listed on the
Pharmaceutical Benefits Scheme (PBS)**

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