IVERMECTIN P02CF01

(1) Does the application adequately address the issue of the public health need for the medicine?

Yes

This application is in support of the inclusion in the core list, adults and children, of ivermectin i) for use against *Strongyloides stercoralis* infection (an infection for which, at the moment, there is no drug indication in the EML); and ii) co-administered with albendazole for use against soil transmitted helminthiasis (i.e. *Ascaris lumbricoides* (roundworm), *Trichuris trichiura* (whipworm), and *Ancylostoma duodenale* and *Necator americanus* (hookworms). Hundreds of millions of people around the world are estimated to be infected by *Strongyloides stercoralis*. Strongyloidiasis is a soil-transmitted helminthiasis that can persist indefinitely in the infected host if not adequately treated, because of a peculiar autoinfective cycle. Chronic infection is characterized by non-specific symptoms of variable intensity (asymptomatic infection can also occur), mainly relating to the gastrointestinal tract. However, strongyloidiasis is particularly relevant because it can cause a severe syndrome in immunocompromised patients, associated with high mortality. Therefore, all infected patients, irrespective of presence of symptoms, should receive a treatment that can guarantee a cure.

(2) Have all important studies that you are aware of been included in the application?

Yes

(3) Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed use?

Yes

Ivermectin is highly efficacious for the treatment of strongyloidiasis and is comparatively more efficacious than albendazole, mebendazole...
and thiabendazole. There is evidence of increased efficacy in children under the age of five. Ivermectin is becoming the drug of choice in many countries due to its more favorable side effects compared with albendazole. Ivermectin co-administered with albendazole is highly efficacious for the treatment of *T. trichiura* and is comparatively more efficacious than albendazole alone. Efficacy of ivermectin and albendazole against *A. lumbricoides* and hookworms are comparable and in some cases more efficacious than albendazole alone.

(4) Is there evidence of efficacy in diverse settings and/or populations?

No

(5) Has the application adequately considered the safety and adverse effects of the medicine? Are there any adverse effects of concern, or that may require special monitoring?

Yes

Adverse events associated with ivermectin treatment are primarily minor and transient. Ivermectin should not be administered to children less than 90 cm or weighing less than 15 kg, pregnant women, lactating women in the first week after birth, severely ill individuals. Severe, sometimes fatal, adverse reactions can occur in people who take ivermectin for the treatment of onchocerciasis and who have a high intensity of *Loa loa* infection. However, the geographical distribution of Loa-Loa is well known and those areas should be excluded from large scale programs.

ADDITIONAL CONSIDERATIONS

(6) Are there special requirements or training needed for the safe, effective and/or appropriate use of the medicine?

Yes

It is very important to assess the level of loiasis endemicity in a community before initiating mass treatment.
Are there any issues regarding the registration of the medicine by regulatory authorities? (e.g., recent registration, new indications, off-label use)

Yes

Not yet approved by EMA but registered in Japan, Australia and USA

Is the medicine recommended for use in a current WHO GRC-approved Guideline (i.e., post 2008)?

No

However a recent update to the 2006 guidelines took place during a WHO Guideline Development Group (GDG) meeting in April 2016. The guidelines will be reviewed at a WHO Guideline Review Committee meeting in January 2017, and released shortly after. The guidelines focus predominantly on the use of single-dose albendazole and mebendazole treatment. However, based on discussions during the GDG meeting, it was clear that we need alternate treatment strategies for improving efficacy against *T. trichiura* and for reducing the risk of insurgence of drug resistance. The inclusion of ivermectin, to be co-administered with albendazole, could appropriately address this gap.

Please comment briefly on issues regarding cost and affordability of this medicine.

The cost for a package of 100 tablets of 3 mg ivermectin is $2.96 (USD 2013). There will be insufficient donated product (“donation program from Merck”) to be used to treat STH. There are no current prequalified products for ivermectin listed

Any additional comments?

None

Please summarise the action you propose the Expert Committee takes.
I propose the inclusion of IVERMECTIN FOR USE IN STRONGYLOIDIASIS AND SOIL-TRANSMITTED HELMINTHIASIS in the 20\textsuperscript{th} WHO Model List of Essential Medicines as well as in the children list.

The proposed formulation of ivermectin is a tablet (scored) in 3 mg doses.