Emerging Drug List
Ruboxistaurin Mesylate Hydrate

Canadian Agency for Drugs and Technologies in Health

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Generic (Trade Name): Ruboxistaurin mesylate hydrate (Arxxant™)

Manufacturer: Eli Lilly and Company

Indication: Ruboxistaurin is being studied for the treatment of diabetic retinopathy.

Current Regulatory Status: A new drug application for ruboxistaurin was submitted to the US Food and Drug Administration in March 2006.[1]

Description: Ruboxistaurin is a specific inhibitor of protein kinase C (PKC)-beta, which is present at high levels in the retina, and is thought to play a critical role in the pathogenesis of diabetic retinopathy (DR).[2] DR is characterized by abnormalities in the microvasculature of the retina, such as vascular leakage and neovascularization.[3,4] Chronic hyperglycemia has been shown to contribute to the pathogenesis of DR, although the mechanism is unknown.[3,4] Several metabolic pathways have been implicated, including increased activation of the PKC pathway[3,4] By inhibiting PKC-beta, ruboxistaurin may prevent the development of DR.[3,4]

Current Treatment: Intensive glycemic control has been shown to reduce the incidence and progression of DR.[5,6] Once vision-threatening DR has been detected, the most common treatment is laser photocoagulation.[4] Pan retinal (scatter) photocoagulation is used to treat proliferative DR. Focal or grid photocoagulation may be used in cases where retinal vessels have become permeable to proteins that have diffused into the retina, causing swelling and macular edema. In some cases, vitrectomy, a surgical procedure to remove clouded fluid from inside the eye, is indicated to prevent blindness or severe visual loss.[7]

Cost: No information about cost is available for ruboxistaurin. The costs for treating DR include those for visits to the physician, ophthalmology consultations, and the use of diagnostic and therapeutic eye procedures. If photocoagulation is used, the cost of treating DR is $379 for proliferative retinopathy, and $423 for macular edema (mean event costs).[8] The event cost increases to $495 if both conditions are present in one patient.[8] In addition, diabetes-related blindness and visual impairment may impose an economic toll, in terms of a patient's lost wages and productivity.[8]

Evidence: The effect of ruboxistaurin in patients with DR has been studied in two phase III randomized controlled trials (RCTs). One trial, the PKC-Diabetic Retinopathy study, was a multicentre, double-blind RCT evaluating ruboxistaurin in 252 patients with moderately severe to very severe nonproliferative DR.[9] Patients received oral ruboxistaurin (8 mg/day, 16 mg/day, or 32 mg/day) or placebo for 36 to 46 months. Efficacy endpoints included progression of DR, moderate visual loss (MVL), and sustained moderate visual loss (SMVL). Ruboxistaurin

did not have a significant effect on the progression of DR compared with placebo. Treatment with 32 mg ruboxistaurin was associated with a delayed occurrence of MVL (log rank p=0.038). In a group of patients with definite diabetic macular edema (DME) at baseline, SMVL occurred less frequently in the 32 mg ruboxistaurin group compared with the placebo group (10% versus 25%; p=0.017). These differences were not observed at lower doses.

In the PKC-Diabetic Macular Edema study (PKC-DME study), ruboxistaurin was evaluated in 686 patients with mild to moderate nonproliferative DR.[10,11] Patients were randomized to receive ruboxistaurin (4 mg/day, 16 mg/day, or 32 mg/day) or placebo for a minimum of 30 months. The primary endpoint of the trial was progression of DME to involve or imminently threaten the centre of the macula, or the application of photocoagulation. Initial results from the trial showed that ruboxistaurin was not associated with a significant reduction in this composite endpoint. When the photocoagulation outcomes were excluded, a significant reduction in the number of patients with progression of DME was observed in the 32 mg ruboxistaurin group compared with the placebo group (37% versus 48%; p=0.046).[10] In an analysis that excluded patients with very poor glycemic control at baseline, 31% of patients had DME progression in the ruboxistaurin group, compared with 45% in the placebo group (p=0.019).[10] The final results of the PKC-DME study are yet to be published.

Adverse Effects:

Harms data from the two trials were pooled (n=938).[9] Of those treatment-related adverse events with an incidence of ≥1%, 14 showed a statistically significant difference between treatment groups. These included coronary artery disease, diarrhea, and asthma. The number of serious adverse events was not statistically different between the treatment groups.

Commentary:

Approximately 40% of Americans with diabetes have DR.[12] In Canada, more than two million individuals have diabetes, and this number is expected to increase to three million by 2010.[13] Because patients with diabetes are living longer, more individuals are at risk of developing DR.[14] Left untreated, DR can lead to vision loss and blindness. DR is the leading cause of blindness in the working-age population, and is responsible for 12% of the new cases of blindness per annum.[15] Although effective, both laser photocoagulation therapy and vitrectomy are invasive interventions that can only be used to treat the disease in the late stages. Both techniques carry a risk of additional vision loss. Ruboxistaurin could be a less invasive treatment option, and it would be used to treat the disease in the earlier stages to prevent or delay the onset of vision loss.

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