Is Lee’s 2008 risk:benefit conclusion for benzbromarone hepatotoxicity still relevant today?

Benzbromarone was approved for use in Europe and Asia, but was not licensed in the United States because of concerns over hepatotoxicity. Benzbromarone was withdrawn by its sponsor in 2003 because of continuing concerns over hepatotoxicity.1–5 The mechanism of benzbromarone hepatotoxicity is believed to be due to its hepatic metabolism by CYP 2C9 and possible effects of the parent compound or its metabolites on mitochondrial function.

While reported cases of hepatotoxicity are sparse,1–5 a review by Lee et al (“Lee”) reports 11 other cases resulting in 9 deaths.6 The authors estimated the incidence of hepatotoxicity from benzbromarone to be around 1 in 17,000 and concluded that adverse events are relatively infrequent but potentially severe.

Lee concluded that the “benefit-risk assessment based on total exposure to the drug does not support the decision by the drug company to withdraw benzbromarone from the market given the paucity of alternative options.”6

PHARMAC’s Pharmacology and Therapeutics Advisory Committee (PTAC) considered an application for reimbursement of benzbromarone in 2010 and again in 2011 wherein they essentially agreed with the conclusions drawn by Lee. PHARMAC subsequently funded benzbromarone as an unregistered medicine from 1 July 2013. However, since PTAC’s recommendation there have been two important developments that call into question the current applicability of the risk:benefit analysis by Lee.

First, Lee’s conclusion was premised on there being a “paucity of alternative options”. Since Lee’s analysis febuxostat has become generally available around the World including UK, USA and in New Zealand from March 2013. There is now available a very real alternative to benzbromarone.

Second, the Pharmaceuticals and Medical Devices Agency (PMDA) from Japan, where benzbromarone has remained on the market, reported in November 2011 that despite warnings in the package insert, Dear Doctor letter warnings, and an advisory for regular LFTs, around 20 cases a year of “serious hepatic disorder” are reported with benzbromarone.7

The contemporary applicability of Lee’s conclusion in 2008 must be seriously called into question and an urgent review of the risk:benefit for benzbromarone undertaken. Although this would ordinarily be the responsibility of Medicines Adverse Reactions Committee (MARC), we are informed by Medsafe that it has no such regulatory powers over benzbromarone due to its unregistered status.

We are left with the haunting question of who is responsible for updating medicine safety when the regulator is powerless?
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**Competing interests:** New Zealand supplier of febuxostat.

**References:**

5. Haring B et al., Benz bromarone: A double-edged sword that cuts the liver? Eur J Gastroenterol Hepatol. 2013 Jan;25(1):119-21. (77 year old woman developed jaundice, fatigue and nausea 4 months after switching from allopurinol to benz bromarone due to hypersensitivity with downhill progression despite best efforts and died 53 days later).