

## Benzbromarone withdrawn from the European market: Another case of "absence of evidence is evidence of absence"?

Sirs,

Gout, already described by Hippocrates, has been one of the most curable disorders of modern rheumatology for years due to potent urate lowering therapeutic options. While in only a minority of our rheumatologically pre-selected patients xanthine oxidase inhibition by allopurinol lowered serum uric acid (SUA) levels sufficiently to prevent gouty attacks, in non-preselected gouty patients 300 mg allopurinol normalized SUA in 85% of patients (1, 2). In most cases gout is caused by inadequate, low uric acid excretion, explaining why uricosuric agents have long been considered the first choice treatment option by many but not all rheumatologists. Not only for reasons of pathophysiology in low excretor gout, but also due to potential hazards associated with the combination of azathioprine and allopurinol, which is clearly not the case when azathioprine is combined with benzbromarone.

Exactly how low should SUA levels become in order to deplete crystal stores and prevent attacks (3)? Li-Yu *et al.* have demonstrated that aiming at SUA levels < 0.36 mM may be suboptimal (3), but it is often clinically quite adequate to aim for levels of < 0.30 mM (2). This is comprehensible when studying the chemico-physical data (4). Perez-Ruiz *et al.* demonstrated in a head-to-head comparison that allopurinol is inferior to benzbromarone in reducing SUA (5). We found similar results in 85 gout patients: SUA levels < 0.30 mM are reached in 79% by benzbromarone monotherapy (100 mg daily), and in just 10% by allopurinol monotherapy (200 mg daily). This may explain why in Europe we all were quite happy with benzbromarone.

Therefore, why was there a sudden withdrawal of this compound from the European market in 2003? Did Sanofi-Synthelabo fear a lawsuit? Or was it due to the lack of commercial profitability?

A PubMed search for fatal outcomes with the main urate lowering treatment options provides us no significant clue (Table I). There are only sporadic reports of hepatic failure secondary to benzbromarone (6); the incidence was about 2 cases per 400 million Europeans, i.e. 1:100,000 benzbromarone prescriptions. Was this the argument for Sanofi-Synthelabo, which owns the patent and therefore has a monopolist position with regard to benzbromarone, to stop its production? In April 2003 the Netherlands Medicine Evaluation Board (MEB) agreed with the request by Sanofi to stop benzbromarone production for the Dutch market, which took place simultaneously in most European countries. In most European

**Table I.** A PubMed search (excluding Japanese papers) for fatal outcome using 4 treatment options: allopurinol, probenecid, benzbromarone, and sulfinpyrazone.

Fatal/death	No. of papers	No. of cases	Year of publication
Allopurinol <sup>a</sup>	14	14	1970-2001
Probenecid <sup>b</sup>	1	1	1957
Benzbromarone <sup>c</sup>	2	3	1995-2000
Sulfinpyrazone <sup>d</sup>	0	0	1976-2004

European registration status: <sup>a</sup>Fully registered for gout.

<sup>b</sup>Registration previously held by MSD, withdrawn due to lack of profitability in the past, but often applicable on special request.

<sup>c</sup>Up to 2003, registration in all of Europe, England excluded. From January 2004 registered only in Spain, and in The Netherlands for strict indications only, i.e. for allopurinol intolerant/allergic gouty patients. <sup>d</sup>Registration held by Novartis (Anturane®) only in England and Ireland, withdrawn from the market in Spain, not registered in other European countries and therefore generally not applicable.

countries neither the uricosuric probenecid nor sulfinpyrazone have been registered for the treatment of gout. An alternative regimen was suggested despite the aforementioned reports in the literature (5): allopurinol, on strict indication combined with probenecid. A peculiar advice since probenecid has not been registered at all in The Netherlands for the treatment of gout.

In clinical practice general practitioners and rheumatologists were left stunned. A lobby by general practitioners and the Dutch Association of Rheumatology has therefore recently brought our MEB to request the pharmaceutical company to restart benzbromarone production for the Dutch market, and their request remarkably was granted. From January 2004 Dutch gouty patients again have the opportunity to be treated with the potent uricosuric benzbromarone. Interestingly, the registration of benzbromarone only has been granted for cases with allopurinol intolerance. But generally allopurinol is well tolerated; only in about 2% of cases, in particular elderly individuals with renal dysfunction, is a pruritic maculopapular eruption with or without fever and facial/tongue swelling encountered. Only for this small group of gout patients will benzbromarone be an option once again according to Sanofi and the Netherlands MEB.

Why did our European MEBs agree so easily with the pharmaceutical company's request to stop a generally safe treatment option? Medico-legal and commercial reasons must cross our minds. One could speculate about a novel class of benzbromarone derivatives on the horizon (7), as the commercial profitability of benzbromarone may be low. If the pharmaceutical company is driven to prevent potential claims in the future, then other companies might follow a similar procedure. This case could serve as a warning for our European MEBs not to bury older drugs before breeding new baby drugs.

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## Polymyositis associated with HIV infection during immune restoration induced by highly active anti-retroviral therapy

Sirs,

Polymyositis associated with human immunodeficiency virus (HIV) infection was first described in 1983, and many reports in the past several years have confirmed this pathologic association (1, 2). It usually occurs early in the course of HIV disease, but may presents at all stages, has a relatively good prognosis, responds well to immunosuppressive therapy, and has little evidence of adverse outcome on the HIV infection (3, 4). However, it is often difficult to distinguish HIV-related polymyositis from myo-