Battle over Fosamax bursts into court

A New York judge has revealed internal Merck discussions about a possible link between its widely prescribed drug and dead jaw syndrome, finds

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A spring evening back in May 1996 was something of a high point for the folks at the global drug company Merck. Three American television networks ran news stories celebrating Merck's latest blockbuster to fight brittle bones—Fosamax, whose generic name is alendronic acid (or alendronate sodium).

Reporters told tens of millions of viewers that the recently approved drug could cut the risk of a hip fracture in half, and one report described this as "almost miraculous."[1] The televangelism proved both efficacious and prophetic: in the years since, the drug became one of Merck's top selling products, with sales in excess of $3bn (£1.8bn; €2.1bn) annually for several years during the past decade.

Fosamax on trial for the first time

Next week, in a district court room not too far away from those same network studios, Merck is scheduled to face the first trial involving its golden goose alendronic acid before Judge John Keenan of the southern district of New York. Approximately 800 cases have been consolidated into a mass action, with plaintiffs claiming that alendronic acid caused them to suffer a rare condition called osteonecrosis of the jaw, or dead jaw syndrome, and Merck failed to properly warn them of this devastating complication. A company spokesperson has told the *BMJ* that Merck is vigorously defending the action, arguing there is no proof of a causal link between the drug and the jaw condition, and that timely and appropriate information about its drug has been provided to consumers and to the medical, scientific, and regulatory communities.

One of the first cases scheduled to be tried involves Shirley Boles, a woman from Florida in her 70s who was first prescribed alendronic acid in 1997 and continued taking it for almost a decade. According to documents filed with the court, after the extraction of two teeth in 2002, Ms Boles had to undergo major oral surgery, and she has developed persistent infections and exposed bone in her jaw that have not healed for many years.

Ms Boles's symptoms are consistent with what is now widely accepted as the signs of osteonecrosis of the jaw, and Merck has received more than 1000 reports of people claiming to have the condition. What is in dispute is whether Merck's drug is the cause. The company's outside counsel, Paul Strain, says Shirley Boles has a history of smoking and medical problems that cause people to develop jaw problems. "The evidence will show that Ms Boles would have experienced dental and jaw-related problems whether she took Fosamax or not."

Does Fosamax cause dead jaw syndrome?

In 2004, following a growing numbers of reports that associated dead jaw and intravenous bisphosphonates used for cancer treatment and the oral versions, including alendronic acid, taken for osteoporosis, the United States Food and Drug Administration released a safety review which found that there may be a "class effect" and urged changes to product labels.[2] In 2005 Merck added new wording to its Fosamax label, though the plaintiff's lawyers say the wording was inadequate. Whether the association is a causal one has been a source of increasing controversy within the medical literature in recent years,[3] made more complicated by the closeness of many leading doctors to the drug manufacturers.

A 2007 task force of the American Society for Bone and Mineral Research concluded that although the association with the condition is "consistent with a role" for bisphosphonates, they have "not been proven to be causal."[4] Three quarters of the authors from the task force disclosed financial ties to multiple drug companies, including Merck. A 2008 Canadian consensus guideline from oral surgeons concluded "a direct causal link has not been established."[5] This time more than a third of the authors declared conflicts of interest: the lead author has worked as a consultant to six drug companies including Merck, and one author declared links to more than 12 companies.

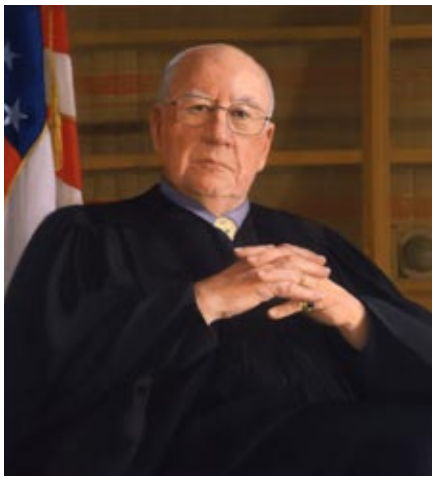
Partly on the basis of these guidelines, Merck has argued strongly in pretrial filings that a causal link is not proved and that expert testimony to this effect from the plaintiff's side should be disallowed at trial. However, in a ruling that ran to over 100 pages, released late in July, Judge John Keenan ruled that testimony on causation from key experts would be allowed, as long as it was not presented as scientifically certain. "Their theory on the mechanism of causation is generally accepted as biologically plausible," the judge wrote.[6] He also ruled it was not the court's role to determine causation in this case, but the jury's.

Discussing the plausibility of a link between the widely prescribed bone drug and the rare dead jaw syndrome, Judge Keenan cited other expert bodies that support a possible causal link, including the American Dental Association.[7]

Importantly, the judge also referred three times to internal Merck documents and comments by one of Merck's own scientists, a Dr Kimmel. At one point in the judge's ruling, he revealed details of internal Merck emails:

"In internal emails in 2005, Dr Kimmel wrote that the reduction of bone remodelling is likely to reduce the jaw's natural ability to heal, and that placing too much of a healing demand on them in patients treated with bisphosphonates can lead to the death of jaw bone."[6]

A spokesperson for Merck told the *BMJ* that Dr Kimmel had examined various theories about the aetiology of osteonecrosis of the jaw, and that "emails from Dr Kimmel can easily be taken out of context in a litigation setting." In addition, the company's general counsel, Bruce N Kuhlik, said Merck had acted responsibly in researching and monitoring Forsamax, conducting clinical trials involving more than 28 000 people.



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Importantly, the judge's ruling also carried some good news for Merck: the judge restricted the nature of the evidence that could be offered in court by several of the plaintiff's nominated experts.

How widespread is dead jaw syndrome?

Alongside the controversy about causality, several surveys have emerged offering tentative suggestions of the prevalence of this rare but distressing problem—which occurs mainly in older women taking bisphosphonates who have undergone dental work. A postal survey from Australia suggested a rate between 1 in 2200 and 1 in 8500, increasing to a rate of approximately 1 in 300-1100 cases if teeth extractions were carried out.[8] A survey conducted by Kaiser Permanente in the United States, currently in press, but cited in court, found osteonecrosis of the jaw occurred in roughly 1 in 1000 respondents with exposure to oral bisphosphonates.[9]

Having just revised its prevalence estimates upwards, Merck today estimates that the rate is between 1.6 per 100 000 and 3.84 per 100 000 patient-treatment years, and in filed documents it argues the surveys don't prove causation as they have no control groups.

However, in the discussion of prevalence in his court ruling, Judge Keenan cited experts who believed the background rate of this condition was "essentially zero," except for cases associated with radiation and a few serious diseases. "The prevalence rates found among persons with osteoporosis offer circumstantial support for the view that oral bisphosphonates increase the risk," he wrote.[6]

A healthy risk-benefit ratio?

Leaving aside the potential risk of dead jaw syndrome, alendronic acid carries well established gastrointestinal side effects, with its label stating "Some patients may develop severe digestive reactions including irritation, inflammation, or ulceration of the esophagus."[10] On the benefit side of the equation, while media and marketing materials often enthusiastically frame risk reductions in relative terms, absolute reductions are much smaller. As a Cochrane review points out, while trials suggest that alendronic acid can reduce hip fractures by one half, in absolute terms it is a reduction from 2% to 1%.[11] Moreover, because this drug is approved to treat and prevent osteoporosis—a condition which is basically a risk factor for future fracture—it has been marketed to many relatively healthy women, for whom the risks become ever more important.

At it turns out, Shirley Boles, the Florida woman who developed osteonecrosis of the jaw, did not even meet the standard definition for having osteoporosis when she was first prescribed the drug. Rather she simply had what is described as osteopenia, essentially being at risk of being at risk of a future fracture. According to filed documents, a gynaecologist prescribed her the drug because a Merck salesperson told him that for osteopenic patients like Ms Boles, Fosamax had proved efficacy—a fact also in dispute in this case.

According to the lawyers representing those who have suffered with osteonecrosis of the jaw, Merck's marketing deliberately targeted many people for whom the drug's benefits would be modest or negligible. A document filed by the lead lawyer for the plaintiffs, Tim O'Brien, claims that "in order to reach its sales targets and projected profits for Fosamax, Merck recognized it had to expand the market for Fosamax beyond osteoporotic women" by "shifting the treatment threshold."[12] The document goes on to provide evidence for this claim by referring to several of Merck's internal marketing and business plan presentations. However the next page and a half of the document, where details of the internal marketing plans are discussed, have been redacted under order of the court—blanked out by thick black ink.

Hopefully, once the trial begins in the New York court room, and the jury weighs the evidence from both sides, a lot of that black ink will be removed, the details of influential marketing strategies will be made public, and a lot more light will be shone on the true risks and benefits of a class of drugs that has been prescribed more than 225 million times.

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