

Translated from *Rev Prescrire* January 2011; 31 (327): 22-23

## Nimesulide: patients still exposed to a risk of severe hepatitis

### Abstract

● **Nimesulide**, a nonsteroidal anti-inflammatory drug (NSAID) that has been marketed in France since 1998, is neither more effective nor better tolerated than other NSAIDs.

● Many reports and reviews published by drug regulatory agencies in Spain, Ireland and Italy have warned of the hepatic adverse effects of *nimesulide*. In early 2008, 17 cases of *nimesulide*-induced liver damage requiring transplantation had been reported in Ireland, Italy, Spain, Finland and France.

● An Italian retrospective study conducted between 1997 and 2001, including about 400 000 patients exposed to NSAIDs, showed that the risk of severe liver damage was twice as high with *nimesulide* as with other NSAIDs.

● The European pharmacovigilance database shows that *nimesulide* is associated with more cases of severe liver damage than other NSAIDs, as well as more cases of liver damage than with cox-2 inhibitors.

● Young women are particularly at risk. In the vast majority of cases of liver damage, the dose of *nimesulide* used was that recommended in the summary of product characteristics (SPC). Liver damage occurred within 15 days after taking the first dose of *nimesulide* in one-third of cases.

● It is unacceptable that *nimesulide* still remains on the market in France and other countries: reports of severe liver damage continue to accumulate, and many other therapeutic options are available.

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**N***imesulide*, a nonsteroidal anti-inflammatory drug (NSAID), has been on the French market since 1998 (1). It is neither more effective nor better tolerated than many other NSAIDs, and has been shown to cause potentially life-threatening liver damage (1-5).

What is known concerning the hepatic adverse effects of *nimesulide* in early 2011?

**An increasing number of reports of liver damage.** Soon after it was first marketed, cases of hepatitis were attributed to *nimesulide*, including a case of fulminant hepatitis (6). The number of reports increased in all countries where *nimesulide* was sold (1,3,4).

In 2010, at *Prescrire*'s request, the European Committee for Human Medicinal Products (CHMP) released a report on the hepatic adverse effects of *nimesulide* (a)(7).

Between 1985 and 29 February 2008, 574 cases of hepatic disorders associated with *nimesulide* were reported, including 17 cases necessitating liver transplantation (6 in Italy, 6 in Ireland, 2 in Finland, 2 in France and 1 in Spain) (b)(7-10).

**Twice the risk of severe liver damage as with other NSAIDs.** A retrospective study of 397 537 Italians using NSAIDs between 1997 and 2001 showed that the risk of severe liver damage was twice as high in patients treated with *nimesulide* as in those using other NSAIDs: the estimated relative risk adjusted for age and gender was 1.9 (95% confidence interval (CI) 1.1 to 3.8). The difference was statistically significant (c)(11).

A case-control study conducted between 2001 and 2004, but not published until 2010, showed a statistically significant 2.5-fold higher risk of hospitalisation for acute liver damage with *nimesulide* than with other NSAIDs, with the exception of *celecoxib*, *rofecoxib*, *diclofenac* and *ibuprofen* (estimated adjusted relative risk 2.63, 95% CI 1.8 to 3.8) (12).

**Severe liver damage at standard doses, especially in young women.** In 2007, the Italian Medicines Agency released Italian pharmacovigilance data showing that hepatic adverse effects represented 13.8% of reports implicating *nimesulide*, compared to only 1.4% for *ibuprofen* and 2.8% for *diclofenac* (3).

The CHMP report published in 2008 included similar findings. Among the 574 reports implicating *nimesulide* recorded in the European EudraVigilance pharmacovigilance database, the proportion of hepatic disorders (cholestasis, jaundice, liver failure, and hepatitis) was higher than with cox-2 inhibitors. The report also emphasised that deaths from liver damage were more frequent with *nimesulide* (7). The CHMP concluded that *nimesulide* had an unfavourable risk-benefit balance.

67% cases of liver damage occurred in women and 39% in patients aged between 12 and 55 years (7,13). In 78% of cases, the daily dose taken was that recommended in the summary of product characteristics (SPC) (14).

**During the first 15 days of treatment in one-third of cases.** In these 574 reports implicating *nimesulide*, onset of adverse effects occurred within 15 days in 31% of cases, from 16 to 29 days in 14% of cases, and after more than 30 days in 37% of cases; time to onset was not known in 18% of cases (8).

As expected, even though the maximum duration of *nimesulide* prescription has been limited to 15 days since September 2007, cases of severe hepatitis continue to occur (3,7,13).

**Unknown mechanism.** The precise mechanism underlying the hepato- ►►

a- Many sections of this document were blacked out, especially numerical data (ref 7).

b- *Nimesulide* was withdrawn from the market in Finland and Spain in 2002, and is no longer available in Argentina, Belgium, Ireland and Singapore (ref 19).

c- Fourteen cases of severe liver damage were reported among patients treated with *nimesulide*, representing a rate of 29 cases per 100 000 patient-years, versus 15.6 cases per 100 000 with other NSAIDs (ref 11).

► toxicity of *nimesulide* is unclear (15). A hypersensitivity reaction has been suggested (13). In addition, the presence of a nitroaromatic nucleus means that *nimesulide* is chemically similar to *nitrofurantoin* and *tolcapone*, both of which are toxic to the liver (15-18).

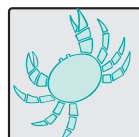
**In practice: use another NSAID.** It is unacceptable to allow *nimesulide* to remain on the market in 2011: reports of severe liver damage continue to accumulate and many other valid therapeutic options exist. If *paracetamol* is inadequately ineffective, oral *ibuprofen* is the NSAID with the best risk-benefit balance when used at standard doses.

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#### Literature search

Our literature search was based on continuous prospective follow-up at the Prescrire library, contents listings of the main international journals, Current Contents-Clinical Medicine, member bulletins of the International Society of Drug Bulletins (ISDB), and systematic consultation of clinical pharmacology textbooks (Martindale The Complete Drug Reference, Stockley's Drug Interactions). We also accessed Medline (2007-August week 5, 2010), Embase/Excerpta Medica Drugs and Pharmacology (2007-2010 3<sup>rd</sup> quarter), Reactions (2007-September 2010) and The Cochrane Library (Central, DARE, HTA, Nhsed; 2010 issue 6; and CDSR, 2010 issue 3).

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## Azathioprine and mercaptopurine: lymphoma

● **Prospective follow-up for a median of 35 months of a French cohort of 19 486 patients with inflammatory bowel disease showed a nearly 4-fold increase in the risk of lymphoma in patients exposed to azathioprine or mercaptopurine (relative risk 3.75; 95% confidence interval 1.59 to 8.85).**

● **This risk should be taken into account when weighing the likely benefits of these drugs in treatment of patients with severe chronic inflammatory bowel disease no longer responding to first-line treatment.**

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**A**zathioprine and its metabolite 6-mercaptopurine are immunosuppressant drugs used to maintain remission in patients with chronic inflammatory bowel disease (ulcerative colitis or Crohn's disease) (1-3).

Immunosuppressants carry an increased risk of infection and cancer in transplant patients (especially lymphoma) (1).

Prospective follow-up of a French cohort of 19 486 inflammatory bowel disease patients for a median of 35 months has provided informative data on the risk of lymphoma associated with *azathioprine* and *mercaptopurine* (4).

**Risk of lymphoma about 4 times higher.** At enrolment in this study, 5867 patients were taking *azathioprine* or *mercaptopurine*, 2809 patients had previously been exposed to these drugs, and 10 810 patients had never taken either drug.

During follow-up, 22 patients developed non-Hodgkin's lymphoma and 1 patient developed Hodgkin's disease. Fifteen of these patients were taking *aza-*

*thioprine* or *mercaptopurine* at the time of lymphoma diagnosis, 2 patients had previously taken one of these drugs, and 6 had never taken either drug. The incidence was 0.9 per 1000 among patients taking *azathioprine* or *mercaptopurine* versus 0.26 per 1000 among patients never exposed to these drugs.

The risk of developing lymphoma was about 4 times higher in patients exposed to *azathioprine* or *mercaptopurine* than in those who had never taken either drug (relative risk 3.75; 95% confidence interval 1.59 to 8.85). After adjustment for variables known to be associated with an increased risk of lymphoma (old age, male sex, longer duration of inflammatory bowel disease), the risk of developing lymphoma was increased by a factor of about 5 in patients exposed to *azathioprine* or *mercaptopurine* (relative risk 5.26; 95% confidence interval 2.20 to 12.6).

**In practice.** *Azathioprine* and *mercaptopurine*, like other immunosuppressants, increase the risk of lymphoma. This risk should be taken into account when weighing the harm-benefit balance of these drugs in patients with severe forms of chronic inflammatory bowel disease no longer responding to first-line treatment.

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