20 January 2012
EMA/73856/2012
Patient Health Protection

Assessment report for Nimesulide containing medicinal products for systemic use

Pursuant to Article 31 of Directive 2001/83/EC, as amended

International Non-proprietary Name: nimesulide

Procedure number: EMEA/H/A-31/1261

Referral under Article 31 of Directive 2001/83/EC, as amended

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Referral of the matter to the CHMP

On 19 January 2010, the European Commission triggered a referral under Article 31 of Directive 2001/83/EC for nimesulide-containing medicinal products for systemic use for a full risk-benefit assessment to be performed further to the review under Article 107 of Directive 2001/83/EC which scope focused on hepatic safety.

The Article 107 of Directive 2001/83/EC was triggered in May 2007 by the Irish Medicines Board on the basis of new safety information regarding cases of fulminant hepatic failure. In this context, the Committee for Medicinal Products for Human Use (CHMP) recommended the maintenance of the Marketing Authorisations for medicinal products containing nimesulide for systemic use, subject to amendments to the Marketing Authorisations. Including introduction of conditions and restrictions for the safe use of these products, namely limit the maximum duration of treatment to 15 days, inclusion of safety warnings and contra indications in the product information and additional safety studies to be performed, amongst other risk minimisation measures. The European Commission (EC) decision (dated 16 October 2009) included further conditions and restrictions for the safe use of these products, in particular the restriction of nimesulide in second line treatment only and the clear obligation upon the Marketing Authorisation Holders to inform health care professionals of the safety risks associated with nimesulide.

Whilst the procedure under Article 107 procedure focused on the hepatic safety, only limited information regarding the gastrointestinal toxicity profile of nimesulide vis-à-vis the gastrointestinal risk of other Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) was considered. Furthermore, given that the use of nimesulide may vary throughout the EU Member States it remained to be ascertained if the additional measures in place to minimise the identified risks are sufficient.

In view of the above, the EC triggered a full benefit-risk assessment of nimesulide-containing medicinal products for systemic use under Article 31 of Directive 2001/83/EC and requested the CHMP to give its opinion on whether the marketing authorisations for medicinal products containing nimesulide for systemic use should be maintained, varied, suspended or withdrawn.

The procedure described in Article 32 of Directive 2001/83/EC, as amended, was applicable.

2. Scientific discussion

2.1. Introduction

Nimesulide is a non-steroidal anti-inflammatory drug (NSAID) with preferred COX-2 inhibition authorised in Europe since 1985. It is indicated as second line treatment for acute pain, symptomatic treatment of painful osteoarthritis and primary dysmenorrhoea. The recommended dosage is 100 mg twice daily and the maximum duration of treatment are 15 days with the shortest duration of treatment recommended.

Background

Nimesulide was subject of an **Article 31 referral** in 2002, following national suspension of the MAs for nimesulide-containing medicinal products in Finland, and subsequently in Spain due to concerns regarding hepatotoxicity.

Further to consideration of all data available at that time, it was agreed that the incidence of hepatic reactions associated with nimesulide treatment was slightly higher when compared to other NSAIDs but that there was no increased incidence in severe hepatic reactions. It was concluded that the risk-benefit balance remained positive subject to amendments to the MAs, including introduction of restrictions for the safe use of the products.

Restriction of the maximum dose to 100 mg twice daily (with withdrawal of the MAs for the 200 mg) and restriction of the therapeutic indications to the three above mentioned were introduced. The use of nimesulide was also contraindicated in patients with known hepatic impairment, in children below 12

years of age, during third trimester of pregnancy and in breast feeding women. Moreover it was recommended discontinuation of treatment in patients who experienced symptoms compatible with hepatic injury or who developed abnormal liver function tests, and to avoid concomitant administration with known hepatotoxic drugs and alcohol abuse during treatment with nimesulide. This procedure was concluded in 2004 (EC decision on 26 April 2004) and the product information was subsequently updated.

In May 2007, following new information regarding cases of fulminant hepatic failure associated with the use of nimesulide, Ireland suspended the MAs for all systemic medicinal products containing nimesulide and a procedure under **Article 107** was started.

The reported cases showed that an association with non-A non-B non-paracetamol-related fulminant hepatic failure requiring liver transplantation in Ireland higher with nimesulide than with any other medicinal product. It was noted that the majority of hepatic disorders (56%) occurred after two weeks of treatment. Overall and further to consideration of the data submitted, it was concluded that a small increase in the absolute risk for hepatotoxic reactions, including severe hepatic reactions, associated with nimesulide could not be excluded.

In the context of this review, limited information on the gastrointestinal toxicity profile of nimesulide in comparison to other NSAIDs, and the possible consequences of switching to other NSAIDs with a higher gastrointestinal toxicity risk was considered.

In view of the uncertainties regarding the magnitude and the determinants of possible nimesulide-induced harm, the risk-benefit balance was considered positive subject to amendments to the product information and introduction of conditions to the MAs for all products containing nimesulide for systemic use:

- The treatment duration was limited to a maximum of 15 days with additional recommendation on the decision to prescribe nimesulide based on an assessment of the individual patient's overall risks. The use of nimesulide was further restricted to second line treatment and contraindications and strengthened warnings were added to limit exposure of nimesulide to those patients without risk factors for hepatic reactions.
- MAHs were asked to conduct further studies and reviews to better characterise the hepatotoxicity profile for nimesulide. Namely, a non-clinical study, a review of epidemiologic data on the hepatoxicity of nimesulide *versus* other NSAIDs and a retrospective study in transplant centers to address the relative risk in respect to other NSAIDs to cause severe hepatic reactions leading to transplants. This retrospective would lead to a prospective study to be conducted in transplant centers.

Moreover, considering that the review and assessment of data available for Article 107 focused on the hepatic safety of nimesulide and that limited information regarding the gastrointestinal toxicity profile of nimesulide was taken into account, it was agreed that a full benefit/risk assessment should be conducted in the framework an Article 31 procedure, where the risks of nimesulide should be weighted vis-à-vis the gastrointestinal risks of other NSAIDs.

The additional measures would contribute to minimising the risks associated with the use of nimesulide whilst awaiting the full risk-benefit assessment of the Article 31 referral.

Therefore, on 19 January 2010, the EC triggered a procedure under Article 31 of Directive 2001/83/EC requesting the CHMP to give its opinion on whether the marketing authorisations for medicinal products containing nimesulide for systemic use should be maintained, varied, suspended or withdrawn.

This report reflects the overall assessment of the data submitted by the MAHs in written and in oral explanations during this procedure.

Marketing status and patient exposure

Nimesulide-containing medicinal products for systemic use are currently marketed in more than 50 countries world-wide mainly in Europe and South America. In the European Union, nimesulide is authorised in 17 Member States on prescription only and marketed in 15 Member States (Bulgaria, Czech Republic, Cyprus, France, Greece, Hungary, Italy, Latvia, Lithuania, Malta, Poland, Portugal, Romania, Slovakia and Slovenia).

Patient exposure based on data provided by nimesulide brand leader MAH shows the highest exposure in Italy, France and Greece. Exposure has been decreasing in Italy since 2002, in Greece since 2004 and in France after rising up until 2008 has modestly been decreasing. In the other countries where nimesulide is marketed, the exposure appears to be stable over time.

Considering all exposure data provided (data from other MAHs account for additional 28% of patient exposure), it is noted that the use of generics of nimesulide seem not to decrease in recent years and Poland has the second highest exposure to nimesulide in the EU.

2.2. Clinical efficacy

Nimesulide is a NSAID therefore with therapeutic effect by decreasing the production of prostaglandins with preferred cox-2 inhibition.

NSAIDs are the most commonly used medication for the treatment of inflammatory conditions and acute pain. NSAIDs are the second line treatment in pain management accordingly with WHO ladder following paracetamol, the first line treatment. Notwithstanding the common analgesic component NSAIDs, as opposed to paracetamol, have an anti-inflammatory action which is against the backdrop of a somewhat higher acute toxicity risk profile.

As previously mentioned in this report, nimesulide is approved as second line treatment for acute pain, symptomatic treatment of painful osteoarthritis and primary dysmenorrhoea. Nimesulide is authorised since 1985. Several published clinical studies including overviews from the Cochrane database, pooled analyses, meta-analyses, reviews and individual clinical studies reports were presented.

These data were submitted for nimesulide when used in different conditions of acute inflammatory pain (such as post-operative dental pain, post-surgical pain, post traumatic conditions and painful extra-articular disorders) and for painful osteoarthritis and primary dysmenorrhoea. These data are summarised hereafter.

2.2.1. Results

Treatment of acute pain

The efficacy of nimesulide in the treatment of acute painful inflammatory conditions has been demonstrated in several short-term treatment (ranging from 1 day to 14 days of treatment) double blind clinical studies, placebo-controlled or active-controlled (other NSAIDs). The efficacy was overall evaluated by measuring pain and signs of inflammation.

The efficacy of nimesulide for the pain and inflammation in **dental surgery** and in **post-operative** states was studied in a certain numbers of studies versus other NSAIDs such as ketoprofen, niflumic acid, mefanamic acid and naproxen as well as in open studies.

The comparison between nimesulide and naproxen conducted in a double blind study of 660 patients with **traumatic lesions of soft tissues** demonstrated a similar efficacy of the two drugs in reducing the intensity of pain and oedema and the degree of functional impairment after 7 days.

The efficacy and tolerability of nimesulide 100 mg bid[1] versus diclofenac 75 mg bid was evaluated in a randomised, double blind double dummy, multicentre study in 343 patients suffering from **acute joint and soft tissue injuries**. Nimesulide and diclofenac demonstrated a similar efficacy after 7 days of treatment.

Three studies involving a total of 444 patients with **acute bursitis and tendinitis** and comparing nimesulide 100 mg bid with naproxen, diclofenac 75 mg bid and diclofenac and naproxen respectively

[1] Twice daily

showed a comparable efficacy of nimesulide with the other NSAIDs. In these studies the duration of treatment was 24 days.

One study[2] performed in 94 patients with **moderate postoperative pain** receiving nimesulide, naproxen or placebo for a maximum of 3 days showed that nimesulide was more effective than naproxen in terms of the summed pain intensity difference within 6 hours and superior in terms of the speed of onset of pain relief. At 1 hour after treatment, more than 70% of nimesulide-treated patients experienced a 50% reduction in pain intensity, compared with less than 50% of patients treated with naproxen and 40% of patients receiving placebo.

Symptomatic treatment of painful osteoarthritis

The efficacy of nimesulide in the treatment of symptoms of osteoarthritis was investigated in placebo-controlled studies and in double blind controlled studies in comparison with piroxicam (20mg once daily), naproxen (500mg bid), diclofenac (50mg bid), ketoprofen (100mg bid) and etodolac (300mg bid). The duration of treatment in these studies varied between 7 days to 12 months. Nimesulide reduced the symptoms of osteoarthritis with an efficacy similar to that of all the comparative drugs tested.

The other studies were particularly discussed by the brand leader MAH: a prospective, randomised, double-blind, within-patient Latin square design study[3] performed in 30 patients for the treatment of symptomatic **osteoarthritis (OA) of the knee**, comparing nimesulide (100mg), celecoxib (200 mg) and rofecoxib (25 mg) during 7 days of treatment and a prospective, randomised, double-blind study , comparing the analgesic effects of nimesulide and celecoxib (200 mg) in 20 patients with **knee osteoarthritis associated with joint effusion** during 14 days of treatment. The results of both studies showed that nimesulide has a rapid onset of analgesic effect.

The data presented showed efficacy of nimesulide for the symptomatic treatment of osteoarthritis. However, concerning the treatment duration, it is noted that of the 8 studies presented only two (above mentioned) had duration of nimesulide not longer than 30 days.

Primary dysmenorrhoea

Amongst women with primary dysmenorrhoea NSAIDs have been demonstrated to be more effective than placebo. According to *Marjoribanks et al.* in a Cochrane review there is insufficient evidence, however, to determine which NSAID is the most effective. According to *Pulkkinen* in another overview numerous studies have given the rationale for the use of nimesulide in the treatment of dysmenorrhoea.

A randomised, double-blind, two-period, parallel group study was performed in 308 women with primary dysmenorrhoea who received up to 300 mg /day of nimesulide or diclofenac 50 mg, for the first three days of the cycle for two menstrual cycles. The results showed a similar analgesic effect for both drugs with reduced pain by 82% with nimesulide and by 79% with diclofenac after two hours with nimesulide showing a faster onset of analgesic activity (at 30 minutes the mean reduction of pain was 35% in nimesulide-treated group *versus* 27% in the diclofenac-treated group).

Overall nimesulide proved to be more effective than placebo and showed an efficacy similar or better to that of the other active comparators.

2.2.2. Discussion

Nimesulide efficacy in the treatment of pain associated with several inflammatory and painful disorders has been shown in mostly short-term studies (up to four weeks) in a limited numbers of patients.

In the literature no unequivocal and clinically meaningful advantage of nimesulide over available NSAIDs in terms of efficacy has been demonstrated. In a Cochrane overview of randomised controlled studies comparisons between rofecoxib and diclofenac (mono- and in a fixed-dose combination with misoprostol), ibuprofen, naproxen, nimesulide, nabumetone, paracetamol and celecoxib did not show consistent differences in efficacy between rofecoxib and any of the active comparators at equivalent doses.

The benefit of a rapid onset of analgesic action associated with the use of nimesulide compared with other NSAIDs has been claimed based on some clinical studies results. However, the clinical relevance of the measured differences in onset of pain relief remains doubtful.

[2] *Binning A.* Clinical Journal of Pain, 2007 Sept 23 (7):565-70
[3] *Bianchi et al.*

It is concluded that the proven efficacy of nimesulide in short-term clinical studies is consistent with the indication for short-term use (i.e. 15 days) as previously restricted to minimise the risks for hepatoxicity. No substantial evidence supported additional clinical benefits over other available NSAIDs and therefore it is concluded that nimesulide has similar efficacy as other available NSAIDs.

2.3. Clinical safety

Overall, the safety data submitted were spontaneous reports, several publications of reported cases, clinical and epidemiological studies, meta-analysis and reviews. The results of the SALT study (*A study of NSAIDs-exposed acute liver failure in European transplant centres*) and of the FVG GI study (Risk of Upper gastrointestinal complications in users of nimesulide and other NSAIDs in Friuli-Venezia Guilia) were provided during this procedure. These data are hereafter presented and discussed.

2.3.1. Results

The overall reporting rate (number of cases per 10 million DDDs sold) for nimesulide for the period 1998-2009 based on data from the WHO-UMC VigiBase NIMBUS from Austria, Belgium, Czech Republic, Finland, France, Greece, Hungary, Ireland, Italy, Poland, Portugal and Spain was 2.5 (corresponding to 1.702 cases for all SOC[4]). This is similar to other NSAIDs namely 2.7 for diclofenac, 3.3. for ibuprofen and 2.3 for naproxen.

The overall reporting rate with regards to all cases with fatal outcome is of 0.05 per 10 million DDD (corresponding to 32 cases) for nimesulide. This is similar to that of most NSAIDs namely diclofenac (0.08), ketoprofen (0.06), ibuprofen (0.04) and naproxen (0.04).

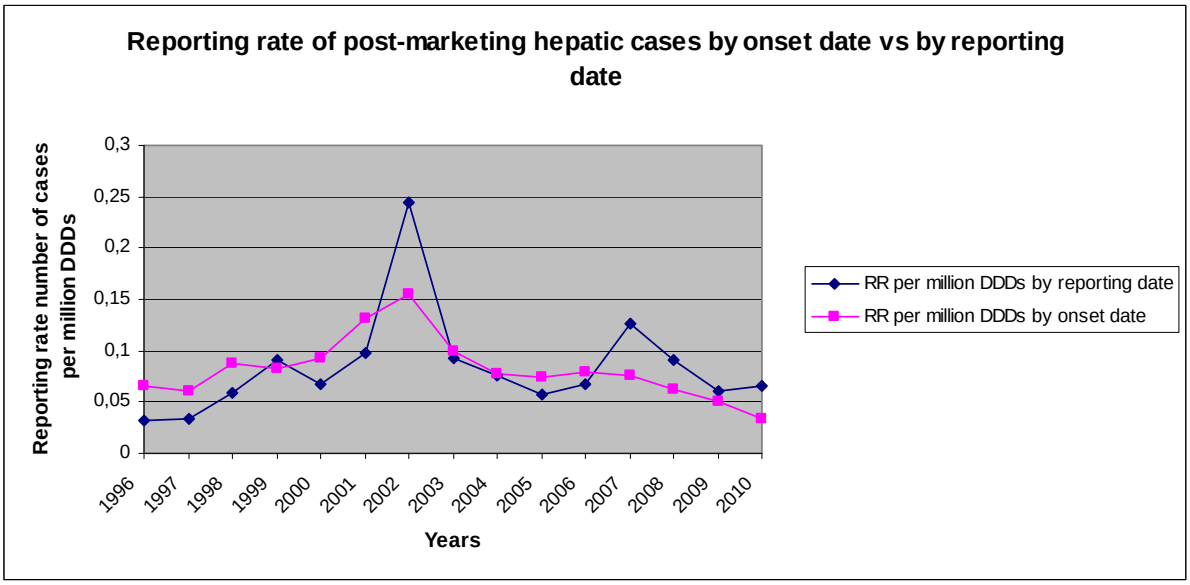
Hepatotoxicity

- *Post marketing data*

A total of 640 serious and non-serious nimesulide **hepatic cases** have been reported up to 14 December 2010 accordingly to the brand leader MAH's safety database. Most cases were reports of hepatitis, jaundice or hepatic failure. Of the 640 cases (477 were serious and 163 non-serious), 536 were considered in the context of the previous referrals procedures under Article 31 and Article 107.

The **reporting rate** regardless of causality, of the most severe hepatic cases with fatal outcome or classified as acute liver failure is overall low (cumulatively 2 and 5 cases per billion DDD, respectively).

The reporting rate of all nimesulide post-marketing hepatic cases from 1996 to (14 December) 2010 per event onset date and *per* event reporting rate is shown in the graphic below. The current reporting rate of hepatic cases is 0.066 per million DDDs considering the reporting date and 0.033 per million DDDs considering the onset date.

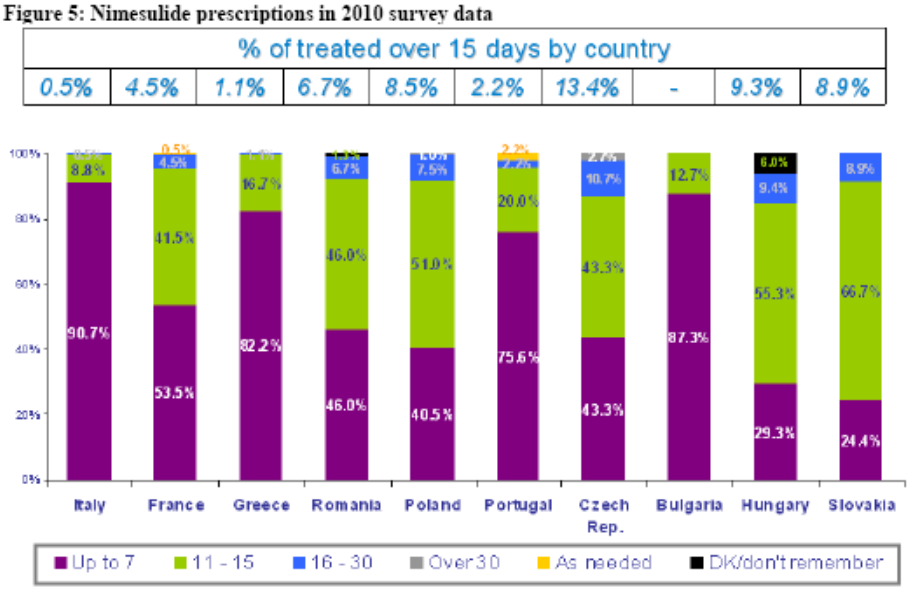


[4] System Organ Class

As previously seen in the other referrals procedures, the majority of cases occurring since 2007 were in female patients with a decrease in the number of cases reported in patients aged more than 55 years old.

According to a survey performed in March 2010 by the brand leader MAH, the majority of the prescribing nimesulide doses in the EU member states where the brand leader MA is marketed do not exceed the recommended daily of 100 mg bid. The following graphic shows the rates of prescribing nimesulide for longer than the 15 days per country.

Figure 5: Nimesulide prescriptions in 2010 survey data



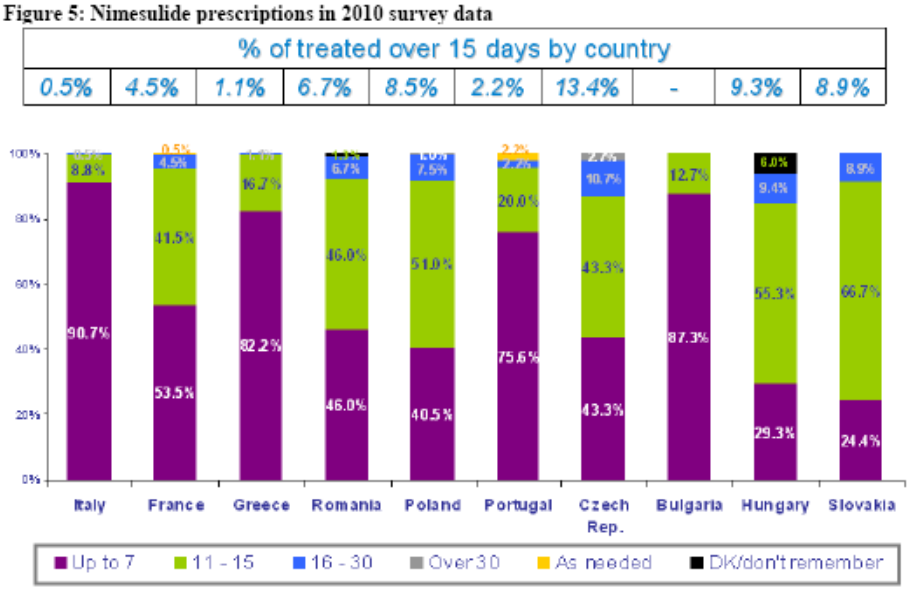
The number of cases with **event time to onset** longer than 15 days has been decreasing since the previous referral procedures as shown in the below table (cut off date of 14 June 2010). The majority of the cases i.e. 46.2% are reported with event time to onset within 15 days.

		Time to onset (days)			
		≤ 15	>15	Unk	Total
1985 to 30 April 2002	No.	87	201	50	338
	%	**25.7**	**59.5**	**14.8**	**100,0**
1 May 2002 to 14 June 2007	No.	91	95	46	232
	%	**39.2**	**40.9**	**19.9**	**100,0**
15 June 2007 to 14 June 2010	No.	30	24	11	65
	%	**46.2**	**36.9**	**16.9**	**100,0**
	Total No.	208	320	107	635
	%	**32.8**	**50.4**	**16.8**	**100,0**

Of the 36.9% of reported cases with time to onset > 15 days, 29.2% equal or more than 30 days while in the previous period of the 40.9% with time to onset > 15 days, 30.2% of cases equal or more than 30 days. It is acknowledged that these data may be confounded by the changes in the nimesulide EU markets over the years and by the different pattern of prescription across countries.

Cases with **treatment duration** up to 15 days were 58.6% of the reported cases between 2007 and 14 June 2010 vs. 26.8% of cases with treatment duration longer than 15 days vs. 14.6% cases with unknown treatment duration.

Figure 5: Nimesulide prescriptions in 2010 survey data



Analysing the reported cases by **therapeutic indication** it is noted that around 23% of the cases involve patients treated for more chronic indications, suggesting that nimesulide is not only being prescribed for acute pain (21.6%) and acute inflammation (21.5%).

Comparison with other NSAIDs

The reporting rate of adverse events on the **hepatobiliary and investigations SOCs** and for **liver injury** with nimesulide has been compared with the cases reported for other NSAIDs using the WHO-UMC NIMBUS (WHO VigiBase) data. The following tables represent the comparison regardless of severity and causality.

VigiBase data: Hepatobiliary and Investigation SOCs

	Hepatobiliary disorders SOC Reporting Rate/ 10^7 DDD	Investigations SOC Reporting Rate / 10^7 DDD
Naproxen	0.08	0.11
Diclofenac	0.12	0.17
Meloxicam	0.15	0.23
Ibuprofen	0.17	0.18
Ketoprofen	0.23	0.31
Paracetamol	0.32	0.39
Piroxicam	0.31	0.51
Nimesulide	0.47	0.37
Indometacin	0.42	0.42
Celecoxib	0.36	0.71
Sulindac	0.80	0.00

': VigiBase data: Liver injury

	Liver injury Total cases	Million DDD sold	Reporting Rate / 10^7 DDD
Naproxen	34	4,598	0.07
Diclofenac	101	10,868	0.09
Meloxicam	24	1,902	0.13
Ibuprofen	177	12,038	0.15
Ketoprofen	93	4,979	0.19
Celecoxib	59	2,152	0.27
Paracetamol	597	22,267	0.27
Piroxicam	62	2,290	0.27
Indometacin	26	819	0.32
Nimesulide	257	6,763	0.38
Sulindac	1	25	0.40

The reporting rate for liver injury associated with nimesulide use is:
- similar to that of indometacin, celecoxib, paracetamol, piroxicam, and sulindac, and
- higher than for ketoprofen, ibuprofen, meloxicam, diclofenac and naproxen;

- *Clinical and epidemiological studies*

No case report of hepatitis or hepatic failure were identified among the 65,449 nimesulide-treated patients in all **MAH-sponsored studies** up to 2010 and included in the database.

No cases of hepatic adverse events were reported in the **40 controlled clinical studies** involving 4,815 nimesulide-treated patients. However, 1.2% of the 1500 patients on nimesulide that were tested showed increased liver enzymes vs. 0% in the placebo group (107 patients) and 0.47% (1063 patients) in the group treated with comparator products, being benzidamine, diclofenac, naproxen, ketoprofen, nimesulide-betacyclodextrin and etodolac, with diclofenac having an event rate of 1.08%. No liver abnormalities were reported ≤ 15 days of treatment. Among patients treated > 15 days no cases fulfilling 'Hy's law[5]' were identified and all reported cases were of mild severity.

In a larger analysis of 173 **controlled clinical trials** including 7,872 patients on nimesulide, four hepatobiliary adverse reactions (of which one was serious - cholelithiasis) were reported (0.05%) vs. 0% in placebo. Hepatic disorders were reported with comparators: 0.08% naproxen vs.0.07%, diclofenac. Increased liver enzymes were observed in 0.2% of nimesulide treated patients (no data for comparators was provided).

Although the above results are regarded of limited value due to the limitations of pooling data across comparative studies of different duration, indication, dose regimens with widely differing number of patients on each treatment and with different study methods, it is noted that the absolute risk for abnormal liver function test with nimesulide is around 1%.

A **review of published and unpublished data** on **spontaneous reporting** cases was presented. This review included 6 publications and 3 internal reports that were previously considered in the procedure under Article 107. In addition, 6 recent studies and 3 case-series have now been included in the review presented.

The 6 recent studies were: Motola D, *et al*. *Influence of Regulatory Measures on the Rate of Spontaneous Adverse Drug Reaction Reporting in Italy* Drug Safety 2008; 31 (7): 609-616; Suzuki A, *et al*. *Drugs associated with hepatotoxicity and their reporting frequency of liver adverse events in VigiBase: unified list based on international collaborative work*. Drug Safety 2010 Jun 1;33(6):503-22; Lee CH, *et al*. *Increased risk of hospitalization for acute hepatitis in patients with previous exposure to NSAIDs*. Pharmacoepidemiology and Drug safety, 2010; 19:708-714; Walker SL, *et al Nimesulide associated fulminant hepatic failure.* Pharmacoepidemiology and Drug Safety. 2008; 17 (11):1108-12; Wang YP, *et al*. *Drug-induced liver disease: an 8-year study of patients from one gastroenterological department*. Journal of Digestive Diseases 2009; 10; 195–200; Licata A., *et al*. *Clinical course and outcomes of drug-induced liver injury: Nimesulide as the first implicated medication* Dig Liver Dis.

The Motola *et al.* (2006) study aiming assessing the extent of drug-induced liver injuries in Italy (period January 1990 to May 2005) by comparing the number of hepatic cases with reports of all other drug related reactions (Reporting Odds Ratio) showed that the drug classes with the highest number of cases were statins (ROR=2.9, 95% CI 2.4–3.5), antiplatelet agents (ROR=3.5; 95% CI 2.6–4.6), NSAIDs (ROR=2.9; 95% CI 2.1–3.9) and macrolides (ROR=1.7; 95% CI 1.2–2.3). Among all NSAIDs a significant disproportionality was found only for nimesulide with 52 cases versus 394 non-cases (ROR 2.9, 95% CI 2.1-3.9). A recent paper (2008) by the author confirmed that the proportion of hepatic adverse reactions increased from about 5% of all nimesulide adverse reaction reports before 2002 to about 20% in the period 2002-2005 and highlighted notoriety bias.

The publication by Suzuki *et al* (2010) the Uppsala Monitoring Centre's Vigibase global spontaneous reporting database (going back to 1968) was used to identify products with a high EGBM (Empirical Bayes Geometric mean) for overall liver injury and for acute liver failure. Relating to NSAIDs the findings are shown in the next tables.

[5] Hy's law: The two 'requirements' for Hy's Law are: 1. Evidence that a drug can cause hepatocellular-type injury, generally shown by a higher rate than control of people with 3 times and greater transaminases elevations over the upper limit of normal (2 times elevations are too common in treated and untreated patients to be discriminating). 2. Cases of increased bilirubin (to at least 2 times ULN) in people with concomitant transaminase elevation to at least 3 times ULN (but it is almost invariably higher) and no evidence of intra-or extra-hepatic bilirubin obstruction (elevated alkaline phosphatase) or Gilbert's syndrome. The patients should have no other reason for the hepatocellular injury, such as viral hepatitis, concomitant use of a hepatotoxic drug, recent marked hypotension, or congestive heart failure, especially right sided. A diligent search for such causes is critical. Pharmacoepidemiology Drug Safety 2006; 15(4): 241-243

liver injury and liver failure data on NSAIDs from Vigibase

	Total no. of reports	Overall liver injury		Acute liver failure	
		No.	EBGM (90% CI)	No.	EBGM (90% CI)
Diclofenac	29 178	2 051	1.6 (1.6, 1.7)	104	1.5 (1.3, 1.8)
Ibuprofen	29 931	880	0.8 (0.7, 0.8)	83	1.2 (1.0, 1.4)
Naproxen	23 545	667	0.6 (0.6, 0.7)	54	0.9 (0.7, 1.1)
Nimesulide	1 500	350	5.5 (5.0, 6.0)	23	4.0 (2.8, 5.6)
Paracetamol	29 636	4 481	4.4 (4.3, 4.5)	1 072	14.2 (13.5, 14.9)
Piroxicam	17 017	565	0.7 (0.7, 0.8)	23	0.7 (0.5, 1.0)

liver injury and liver failure data on NSAIDs from Vigibase – data derived from published study tables

	Total no. of reports	Overall liver injury		Acute liver failure	
		No.	% of total reports	No.	% of total reports
Diclofenac	29 178	2 051	7.0	104	0.4
Ibuprofen	29 931	880	2.9	83	0.3
Naproxen	23 545	667	2.8	54	0.2
Nimesulide	1 500	350	23.3	23	1.5
Paracetamol	29 636	4 481	15.1	1 072	3.6
Piroxicam	17 017	565	3.3	23	0.1

The higher EGBM for nimesulide compared to other NSAIDs shows that the proportion of hepatic reports for nimesulide is higher than for other NSAIDs, i.e. that compared to other NSAIDs relatively to the total reports submitted for nimesulide more hepatic reports are submitted to the UMC.

Results of these two studies based on spontaneous reporting (*Motola* and *Suzuki*) are consistent with an increased risk for hepatotoxicity of nimesulide compared to other NSAIDs based on spontaneous reporting data.

The epidemiological case-crossover study by *Lee et al* (2010) conducted in Taiwan identified a total of 4,519 cases of hospitalization for acute hepatitis between April 2001 and December 2004, of which 30 were taking nimesulide. Current use of all NSAIDs was associated with an elevated risk of acute hepatitis, with a range of OR from 1.60 [1.01-2.51] for rofecoxib to 2.63 [1.83-3.77] for nimesulide, in a similar magnitude as ibuprofen with OR of 2.51 [2.23-2.82] and diclofenac of 2.22 [2.05-2.42].

A **systematic review of epidemiological studies** on the risk of liver injury associated with the use of nimesulide and other NSAIDs covering the period from 1985 up to 15 November 2010 was presented. This review consisted of 10 published studies. Results for individual NSAIDs with relative risk estimates from more than one study were presented.

Overall only two studies provided data on the risk of acute liver injury associated with the use of nimesulide (*Lee et al.,* 2010; *Traversa et al*., 2003). As discussed above, the Lee et al study showed a a risk for hospitalisation for acute non-viral hepatitis higher for nimesulide (2.63) similar to that of diclofenac (2.22) and ibuprofen (2.51).

The *Traversa et al*. (2003) was a retrospective cohort study previously considered during the review under Article 107, that including 187,312 users of nimesulide in Italy. The incidence rate of acute liver injury in users of nimesulide was 33.1 per 100,000 person-years. Users of nimesulide had a 2-fold greater risk of acute liver injury over past users of NSAIDs. This risk increase was similar to the one reported for ketorolac and in between the increases associated with the use of diclofenac and ibuprofen in the same study. In an additional analysis, the risk of severe acute liver injury with nimesulide use was about two-fold higher than the risk for all other NSAIDs aggregated in a single category. All other NSAIDs were grouped in the reference group, therefore direct comparisons between nimesulide and individual NSAIDs for severe acute liver injury were not conducted in this study.

Overall the results of the systematic review of epidemiological studies support the conclusion that nimesulide is associated with an increased risk of liver injury compared to past use, as well as to other NSAIDs aggregated as a single category.
Based on Traversa et al., 2003, the absolute risk for hospital admission for hepatopathy is approximately 30-35 per 100,000 person-years.

Data from these epidemiologic studies only allow for indirect comparisons between NSAIDs. Pooled data on the relative risks from the individual NSAIDs vs. no use (using random effects model – see table below) suggests that the risk for liver injury associated with nimesulide to be:

- comparable to ibuprofen, diclofenac and indomethacin;
- higher than for celecoxib, naproxen or ketoprofen, and;
- lower than for sulindac;

	Traversa	Lee	Carlson	Perez	de Abajo	Pooled
Naproxen	0.9 [0.1-6.2]	-	0.6 [0.0-4.5]	1.7 [0.5-6.4]	1.7 [0.3-9.1]	1.3 [0.5-2.9]
Ketoprofen	1.4 [0.5-3.8]	-	-	-	-	1.4 [0.5-3.8]
Celecoxib	1.0 [0.1-7.3]	1.9 [1.4-2.7]	-	-	-	1.9 [1.3-2.6]
Diclofenac	1.5 [0.7-3.2]	2.2 [2.1-2.4]	-	2.0 [0.2-17.4]	4.1 [1.9-8.8]	2.2 [1.7-2.9]
Ibuprofen	3.0 [0.7-12.4]	2.5 [2.2-2.8]	1.3 [0.2-5.5]	1.2 [0.1-12.0]	-	2.5 [2.2-2.8]
Nimesulide	2.2 [1.3-3.9]	2.6 [1.8-3.8]	-	-	-	2.5 [1.8-3.4]
Indomethacin	-	-	-	2.6 [0.8-8.6]		2.6 [0.8-8.6]
Sulindac	-	-	4.1 [0.6-22.4]	5.0 [1.3-18.5]	-	4.6 [1.6-13.1]

It is noted that data from these observational studies allow for adjustments by age, sex, co-medication and co-morbidities as well as to see the effect of dose and duration at a patient level. Data over event rates per gross patient exposure calculations such or the spontaneous reporting rate does not allow such stratifications of the results.

SALT (*Study of Acute Liver Transplant) **- A study of NSAIDs-exposed acute liver failure in European transplant centres***

Design

The SALT-1 study was a non-interventional retrospective study requested as follow up of the procedure under Article 107 to provide estimates of the rates of case of acute liver failure (ALF) leading to registration for liver transplantation in patients exposed to NSAIDs within 30 days before first clinical symptom of liver injury.

The study, conducted by the University of Bordeaux was a case-population study of all adult patients registered for liver transplantation in France, Greece, Ireland, Italy, the Netherlands, Portugal and in the United Kingdom, in the 3-year retrospective period 2005-2007. The study protocol was approved by the CHMP in November 2008. Data was collected from the period from June 2009 to January 2011 and the final results were now submitted.

Objectives

Primary objectives were to estimate the absolute frequency of ALF leading to registration for transplantation in patients exposed to nimesulide and to compare the population incidence rates of hepatic transplantation after nimesulide exposure to that of other NSAIDs.

Methodology

Case exposure was considered within a 30-day period before onset of clinical symptoms (index date). Population exposure was derived from IMS sales data over the three-year period. Study population were all adult patients (≥18 years of age) resident in the country, register in the transplant center and who were identified, assessed and classified as chronic or acute liver failure (CLF or ALF) for whatever reason. Cases were reviewed and validated by a national case classification hepatologist who defined the date of onset of liver disease (i.e. index date).

Results

Overall, of the 57 centres eligible for inclusion, 54 agreed to participate (France 20/21, Italy 19/20, Portugal 2/3, Greece, 2/2, Ireland 1/1, NL 3/3, UK 7/7). Data collected was however, not provided by 4 of the centers (3 in the UK and 1 in Italy) due to administrative delays.

A total of 8824 cases registered for transplantation were evaluated and 500 cases of acute liver failure were identified. Of these, 288 cases without clinical cause, 197 with identified clinical cause and 15 had medical files incomplete. Of the 288 cases, 241 had drug exposure: 34 cases were exposure to NSAIDs (≥1 NSAIDs) within 30 days before the onset of symptoms, 123 cases identified without exposure to NSAIDs and the remaining 84 were due to acute drug intoxication. In the 34 cases there was exposure to 37 NSAIDs. Twenty nine of the 34 exposed to NSAIDs had also been exposed to other drugs including paracetamol in 18 cases.

In the studied period and considering all 7 countries in the study, nimesulide was the second most sold NSAID after ibuprofen. Among the top five most commonly used NSAIDs the overall event rates of acute liver failure (ALF) per million treatment-years were: 4.46 [95% CI 1.45; 10.41] for diclofenac, 4.67 [95% CI 0.96; 13.64] for ketoprofen, 5.35 [95% CI 0.64; 19.35] for naproxen, 5.64 [95% CI 2.43; 11.11] for nimesulide and 5.77 [95% CI 2.77; 10.61] for ibuprofen. The overall event rate for NSAIDs was 4.37 [95% CI 3.02; 6.10] per million treatment year corresponding to 4.02 cases per billion DDD. The following table presents the ALF incidence rate per million treatment-years and the correspondent cases per billion DDD (within 30 days – index date).

NSAID	Number of DDD (IMS)	Number of treatment-years	Number of cases	Cases per billion DDD	Rate per million treatment-years [CI 95%]
Celecoxib	357 873 149	287 531	1	2.79	3.48 [0.10; 19.37]
Diclofenac*	1 514 709 881	1 120 803	5	3.30	4.46 [1.45; 10.41]
Ketoprofen	899 161 612	642 962	3	3.34	4.67 [0.96; 13.64]
Naproxen	647 295 878	373 640	2	3.09	5.35 [0.64; 19.35]
Nimesulide	1 356 255 833	1 418 253	8	5.90	5.64 [2.43; 11.11]
Ibuprofen	1 219 162 429	1 732 791	10	8.20	5.77 [2.77; 10.61]
Indometacin	80 584 130	76 318	1	12.41	13.10 [0.39; 72.98]
Niflumic acid	62 794 037	69 274	1	15.93	14.44 [0.43; 80.41]
Etodolac	70 791 098	44 526	1	14.13	22.46 [0.67; 125.1]
Ketorolac	38 652 374	34 302	2	51.74	58.31 [7.00; 210.8]
NSAID (INN unknown)	-	-	3	-	-
Other NSAIDs	2 214 631 861	1 984 220	0	-	0.00 [0.00; 1.86]
Total	8 461 912 281	7 784 621	34	4.02	4.37 [3.02; 6.10]

The rate of ALF cases exposed to paracetamol over the same period, excluding overdoses was 9.80 [95% CI 7.66 – 12.37]. It is noted to be twice higher than the rate in patients exposed to all NSAIDs.

The incidence rate per million treatment-years of NSAIDs (cases exposed 15 days prior index date) in NSAID-exposed patients for the studied period and in all countries is found in the below table.

Table 202. ALF incidence rate per million treatment-years of NSAID (cases exposed 15 days prior to index date) in NSAID-exposed patients for the years 2005, 2006, 2007, all countries

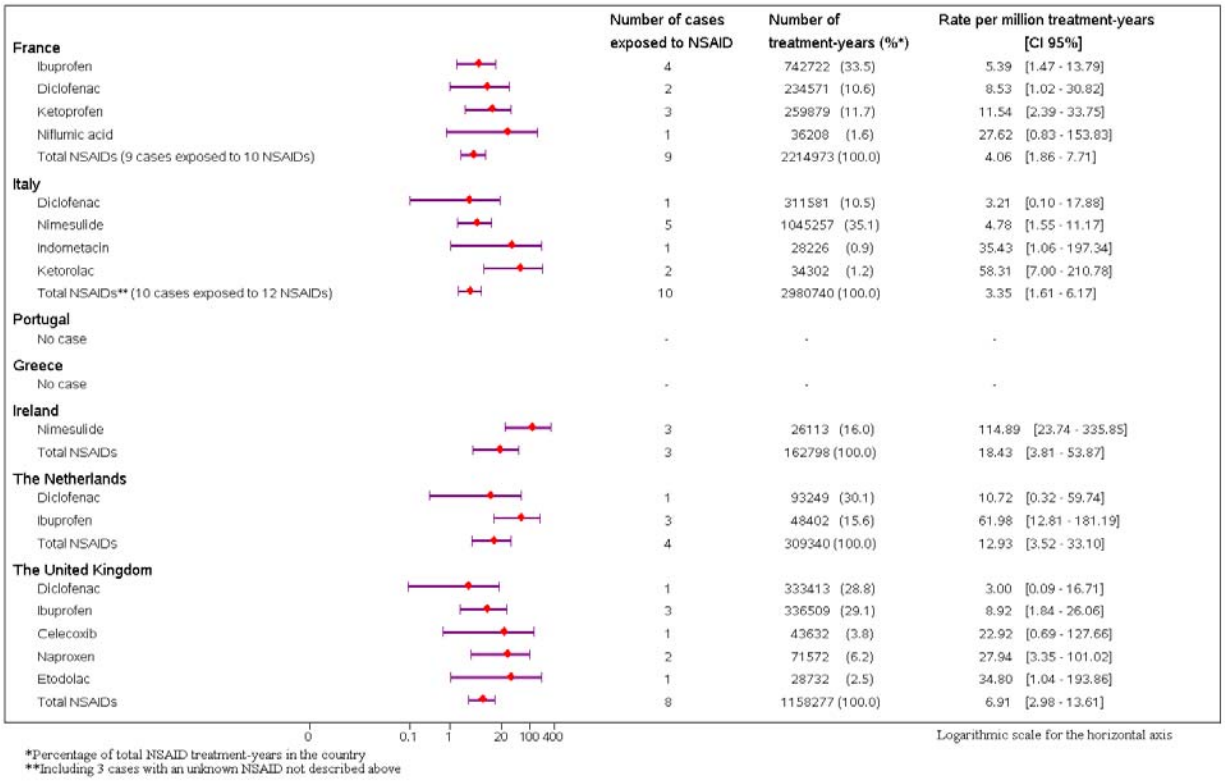
NSAID	Number of units (IMS) [1]	Number of DDD (IMS) [2]	% DDD	Number of treatment-years [3]	% treatment-years	Number of cases exposed to NSAIDs (SALT- I study) [4]	% case exposed to NSAIDs	Case per billion DDD for 3 years [5]	Rate per million treatment-years [CI 95%] [6]
Nimesulide	2 714 082 676	1 356 255 833	16.03	1 418 253	18.22	7	22.58	5.16	4.94 [1.98; 10.17]
Celecoxib	396 017 923	357 873 149	4.23	287 531	3.69	1	3.23	2.79	3.48 [0.10; 19.37]
Diclofenac*	2 430 307 644	1 514 709 881	17.90	1 120 803	14.40	4	12.90	2.64	3.57 [0.97; 9.14]
Etodolac	68 705 974	70 791 098	0.84	44 526	0.57	1	3.23	14.13	22.46 [0.67; 125.10]
Ibuprofen	5 122 263 733	1 219 162 429	14.41	1 732 791	22.26	8	25.81	6.56	4.62 [1.99; 9.10]
Indometacin	164 354 111	80 584 130	0.95	76 318	0.98	1	3.23	12.41	13.10 [0.39; 72.98]
Ketoprofen	1 163 210 499	899 161 612	10.63	642 962	8.26	3	9.68	3.34	4.67 [0.96; 13.64]
Ketorolac	51 021 224	38 652 374	0.46	34 302	0.44	2	6.45	51.74	58.31 [7.00; 210.78]
Naproxen	741 921 987	647 295 878	7.65	373 640	4.80	2	6.45	3.09	5.35 [0.64; 19.35]
Niflumic acid	189 356 812	62 794 037	0.74	69 274	0.89	1	3.23	15.93	14.44 [0.43; 80.41]
NSAID (molecule name unknown)	-	-	-	-	-	3	9.68	-	-
Other NSAIDs	3 584 501 362	2 214 631 861	26.17	1 984 220	25.49	0	-	-	0.00 [0.00; 1.86]
Total NSAIDs	16 625 743 947	8 461 912 281	100.00	7 784 621	100.00	31	100.00	3.66	3.98 [2.71; 5.65]

* 1 case with diclofenac in topical form

[1] Number of units (IMS) = total number of units
[2] Number of DDD (IMS) = total number of DDD
[3] Number of treatment - years = total number of treatment-years
[4] Number of cases exposed to NSAIDs = 31 cases exposed to 33 NSAIDs (1 case with Nimesulide + Indometacine and 1 case with Nimesulide + Ketorolac)
[5] Case per billion DDD for 3 years = (number of cases exposed to NSAIDs / number of DDD) * 10^9
[6] Rate per million treatment-years [CI 95%] = (number of cases exposed to NSAIDs /number of treatment-years) * 10^5 [95% confidence interval from a Poisson distribution]

No difference in event rates per billion DDD or million treatment years between the NSAIDs was observed, especially for NSAIDs such as ibuprofen, ketoprofen, diclofenac, naproxen or nimesulide for all of which point estimates were below 10 per billion DDD or million treatment years. These results remained consistent with various sensitivity analyses presented, such as increasing the exposure window to 90 days or reducing it to 7 days.

The following figure shows the ALF incidence rate per million treatment-years of NSAID per country (cases exposed 30 days prior to index date) in NSAID-exposed patients for the years 2005, 2006, 2007.



*Percentage of total NSAID treatment-years in the country
**Including 3 cases with an unknown NSAID not described above

A higher event rate for nimesulide is observed only in Ireland, but higher rates in comparison with other countries were found also for all-causes ALF, in particular for drug-exposed ALF. Of note, event rates for all NSAIDs pooled were higher in Ireland and in the Netherlands than in other countries, respectively 4.4 [95%CI 1.4 – 14.3] and 3.1 [95%CI 1.1-8.7] times more than all countries pooled.

Overall the results of the SALT study show that:

- The absolute risk for ALF indicated for transplantation associated with nimesulide use is 5.64 [2.43-11.11] per million person-years;
- Taking into account average dose per country, the absolute risk for ALF indicated for transplantation is 5.90 per billion DDDs;
- Comparing the incidence rates per million person years, the risk for ALF of nimesulide is in the range of that for diclofenac (4.46 [1.45; 10.41]) and ketoprofen (4.67 [0.96; 13.64]), naproxen (5.35 [0.64; 19.35]) and ibuprofen (5.77 [2.77; 10.61]);
- Comparing the incidence rates per billion DDDs the risk for ALF of nimesulide is higher than for diclofenac (3.30), ketoprofen (3.34) and naproxen (3.09), and lower than for ibuprofen (8.20);
- In both models the risk for ALF of nimesulide is higher than for celecoxib (3.48 [0.10; 19.37] per million person years and 2.79 per billion DDDs);
- In both models the risk for ALF of nimesulide is lower than for paracetamol (intoxications excluded) (9.80 [7.66; 12.37] per million person years and 12.82 per billion DDDs) and indomethacin (12.10 [0.39-72.98] per million person years and 12.41 per billion DDDs);
- These comparisons between NSAIDs are consistent according to exposure window (90 days, 15 days, 7 days), and in several sensitivity analyses;

The results depend on the method used to calculate incidence rates. The rates that take into account average dose per country are regarded to be the most appropriate. The high incidence rate of ALF cases exposed to nimesulide observed in Ireland, is not observed in any of other countries studied. The average daily dose of nimesulide in Ireland (1.980) is comparable to the other countries where ALF risks were lower (France: 1.933, Italy: 1.678, Portugal: 2.030, Greece: 1.878).

All presented results are crude incidence rates for the years 2005 to 2007, and do not take into account duration of use or any confounding factors, such as co-medication or co-morbidities. Dose was only partially considered in the calculation of cases per billion DDDs (only adjusted for the mean dose in the population and not able to calculate dose specific risks).

Overall, the pooled risk estimates that take into account average dose per country, suggest that the risk for ALF (indicated for transplantation) associated with nimesulide is higher than for celecoxib, diclofenac, ketoprofen and naproxen, and lower than for ibuprofen, paracetamol and indomethacin.

The SALT-1 study has several limitations namely small number of cases, all severe cases are of acute liver failure and very wide confidence intervals. This leads to uncertainties with regards the robustness of the data and its results.

- *Possible mechanisms of hepatotoxicity of nimesulide*

The pathogenesis of low-incidence, high-severity nimesulide hepatotoxicity is largely unknown.

Because liver injury from nimesulide is not predictable and, unlike paracetamol, lacks a dose-response relationship, nimesulide-induced liver injury is considered as an example of idiosyncratic drug toxicity. Idiosyncratic hepatotoxicity is a rare and unpredictable event of liver injury affecting generally less than 1 in 10,000 patients treated with certain drugs. However, it is a serious clinical problem as it accounts for 10% of all drug-induced liver failure cases.

The currently favoured concept of **idiosyncratic hepatotoxicity** assumes that the injury is caused by a combination of certain genetic and environmental factors, which sufficiently enhance an individual's susceptibility to otherwise clinically silent adverse effects of a drug. There are no animal models available to study the hepatic toxicity of NSAIDs. Several of the studies on mechanism of hepatotoxicity are based on studies with other NSAIDs than nimesulide. The relevance of some *in vitro* studies using nimesulide may be limited because of the use of relative high nimesulide concentrations, around 1-100 mM, which are well above its usual therapeutic plasma concentrations.

Several molecular mechanisms have been postulated to be implicated in NSAIDs including nimesulide hepatotoxicity. These mechanisms are: (1) mitochondrial toxicity leading to activation of cell death-signaling pathways, (2) induction of oxidant stress and induction of apoptosis, (3) formation of a reactive metabolite which bind to proteins and subsequent induction of hepatotoxicity (4) interference

of NSAIDs with hepatobiliary transport leading to intracellular accumulation of endogenous and/or exogenous compounds (including nimesulide).

Nimesulide has been shown to cause mitochondrial damage by major mechanisms of uncoupling of oxidative phosphorylation, opening of the mitochondrial permeability transition pore (mPT), and inhibition of mitochondrial β-oxidation. In terms of induction of oxidant stress, there is no consensus on whether nimesulide induces the formation of reactive oxygen species or not. Some reports found no evidence (e.g. Kale 2010) while others did find a depletion of GSH levels and ROS formation (Tripathi 2010, Singh 2010).
Nimesulide formed covalent adducts with human liver microsomal proteins and cellular proteins in a cultured human hepatocyte cell line (Kale 2010, Gan 2009). The formation of these covalent adducts was dependent on CYP2C. Overall, the extent of binding was modest and similar or lower than that obtained with other drugs, including drugs that have not been associated with liver injury.
In principle covalent protein binding could lead to hapten formation, and thus immune activation. However the mechanisms underlying breaking of tolerance are poorly understood. Protein binding could also induce pro-toxicant pathways and/or protective pathways. This has not been studied yet for nimesulide.
The main carrier involved in the hepatobiliary excretion of nimesulide and its metabolites in rats is Mrp2. It is likely that nimesulide hepatobiliary excretion in man is via the equivalent human carrier, i.e. MRP2. Nimesulide does not impair the biliary secretion of bile salts via BSEP and phospholipids and cholesterol via Mdr2. It was considered unlikely that nimesulide –induced hepatotoxicity can be triggered by interference with the biliary secretion machinery nevertheless it cannot be ruled out that nimesulide may interfere with its own excretion causing high hepatic exposure to or increased retention. This may then lead to oxidative stress, mitochondrial toxicity and/or protein adduct at such levels that cannot be compensated.

As a follow up of the Article 107, a non-clinical study on the mechanisms of nimesulide hepatotoxicity - possible role of reactive metabolites was performed. It was found that nimesulide forms a reactive metabolite that covalently binds to hepatocellular protein, but that the extent of binding was relatively small. Furthermore, this electrophile stress caused activation of the transcription factor Nrf2 in hepatocytes and in mice; however, inactivation of this defense pathway did not render cells or mice more susceptible to nimesulide toxicity, suggesting that the formation of this nimesulide reactive metabolite may not be a major pathway leading to liver injury in normal hepatocytes or normal healthy mice.

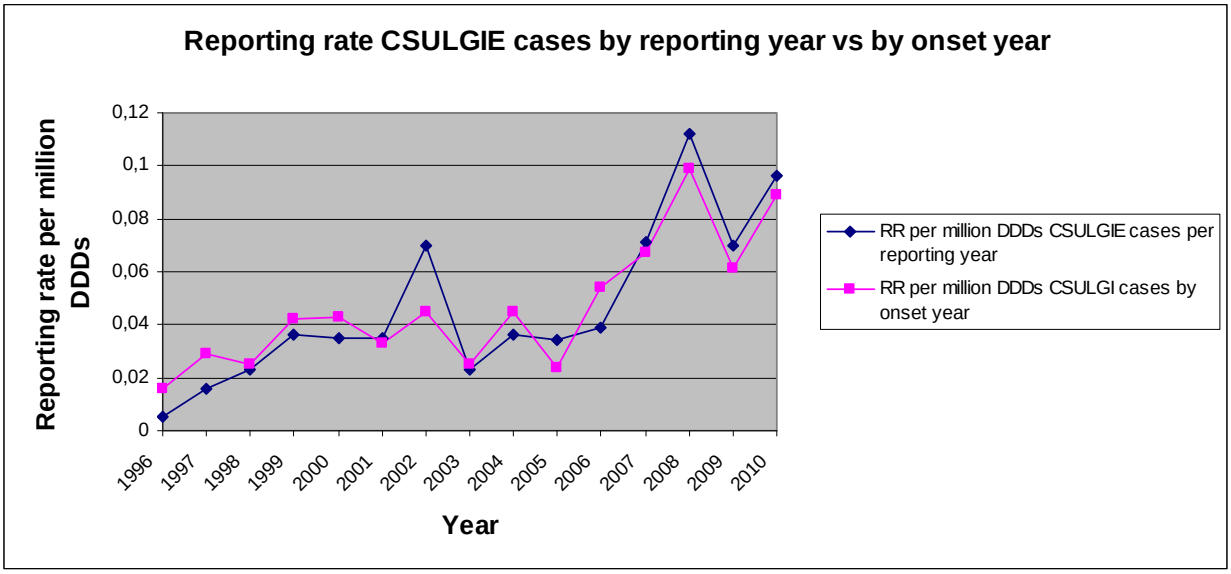
Considering the above mentioned data, the mechanism of action for nimesulide induced hepatotoxicity is still not clear. It may be possible that several of the described mechanisms all contribute to the nimesulide induced hepatotoxicity. Because of this lack of understanding it is not possible to determine or predict the risk for nimesulide-associated liver liability at the individual patient level.

Gastrointestinal toxicity

- *Post marketing data*

A total of 1217 serious and non-serious adverse events pertaining to the Gastrointestinal SOC have been registered in the brand leader MAH's safety database up to 2010 (14 December). This represents 21% of the overall adverse events reported.

A total of 350 nimesulide clinically significant **upper and lower GI cases** (CSULGIE cases) have been identified. Corresponding to a CSULGIE reporting rate (per event onset year) of 0.048 cases per million DDDs. Reporting rate of CSULGIE cases over time and by reporting year and reporting onset year are presented in the following graph.



In the majority of the reported cases it was noted the concomitant use of products known for increasing the risk of gastrointestinal toxicity such as other NSAIDS, antiplatelet agents etc, which can explain the increasing number of CSULGIE cases reported over the years.

Reporting rate for nimesulide regardless of severity or causality in VigiBase (1998 – 2009) is 1.13 per 10 million DDDs. As for almost all NSAIDs, this is the SOC with the highest reporting rate of adverse reactions. Of the comparators only paracetamol (0.40 per 10 million DDDs) and naproxen (1.07 per have lower scores.

Reporting rate for nimesulide (0.32 per 10 million DDDs) with regards **GI perforation, ulceration or bleeding cases** (PUB cases in Vigi Base) is found higher than for paracetamol (0.04), similar to naproxen (0.37), ibuprofen(0.40) and diclofenac (0.49), and lower than for indomethacin (0.79), ketoprofen (0.72), meloxicam(0.72), celecoxib (0.99), sulindac (1.20) and piroxicam (1.96). The reporting rate for GI toxicity for nimesulide based on VigiBase data (0.32 per 10 million DDDs) is in line with that found for CSULGIE cases (0.048 per million DDDs).

- *Clinical and epidemiological studies*

Endoscopy studies suggest less mucosal damage associated with treatment with nimesulide (200 mg/day) compared to indomethacin (150 mg/day) and naproxen (1000 mg/day). No difference was found when nimesulide 200 mg/day was compared to diclofenac 150 mg/day. As indomethacin was regarded a positive control, and naproxen was used in a double dose (1000 mg per day, 2DDD), no clear beneficial effect from the endoscopy studies can be concluded for nimesulide.

Pooled analysis performed by the "Safety Of non Steroidal anti-inflammatory drugs (SOS) project" funded in 2008 by the EC was presented. The **meta-analysis** included 26 studies comparing the risk of UGIC between users and nonusers of NSAIDs (of a total of 2,540 studies published between 1980 and 2008). Pooled relative risks (RR) for each individual NSAID were estimated using random-effect models. The results showed RRs ranging from 1.49 (95% CI 1.07-2.08) for celecoxib to 18.45 (10.99-30.97) for azapropazone. RRs were less than 2 for celecoxib and ibuprofen; from 2 to less than 4 for rofecoxib, diclofenac, sulindac and nimesulide (3.8); from 4 to 5 for meloxicam, tenoxicam, ketoprofen, naproxen, diflunisal and indometacin; and greater than 5 for piroxicam, ketorolac and azapropazone. It is noted that the effect of dose was not adjusted and may have caused variation in identified risks, especially for drugs that are being applied for both analgesia and anti-inflammation.

A **new epidemiological study** - risk of Upper gastrointestinal complications in users of nimesulide and other NSAIDs in Friuli-Venezia Guilia (FVG GI study) was submitted. This was a retrospective cohort and nested case-control study. A total of 588,827 subjects who received at least one prescription for a systemic NSAID between 1 January 2001 and 31 December 2008 were included in the final cohort with 251,013 users of nimesulide followed by 226,805 users of diclofenac, 150,062 for ketoprofen, 121,117 for piroxicam, 97, 527 for celecoxib, 94,148 for ibuprofen, 67,705 for etoricoxib,

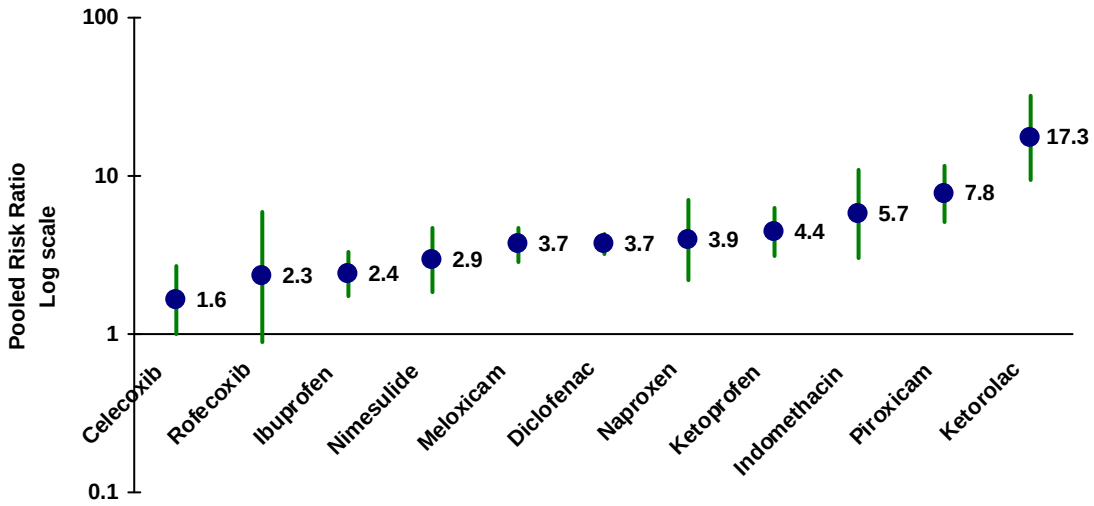
61,759 for ketorolac, 57,242 for rofecoxib, 56,289 for aceclofenac, 48,498 for meloxicam, 37,216 for indomethacin, 31, 207 for naproxen.

Among this cohort, cases of upper gastrointestinal (GI) complications (UGIC) were identified and validated. The case-control analysis was restricted to those cases aged 20 to 84 years and included 2,735 cases and 27,011 controls that were selected using density-based sampling. Current use of different NSAIDs was compared to non-use in logistic regression analyses. The following table shows the adjusted relative risk of UGIC associated with the use of individual NSAIDs.

Use of NSAIDs	Cases (n = 2,735)		Controls (n = 27,011)		Adjusted RR (by age, sex, and risk factors) (95% CI)		
	n	%	n	%	RR	LL	UL
Nonuse	1357	49.6	17215	63.7	1.00	-	-
Current single	353	12.9	1510	5.6	2.83	2.43	3.29
Rofecoxib	10	0.4	109	0.4	0.84	0.41	1.74
Celecoxib	24	0.9	170	0.6	1.38	0.85	2.24
Nimesulide	42	1.5	412	1.5	1.53	1.08	2.18
Naproxen	8	0.3	39	0.1	2.74	1.14	6.59
Ibuprofen	24	0.9	84	0.3	3.04	1.81	5.12
Diclofenac	81	3.0	271	1.0	3.24	2.40	4.36
Etoricoxib	16	0.6	55	0.2	3.27	1.72	6.19
Meloxicam	13	0.5	36	0.1	4.47	2.16	9.27
Ketoprofen	30	1.1	72	0.3	5.45	3.29	9.05
Piroxicam	37	1.4	100	0.4	5.70	3.65	8.89
Ketorolac	47	1.7	26	0.1	21.76	11.93	39.70
Other NSAIDs	21	0.8	136	0.5	1.72	1.02	2.90

The results indicate that the risk associated with nimesulide is comparable to that of NSAIDs in the mid and lower range of risk for UGICs.

The MAH provided a pooled analysis of UGIC epidemiological studies in which the final results of the FVG GI study were also included (see below figure). Pooled relative risks for UGIC were estimated from 5 studies (Friuli Venezia Giulia, 2011; Salmivaara et al., 2007; Laporte et al., 2004; García Rodríguez et al., 1998; Menniti-Ippolito et al., 1998).



According to pooled analyses of epidemiological studies, nimesulide risk for UGIC appears comparable to that of NSAIDs in the lower range. The point estimates of the pooled analysis considering the interim final results of the FVG GI study, the risk for UGIC associated with nimesulide (2.98 [1.96-4.53]) is found lower than or comparable to naproxen (3.85 [2.12-6.99]), diclofenac (3.62 [3.10-4.23]) and ketoprofen (4.62 [3.07-6.96]),comparable to or higher than that for ibuprofen (2.29 [1.73-3.04]) and higher than that for celecoxib (1.65 [1.02-2.69]). However, no direct comparisons are available, and confidence intervals are overlapping considerably.

The pooled analysis do not allow for calculation of the absolute risk due to the majority of the studies being case-control and only provided relative risk estimates. Therefore the incidence rate of UGIC for Nimesulide was estimated by multiplying the pooled relative risks by the absolute background incidence for UGIC (100 in 100,000 person years). This was considered the most robust method since more information from different studies is considered and not only from the only considered cohort study by Menniti-Ippolito. Both methods are presented in the following table.

	Menniti-Ippolito crude rates			*Extrapolated pooled relative risks*		
	Events	PY	Incidence rate /100 000py	Pooled RR	Background incidence	Incidence rate /100 000py
Celecoxib	-	-		1.65	1/100000	165
Ibuprofen	-	-		2.29	1/100000	229
Nimesulide	14	8047	174	2.98	1/100000	298
Diclofenac	33	11730	278	3.62	1/100000	362
Naproxen	8	3940	203	3.85	1/100000	385
Ketoprofen	9	3233	281	4.62	1/100000	462
Indomethacin	-	-		5.70	1/100000	570

Hence, the incidence rate for UGIC associated with nimesulide is estimated to be approximately 300 per 100,000 person years.

Cardiovascular toxicity

- *Post marketing data*

A total of 202 serious and non-serious adverse reactions pertain to the Cardiac and Vascular SOCs have been registered in the brand leader MAH's safety database up to 2010 (14 December). This represents 3.4 % of the overall adverse events reported.

Based on the WHO VigiBase data, the event reporting rates for cardiac disorders events per 10 million DDDs nimesulide is 0.05 and for vascular disorsers 0.09. The cardiovascular reporting rate for nimesulide is similar to that of naproxen, ibuprofen, diclofenac and paracetamol, and lower than for piroxicam, meloxicam, ketoprofen, indometacin and celecoxib. The case reporting rate for cardiac and cerebral ischaemia was very low overall, with a higher rate for celecoxib (0.35), indomethacin (0.04), meloxicam, ketoprofen and piroxicam than for nimesulide (0.01).

Based on spontaneous reporting data it does not seem to be a concern with respect to nimesulide's cardiotoxicity as compared to other NSAIDs.

- *Clinical and epidemiological studies*

An epidemiological study assessing cardiovascular safety of nimesulide using the Finnish database assessed the risk for first hospitalisation for Myocardial Infarction associated with NSAIDs, considering both duration of therapy and the age of the user. Among individual substances, the mean adjusted odds ratio associated with the current use of nimesulide vs. non use was 1.69 (95% CI: 1.43-1.99), with indomethacin 1.56 (95% CI: 1.21-2.03), with rofecoxib 1.44 (95% CI: 1.20-1.72), with ibuprofen 1.41 (95% CI: 1.28-1.55), with diclofenac 1.35 (95% CI: 1.18-1.54), and with naproxen 1.19 (95% CI: 1.02-1.38).

The cardiovascular risk profile of nimesulide is not better than for other NSAIDs: naproxen, ibuprofen and diclofenac.

Renal toxicity

- *Post marketing data*

A total of 255 serious and non-serious adverse reactions pertain to the Renal SOC have been registered in the brand leader MAH's safety database up to 2010 (14 December). This represents 4.4 % of the overall adverse events reported. The reports include 117 cases of some type of renal failure and several cases with interstitial or other forms of nephritis. Also in the Investigations SOC, there were 23 reports with some form of renal abnormalities. Effects of nimesulide on hemodynamic and renal functions are comparable to those observed with other NSAIDs. Inhibition of renal prostaglandins accounts for most of the renal effects of NSAIDs which are mostly temporary effects, as resulted by the analysis of the nimesulide cases.

Based on the WHO VigiBase data, the event reporting rates for Renal SOC per 10 million DDDs nimesulide is 0.17. This is similar to that seen for meloxicam (0.15), naproxen (0.16), ibuprofen (0.20) and diclofenac (0.20). The event reporting rate of acute renal failure for nimesulide (0.09 per 10million DDD) as compared to other NSAIDs is in line with that observed for the general SOC.

- *Clinical and epidemiological studies*

Results from pooled randomised clinical studies did not identify any report of nephritis or renal failure. In the large observational studies, no signals were identified involving the renal system.
The absolute incidence of serious renal adverse events is at least 0.5 per 10 million DDD, and 0.02 per million DDDs for acute renal failure.

Skin toxicity

- *Post marketing data*

A total of 1462 adverse events pertaining to the skin SOC have been registered in the brand leader MAH's safety database up to 2010 (14 December). This represents 25.1% of the overall adverse events reported. There were 34 reports of Stevens-Johnson Syndrome (SJS) and 15 of toxic epidermal necrolysis (TEN) as well as a small number of other severe cutaneous adverse reaction reports.

Based on the WHO VigiBase data, the event reporting rates for skin SOC per 10 million DDDs nimesulide is 1.00. This is comparable with that of other NSAIDs such as diclofenac (1.12), naproxen (1.02) and paracetamol (1.13) and better than that of ibuprofen (1.60), sulindac, piroxicam, ketoprofen or indometacin. The event reporting rate for severe cutaneous adverse reactions acute for nimesulide (0.09 per 10million DDD) was similar to that for ibuprofen (0.16), paracetamol (0.12), naproxen (0.8), diclofenac (0.07) and meloxicam (0.05).

- *Clinical and epidemiological studies*

The pooled clinical studies provided did not identify reports of serious skin reactions such as SJS or toxic TEN. There were single reports of bullous dermatitis for nimesulide and for diclofenac. Most of the skin events comprised pruritus, rash and urticaria. None of the reports was classified as serious. In the large observational studies, serious skin reactions were not reported in association with nimesulide.

Immune system disorders

- *Post marketing data*

A total of 96 reports with adverse reactions from the immune system disorders SOC have been registered in the brand leader MAH's safety database up to 2010 (14 December). This includes 44 reports describing anaphylactic/ anaphylactoid reactions.

Based on the WHO VigiBase data, the event reporting rates for immune disorders SOC per 10 million DDDs nimesulide is 0.05 which is the lowest of all NSAIDs and similar to meloxicam (0.05), indomethacin (0.06) and paracetamol (0.07). The event reporting rate of anaphylaxis for nimesulide (0.04 per 10 million DDD) was similar to that for ibuprofen (0.06), paracetamol (0.05), indomethacin (0.05) and piroxicam (0.03).

- *Clinical and epidemiological studies*

There was a very low incidence of immune system events among the 64,000 nimesulide treated patients in a pooled clinical studies review. In total 14 patients reported unspecified hypersensitivity, face oedema and angioneurotic oedema. None of these was serious and there were no reports of anaphylaxis.

Nervous system disorders

- *Post marketing data*

A total of 254 reactions belonging to the Nervous system SOC, including 46 reports of dizziness, 44 of headache, 32 of somnolence and 18 of tremor were identified from the MAH's safety database up to 2010 (14 December). In addition, a cumulative review of suspected neurological events of 'paraesthesia' (21) and 'presyncope' (12), regardless of seriousness and considering both primary and secondary events was conducted to be submitted in the six-month PSUR 34.

Based on the WHO VigiBase data, the event reporting rates for Nervous system disorders SOC per 10 million DDDs nimesulide is 0.15 which is a low reporting rate of nervous system disorders, similar to those of paracetamol, naproxen, ketoprofen and ibuprofen, and half or less those of diclofenac, piroxicam, meloxicam, indometacin and celecoxib.

2.3.2. Discussion

Hepatoxicity

The safety data provided support that nimesulide is associated with an increased risk for hepatotoxicity vs. no-use or past use.

Nimesulide has shown a higher risk for hospital admission for hepatoxicity when compared to other NSAIDs combined as a single category (Travessa, 2003). Pooled data from epidemiological studies shows that nimesulide risk for hospital admission for hepatoxicity is comparable to ibuprofen, diclofenac and indomethacin, higher than for naproxen or ketoprofen and lower than for sulindac.

The absolute risk for hospital admission for hepatopathy associated with nimesulide is approximately 30-35 per 100,000 person-years.

Results of the SALT study suggest that the (crude) incidence rate per billion DDDs for acute liver failure indicated for transplantation associated with nimesulide is higher than for celecoxib, diclofenac, ketoprofen, and naproxen and lower than for ibuprofen, paracetamol and indomethacin.

The absolute risk for acute liver failure indicated for transplantation with nimesulide is 5.64 [2.43-11.11] per million person-years and 5.90 per billion DDDs.

The SALT-1 study has several limitations namely a small number of cases, only severe cases of liver failure and very wide confidence intervals.

The absolute risk for abnormal liver function tests with nimesulide is approximately 1%.

Spontaneous reporting rates per 10 million DDDs suggest that the risk for liver injury is higher than for ketoprofen, ibuprofen, meloxicam, diclofenac and naproxen and similar to celecoxib, piroxicam, paracetamol and sulindac.

Overall, nimesulide seems to have a worse safety profile for hepatotoxicity compared to diclofenac and naproxen. The hepatotoxic profile compared to ibuprofen varies from worse profile in spontaneous reports data, to comparable or slightly better in pooled epidemiological studies and in the SALT study.

There are several possible mechanisms of action for nimesulide-induced hepatoxicity. Data presented including a recent study on possible role of reactive metabolites, suggest that several of the described mechanisms may all contribute to the nimesulide induced hepatotoxicity. The mechanism of action for nimesulide induced hepatotoxicity is still not clear. Due to this lack of current understanding it is not possible to determine or predict the risk for nimesulide-associated liver liability at the individual patient level.

Gastrointestinal toxicity

The risk for Upper Gastrointestinal Complication (UGIC) associated with nimesulide appears to be lower than or comparable to that for naproxen, diclofenac, and ketoprofen, comparable to or higher than that for ibuprofen, and higher than that for celecoxib, as shown in pooled analysis of epidemiological studies including the recent GI study conducted in Fruili-Venezia Gulia. However, it must be noted that no direct comparisons are available, and confidence intervals are overlapping considerably.

The incidence rate for UGIC associated with nimesulide is estimated to be approximately 300 per 100,000 person years.

Based on data available, the risk of gastrointestinal complications due to nimesulide is lower than for ketorolac, piroxicam, indomethacin and azopropazone, but not proven consistently different from other NSAIDs such as celecoxib, ibuprofen, naproxen, ketoprofen, diclofenac, sulindac and meloxicam. Overall, the gastrointestinal toxicity of nimesulide is regarded to be no worse or better than most of the other available NSAIDs.

When combining both liver injury and GI toxicity nimesulide falls in the mid range of the other NSAIDs. This is presented in the below table that combines VigiBase data on liver injury with nimesulide (0.38 per 10 million DDDs) and on GI perforation, ulceration or bleeding cases (PUB) associated with nimesulide (0.32 per 10 million DDDs).

	Reporting rate / 10^7 DDD
Paracetamol	0.31
Naproxen	0.44
Ibuprofen	0.55
Diclofenac	0.58
Nimesulide	0.70
Meloxicam	0.85
Ketoprofen	0.91
Indometacin	1.11
Celecoxib	1.26
Sulindac	1.60
Piroxicam	2.23

Other risks

Based on all the data submitted, it is concluded that the **cardiovascular risk** profile of nimesulide is not better than for naproxen, ibuprofen and diclofenac. Celecoxib, indomethacin and sulindac may be associated with a worse cardiovascular risk profile. However, the risk for first time MI associated with celecoxib appears to be lower than for nimesulide, whereas spontaneous reports suggest a worse cardiovascular risk profile for celecoxib.
The absolute incidence for CV events cannot be estimated accurately, but according to the VigiBase analyses the frequency of cardiac and cerebral thrombotic events combined is at least 0.01 per 10 million DDDs.

The **renal safety profile** for nimesulide is regarded as comparable to other NSAIDs. Absolute incidence of serious renal adverse events with nimesulide is at least 0.5 per 10 million DDD, and 0.02 per million DDDs for acute renal failure.

Nimesulide has a comparable slightly favourable **skin safety profile** to other NSAIDs. The absolute incidence of serious skin adverse events with nimesulide is at least 1 per 10 million DDD.

The **immunological safety** of nimesulide is comparable or slightly favourable to other NSAIDs. Absolute incidence of allergic conditions is at least 0.03 per 10 million DDDs.

Overall Safety vs Other NSAIDs

The overall reporting rate of all adverse reactions (WHO VigiBase) per 10 million DDDs for nimesulide was similar to that for diclofenac, ibuprofen, naproxen, meloxicam and paracetamol and lower than for

celecoxib, indometacin, piroxicam and sulindac. Considering all data, the overall safety profile for nimesulide compared to other NSAIDs can be summarised as shown in the below table.

	diclofenac	ibuprofen	ketoprofen	celecoxib	sulindac	naproxen	indomethacin	paracetamol
GI	=	≤	≥	≤ ≥	=	≥	≥	<
Hepat	≤	≤ to ≥	≤	<	>	<	≥	>
CV	≤	≤	≤	< >	< >	≤	≥	=
Renal	≤	≤	>	>	≤	≤	>	≥
Skin	=	≥	>	>	≤	=	≥	=
Immuno	≥	=	=	≥	>	=	=	=
CNS	≥	≥	≥	>	≤	≥	>	=

Nimesulide is: > beneficial; ≥ at least comparable; = comparable; ≤ not better; < worse.

Note: This table reflects the cumulative safety profile of nimesulide as seen at this time point and does not take into account time trends to assess the effects of regulatory actions that have been taken following the previous referrals.

Comparisons for gastrointestinal and hepatic safety are based on both clinical, epidemiological studies as well as spontaneous reporting data. The comparisons for the other safety issues and the combined GI hepatic safety profiles are mainly based on spontaneous reporting only, hence the evidence is regarded to be limited. Additionally, it should be noted that not all NSAIDs are indicated for acute pain indications as nimesulide. Market leaders in the EU are diclofenac and ibuprofen, while naproxen and ketoprofen are also widely used for these indications. Celecoxib is not indicated for acute pain.

Compared to diclofenac and naproxen, nimesulide has a worse safety profile both for hepatoxicity alone as when combining (more severe) GI and hepatic toxicity data.

2.4. Overall benefit/risk assessment

Efficacy

Nimesulide efficacy in the treatment of pain associated with several inflammatory and painful disorders has been shown in mostly short-term studies (up to four weeks) with limited numbers of patients. Although there are some results of clinical studies that may suggest rapid onset of analgesic action associated with the use of nimesulide compared with other NSAIDs, the clinical relevance of the measured differences in onset of pain relief is doubtful.

Based on available data, it is concluded that the proven efficacy of nimesulide in short-term clinical studies is consistent with the indication for short-term use only (i.e. maximum 15 days of treatment) as previously restricted to minimise the risks for hepatoxicity. No unequivocal and clinically meaningful advantage over other NSAIDs has been demonstrated and, therefore the Committee considered the efficacy of nimesulide to be similar to other NSAIDs available.

Safety

Nimesulide is associated with an increased risk of hepatotoxicity versus no-use or past use. Further to the review of all available data, it is overall concluded that nimesulide seems to have a worst safety profile for hepatotoxicity compared to diclofenac and naproxen, both for severe liver injury requiring transplant and for hospitalisation for liver injury. The hepatotoxic profile compared to ibuprofen varies from worse in spontaneous reports, to comparable with respect to hospitalisations for liver injury or slightly better with respect to severe liver injury requiring transplant.

The absolute risk for acute liver failure indicated for transplantation is 5.64 [2.43-11.11] per million person-years and 5.90 per billion DDDs. The absolute risk for hospital admission for hepatoxicity is approximately 30-35 per 100,000 person-years and the absolute risk for abnormal liver function tests is approximately 1%.
The hepatoxicity of nimesulide was previously assessed under the Article 107 procedure triggered by the new information regarding cases of fulminant hepatic failure associated with its use in Ireland and the consequent suspension of the marketing authorisations for nimesulide in that Member State. At that time the magnitude of the increased risk of severe hepatic adverse reactions with nimesulide compared to other NSAIDs seen in spontaneous reporting, clinical and epidemiological studies seemed slight, with the exception of the signal raised by Ireland. Further to that the results of the SALT study became available. In this regard the SALT study was a key piece of data expected to provide further insight. As discussed throughout this report, the SALT study presented several limitations such as small number of identified cases, all severe cases are of acute liver failure and very wide confidential

intervals making the results not being robust. Nevertheless, the SALT study did confirm the signal seen in Ireland which was not seen in any other country involved in the study. This signal could possibly be due to environmental, genetic factors involved and it remains to be explained.

Data available including a new epidemiological study (FVG GI study) confirms that all NSAIDs can induce damage to the gastroduodenal mucosa and increase the risk of upper gastrointestinal complications (UGIC). The risk of gastrointestinal complications due to nimesulide is lower than for ketorolac, piroxicam, indomethacin and azopropazone, but not proven to be consistently different from other NSAIDs such as celecoxib, ibuprofen, naproxen, ketoprofen, diclofenac, sulindac and meloxicam. However, it must be noted that no direct comparisons are available, and confidence intervals are overlapping considerably.

Overall, gastrointestinal toxicity of nimesulide is regarded to be comparable to other available NSAIDs. When combining both liver injury and GI toxicity nimesulide falls in the mid range of the other NSAIDs. The safety profile in terms of hepatotoxicity and gastro intestinal toxicity for nimesulide is shown as worse than alternative NSAIDs such as diclofenac and naproxen.

No new safety issue with respect to cardiovascular disorders, renal safety, skin, immunological and nervous system safety has arisen from the data submitted during this review. It seems that the risk profile of nimesulide is not better than for other NSAIDs with regards to cardiovascular disorders. Data suggests that that the renal safety for nimesulide is comparable to other NSAIDs and also comparable or slightly favourable with regards to skin, immunological and nervous system safety.

Benefit/risk balance

Nimesulide efficacy is proven in short-term clinical studies which is consistent with the indication for short-term use (i.e. maximum 15 days of treatment) previously introduced to minimise the risks for hepatoxicity. Overall nimesulide is at least as effective as other NSAIDs in short-term use indications for pain.

There is an increased risk of hepatoxicity associated with nimesulide whose magnitude still raises uncertainties. It is noted that 23% of the hepatic cases reported for nimesulide involved patients treated for more chronic indications. Therefore the committee concluded that nimesulide use should be restricted to acute conditions only i.e. treatment of acute pain and primary dysmenorrhoea. In view of the risk of chronic use in the treatment of osteoarthritis and aiming further minimisation of the risks associated with nimesulide, the CHMP concluded that nimesulide has no longer a positive risk- benefit in this indication.

2.5. Risk management plan

The Risk Management Plan in place for nimesulide-containing medicinal products for systemic use is amended to reflect that nimesulide is no longer indicated for the symptomatic treatment of painful osteoarthritis. Furthermore one of the ongoing minimisation measures previously introduced under Article 107 - A survey on the identification of the mode of use of nimesulide by General Practitioners – will be performed 9 months after the CHMP Opinion on this procedure under Article 31.

2.6. Changes to the product information

The relevant section of the SmPC and Package Leaflet for nimesulide-containing products for systemic use are amended to reflect that nimesulide is no longer indicated for the symptomatic treatment of painful osteoarthritis. Furthermore, the frequency of the gastro intestinal perforation, ulceration or bleeding cases (PUB cases) is amended to "uncommon" in line with the data presented under the gastrointestinal toxicity subheading of section 2.3.1 of this report.

The following wording is deleted (~~strikethrough text~~), added or moved (<u>underlined text</u>) within the same section of the SmPC and PL as follows:

Summary of Product Characteristics

[…]
4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of acute pain (see section 4.2)
~~Symptomatic treatment of painful osteoarthritis (see section 4.2)~~
Primary dysmenorrhoea

Nimesulide should only be prescribed as second line treatment. The decision to prescribe nimesulide should be based on assessment of the individual patient's overall risks (see section 4.3 and 4.4).
[…]

4.8 Undesirable effects
[…]

Gastrointestinal disorders
[…]
Uncommon: Gastrointestinal bleeding, Duodenal ulcer and perforation, Gastric ulcer and perforation
[…]
Hepato-biliary disorders
Common: Hepatic enzymes increased
[…]

Package Leaflet
[…]
1. WHAT *{(INVENTED) NAME}* IS AND WHAT IT IS USED FOR

{(Invented) name} is a non-steroidal anti-inflammatory drug ("NSAID") with pain-killing properties. It is used for the treatment of acute pain~~, for the treatment of symptoms of painful osteoarthritis~~ and for the treatment of period pains.
[…]

4. POSSIBLE SIDE EFFECTS
[…]
Side effects that may occur with {(Invented) name} are:
[…]
Uncommon: bleeding from stomach or bowel; duodenal or stomach ulcers and burst ulcers.
[…]

2.7. Communication plan

As part of this referral procedure, the CHMP agreed the wording of a 'Dear healthcare professional' communication designed to inform prescribers of the positive risk-benefit of nimesulide in short-treatment indications only (i.e. acute pain and primary dysmenorrhoea) and on the no longer favourable risk-benefit balance for the symptomatic treatment of osteoarthritis in view of the hepatotoxicity risks in chronic use.

A harmonised release date of the communication as also been agreed.

3. Overall conclusion

Having considered the overall submitted data provided by the MAHs in writing and in the oral explanation, the CHMP concluded:

- that evidence of the clinically efficacy of nimesulide-containing products for systemic use in the indications for short-term treatment has been shown. No unequivocal and clinically meaningful advantage over other NSAIDs has been demonstrated and, therefore the Committee considered the efficacy of nimesulide to be similar to other NSAIDs available.

- that nimesulide overall gastrointestinal toxicity is comparable to other NSAIDs but that nimesulide is associated with an increased risk for hepatotoxicity. The combined safety profile in terms of hepatotoxicity and gastro intestinal toxicity for nimesulide is shown as worse than some other alternative NSAIDs such as diclofenac and naproxen. Furthermore, the limitations of the current available data lead to uncertainties on hepatotoxicity, and concerns remain especially with prolonged use of nimesulide.

- Considering the maximum duration of 15 days of treatment to minimise the risk for hepatotoxicity and aiming a further minimisation of the risks associated with nimesulide, the Committee considered that nimesulide use should be restricted to acute conditions only i.e. treatment of acute pain and primary dysmenorrhoea.

- That in light of the above, considered that there is a risk of chronic use of nimesulide in "symptomatic treatment of painful osteoarthritis" and concludes that the risk-benefit balance of nimesulide-containing medicinal products for systemic use is no longer favourable in this indication.

Therefore, the CHMP recommended the variation to the terms of the marketing authorisations for the medicinal products referred to in Annex I of the Opinion, for which amendments to the relevant sections of the summary of product characteristics and package leaflet are set out in Annex III to the opinion.

The conditions affecting the marketing authorisations are set out in Annex IV of the Opinion.

Appendix

DIVERGENT POSITIONS

DIVERGENT POSITIONS

The undersigned members of CHMP did not agree with the Committee's opinion.

The reasons for divergent opinion were the following:

Liver-related toxicity remains worrying: results from epidemiological studies show that nimesulide has a worse profile for hepatotoxicity compared to other available non-steroidal anti-inflammatory drugs and the data from the SALT-1 study confirm the concern on fatal or nearly fatal (hepatic transplant) cases reported by Ireland and other member States.

Nimesulide has not convincingly demonstrated superior efficacy that may outweigh the increased risk.

The major concern is that there are no specific risk factors that could be identified, that would explain the signal seen in Ireland (and possibly Finland) and that could be used to predict idiosyncratic hepatotoxicity and develop specific risk minimisation measures. Nimesulide, even with limited indications, could be introduced in Member States where it was not authorised before. In such cases, it cannot be excluded that the newly exposed patient populations will not have similar reactions to the Irish patients and it is highly likely that idiosyncratic hepatotoxicity could occur more frequently.

The frequency of idiosyncratic hepatotoxicity, the lack of specific risk minimization measures and the resulting uncertainty, without the therapeutic added value make the benefit risk balance negative.

London, 23 June 2011

……
Dr. George Aislaitner

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Dr. Pieter Neels

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Dr. Christian Schneider

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Dr. Sol Ruiz

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Dr. Concepcion Prieto Yerro

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Dr. David Lyons

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Dr. Pierre Demolis

……

Prof. Metoda Lipnik-Stangelj

……

Dr. Jean-Louis Robert

……

Dr. Alar Irs

……

Dr. Harald Enzmann

……

Dr. Milena Stain

……

Dr. Barbara van Zwieten-Boot

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London, 23 June 2011

……
Dr. Kolbeinn Gudmundsson

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The major concern is that there are no specific risk factors that could be identified, that would explain the signal seen in Ireland (and possibly Finland) and that could be used to predict idiosyncratic hepatotoxicity and develop specific risk minimisation measures. Nimesulide, even with limited indications, could be introduced in Member States where it was not authorised before. In such cases, it cannot be excluded that the newly exposed patient populations will not have similar reactions to the Irish patients and it is highly likely that idiosyncratic hepatotoxicity could occur more frequently.

The frequency of idiosyncratic hepatotoxicity, the lack of specific risk minimization measures and the resulting uncertainty, without the therapeutic added value make the benefit risk balance negative.

London, 23 June 2011

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Prof. Eva Skovlund