HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

17 October 2012

Examination of the dossier for proprietary medicinal products included for a 5-year period starting on 7 August 2007 (Official Gazette of 23 April 2009)

MOBIC 7.5 mg, tablets
B/14 (CIP code: 339 608-5)

MOBIC 15 mg, scored tablets
B/14 (CIP code: 338 906-2)

MOBIC 15 mg/1.5 ml, solution for injection
B/3 ampoules (CIP code: 353 974-5)

Applicant: BOEHRINGER INGELHEIM

meloxicam

ATC code: M01AC06 (NSAIDs)

List I

Date of Marketing Authorisation (mutual recognition procedure):
08/05/1995 MOBIC 7.5 mg - 15 mg tablets
20/03/2000 MOBIC 15 mg/1.5 ml solution for injection

Reason for request:

- renewal of inclusion on the list of medicines refundable by National Health Insurance;
- re-assessment of Actual Benefit at the request of the Transparency Committee in accordance with article R 163-21 of the Social Security Code.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

meloxicam

1.2. Indications

"MOBIC 7.5 mg tablets and MOBIC 15 mg scored tablets:
- Short-term symptomatic treatment of acute exacerbations of osteoarthritis;
- Long-term symptomatic treatment of rheumatoid arthritis or ankylosing spondylitis."

MOBIC 15 mg/1.5 ml solution for injection
"Short-term symptomatic treatment of acute exacerbations of rheumatoid arthritis or ankylosing spondylitis, where treatment cannot be administered orally or rectally."

1.3. Dosage

15 mg and 7.5 mg tablets
"For oral use.
The total daily dose should be taken as a single dose, with water or another liquid, during a meal.
Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms.
The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically, especially in patients with osteoarthritis.

- Acute exacerbations of osteoarthritis: 7.5 mg/day (one 7.5 mg tablet or half a 15 mg tablet). If necessary, in the absence of improvement, the dose may be increased to 15 mg/day (two 7.5 mg tablets or one 15 mg tablet).

- Rheumatoid arthritis, ankylosing spondylitis: 15 mg/day (two 7.5 mg tablets or one 15 mg tablet) (see also section "Special populations" below).

According to the therapeutic response, the dose may be reduced to 7.5 mg/day (one 7.5 mg tablet or half a 15 mg tablet). Do not exceed the dose of 15 mg/day.

Special populations
Elderly patients and patients with increased risks for adverse reaction
The recommended dose for long-term treatment of rheumatoid arthritis and ankylosing spondylitis in elderly patients is 7.5 mg per day. Patients with increased risks for adverse reactions should start treatment with 7.5 mg per day.

Renal impairment
In dialysis patients with renal failure, the dose should not exceed 7.5 mg per day. No dose reduction is required in patients with mild to moderate renal impairment (i.e. patients with a creatinine clearance greater than 25 ml/min). (For patients with non-dialysed severe renal failure, see section 4.3 of the SPC.)

Hepatic impairment
No dose reduction is required in patients with mild to moderate hepatic impairment. (For patients with severely impaired liver function, see section 4.3 of the SPC.)

Children and adolescents
MOBIC is contraindicated in children and adolescents aged under 16 years.
This medicinal product exists in other forms and dosages, which may be more appropriate."

15 mg solution for injection
"Intramuscular administration.
One 15 mg ampoule once daily.
DO NOT EXCEED THE DOSE OF 15 MG/DAY.
Treatment is normally limited to a single injection to initiate treatment, with a maximum duration of 2 to 3 days in exceptional cases (for example, when treatment cannot be administered orally or rectally).
Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms.
The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically.

Special populations
Elderly patients and patients with increased risks for adverse reaction
The recommended dose in elderly patients is 7.5 mg/day. Patients with increased risks for adverse reactions should start treatment with 7.5 mg per day (half a 15 mg ampoule).
Renal impairment
In dialysis patients with renal failure, the dose should not exceed 7.5 mg per day (half a 15 mg ampoule). No dose reduction is required in patients with mild to moderate renal impairment (i.e. patients with a creatinine clearance of greater than 25 ml/min). (For patients with non-dialysed severe renal failure, see section 4.3.)
Hepatic impairment
No dose reduction is required in patients with mild to moderate hepatic impairment. (For patients with severely impaired liver function, see section 4.3.)
Children and adolescents
MOBIC 15 mg/1.5 ml solution for injection is contraindicated in children and adolescents aged under 18 years.

Method of administration
The medicinal product should be injected deeply and slowly, under strict aseptic conditions, into the external part of the superior external quadrant of the thigh. For repeated injections, it is recommended to change sides with each injection. It is important to aspirate before injecting, in order to ensure that the tip of the needle is not in a blood vessel.
If severe pain occurs during the injection, stop immediately.
In patients with a hip prosthesis, the injection should be given in the opposite side."

2 REMINDER OF COMMITTEES OPINIONS AND CONDITIONS OF INCLUSION

Committee Opinion of 3 March 1999

Since pharmacovigilance data has led to changes to the wording of the Summary of Product Characteristics, the 7.5 mg and 15 mg tablets do not offer any improvement in actual benefit (IAB) over comparator medicines.

Committee Opinion of 6 December 2000:

Inclusion of solution for injection. This is a product line extension: improvement in actual benefit (IAB) level V.

Committee Opinion of 24 April 2002 – renewal of inclusion

The actual benefit of the 7.5 mg and 15 mg tablets is substantial. The actual benefit of the solution for injection is moderate.

Committee Opinion of 16 April 2003 – renewal of inclusion

The actual benefit of the 7.5 mg and 15 mg tablets is substantial. The actual benefit of the solution for injection is moderate.

Committee Opinion of 18 April 2007 – renewal of inclusion

The actual benefit of the 7.5 mg and 15 mg tablets is substantial. The actual benefit of the solution for injection is moderate.

Committee Opinion of 5 October 2011 – removal from the list

Removal from the list, following market withdrawal, of MOBIC 7.5 mg and 15 mg suppositories.

3 SIMILAR MEDICINAL PRODUCTS

3.1. ATC Classification (2012)

M	Musculo-skeletal system
M01	Anti-inflammatory and antirheumatic products
M01A	Anti-inflammatory and antirheumatic products, non-steroids
M01AC	Oxicams
M01AC06	Meloxicam

3.2. Medicines in the same therapeutic category

These are non-steroidal anti-inflammatory drugs from the oxicam family.

3.3. Medicines with a similar therapeutic aim

All other proprietary medicinal products used in the management of the conditions targeted by MOBIC.

4 UPDATE ON THE DATA AVAILABLE SINCE THE PREVIOUS OPINION

4.1. Evaluation background

Mechanism of action
Meloxicam is a non-steroidal anti-inflammatory drug from the oxicam family. Like nimesulide and nabumetone, it is sometimes classed as a preferential COX-2 inhibitor, i.e. inhibiting COX-2 more than COX-1.

Reminder of European evaluations
Like all NSAIDs, MOBIC has been subject to several re-evaluations of its risk/benefit ratio by the European Medicines Agency (EMA).

In October 2005, the Committee for Medicinal Products for Human Use (CHMP) delivered the conclusions of its evaluation of safety data for non-selective NSAIDs, carried out at the request of the European Commission with the aim of identifying their possible risks, particularly cardiovascular, gastrointestinal and dermatological risks. The CHMP concluded that "the therapeutic benefit of these medicinal products was not called into question and their risk/benefit ratio remained favourable". However, the decision was made to standardise the summaries of product characteristics (SPCs) for all NSAIDs, due to the disparities observed between the countries of the European Union. This standardisation led to the addition of information about the risks of heart failure and hypertension, gastrointestinal complications and severe skin reactions.

The CHMP also concluded that there was a need for in-depth evaluation of the risk/benefit ratio for some NSAIDs (piroxicam, ketoprofen and ketorolac). Although, like piroxicam, it belongs to the oxicam class, meloxicam was not included in this re-evaluation.
The review, completed in June 2006, revealed a potentially increased risk of gastrointestinal and skin reactions (including a bullous eruption that can be fatal) with systemic forms of piroxicam in comparison with other non-selective NSAIDs (CHMP conclusions, published 21 June 2007). The CHMP nonetheless deemed that "the risk/benefit ratio for piroxicam remains favourable in the symptomatic treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis, subject to modification of the conditions of use of these medicines (second-line therapy when an NSAID is indicated, and the treatment must be reconsidered after 14 days of treatment). For the treatment of other diseases in the acute phase, the risk/benefit ratio was considered to be unfavourable due to piroxicam's long half-life (50 hours) and its safety profile."

In 2006, the EMA conducted an evaluation of new data regarding the cardiovascular safety of some traditional non-steroidal anti-inflammatory drugs (NSAIDs) including meloxicam. The conclusions of this evaluation were that "the risk/benefit ratio for NSAIDs remains favourable, although they may be associated with a slightly increased risk of arterial thrombosis (myocardial infarction or cerebrovascular accident)".[1]
As regards meloxicam, the report[2] indicated that:
"New data comprising the final report of three epidemiological studies on the risk of myocardial infarction have recently become available. These data were presented during the 22nd International Conference on Pharmacoepidemiology & Therapeutic Risk Management, held in August 2006 in Lisbon. Two comparisons have been performed: meloxicam with

[1] AFSSAPS: news update. Evaluation des nouvelles données de tolérance cardiovasculaire : le rapport bénéfice/risque des AINS reste favorable mais les précautions d'emploi doivent être renforcées. 24 October 2006.
[2] EMEA. Public CHMP assessment report for medicinal products containing non-selective non steroidal anti-inflammatory drugs (NSAIDs). Procedure No. EMEA/H/A-5.3/800. November 2006.

diclofenac in one report, and meloxicam with non-use in another report. Three databases in three different countries were used: - the GPRD (General Practitioner Research Database) in the UK, based on data from general practitioners (GPs). It contains information on 9 million patients (3 million current) and 400 general practices; - the RAMQ (Règles de l'Assurance Maladie au Québec), based on hospital cases and covering 7.4 million patients on 01/07/04; - the VA (Veteran's Administration) in the USA, based on hospital cases. It cares for over 7 million patients who have served in the armed forces of the US.
New epidemiological data for meloxicam, based on analyses in three independent databases, do not indicate that meloxicam is associated with an increased risk of thrombotic cardiovascular disease, in relation to non-use or to use of diclofenac. However, the data are rather inconsistent as regards outcomes for other NSAIDs and there are no details on the duration or dose of use or of time to event. Therefore, these new data, although reassuring, do not permit firm conclusions to be made. Thus, there is still uncertainty about the thrombotic cardiovascular risk profile for meloxicam."

In December 2007, the SPC was changed as part of the standardisation of NSAID SPCs, with added information about cardiovascular, gastrointestinal and dermatological safety.

In 2009, the SPC was changed to add contraindications in the 3rd trimester of pregnancy and in children and adolescents aged under 16 years (see annex).

In October 2011, the EMA announced that a new re-evaluation of the cardiovascular risk from traditional NSAIDs was underway in order to update their 2006 recommendations.
At the date of writing, this re-evaluation is still ongoing.

Transparency Committee evaluation context
Following the EMA re-evaluation of systemic forms of piroxicam in 2006, the Transparency Committee re-evaluated the actual benefit of these medicinal products in April 2009. Its conclusions were as follows:

- Where an NSAID is indicated, piroxicam should only be chosen as a second-line therapy due to its risk of severe gastrointestinal and dermatological adverse effects.
- As second-line therapy where an NSAID is indicated in rheumatoid arthritis, ankylosing spondylitis and symptomatic osteoarthritis of the hip and knee, the **actual benefit of oral forms of piroxicam is moderate and the actual benefit of IV and rectal forms is low**. In other types of osteoarthritis, the actual benefit is insufficient.

As part of the examination for the renewal of inclusion of the MOBIC proprietary medicinal products, which belong to the same class as piroxicam, the Transparency Committee sought to re-evaluate the actual benefit of these medicinal products in accordance with article R. 163-21.

4.2. Efficacy

Since the last Committee opinion of 2007 (renewal of inclusion), no clinical studies evaluating the efficacy and safety of meloxicam in its Marketing Authorisation indications have been published. Three clinical studies were performed in China with the aim of obtaining Marketing Authorisation, in which the injectable form was compared to the oral form.

The pharmaceutical company cited the following data, which will not be described:

- a summary of a study presented at a conference in 2007, with the study report not provided;
- an English guideline for the management of osteoarthritis published in 2008, of little relevance for assessing the efficacy and safety of meloxicam.

The pharmaceutical company also provided a literature review published in 2008, described below.

Review by Chen et al 2008[3]

The aim of this literature review was to evaluate the efficacy and cost-effectiveness of COX-2 selective non-steroidal anti-inflammatory drugs (etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib) in the treatment of osteoarthritis or rheumatoid arthritis. Only the efficacy results for meloxicam will be presented.

Sixteen (16) randomised controlled studies comparing meloxicam 7.5 - 22.5 mg/day to placebo or to some traditional NSAIDs (diclofenac 100 mg/day, naproxen 750 mg/day, nabumetone 1g/day or piroxicam 20 mg/day) were included in this analysis. Twelve of these studies involved patients with osteoarthritis and 4 involved patients with rheumatoid arthritis.

Compared to traditional NSAIDs, meloxicam had inferior or equivalent efficacy (VAS difference 1.7 [0.8; 2.7], overall efficacy -0.05 [-0.25; 0.15]). There were fewer symptomatic gastrointestinal events (RR = 0.53, 95% CI: [0.29; 0.97]. Combined analysis did not demonstrate any difference for complicated gastrointestinal events (RR = 0.56, 95% CI: [0.27; 1.15]). There was an insufficient number of events to draw any conclusions on the risk of myocardial infarction.

4.3. Adverse effects

The pharmaceutical company submitted data from three PSURs covering the period November 2004 to July 2010 and all forms marketed around the world. The most frequently reported serious adverse effects were gastrointestinal disorders (12.4%) and skin disorders (4.6%).

A review of deaths of gastrointestinal or dermatological origin has been ongoing since 1993.

No deaths of dermatological origin have been attributed to meloxicam. Rare cases of bullous eruptions such as Stevens-Johnson syndrome and more rarely toxic epidermal necrolysis have been reported.

Between 30/08/1993 and 08/11/2004, 141 deaths including 78 deaths of gastrointestinal origin (55%) were reported. Between 09/11/2004 and 09/07/2007, 46 deaths including 10 deaths of gastrointestinal origin (22%) were reported. Between 10/09/2009 and 09/07/2010, 5 deaths of which none were of gastrointestinal origin were reported, and between 10/07/2010 and 31/01/2011, 7 deaths of which none were of gastrointestinal origin were reported.

Cases of agranulocytosis and aplastic anaemia were and are subject to special monitoring.

The pharmaceutical company also provided a publication on the dermatological safety of NSAIDs (Ward 2010), which did not specifically include meloxicam, and a publication on their renal safety (Lafrance 2009[4]).

The Lafrance et al (2009) publication included 15 cases involving meloxicam. This American epidemiological study showed that the risk of acute kidney injury was higher in patients who had recently used NSAIDs than in non-users (OR: 1.82 [1.68; 1.98]). This risk of acute kidney injury was variable: rofecoxib (0.95 [0.64; 1.42]), celecoxib (0.96 [0.63; 1.47]), meloxicam (1.13 [0.63; 2.05]), etodolac (1.31 [1.08; 1.59]), diclofenac (1.11 [0.84; 1.48]), piroxicam (1.53 [1.05; 2.23]), salsalate (1.51 [1.22; 1.87]), sulindac (1.61 [1.12; 2.30]), ibuprofen (2.25 [2.04; 2.49]), naproxen (1.72 [1.52; 1.95]), low-dose aspirin (3.64 [2.46; 5.37]), indomethacin (1.94 [1.56; 2.42]), ketorolac (2.07 [1.78; 2.41]). Patients using several NSAIDs appeared to be at greater risk (2.90 [2.62; 3.22]).

[3] Chen, Y.F. et al. Cyclooxygenase-2 selective non-steroidal anti-inflammatory drugs (etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib) for osteoarthritis and rheumatoid arthritis: a systematic review and economic evaluation. HTA 2008; 12(11).

[4] Lafrance et al. Selective and non-selective non-steroidal anti-inflammatory drugs and the risk of acute kidney injury Pharmacoepidemiol Drug Saf 2009; 18: 923-31.

The ANSM pharmacovigilance department was consulted, and after checking the available databases, no safety alerts concerning meloxicam were found.

5 MEDICINAL PRODUCT USAGE DATA

Prescribing data:

According to IMS-EPPM data (moving annual total November 2011), 321,000 prescriptions have been issued for these proprietary medicinal products, comprising 142,000 for the 7.5 mg tablets, 94,000 for the 15 mg tablets and 84,000 for the injectable form. The average dose was 1.1 units per day.

6 TRANSPARENCY COMMITTEE CONCLUSIONS

6.1. Re-evaluation of actual benefit

MOBIC 7.5 mg and 15 mg tablets

Rheumatoid arthritis is a potentially serious and disabling chronic inflammatory disease, which mostly affects women.

Ankylosing spondylitis is a chronic inflammatory disease that mainly affects the vertebral column and sacroiliac joints (axial form) as well as the peripheral entheses (particularly in the heel). The disease generally starts between the ages of 15 and 40, and it affects men three times as often as women.

Osteoarthritis is a joint disorder. Its prevalence increases with age. It can be painful and is characterised by potential progression to disability and/or a marked deterioration in quality of life. The disabling forms, particularly those of the hip and knee, require surgery.

These proprietary medicinal products are intended as symptomatic treatment.

They are first-line or second-line therapies.

Their adverse effects are those which are typical of NSAIDs: gastrointestinal disorders, hypersensitivity reactions (dermatological, respiratory and general), effects on the central nervous system, skin and mucosal reactions, altered laboratory test values (liver function, kidney function and haematology), and cardiovascular effects (increased risk of arterial thrombotic events, particularly myocardial infarction and CVA).

The efficacy/adverse effects ratio for these medicinal products **remains high** in the treatment of rheumatoid arthritis and ankylosing spondylitis, and **remains modest** in the treatment of osteoarthritis.

The actual benefit of these medicinal products **remains substantial** in the Marketing Authorisation indications (exacerbations of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis).

MOBIC solution for injection
Rheumatoid arthritis is a potentially serious and disabling chronic inflammatory disease, which mostly affects women.
Ankylosing spondylitis is a chronic inflammatory disease that mainly affects the vertebral column and sacroiliac joints (axial form) as well as the peripheral entheses (particularly in the heel). The disease generally starts between the ages of 15 and 40, and it affects men three times as often as women.

This proprietary medicinal product is intended as symptomatic therapy.

It is a second-line drug to be used where the administration of oral medicines is impossible.

Its adverse effects are those which are typical of NSAIDs: gastrointestinal disorders, hypersensitivity reactions (dermatological, respiratory and general), effects on the central nervous system, skin and mucosal reactions, altered laboratory test values (liver function, kidney function and haematology), and cardiovascular effects (increased risk of arterial thrombotic events, particularly myocardial infarction and CVA).

The efficacy/adverse effects ratio for this medicinal product **remains modest**.

The actual benefit of this medicinal product **remains moderate for treatment not exceeding 3 days; beyond that, its actual benefit is insufficient**.

6.2. Transparency Committee recommendations

The Transparency Committee recommends continued inclusion on the list of medicines refundable by National Health Insurance in all the indications and at the dosages in the Marketing Authorisation.

6.2.1. Packaging: Appropriate for the prescription conditions.
The Committee hopes that, for patients requiring fewer than three injections, the solution for injection will be made available as a box of one ampoule in addition to the box of three ampoules.

6.2.2. Reimbursement rate:
65% (7.5 mg tablets; 15 mg scored tablets).
30% (15 mg/1.5 ml solution for injection).

Table of changes made to the SPC for the medicinal product MOBIC

2007 SPC	2009 SPC
4.3. Contraindications This medicinal product is contraindicated in the following situations: • Pregnancy and breastfeeding (see section 4.6); • Hypersensitivity to meloxicam or to one of the excipients or hypersensitivity to substances with a similar action, e.g. other NSAIDs, aspirin. MOBIC should not be given to patients who have developed signs of asthma, nasal polyps, angioneurotic oedema or urticaria following the administration of aspirin or other NSAIDs; • History of gastrointestinal bleeding or perforation, related to previous NSAID therapy; • Active peptic ulcer, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding); • Gastrointestinal bleeding, cerebrovascular bleeding or other bleeding disorders; • Severely impaired liver function; • Non-dialysed severe renal failure; • Severe heart failure.	**4.3. Contraindications** This medicinal product is contraindicated in the following situations: • Third trimester of pregnancy (see section 4.6); • Children and adolescents aged under 16 years; • Hypersensitivity to meloxicam or to one of the excipients or hypersensitivity to substances with a similar action, e.g. other NSAIDs, aspirin. MOBIC should not be given to patients who have developed signs of asthma, nasal polyps, angioneurotic oedema or urticaria following the administration of aspirin or other NSAIDs; • History of gastrointestinal bleeding or perforation, related to previous NSAID therapy; • Active or recent peptic ulcer, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding); • Gastrointestinal bleeding, history of cerebrovascular bleeding or other bleeding disorders; • Severely impaired liver function; • Non-dialysed severe renal failure; • Severe heart failure.
4.4. Special warnings and precautions for use • Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2 and the paragraphs “Gastrointestinal effects” and “Cardiovascular and cerebrovascular effects” below). • The recommended maximum daily dose should not be exceeded in case of insufficient therapeutic effect, nor should an additional NSAID be added to the therapy because this may increase the toxicity while therapeutic advantage has not been proven. The use of MOBIC with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided. In the absence of improvement after several days, the clinical benefit of the treatment should be reassessed. • If there is a history of oesophagitis, gastritis and/or peptic ulcer, complete healing must be ensured before starting treatment with meloxicam. Patients treated with meloxicam and with a past history of this type should be routinely monitored for any recurrence.	**4.4. Special warnings and precautions for use** • Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2 and the paragraphs “Gastrointestinal effects” and “Cardiovascular and cerebrovascular effects” below). • The recommended maximum daily dose should not be exceeded in case of insufficient therapeutic effect, nor should an additional NSAID be added to the therapy because this may increase the toxicity while therapeutic advantage has not been proven. The use of meloxicam with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided. Meloxicam is not appropriate for the treatment of acute pain. In the absence of improvement after several days, the clinical benefit of the treatment should be reassessed. • If there is a history of oesophagitis, gastritis and/or peptic ulcer, complete healing must be ensured before starting treatment with meloxicam. Patients treated with meloxicam and with a past history of this type should be routinely monitored for any recurrence.

Gastrointestinal effects GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at any time during treatment, with or without warning symptoms or a previous history of serious GI events. The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low-dose aspirin, or other drugs likely to increase gastrointestinal risk (see below and section 4.5). Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment. Caution is advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as orally administered corticosteroids, oral anticoagulants such as warfarin, selective serotonin reuptake inhibitors (SSRIs) and antiplatelet drugs such as acetylsalicylic acid (see section 4.5). When GI bleeding or ulceration occurs in patients receiving MOBIC, the treatment should be withdrawn. NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) and these patients should be closely monitored, as these conditions may be exacerbated (see section 4.8). **Cardiovascular and cerebrovascular effects** Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy. Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long-term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). There are insufficient data to exclude such a risk for meloxicam. Patients with uncontrolled hypertension, congestive heart failure, ischaemic heart disease, peripheral arterial disease, and/or a history of cerebrovascular accident (including transient ischaemic attack) should only be treated with	**Gastrointestinal effects** GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at any time during treatment, with or without warning symptoms or a previous history of serious GI events. The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low-dose aspirin, or other drugs likely to increase gastrointestinal risk (see below and section 4.5). Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment. Caution is advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as ~~orally administered corticosteroids~~ heparin as curative treatment or given in geriatrics, ~~oral~~ anticoagulants such as warfarin, ~~selective serotonin reuptake inhibitors (SSRIs) and antiplatelet drugs such as acetylsalicylic acid~~ or other non-steroidal anti-inflammatory drugs, including acetylsalicylic acid given at anti-inflammatory doses (≥ 1g as single intake or ≥ 3g as total daily amount) (see section 4.5). When GI bleeding or ulceration occurs in patients receiving meloxicam, the treatment should be withdrawn. NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) and these patients should be closely monitored, as these conditions may be exacerbated (see section 4.8). **Cardiovascular and cerebrovascular effects** Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy. Clinical monitoring of blood pressure for patients at risk is recommended during treatment with meloxicam and especially during treatment initiation. Clinical trial and epidemiological data suggest that use of some NSAIDs including meloxicam (particularly at high doses and in long-term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). There are insufficient data to exclude such a risk for meloxicam. Patients with uncontrolled hypertension, congestive heart failure, ischaemic heart disease, peripheral arterial disease, and/or a history of cerebrovascular accident

meloxicam after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).	(including transient ischaemic attack) should only be treated with meloxicam after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).
Skin reactions Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (see section 4.8). Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. MOBIC should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.	**Skin reactions** Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (see section 4.8). Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Meloxicam should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.
	Parameters of liver and renal function As with most NSAIDs, occasional increases in serum transaminase levels, increases in serum bilirubin or other liver function parameters, and increases in serum creatinine and blood urea nitrogen and other laboratory disturbances have been reported. The majority of these instances involved transitory and slight abnormalities. Should any such abnormality prove significant or persistent, the administration of meloxicam should be stopped and appropriate investigations undertaken.
Functional renal failure NSAIDs, by inhibiting the vasodilating effect of renal prostaglandins, may induce functional renal failure by reduction of glomerular filtration. This adverse event is dose-dependent. At the beginning of the treatment, or after dose increase, careful monitoring of diuresis and renal function is recommended in patients with the following risk factors: • elderly; • concomitant treatment with ACE inhibitors, angiotensin II antagonists, sartans or diuretics (see section 4.5); • hypovolaemia (whatever the cause); • congestive heart failure; • renal failure; • nephrotic syndrome; • lupus nephropathy;	**Functional renal failure** NSAIDs, by inhibiting the vasodilating effect of renal prostaglandins, may induce functional renal failure by reduction of glomerular filtration. This adverse event is dose-dependent. At the beginning of the treatment, or after dose increase, careful monitoring of diuresis and renal function is recommended in patients with the following risk factors: • elderly; • concomitant treatment with ACE inhibitors, angiotensin II antagonists, sartans or diuretics (see section 4.5); • hypovolaemia (whatever the cause); • congestive heart failure; • renal failure; • nephrotic syndrome;

• severe hepatic dysfunction (serum albumin < 25 g/l or Child-Pugh score ≥ 10).	• lupus nephropathy;
	• severe hepatic dysfunction (serum albumin < 25 g/l or Child-Pugh score ≥ 10).
In rare instances NSAIDs may be the cause of interstitial nephritis, glomerulonephritis, renal medullary necrosis or nephrotic syndrome.	In rare instances NSAIDs may be the cause of interstitial nephritis, glomerulonephritis, renal medullary necrosis or nephrotic syndrome.
	The dose of meloxicam in patients with end-stage renal failure on haemodialysis should not be higher than 7.5 mg. No dose reduction is required in patients with mild or moderate renal impairment (i.e. in patients with a creatinine clearance of greater than 25 ml/min).
Sodium and water retention	**Sodium, potassium and water retention**
Induction of sodium and water retention with possible oedema, hypertension or aggravation of existing hypertension, or aggravation of heart failure. Clinical monitoring is necessary from the start of treatment in cases of hypertension or heart failure. A decrease in the effect of antihypertensive drugs can occur (see section 4.5).	Induction of sodium, potassium and water retention and interference with the natriuretic effects of diuretics may occur with NSAIDs. Furthermore, a decrease of the antihypertensive effect of antihypertensive drugs can occur (see section 4.5). Consequently, ~~with possible oedema, hypertension or aggravation of existing hypertension, or aggravation of heart failure,~~ cardiac failure or hypertension may be precipitated or exacerbated in susceptible patients. Clinical monitoring is therefore necessary ~~from the start of treatment in cases of hypertension or heart failure. A decrease in the effect of antihypertensive drugs can occur (see section 4.5).~~
Aggravation of the condition of patients with heart failure or hypertension may be observed with NSAIDs following sodium, potassium and water retention and interference with the natriuretic effects of diuretics (see sections 4.2 and 4.3).	~~Aggravation of the condition of patients with heart failure or hypertension may be observed with NSAIDs following sodium, potassium and water retention and interference with the natriuretic effects of diuretics for patients at risk~~ (see sections 4.2 and 4.3).
Hyperkalaemia	**Hyperkalaemia**
Hyperkalaemia may be induced in cases of diabetes or concomitant treatment with medicines known to increase serum potassium (see section 4.5). Regular monitoring of potassium values should be performed in such cases.	Hyperkalaemia may be induced in cases of diabetes or concomitant treatment with medicines known to increase serum potassium (see section 4.5). Regular monitoring of potassium values should be performed in such cases.
Elderly patients	~~**Elderly patients**~~
Adverse reactions are often less well tolerated in elderly, fragile or weakened individuals, who therefore require careful monitoring. As with other NSAIDs, particular caution is required in the elderly, in whom renal, hepatic and cardiac functions are frequently impaired.	~~Adverse reactions are often less well tolerated in elderly, fragile or weakened individuals, who therefore require careful monitoring. As with other NSAIDs, particular caution is required in the elderly, in whom renal, hepatic and cardiac functions are frequently impaired.~~
The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (see section 4.2).	~~The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (see section 4.2).~~
• As with most NSAIDs, occasional increases in serum transaminase levels, increases in serum bilirubin or other liver function parameters, and increases in serum creatinine and blood urea nitrogen and other laboratory disturbances have been reported. The majority of these instances involved transitory and slight abnormalities. Should any such abnormality prove significant or	• ~~As with most NSAIDs, occasional increases in serum transaminase levels, increases in serum bilirubin or other liver function parameters, and increases in serum creatinine and blood urea nitrogen and other laboratory disturbances have been reported. The majority of these instances involved transitory and slight abnormalities. Should any such abnormality prove significant or persistent, the administration of meloxicam should be stopped and appropriate investigations undertaken.~~

persistent, the administration of meloxicam should be stopped and appropriate investigations undertaken. • Meloxicam, as any other NSAID, may mask symptoms of an underlying infectious disease. • The use of meloxicam, as with any drug known to inhibit cyclooxygenase / prostaglandin synthesis, may impair fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving, or who are undergoing investigation of infertility, withdrawal of meloxicam should be considered. • Patients with rare hereditary problems of galactose intolerance, the Lapp-lactase deficiency or glucose-galactose malabsorption should not take this medicine.	• ~~Meloxicam, as any other NSAID, may mask symptoms of an underlying infectious disease.~~ • ~~The use of meloxicam, as with any drug known to inhibit cyclooxygenase / prostaglandin synthesis, may impair fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving, or who are undergoing investigation of infertility, withdrawal of meloxicam should be considered.~~ • ~~Patients with rare hereditary problems of galactose intolerance, the Lapp-lactase deficiency or glucose-galactose malabsorption should not take this medicine.~~ Other warnings and precautions ~~Elderly patients~~ Adverse reactions are often less well tolerated in elderly, fragile or weakened individuals, who therefore require careful monitoring. As with other NSAIDs, particular caution is required in the elderly, in whom renal, hepatic and cardiac functions are frequently impaired. The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (see section 4.2). Meloxicam, as any other NSAID, may mask symptoms of an underlying infectious disease. The use of meloxicam, as with any drug known to inhibit cyclooxygenase / prostaglandin synthesis, may impair fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving, or who are undergoing investigation of infertility, withdrawal of meloxicam should be considered. MOBIC 15 mg tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp-lactase deficiency or glucose-galactose malabsorption should not take this medicine.
4.5. Interaction with other medicinal products and other forms of interaction **Pharmacodynamic Interactions:** **+ Other NSAIDs, including salicylates (acetylsalicylic acid > 3g/day):** Co-administration of several NSAIDs can increase the risk of gastrointestinal ulcers and bleeding, through a synergistic effect. Meloxicam should not be administered simultaneously with other NSAIDs (see section 4.4). **+ Orally administered corticosteroids:** Increased risk of bleeding or gastrointestinal ulceration (see section 4.4).	**4.5. Interaction with other medicinal products and other forms of interaction** Interaction studies have only been performed in adults. **Pharmacodynamic Interactions:** **+ Other non-steroidal anti-inflammatory drugs (NSAIDs) and acetylsalicylic acid > 3g/day:** Combination (see section 4.4) with other non-steroidal anti-inflammatory drugs, including acetylsalicylic acid given at anti-inflammatory doses (≥ 1 g as single intake or ≥ 3 g as total daily amount) is not recommended (see section 4.4). **+ Corticosteroids (e.g. glucocorticoids):** Concomitant use with corticosteroids requests caution because of an increased risk of bleeding or gastrointestinal ulceration.

+ Oral anticoagulants: Increased risk of bleeding, via inhibition of platelet function and damage to the gastroduodenal mucosa. NSAIDs may enhance the effects of anticoagulants, such as warfarin (see section 4.4). The concomitant use of NSAIDs and anticoagulants is not recommended (see section 4.4). Careful monitoring of the INR is required if it proves impossible to avoid such a combination.	**+ Anticoagulants or heparin administered in geriatrics or at curative doses:** Considerably increased risk of bleeding, via inhibition of platelet function and damage to the gastroduodenal mucosa. NSAIDs may enhance the effects of anticoagulants, such as warfarin (see section 4.4). The concomitant use of NSAIDs and anticoagulants or heparin administered in geriatrics or at curative dose is not recommended (see section 4.4). In remaining cases of heparin use, caution is necessary due to an increased bleeding risk. Careful monitoring of the INR is required if it proves impossible to avoid such a combination.
+ Thrombolytics and antiplatelet drugs: Increased risk of bleeding, via inhibition of platelet function and damage to the gastroduodenal mucosa.	**+ Thrombolytics and antiplatelet drugs:** Increased risk of bleeding, via inhibition of platelet function and damage to the gastroduodenal mucosa.
+ Selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding (see section 4.4).	**+ Selective serotonin reuptake inhibitors (SSRIs):** Increased risk of gastrointestinal bleeding.
+ Diuretics, ACE inhibitors and angiotensin II antagonists: NSAIDs may reduce the effect of diuretics and other antihypertensive drugs. In some patients with compromised renal function (e.g. dehydrated patients or some elderly patients) the co-administration of an ACE inhibitor or angiotensin II antagonist and agents that inhibit cyclooxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter (see also section 4.4).	**+ Diuretics, ACE inhibitors and angiotensin II antagonists:** NSAIDs may reduce the effect of diuretics and other antihypertensive drugs. In some patients with compromised renal function (e.g. dehydrated patients or some elderly patients) the co-administration of an ACE inhibitor or angiotensin II antagonist and agents that inhibit cyclooxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter (see also section 4.4).
+ Other antihypertensive drugs (e.g. beta-blockers): As with ACE inhibitors and angiotensin II antagonists, a decrease in the antihypertensive effect of beta-blockers (due to inhibition of prostaglandins with vasodilatory effect) can occur.	**+ Other antihypertensive drugs (e.g. beta-blockers):** As with ACE inhibitors and angiotensin II antagonists, a decrease in the antihypertensive effect of beta-blockers (due to inhibition of prostaglandins with vasodilatory effect) can occur.
+ Ciclosporin Nephrotoxicity of ciclosporin may be enhanced by NSAIDs via renal prostaglandin mediated effects. During combined treatment renal function should be monitored, especially in the elderly.	**+ Calcineurin inhibitors (e.g. ciclosporin, tacrolimus):** Nephrotoxicity of calcineurin inhibitors may be enhanced by NSAIDs via renal prostaglandin mediated effects. During combined treatment renal function should be monitored, especially in the elderly.
	+ Intrauterine devices: NSAIDs have been reported to decrease the efficacy of intrauterine devices. A decrease of the efficacy of intrauterine devices by NSAIDs has been previously reported but needs further confirmation.

+ Intrauterine devices: NSAIDs have been reported to decrease the efficacy of intrauterine devices. A decrease of the efficacy of intrauterine devices by NSAIDs has been previously reported but needs further confirmation.	
Pharmacokinetic Interactions (effect of meloxicam on the pharmacokinetics of other drugs) **+ Lithium** NSAIDs have been reported to increase blood lithium levels (via decreased renal excretion of lithium), which may reach toxic values. The concomitant use of lithium and NSAIDs is not recommended (see section 4.4). If this combination cannot be avoided, lithium plasma concentrations should be monitored carefully during the initiation, ongoing course and withdrawal of meloxicam treatment.	**Pharmacokinetic Interactions (effect of meloxicam on the pharmacokinetics of other drugs)** **+ Lithium** NSAIDs have been reported to increase blood lithium levels (via decreased renal excretion of lithium), which may reach toxic values. The concomitant use of lithium and NSAIDs is not recommended (see section 4.4). If this combination cannot be avoided, lithium plasma concentrations should be monitored carefully during the initiation, ongoing course and withdrawal of meloxicam treatment.
+ Methotrexate NSAIDs can reduce the tubular secretion of methotrexate thereby increasing the plasma concentrations of methotrexate. For this reason, for patients on high dosages of methotrexate (more than 15 mg/week) the concomitant use of NSAIDs is not recommended (see section 4.4). The risk of an interaction between NSAID preparations and methotrexate should be considered also in patients on low doses of methotrexate, especially in patients with impaired renal function. In the case of combination treatment, blood cell count and renal function should be monitored. Special precautions are required if methotrexate and NSAIDs are administered simultaneously for three consecutive days, due to the risk of toxicity from increased plasma levels of methotrexate. Although the pharmacokinetics of methotrexate (15 mg/week) were not significantly affected by concomitant meloxicam treatment, it should be considered that the haematological toxicity of methotrexate can be amplified by treatment with NSAID drugs (see above) (see section 4.8).	**+ Methotrexate** NSAIDs can reduce the tubular secretion of methotrexate thereby increasing the plasma concentrations of methotrexate. For this reason, for patients on high dosages of methotrexate (more than 15 mg/week) the concomitant use of NSAIDs is not recommended (see section 4.4). The risk of an interaction between NSAID preparations and methotrexate should be considered also in patients on low doses of methotrexate, especially in patients with impaired renal function. In the case of combination treatment, blood cell count and renal function should be monitored. Special precautions are required if methotrexate and NSAIDs are administered simultaneously for three consecutive days, due to the risk of toxicity from increased plasma levels of methotrexate. Although the pharmacokinetics of methotrexate (15 mg/week) were not significantly affected by concomitant meloxicam treatment, it should be considered that the haematological toxicity of methotrexate can be amplified by treatment with NSAID drugs (see above).
Pharmacokinetic Interactions (effect of other drugs on the pharmacokinetics of meloxicam) **+ Cholestyramine** Cholestyramine accelerates the elimination of meloxicam by interrupting the enterohepatic circulation so that meloxicam clearance increases by 50% and the half-life decreases to 13±3 hrs. This interaction is of clinical significance.	**Pharmacokinetic Interactions (effect of other drugs on the pharmacokinetics of meloxicam)** **+ Cholestyramine** Cholestyramine accelerates the elimination of meloxicam by interrupting the enterohepatic circulation so that meloxicam clearance increases by 50% and the half-life decreases to 13±3 hrs. This interaction is of clinical significance. No clinically relevant pharmacokinetic drug-drug interactions were detected with respect to the concomitant administration of antacids, cimetidine or digoxin.

No clinically relevant pharmacokinetic drug-drug interactions were detected with respect to the concomitant administration of antacids, cimetidine or digoxin.	
4.8. Undesirable effects **a) General Description** Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4). Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment. The most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4) have been reported following the administration of NSAIDs. Less frequently, gastritis has been observed. The frequencies of adverse drug reactions given below are based on corresponding occurrences of reported adverse events in clinical trials. The information is based on clinical trials involving 3750 patients who have been treated with daily oral doses of 7.5 or 15 mg meloxicam tablets or capsules over a period of up to 18 months (mean duration of treatment 127 days). Adverse reactions that have come to light from spontaneous reporting after the marketing of the product are also included. Adverse reactions have been ranked under headings of frequency using the following convention: Very common (> 1/10); common (> 1/100 to < 1/10); uncommon (> 1/1,000 to < 1/100); rare (> 1/10,000 to < 1/1,000); very rare (< 1/10,000). **b) Table of adverse reactions** Blood and lymphatic system disorders Common: Anaemia Uncommon: Blood count abnormal: leukopenia, thrombocytopenia, agranulocytosis (see section c) "Information characterising individual serious and/or frequently occurring adverse reactions").	**4.8. Undesirable effects** **a) General Description** Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long-term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4). Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment. The most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4) have been reported following the administration of NSAIDs. Less frequently, gastritis has been observed. The frequencies of adverse drug reactions given below are based on corresponding occurrences of reported adverse events in 27 clinical trials with a treatment duration of at least 14 days. The information is based on clinical trials involving 15,197 patients who have been treated with daily oral doses of 7.5 or 15 mg meloxicam tablets or capsules over a period of up to one year. Adverse reactions that have come to light from spontaneous reporting after the marketing of the product are also included. Adverse reactions have been ranked under headings of frequency using the following convention: Very common (> 1/10); common (> 1/100 to < 1/10); uncommon (> 1/1,000 to < 1/100); rare (> 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data). **b) Table of adverse reactions** *Blood and lymphatic system disorders* Uncommon: Anaemia Rare: Blood count abnormal (including differential white cell count): leukopenia, thrombocytopenia. Very rare cases of agranulocytosis have been reported (see section c).

Immune system disorders Rare: Anaphylactic reaction, anaphylactoid reaction. Psychiatric disorders Rare: Mood disorders, insomnia, nightmares. Nervous system disorders Common: Light-headedness, headache. Uncommon: Vertigo, tinnitus, somnolence. Rare: Confusion.	*Immune system disorders* Uncommon: Allergic reactions other than anaphylactic or anaphylactoid reactions. Not known: Anaphylactic reaction, anaphylactoid reaction. *Psychiatric disorders* Rare: Mood altered, nightmares. Not known: Confusional state, disorientation. *Nervous system disorders* Common: ~~Light-headedness,~~ headache. Uncommon: Dizziness, somnolence.
Eye disorders Rare: Visual disturbance including blurred vision. Cardiac disorders Uncommon: Palpitations. Vascular disorders Uncommon: Blood pressure increased (see section 4.4), flushing. Respiratory, thoracic and mediastinal disorders Rare: Asthma attacks in individuals allergic to aspirin or other NSAIDs. Gastrointestinal disorders Common: Dyspepsia, nausea, vomiting, abdominal pain, constipation, flatulence, diarrhoea. Uncommon: Gastrointestinal bleeding, gastroduodenal ulcer, oesophagitis, stomatitis. Rare: Gastrointestinal perforation, gastritis, colitis. Gastroduodenal ulcers, perforation and bleeding, when they occur, can sometimes be severe, particularly in elderly patients (see section 4.4). Hepatobiliary disorders Rare: Hepatitis. Skin and subcutaneous tissue disorders Common: Pruritus, rash. Uncommon: Urticaria. Rare: Stevens-Johnson syndrome, toxic epidermal necrolysis, angioedema, bullous reactions such as erythema multiforme, photosensitivity reactions. Renal and urinary disorders Uncommon: Sodium and water retention, hyperkalaemia (see sections 4.4 and 4.5). Rare: Acute functional renal failure in some patients with risk factors (see section 4.4). General disorders and administration site conditions Common: Oedema including oedema of the lower limbs.	*Eye disorders* Rare: Visual disturbance including blurred vision, conjunctivitis. *Ear and labyrinth disorders* Uncommon: vertigo. Rare: Tinnitus. *Cardiac disorders* Rare: Palpitations. Cardiac failure has been reported in association with NSAID treatment. *Vascular disorders* Uncommon: Blood pressure increased (see section 4.4), flushing. *Respiratory, thoracic and mediastinal disorders* Rare: Asthma in individuals allergic to aspirin or other NSAIDs. *Gastrointestinal disorders* Very common: Dyspepsia, nausea, vomiting, abdominal pain, constipation, flatulence, diarrhoea. Uncommon: Occult or macroscopic gastrointestinal haemorrhage, stomatitis, gastritis, eructation. Rare: Colitis, gastroduodenal ulcer, oesophagitis. Very rare: Gastrointestinal perforation. Gastrointestinal haemorrhage, ulceration or perforation may sometimes be severe and potentially fatal, especially in elderly patients (see section 4.4). *Hepatobiliary disorders* Uncommon: Abnormal liver function (e.g. raised transaminases or bilirubin). Very rare: Hepatitis. *Skin and subcutaneous tissue disorders* Uncommon: Angioedema, pruritus, rash. Rare: Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria.

	Very rare: Dermatitis bullous, erythema multiforme. Not known: Photosensitivity reaction. *Renal and urinary disorders* Uncommon: Sodium and water retention, hyperkalaemia (see sections 4.4 and 4.5), renal function test abnormal (increased serum creatinine and/or serum urea). Very rare: Acute renal failure in particular in patients with risk factors (see section 4.4). *General disorders and administration site conditions* Uncommon: Oedema including oedema of the lower limbs. **c) Information characterising individual serious and/or frequently occurring adverse reactions** Very rare cases of agranulocytosis have been reported in patients treated with meloxicam and other potentially myelotoxic drugs (see section 4.5). **d) Adverse reactions which have not been observed yet in relation to the product, but which are generally accepted as being attributable to other compounds in the class** Organic renal injury resulting in acute renal failure: very rare cases of interstitial nephritis, acute tubular necrosis, nephrotic syndrome, and papillary necrosis have been reported (see section 4.4).