

The legally binding text is the original French version

**TRANSPARENCY COMMITTEE**  
**Opinion**  
**5 February 2014**

**FLECTOR 50 mg, granules for oral solution in single-dose sachets**

B/21 (CIP: 34009 352 642 9 9)

Applicant: GENEVRIER

INN	diclofenac epolamine
ATC code (2012)	M01AB05 (Antiinflammatory and antirheumatic products, non-steroids)
Reason for the review	<b>Re-assessment of the Actual Benefit of all systemically administered diclofenac-based medicines at the Committee's request, in compliance with Article R-163-21 of the French Social Security Code</b>
Lists concerned	<b>National Health Insurance</b> (French Social Security Code L.162-17) <b>Inclusion for hospital use</b> (French Public Health Code L.5123-2)
Indications concerned	<b>"In adults (aged over 15 years): short-term symptomatic treatment of acute episodes of:</b> - extra-articular rheumatism such as scapulohumeral periarthritis, tendonitis, bursitis; - microcrystalline arthritis; - osteoarthritis; - lumbar pain; - radicular pain."

<p>AB</p>	<p>✓ <b>Extra-articular rheumatism such as scapulothoracic periarthritis, tendonitis and bursitis</b>  <b>The actual benefit of FLECTOR in these indications remains <u>moderate</u>.</b>  <b>It is <u>insufficient</u> in the subpopulation of patients who have risk factors for cardiovascular events.</b></p> <p>✓ <b>Lumbar pain</b>  <b>The actual benefit of FLECTOR in this indication remains <u>moderate</u>.</b>  <b>It is <u>insufficient</u> in the subpopulation of patients who have risk factors for cardiovascular events.</b></p> <p>✓ <b>Microcrystalline arthritis</b>  <b>The actual benefit of FLECTOR in this indication remains <u>substantial</u>.</b>  <b>It is <u>insufficient</u> in the subpopulation of patients who have risk factors for cardiovascular events.</b></p> <p>✓ <b>Osteoarthritis</b>  <b>The actual benefit of FLECTOR in this indication remains <u>substantial</u>.</b>  <b>It is <u>insufficient</u> in the subpopulation of patients who have risk factors for cardiovascular events.</b></p> <p>✓ <b>Radicular pain</b>  <b>The actual benefit of FLECTOR in this indication remains <u>substantial</u>.</b>  <b>It is <u>insufficient</u> in the subpopulation of patients who have risk factors for cardiovascular events.</b></p>
<p>Therapeutic use</p>	<p>Taking into account:</p> <ul style="list-style-type: none"> <li>- new data on the cardiovascular safety of systemically administered diclofenac, which establish that the cardiovascular risk of diclofenac is similar to that observed with coxibs, when treatment is prescribed in the long term, at the maximum dose, and in particular in patients with cardiovascular risk factors;</li> <li>- the existence of other comparators in the same therapeutic category for which no similar cardiovascular safety alerts have emerged;</li> </ul> <p>the Committee considers that diclofenac has no role in the therapeutic strategy for diseases treated with NSAIDs in patients with significant risk factors for cardiovascular events (particularly permanent treated or untreated arterial hypertension, dyslipidaemia, treated or untreated diabetes, and current use of tobacco or cessation within the past 3 years).</p>

## ADMINISTRATIVE AND REGULATORY INFORMATION

<p>Marketing Authorisation (procedure)</p>	<p>Date of Marketing Authorisation (national procedure): 08/11/1999</p>
<p>Prescribing and dispensing conditions/special status</p>	<p>LIST II</p>

# TRANSPARENCY COMMITTEE

## Assessment report 5 February 2014

### 01 BACKGROUND AND PURPOSE OF THE RE-ASSESSMENT

---

The Transparency Committee (TC) of HAS assesses medicinal products that have obtained Marketing Authorisation when the company marketing them wishes them to be included on the list of medicines refundable by National Health Insurance (articles L.162-17 of the Social Security Code and L.5123-2 of the Public Health Code) or on request.

The TC is a scientific body comprised of medical practitioners, pharmacists and specialists in methodology and epidemiology.

Its objectives are:

- to provide an opinion to ministers responsible for health and social security on the justification for reimbursement of medicinal products by social security and/or for their use in hospital, with particular regard to their actual benefit (AB) and to the improvement in actual benefit (IAB) they are likely to offer over treatments that are already available;
- to contribute to the proper use of medicinal products by publishing relevant, independent scientific information on the products.

These objectives are defined in the Social Security Code, in particular in articles R.163-2 to R.163-21, L.161-37, L.161-39 and L.161-41.

According to articles L.162-17, L.161-37, L.161-39, L.161-41, L.161-44, R.163-2 to R.163-21, R.161-71, R.161-76 and R.161-85 of the Social Security Code and articles L.5123-2 and L.5123-3 of the Public Health Code, the opinions of the TC specify the actual benefit and improvement in actual benefit provided by the medicinal products.

This assessment is performed on the basis of a critical analysis of the scientific data available using evidence-based medicine and expert opinion, in accordance with the indications and dosages in the Marketing Authorisation.

#### 01.1 History and background to the re-assessment

In 2002, new safety data resulted in France activating a procedure to re-assess the risk/benefit ratio of coxibs at European level. In 2004, the EMA assessment of the cardiovascular safety of cyclooxygenase-2 inhibitors (coxibs) concluded that the coxib class could have a higher risk of thrombotic events than placebo and some NSAIDs, which could be related to the dose and duration of use. In France, rofecoxib (VIOXX), the first coxib marketed in April 2000, was withdrawn from the market in 2004 due to an increased risk of cardiovascular events during long-term treatment. This assessment was then extended to NSAIDs. In 2005, the conclusions stated that the effect of NSAIDs on the kidneys was likely to have a negative cardiovascular impact in the long term. In 2006, the possibility of a slight increase in the absolute risk of thrombotic events during long-term use and at high doses of NSAIDs was suggested.

The available data suggested that diclofenac (150 mg/day) was associated with the highest risk of a thrombotic event among the NSAIDs and with a similar risk to the coxibs, and that it might be associated with an increased risk of an arterial thrombotic event (myocardial infarction). The risk of a thrombotic event was added to the summaries of product characteristics (SPCs) for all NSAIDs.

At the request of the European Medicines Agency (EMA), the European Commission funded an independent epidemiological research project called the SOS (Safety Of non-Steroidal anti-inflammatory drugs) project<sup>1</sup> involving 12 research groups across 7 European countries. This project was based on a review of published meta-analyses and was undertaken between 2008 and 2012; its primary objective was to evaluate the cardiovascular and gastrointestinal risks associated with the use of NSAIDs and more specifically coxibs.

Since 2006, new published studies and the results of the independent SOS project have been examined by the CHMP [Committee for Medicinal Products for Human Use]. Despite differences in methodology between the studies, the data are consistent and demonstrate that diclofenac has a similar level of risk to the coxibs. This risk is present at doses above 75 mg/day. The studies did not examine topical diclofenac use; it was considered that the slight systemic exposure from this route of administration would lead to a minimal risk.

Following the CHMP conclusions,<sup>2</sup> in October 2012 the Pharmacovigilance Risk Assessment Committee (PRAC) ordered a review of the data for systemically administered diclofenac at the request of the British health authorities, pursuant to article 31 of Directive 2001/83/EU.

In June 2013, the PRAC<sup>3</sup> delivered the following conclusions:

- Regarding the arterial thrombotic risks of diclofenac, the data available to date, from randomised clinical trials, observational studies and individual epidemiological studies, including a meta-analysis of these studies, allow us to conclude that diclofenac is associated with increased cardiovascular risks. These risks are similar to those associated with COX-2 inhibitors.
- Medicines containing diclofenac are effective in their approved indications.
- In view of the currently available safety data, to maintain a favourable risk/benefit ratio, medicines containing diclofenac should be contraindicated in patients with established congestive heart failure (NYHA [New York Heart Association] class II-IV), ischaemic heart disease, peripheral arterial disease and/or cerebral vascular disease.
- Patients with certain cardiovascular risk factors (hypertension, hyperlipidaemia, diabetes mellitus, tobacco use) should only take diclofenac after meticulous consideration.
- This information should be communicated directly to healthcare professionals.

The conclusions of the PRAC were endorsed by the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) of the EMA on 28 June 2013.<sup>4</sup> In agreement with the PRAC, the CMDh emphasised that, although the benefits of systemically administered diclofenac continue to outweigh the risks, similar precautions should be taken as with COX-2 inhibitors. A decision of the European Commission was adopted on 25 September 2013.

In August 2013, the ANSM [National Medicines and Health Product Safety Agency] placed restrictions on the use of systemically administered medicinal products containing diclofenac. Diclofenac is now contraindicated in patients with established congestive heart failure (NYHA [New York Heart Association] class II-IV), ischaemic heart disease, peripheral arterial disease and/or cerebral vascular disease. Treatment with diclofenac should only be started after careful consideration in patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus and tobacco use). The lowest effective dose of diclofenac should be used for the shortest period necessary to control patients' symptoms.

---

<sup>1</sup> Project led by Erasmus University, Rotterdam.

<sup>2</sup> European Medicines Agency. Assessment report for Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and cardiovascular risk. 18 October 2012. EMA/653433/2012.

<sup>3</sup> European Medicines Agency. PRAC recommends the same cardiovascular precautions for diclofenac as for selective COX-2 inhibitors. 14 June 2013. EMA/353084/2013.

<sup>4</sup> European Medicines Agency. New safety advice for diclofenac – CMDh endorses PRAC recommendation. 28 June 2013. EMA/380947/2013.

In this context, the Transparency Committee wished to re-assess the actual benefit of systemically administered diclofenac-based proprietary medicinal products.<sup>5</sup>

The proprietary medicinal products involved are:

ARTOTEC 50 mg/0.2 mg, tablet (B/30)

ARTOTEC 75 mg/0.2 mg, tablet (B/20)

FLECTOR 50 mg, granules for oral solution in single-dose sachets (B/21)

VOLTARENDOLO 12.5 mg (formerly VOLTADOL), coated tablet (B/30)\*

VOLTARENE 25 mg, gastro-resistant coated tablet (B/30)\*

VOLTARENE 50 mg, gastro-resistant coated tablet (B/30)\*

VOLTARENE LP 75 mg, prolonged-release coated tablet (B/30)

VOLTARENE LP 100 mg, prolonged-release coated tablet (B/15)

VOLTARENE 25 mg, suppository (B/10)

VOLTARENE 100 mg, suppository (B/10)

VOLTARENE 75 mg/3 ml, solution for injection (B/2)

*\* these proprietary medicinal products are available as generics*

The administrative and regulatory information for the systemically administered diclofenac-based proprietary medicinal products affected by the re-assessment is given in Table 1.

Diclofenac is a non-steroidal anti-inflammatory and phenylacetic acid derivative belonging to the aryl carboxylic acid group. It is a non-selective NSAID with analgesic, antipyretic, anti-inflammatory and short-term antiplatelet properties. These properties are related to the inhibition of prostaglandin synthesis.

The proprietary medicinal products affected by the re-assessment are indicated to relieve pain of varying severity and inflammation in a wide range of conditions, particularly arthritic diseases (such as rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and acute gout), acute musculoskeletal disorders (such as peri-arthritis, tendonitis, tenosynovitis and bursitis) and other painful disorders resulting from trauma (such as fractures, lumbar pain, sprains, dislocations, and orthopaedic, dental and other minor surgery), as well as in the treatment of primary dysmenorrhoea after an aetiological assessment.

---

<sup>5</sup> It should be noted that aceclofenac (marketed under the brand name CARTREX 100 mg, tablet) has not been included in this re-assessment. According to the SPC, "Approximately two thirds of the administered dose is excreted via the urine, mainly as hydroxymetabolites. After a single oral dose, only 1% is excreted unchanged. Aceclofenac is most likely metabolised through CYP2C9 into its main metabolite 4'-OH-aceclofenac, which probably has negligible clinical activity. Diclofenac and 4'-OH-diclofenac have been detected among its metabolites."

In its October 2012 analysis, the CHMP mentions aceclofenac: "For aceclofenac, dexibuprofen, ketoprofen, ketorolac, lornoxicam, nimesulide and tenoxicam results were presented only for the two Italian databases... Of these drugs ketorolac was the only one for which very high risks were seen."

**Table 1: Systemically administered diclofenac-based proprietary medicinal products**

<b>Proprietary medicinal product</b>	<b>Indications</b>	<b>Dosage</b>	<b>Prescribing conditions</b>	<b>Marketing authorisation date (procedure)</b>	<b>List</b>
<b>ARTOTEC 50 mg/0.2 mg, tablet B/20  PFIZER</b>	Symptomatic treatment of rheumatic diseases in at-risk patients (particularly those aged > 65 years or with a history of peptic ulcer or intolerance to NSAIDs) for whom anti-inflammatory treatment is essential.	Adverse effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms.  One tablet, 2 to 3 times daily.  The maximum daily dose of 150 mg diclofenac must not be exceeded.	List I	03/08/1993 (national)	National Health Insurance (15%) Hospital use
<b>ARTOTEC 75 mg/0.2 mg, tablet B/20  PFIZER</b>	Symptomatic treatment of acute episodes of rheumatic diseases in at-risk patients (particularly those aged > 65 years or with a history of peptic ulcer or intolerance to NSAIDs) for whom anti-inflammatory treatment is essential.	Adverse effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms.  One tablet, 2 to 3 times daily.  The maximum daily dose of 150 mg diclofenac must not be exceeded.	List I	22/11/1999 (national)	National Health Insurance (15%) Hospital use
<b>FLECTOR 50 mg, granules for oral solution in single-dose sachets B/21  GENEVRIER</b>	These result from diclofenac's anti-inflammatory activity, the significance of signs of intolerance caused by the medicine and its place in the range of anti-inflammatory products currently available.  In adults (aged over 15 years), they are restricted to the short-term symptomatic treatment of acute episodes of:  extra-articular rheumatism such as scapulohumeral peri-arthritis, tendonitis, bursitis, microcrystalline arthritis, osteoarthritis, lumbar pain and radicular pain.	Adverse effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms.  150 mg/day (One sachet 3 times daily)	List II	08/11/1999 (national)	National Health Insurance (65%) Hospital use
<b>VOLTARENE 25 mg, gastro-resistant</b>	These result from diclofenac's anti-inflammatory activity, the significance of signs of intolerance caused by the	Adverse effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms.	List II	08/12/1997 (national)	National Health Insurance (65%)

Proprietary medicinal product	Indications	Dosage	Prescribing conditions	Marketing authorisation date (procedure)	List
<p><b>coated tablet B/30</b></p> <p><b>NOVARTIS PHARMA SAS</b></p>	<p>medicine and its place in the range of anti-inflammatory products currently available.</p> <p>In adults and children aged 15 years and over, they are restricted to:</p> <p>Long-term symptomatic treatment:</p> <ul style="list-style-type: none"> <li>- chronic inflammatory rheumatic diseases, particularly rheumatoid arthritis, ankylosing spondylitis or related syndromes such as Reiter's syndrome and psoriatic arthritis;</li> <li>- some painful and disabling forms of osteoarthritis.</li> </ul> <p>Short-term symptomatic treatment of acute episodes of:</p> <ul style="list-style-type: none"> <li>- extra-articular rheumatism (acute shoulder pain, tendonitis, bursitis);</li> <li>- microcrystalline arthritis;</li> <li>- osteoarthritis;</li> <li>- lumbar pain and severe radicular pain.</li> </ul> <p>Treatment of primary dysmenorrhoea, after aetiological assessment.</p> <p>In children aged 6 years and over, the indication is restricted to juvenile inflammatory rheumatic diseases.</p>	<p><b>Adults</b></p> <p><b>Rheumatology:</b></p> <p>Treatment of acute episodes: 150 mg for a maximum of 7 days, i.e. 2 x 25 mg tablets 3 times daily for 7 days.</p> <p>In the case of an acute flare-up, tablets should be taken before meals.</p> <p>Maintenance treatment (or initial treatment in some patients): 75 to 100 mg daily, i.e. 3 to 4 x 25 mg tablets daily in two or three divided doses.</p> <p><b>Primary dysmenorrhoea:</b> 100 mg daily in two divided doses, i.e. 2 x 25 mg tablets morning and evening.</p> <p><b>Children aged 6 years and over:</b></p> <p>Inflammatory rheumatic disease: 2 to 3 mg/kg/day, divided into two or three doses, for example as an illustration:</p> <ul style="list-style-type: none"> <li>up to 25 kg (about 8 years): 1 x 25 mg tablet twice daily, i.e. 50 mg per day;</li> <li>- 25 to 30 kg (about 8 to 10 years): 1 x 25 mg tablet 2 to 3 times daily, i.e. 50 to 75 mg per day;</li> <li>- 30 to 35 kg (about 10 to 12 years): 1 x 25 mg tablet 3 times daily to 2 x 25 mg tablets twice daily, i.e. 75 to 100 mg per day;</li> <li>- 35 to 50 kg (about 12 to 15 years): 2 x 25 mg tablets 2 to 3 times daily, i.e. 100 to 150 mg per day.</li> </ul> <p>The maximum daily dose of 150 mg must not be exceeded.</p>			Hospital use
<b>VOLTARENE</b>	These result from diclofenac's	Adverse effects may be minimised by using	List II	10/04/1980	National Health

Proprietary medicinal product	Indications	Dosage	Prescribing conditions	Marketing authorisation date (procedure)	List
<p><b>50 mg, gastro-resistant coated tablet B/30</b></p> <p><b>NOVARTIS PHARMA SAS</b></p>	<p>anti-inflammatory activity, the significance of signs of intolerance caused by the medicine and its place in the range of anti-inflammatory products currently available.</p> <p>In adults and children aged 15 years and over, they are restricted to:</p> <p>Long-term symptomatic treatment:</p> <ul style="list-style-type: none"> <li>- chronic inflammatory rheumatic diseases, particularly rheumatoid arthritis, ankylosing spondylitis or related syndromes such as Reiter's syndrome, and psoriatic arthritis;</li> <li>- some painful and disabling forms of osteoarthritis.</li> </ul> <p>Short-term symptomatic treatment of acute episodes of:</p> <ul style="list-style-type: none"> <li>- extra-articular rheumatism (acute shoulder pain, tendonitis, bursitis);</li> <li>- microcrystalline arthritis;</li> <li>- osteoarthritis;</li> <li>- lumbar pain and severe radicular pain.</li> </ul> <p>Treatment of primary dysmenorrhoea, after aetiological assessment.</p> <p>In children weighing 35 kg and over (i.e. about 12 years of age), the indication is restricted to juvenile inflammatory rheumatic diseases.</p>	<p>the lowest effective dose for the shortest duration necessary to control symptoms.</p> <p><b>Adults</b> <b>Rheumatology:</b> Treatment of acute episodes: 150 mg for a maximum of 7 days, i.e. 1 x 50 mg tablet 3 times daily for 7 days. In the case of an acute flare-up, tablets should be taken before meals.</p> <p>Maintenance treatment (or initial treatment in some patients): 75 to 100 mg daily, i.e. 3 x 25 mg tablets to 2 x 50 mg tablets daily in two or three divided doses.</p> <p><b>Primary dysmenorrhoea:</b> 100 mg daily in two doses, i.e. 1 x 50 mg tablet morning and evening.</p> <p><b>Children weighing 35 kg to 50 kg (i.e. 12 to 15 years):</b> Inflammatory rheumatic disease: 2 to 3 mg/kg/day, divided into two or three doses, for example as an illustration: 1 x 50 mg tablet 2 to 3 times daily, i.e. 100 to 150 mg per day.</p> <p>The maximum daily dose of 150 mg must not be exceeded.</p>		(national)	Insurance (65%) Hospital use
<p><b>VOLTARENE LP 75 mg, prolonged-release coated tablet</b></p>	<p>These result from diclofenac's anti-inflammatory activity, the significance of signs of intolerance caused by the medicine and its place in the range of</p>	<p>Adverse effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms.</p>	List II	09/12/1993 (national)	National Health Insurance (65%) Hospital use



Proprietary medicinal product	Indications	Dosage	Prescribing conditions	Marketing authorisation date (procedure)	List
<b>B/30</b>  <b>NOVARTIS PHARMA SAS</b>	<p>anti-inflammatory products currently available.</p> <p>In adults and children aged 15 years and over, they are restricted to:</p> <p>Maintenance treatment of chronic rheumatic diseases where, during use of the 25 mg and 50 mg forms, a dosage of 75 mg daily was found to be adequate.</p> <p>Short-term symptomatic treatment of acute episodes of osteoarthritis.</p>	<p>Maintenance treatment: 1 x 75 mg tablet daily.</p> <p>If symptoms are more pronounced during the night, the tablet should be taken in the evening.</p> <p>Treatment of acute episodes: 1 x 75 mg tablet morning and evening for a maximum of 7 days.</p> <p>The maximum daily dose of 150 mg must not be exceeded.</p>			
<b>VOLTARENE LP 100 mg, prolonged-release coated tablet B/15</b>  <b>NOVARTIS PHARMA SAS</b>	<p>These result from diclofenac's anti-inflammatory activity, the significance of signs of intolerance caused by the medicine and its place in the range of anti-inflammatory products currently available.</p> <p>In adults and children aged 15 years and over, they are restricted to:</p> <p>Maintenance treatment of chronic rheumatic diseases where, during use of the 25 mg and 50 mg forms, a dosage of 100 mg daily was found to be adequate.</p>	<p>Adverse effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms.</p> <p>1 x 100 mg tablet daily.</p> <p>If symptoms are more pronounced during the night, the tablet should be taken in the evening.</p> <p>The maximum daily dose of 150 mg must not be exceeded.</p>	List II	11/06/1981 (national)	National Health Insurance (65%) Hospital use
<b>VOLTARENE 25 mg, suppository B/10</b>  <b>NOVARTIS PHARMA SAS</b>	<p>These result from diclofenac's anti-inflammatory activity, the significance of signs of intolerance caused by the medicine and its place in the range of anti-inflammatory products currently available.</p> <p>They are restricted to juvenile inflammatory rheumatic diseases in children weighing over 16 kg (i.e. about 4 years old).</p>	<p>Adverse effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms.</p> <p>2 to 3 mg/kg/day, divided into two or three doses.</p> <p>For example, in a child weighing 16 to 35 kg, 1 x 25 mg suppository 2 to 3 times daily.</p> <p>The duration of use of the rectal route of administration should be as short as possible due to the risk of local toxicity.</p>	List II	15/12/1978 (national)	National Health Insurance (30%) Hospital use

Proprietary medicinal product	Indications	Dosage	Prescribing conditions	Marketing authorisation date (procedure)	List
<p><b>VOLTARENE 100 mg, suppository B/10</b></p> <p><b>NOVARTIS PHARMA SAS</b></p>	<p>These result from diclofenac's anti-inflammatory activity, the significance of signs of intolerance caused by the medicine and its place in the range of anti-inflammatory products currently available.</p> <p>In adults and children aged 15 years and over, they are restricted to:</p> <p>Long-term symptomatic treatment:</p> <ul style="list-style-type: none"> <li>- chronic inflammatory rheumatic diseases, particularly rheumatoid arthritis, ankylosing spondylitis or related syndromes such as Reiter's syndrome, and psoriatic arthritis;</li> <li>- some painful and disabling forms of osteoarthritis.</li> </ul> <p>Short-term symptomatic treatment of acute episodes of:</p> <ul style="list-style-type: none"> <li>- extra-articular rheumatism (acute shoulder pain, tendonitis, bursitis);</li> <li>- microcrystalline arthritis;</li> <li>- osteoarthritis;</li> <li>- lumbar pain and severe radicular pain.</li> </ul>	<p>Adverse effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms.</p> <p>Acute treatment: 150 mg in two doses, i.e. one 100 mg suppository supplemented with an oral form.</p> <p>Maintenance treatment (or initial treatment in some patients): 1 x 100 mg suppository daily, in the evening at bedtime.</p> <p>The duration of use of the rectal route of administration should be as short as possible due to the risk of local toxicity.</p>	List II	29/06/1978 (national)	National Health Insurance (30%) Hospital use
<p><b>VOLTARENE 75 mg/3 ml, solution for injection B/2 ampoules</b></p> <p><b>NOVARTIS PHARMA SAS</b></p>	<p>These result from diclofenac's anti-inflammatory activity, the significance of signs of intolerance caused by the medicine and its place in the range of anti-inflammatory products currently available.</p> <p>In adults and children aged over 15 years, they are restricted to the short-term symptomatic treatment of:</p> <ul style="list-style-type: none"> <li>- episodes of inflammatory rheumatic disease;</li> </ul>	<p>Adverse effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms.</p> <p>1 x 75 mg ampoule per day as a single injection. Treatment may be supplemented with one diclofenac 50 mg tablet if necessary.</p> <p>The duration of treatment is 2 to 3 days (allowing time for orally or rectally administered follow-on treatment to be started if necessary).</p>	List II	20/10/1980 (national)	National Health Insurance (30%) Hospital use

Proprietary medicinal product	Indications	Dosage	Prescribing conditions	Marketing authorisation date (procedure)	List
	<ul style="list-style-type: none"> <li>- acute lumbar pain;</li> <li>- radicular pain;</li> <li>- attacks of renal colic.</li> </ul>				
<b>VOLTARENDOLO 12.5 mg (formerly VOLTADOL), coated tablet, B/30</b>  <b>NOVARTIS SANTE FAMILIALE SAS</b>	Symptomatic treatment of mild to moderate pain and/or fever.	<p>Adverse effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms.</p> <p>RESTRICTED TO ADULTS (aged over 15 years).</p> <p>One tablet, to be repeated if necessary after 4 to 6 hours.</p> <p>In case of more severe pain or fever, two tablets may be taken as a single dose, to be repeated if necessary after 4 to 6 hours. In all cases, do not exceed six tablets per day.</p>	List II	05/02/2001 (national)	National Health Insurance (65%) Hospital use

## 01.2 Summary of previous assessments

The previous assessment undertaken by the Transparency Committee is summarised below.

### ARTOTEC 50 mg/0.2 mg, tablet ARTOTEC 75 mg/0.2 mg, tablet

	ARTOTEC 50 mg/0.2 mg, tablet	ARTOTEC 75 mg/0.2 mg, tablet
<b>Date of opinion</b> (reason for review)	<b>02/06/2010</b> (Renewal)	
<b>Indications</b>	Symptomatic treatment of rheumatic diseases in at-risk patients (particularly those aged > 65 years or with a history of peptic ulcer or intolerance to NSAIDs) for whom anti-inflammatory treatment is essential.	Symptomatic treatment of acute episodes of rheumatic diseases in at-risk patients (particularly those aged > 65 years or with a history of peptic ulcer or intolerance to NSAIDs) for whom anti-inflammatory treatment is essential.
<b>AB</b>	Pending further data, the Transparency Committee considers that the actual benefit of the ARTOTEC proprietary medicinal products remains <b>low</b> .	
<b>IAB</b>	-	

### FLECTOR 50 mg, granules for oral solution in single-dose sachets

<b>Date of opinion</b> (reason for review)	<b>16 June 2010</b> (Renewal)	
<b>Indications</b>	<p>These result from diclofenac's anti-inflammatory activity, the significance of signs of intolerance caused by the medicine and its place in the range of anti-inflammatory products currently available.</p> <p>In adults (aged over 15 years), they are restricted to the short-term symptomatic treatment of acute episodes of:</p> <ul style="list-style-type: none"> <li>- abarticular rheumatism such as scapulohumeral peri-arthritis, tendonitis, bursitis;</li> <li>- microcrystalline arthritis;</li> <li>- osteoarthritis;</li> <li>- lumbar pain;</li> <li>- radicular pain.</li> </ul>	
<b>AB</b>	<p>As in the opinions delivered for proprietary medicinal products in the same category, the actual benefit of this proprietary medicinal product is <b>substantial</b> in the following indications:</p> <ul style="list-style-type: none"> <li>- microcrystalline arthritis;</li> <li>- osteoarthritis;</li> <li>- radicular pain.</li> </ul> <p>The actual benefit of this proprietary medicinal product remains <b>moderate</b> in the following indications:</p> <ul style="list-style-type: none"> <li>- extra-articular rheumatism such as scapulohumeral peri-arthritis, tendonitis, bursitis;</li> <li>- lumbar pain.</li> </ul>	
<b>IAB</b>	-	

### VOLTARENDOLO 12.5 mg, coated tablet

<b>Date of opinion</b> (reason for review)	<b>01/03/2006</b> (Renewal)
<b>Indications</b>	Symptomatic treatment of mild to moderate pain and/or fever.
<b>AB</b>	Pain and fever lead to a marked deterioration in quality of life. This proprietary medicinal product is intended as a symptomatic therapy. It may be used as a first-line or second-line treatment. Its adverse effects are mainly gastrointestinal disorders, hypersensitivity reactions, central nervous system effects, skin reactions and renal effects. The efficacy/adverse effects ratio for this medicinal product is modest in the symptomatic treatment of mild to moderate pain and/or fever.  The actual benefit is <b>substantial</b> in this indication.
<b>IAB</b>	-

**VOLTARENE 25 mg, gastro-resistant coated tablet (B/30)**  
**VOLTARENE 50 mg, gastro-resistant coated tablet (B/30)**  
**VOLTARENE LP 75 mg, prolonged-release coated tablet (B/30)**  
**VOLTARENE LP 100 mg, prolonged-release coated tablet (B/15)**  
**VOLTARENE 25 mg, suppository (B/10)**  
**VOLTARENE 100 mg, suppository (B/10)**  
**VOLTARENE 75 mg/3 ml, solution for injection (B/2)**

<b>Date of opinion</b> (reason for review)	<b>05/01/2011</b> (Renewal)
<b>Indications</b>	<p><u>VOLTARENE 25 mg, gastro-resistant coated tablet, VOLTARENE 50 mg, gastro-resistant coated tablet:</u>  In adults and children aged 15 years and over, they are restricted to:  - Long-term symptomatic treatment:  chronic inflammatory rheumatic diseases, particularly rheumatoid arthritis, ankylosing spondylitis or related syndromes such as Reiter's syndrome and psoriatic arthritis; some painful and disabling forms of osteoarthritis.  - Short-term symptomatic treatment of acute episodes of:  abarticular rheumatism (acute shoulder pain, tendonitis, bursitis);  microcrystalline arthritis;  osteoarthritis;  lumbar pain;  severe radicular pain.  - Treatment of primary dysmenorrhoea, after aetiological assessment.</p> <p>In children, the indication is restricted to juvenile inflammatory rheumatic diseases:  from the age of 6 years, for the 25 mg tablet form;  from 35 kg (i.e. about 12 years), for the 50 mg tablet form.</p> <p><u>VOLTARENE LP 75 mg, prolonged-release coated tablet and VOLTARENE LP 100 mg, prolonged-release coated tablet:</u>  In adults and children aged 15 years and over, these are restricted to:  - Maintenance treatment of chronic rheumatic diseases where, during use of the 25 mg and 50 mg forms, a dosage of 75 mg or 100 mg daily was found to be adequate.  - Short-term symptomatic treatment of acute episodes of osteoarthritis (75 mg form only).</p> <p><u>VOLTARENE 100 mg, suppository:</u>  “In adults and children aged 15 years and over, they are restricted to:  • Long-term symptomatic treatment:  - chronic inflammatory rheumatic diseases, particularly rheumatoid arthritis, ankylosing spondylitis or related syndromes such as Reiter's syndrome, and</p>

	<p>psoriatic arthritis;</p> <ul style="list-style-type: none"> <li>- some painful and disabling forms of osteoarthritis.</li> <li>• Short-term symptomatic treatment of acute episodes of:</li> <li>- abarticular rheumatism (acute shoulder pain, tendonitis, bursitis);</li> <li>- microcrystalline arthritis;</li> <li>- osteoarthritis;</li> <li>- lumbar pain and severe radicular pain.”</li> </ul> <p><u>VOLTARENE ENFANT, suppository:</u> They are restricted to juvenile inflammatory rheumatic diseases in children weighing over 16 kg (i.e. about 4 years old).</p> <p><u>VOLTARENE 75 mg/3 ml, solution for injection:</u> They are restricted, in adults and children aged over 15 years, to the short-term symptomatic treatment of: episodes of inflammatory rheumatic disease, acute lumbar pain, radicular pain, attacks of renal colic.</p>
AB	<p><u>Oral forms:</u> The actual benefit of these proprietary medicinal products remains <b>substantial</b> in all indications, except for abarticular rheumatism and lumbar pain, where it remains <b>moderate</b>.</p> <p><u>Rectal forms:</u> The actual benefit remains <b>moderate</b>.</p> <p><u>Injectable form:</u> The actual benefit of this proprietary medicinal product remains <b>moderate</b> in all indications, except for renal colic where it remains <b>substantial</b>.</p>
IAB	-

## 01.3 International information on the medicinal product

Marketing Authorisation (Country)	REIMBURSEMENT	
	YES/NO If no, why not	Indication reimbursed
<p><b>ARTOTEC 50 mg/0.2 mg:</b> Spain, United Kingdom, Italy</p> <p><b>ARTOTEC 75 mg/0.2 mg:</b> Germany, United Kingdom, Italy</p>	<p>Yes: ARTOTEC 50 mg/0.2 mg: Spain, United Kingdom, Italy ARTOTEC 75 mg/0.2 mg: United Kingdom, Italy</p>	
<p><b>FLECTOR 50 mg:</b> Available in 25 mg and 50 mg doses in 13 countries: Czech Republic, Hungary, Italy, Lebanon, Slovakia, Switzerland, Argentina, Ecuador, Mexico, Paraguay, Uruguay, Honduras, Dominican Republic</p>	<p>Yes: Slovakia</p>	<p>Same as in France</p>
<p><b>VOLTARENDOLO 12.5 mg,</b> coated tablet Germany, Bulgaria, Cyprus, Denmark, Estonia, Greece, Hungary, Ireland, Iceland, Latvia, Lithuania, Norway, Netherlands, Poland, Portugal, Czech Republic, United Kingdom, Slovenia, Sweden</p>	<p>Yes: Germany, Greece, Ireland</p> <p>No: Bulgaria (OTC), Denmark, Estonia, Hungary, Iceland, Latvia, Lithuania, Norway, Netherlands, Poland, Portugal, Czech Republic, Slovenia (not marketed), Sweden (not marketed)</p>	<p>Germany: In children aged up to 12 years or children aged up to 18 years with a developmental disorder</p> <p>Greece: Back pain, dental pain, dysmenorrhoea, headache, joint pain, muscular pain, rheumatic pain</p> <p>Ireland: Dental pain, headache, muscular pain, period pain, reduction of fever, relief of painful conditions, colds, relief of influenza symptoms, rheumatic pain</p> <p>United Kingdom: Back pain, dental pain, headache, muscular pain, period pain, reduction of fever, colds, relief of influenza symptoms, rheumatic pain</p>
<p><b>VOLTARENE</b> United Kingdom, Germany, Italy, Spain, USA, Canada, Switzerland</p>	<p>Yes: United Kingdom, Spain, Canada</p> <p>No: USA, Switzerland, Germany, Italy</p>	<p>N/A</p>

## 02 LITERATURE SEARCH

---

### 02.1 Data submitted by the pharmaceutical companies

The licence holders were asked to provide HAS with all the clinical information necessary to re-assess the actual benefit of systemically administered diclofenac-based proprietary medicinal products.

✓ **ARTOTEC 50 mg/0.2 mg, ARTOTEC 75 mg/0.2 mg, tablet**

The company submitted:

- comparative data on the efficacy of misoprostol in preventing NSAID-induced gastrointestinal toxicity (a meta-analysis<sup>6</sup> and four old clinical trials<sup>7,8,9,10</sup>) the results of which are not presented here because they do not specifically concern diclofenac;
- a clinical trial<sup>11</sup> examining the efficacy and safety of diclofenac versus diclofenac combined with misoprostol in rheumatoid arthritis, the results of which have not been taken into account here because the objective was to evaluate the benefit, in terms of gastroduodenal safety, of adding misoprostol.

✓ **FLECTOR 50 mg, granules for oral solution in single-dose sachets**

The company submitted:

- two studies from the Marketing Authorisation dossier (Dreiser 1995, Treves 1989);
- a summary of nine studies published between 1988 and 1991, from the Marketing Authorisation dossier;
- two open-label, non-controlled, unpublished clinical studies (Murena 1986-1987);
- two publications.<sup>12,13</sup>

These data, which have already been assessed by the Transparency Committee, are not discussed again in this report.

---

<sup>6</sup> Rostom A et al. Prevention of NSAID-induced gastroduodenal ulcers. The Cochrane Library 2011.

<sup>7</sup> Silverstein Fred E. et al. Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs. *Ann Intern Me*, 1995; 123: 241-249.

<sup>8</sup> Graham David Y et al. Prevention of NSAID induced gastric ulcer with misoprostol: multicentre, double blind, placebo-controlled trial. *The Lancet*, December 3, 1988.

<sup>9</sup> Jeffrey B. Raskin et al. Misoprostol dosage in the prevention of nonsteroidal anti-inflammatory drug induced gastric and duodenal ulcers: a comparison of three regimens. *Ann Intern Med*. 1995; 123: 344-350.

<sup>10</sup> Agrawal Naurang M et al. Misoprostol coadministered with Diclofenac for prevention of gastroduodenal ulcers. A one-year study. *Digestive Diseases and Sciences*. Vol. 40, No. 5, May 1995.

<sup>11</sup> W. Verdickt et al. A double-blind comparison of the gastroduodenal safety and efficacy of diclofenac and a fixed dose combination of diclofenac and misoprostol in the treatment of rheumatoid arthritis. *Scand J Rheumatol*. 1992; 21: 85-91.

<sup>12</sup> Pertuiset E. Intérêt de l'utilisation d'un nouveau sel de diclofénac, le diclofénac hydroxyéthylpyrrolidine, dans le traitement par voie orale des pathologies lombaires aiguës. *Rev Rhum* 2001; 68 (Suppl. 2): 31-9.

<sup>13</sup> Vecsei L et al. Diclofenac epolamine is effective in the treatment of acute migraine attacks. A randomised, crossover, double blind, placebo-controlled, clinical study. *Cephalalgia* 2007; 27: 29-34.



✓ **VOLTARENDOLO 12.5 mg, coated tablet**

The company submitted:

- efficacy and safety data for diclofenac from three studies using different models of pain<sup>14,15,16</sup>
- two studies in febrile condition.<sup>17,18</sup>

All of these studies included an active comparator arm (paracetamol or ibuprofen). A review summarised all of those studies undertaken using VOLTARENDOLO.<sup>19</sup> These studies, which were already assessed by the Transparency Committee as part of its assessment of the application for inclusion in 2004, are not discussed again here. The company also submitted the results of two meta-analyses examining single-dose diclofenac in acute postoperative pain,<sup>20,21</sup> a meta-analysis examining NSAIDs (and not only diclofenac) in acute lumbar pain,<sup>22</sup> and a review of diclofenac as a single 50 mg dose in headaches.<sup>23</sup> These meta-analyses, which do not call into question the analgesic efficacy of low-dose diclofenac potassium, are not discussed here.

---

<sup>14</sup> Kubitzek F et al. Analgesic efficacy of low-dose diclofenac versus paracetamol and placebo in postoperative dental pain. *J Orofac Pain*. 2003 Summer; 17(3): 237-44.

<sup>15</sup> Kubitzek F et al. Low-dose diclofenac potassium in the treatment of episodic tension-type headache. *Eur J Pain* 2003; 7(2): 155-62.

<sup>16</sup> Dreiser RL et al. Relief of acute lumbar pain with diclofenac-K 12.5 mg tablets: a flexible dose, ibuprofen 200 mg and placebo-controlled clinical trial. *Int J Clin Pharmacol Ther*. 2003 Sep; 41(9): 375-85.

<sup>17</sup> Grebe W et al. A multicenter, randomized, double-blind, double-dummy, placebo-and-active-controlled, parallel-group comparison of diclofenac-K and ibuprofen for the treatment of adults with influenza-like symptoms. *Clin Ther*. 2003 Feb; 25(2): 444-58.

<sup>18</sup> Gehanno P, Dreiser RL, Ionescu E, Gold M, Liu JM. Lowest effective single dose of diclofenac for antipyretic and analgesic effects in acute febrile sore throat. *Clin Drug Investig*. 2003; 23(4): 263-71.

<sup>19</sup> Moore N. Diclofenac potassium 12.5 mg tablets for mild to moderate pain and fever. A review of its pharmacology, clinical efficacy and safety. *Clin Drug Invest* 2007; 27: 163-195.

<sup>20</sup> Derry P et al. Single dose oral diclofenac for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009. Issue 2.

<sup>21</sup> Moore RA, et al. Single dose oral analgesics for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2011, Issue 9. Art. No.: CD008659. DOI: 10.1002/14651858.CD008659.pub2.

<sup>22</sup> Roelofs PDDM et al. Non-steroidal anti-inflammatory drugs for lumbar pain. *Cochrane Database of Systematic Reviews* 2008, Issue 1. Art. No.: CD000396. DOI: 0.1002/14651858.CD000396.pub3.

<sup>23</sup> Derry S, Rabbie R, Moore RA. Diclofenac with or without an antiemetic for acute migraine headaches in adults. *Cochrane Database of Systematic Reviews* 2013, Issue 4. Art. No.: CD008783. DOI: 10.1002/14651858.CD008783.pub3.

In addition, the company submitted:

- the results of a pooled analysis of safety data from clinical studies carried out using diclofenac potassium;
- published data from the European SOS (Safety Of non-Steroidal anti-inflammatory medicines) project;
- data from pharmacoepidemiological studies, some of which were submitted and analysed by the company as part of its communication with the PRAC. Six of these studies<sup>24,25,26,27,28,29</sup> are not discussed in this report, as they are retrospective case-control studies based on data extracted from reimbursement databases: the results of these studies are subject to interpretation;
- data from two actual use studies (one carried out in Norway<sup>30</sup> and the other in New Zealand<sup>31</sup>) evaluating the efficacy and safety of diclofenac used as an over-the-counter medicine. These two prospective and non-interventional studies were based on a patient questionnaire either provided by the pharmacist at the time of purchase (Norwegian study) or sent by post one week after purchase (New Zealand study). Their results are not presented here.

---

<sup>24</sup> Bak S et al. Risk of stroke associated with nonsteroidal anti-inflammatory drugs. A nested case-control study. *Stroke* 2003; 34: 379-86.

<sup>25</sup> Fosbøl EL et al. Cause-specific cardiovascular risk associated with nonsteroidal anti-inflammatory drugs among healthy individuals. *Circulation Cardiovascular Quality and Outcomes* 2010; 3: 395-405.

<sup>26</sup> Fosbøl EL et al. Risk of myocardial infarction and death associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs) among healthy individuals: a nationwide cohort study. *Clinical Pharmacology & Therapeutics* 2009; 85: 190-7.

<sup>27</sup> Garcia Rodriguez LA et al. Role of dose potency in the prediction of risk of myocardial infarction associated with nonsteroidal anti-inflammatory drugs in the general population. *Journal of the American College of Cardiology* 2008; 52: 1628-36.

<sup>28</sup> Fischer LM et al. Current use of nonsteroidal antiinflammatory drugs and the risk of acute myocardial infarction. *Pharmacotherapy* 2005; 25: 503-10.

<sup>29</sup> Varas-Lorenzo C et al. The use of selective cyclooxygenase-2 inhibitors and the risk of acute myocardial infarction in Saskatchewan, Canada. *Pharmacoepidemiology and Drug Safety* 2009; 18: 1016-25.

<sup>29</sup> Van der Linden NW et al. The balance between severe cardiovascular and gastrointestinal events among users of selective non-steroidal anti-inflammatory drugs. *Ann Rheum Dis* 2009; 68: 668-73.

<sup>30</sup> Hasford J et al. Safety and usage pattern of low-dose diclofenac when used as an over-the-counter medication: results of an observational cohort study in a community-based pharmacy setting. *International Journal of Clinical Pharmacology and Therapeutics* 2004; 42: 415-22.

<sup>31</sup> Gauld NJ et al. Surveillance of a recently switched non-prescription medicine (diclofenac) using a pharmacy-based approach. *Pharmacoepidemiology and Drug Safety* 2000; 9: 207-14.

✓ **VOLTARENE oral, injectable and suppository forms:**

The company retained the following references from a literature search:

- three meta-analyses,<sup>32,33,34</sup> one case-control study<sup>35</sup> and two reviews<sup>36,37</sup> evaluating the cardiovascular risk of treatment with NSAIDs. Some of these data were presented during the re-assessment of diclofenac by the CHMP and the PRAC;
- five studies evaluating the gastrointestinal risk of treatment with NSAIDs (two randomised studies<sup>38,39</sup> and three meta-analyses<sup>40,41,42</sup>);
- one study evaluating the teratogenicity of diclofenac during the 1<sup>st</sup> trimester of pregnancy;<sup>43</sup>
- one study evaluating the association between NSAID use and liver transplantation<sup>44</sup>, not detailed here because it was a retrospective study examining a range of prescriptions, with only 6 of the 301 patients included having received diclofenac.

Overall, the references submitted by the companies related to the safety of systemically administered diclofenac. No new clinical efficacy data were identified.

## 02.2 Literature search strategy and results

As there had been a recent evaluation of the data on systemically administered diclofenac, a systematic literature search was not undertaken. A search was carried out on the PubMed website using the keywords “diclofenac”, “randomised controlled trial” and “meta-analysis” for references published in the last 5 years. This supplementary literature search identified a meta-analysis of observational studies relating to the risk of myocardial infarction with NSAIDs published as part of the SOS project.<sup>45</sup>

In addition, the following websites were consulted:

- Cochrane Library
- “Safety Of non-Steroidal anti-inflammatory drugs” (SOS) project

---

<sup>32</sup> Trelle S et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. *BMJ* 2011. 342: c7086.

<sup>33</sup> Varas-Lorenzo C et al. Stroke risk and NSAIDs: a systematic review of observational studies. *Pharmacoepidemiology and Drug Safety* 2011. 20: 1225–1236.

<sup>34</sup> Coxib and traditional NSAID Trialists’ (CNT) Collaboration. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *Lancet* 2013; 382: 769-79.

<sup>35</sup> Grimaldi-Bensouda L et al. Risk of ST versus non-ST elevation myocardial infarction associated with non-steroidal anti-inflammatory drugs. *Heart* 2011; 97: 1834-1840.

<sup>36</sup> Salvo F et al. Cardiovascular and Gastrointestinal Safety of NSAIDs: A Systematic Review of Meta-Analyses of Randomized Clinical Trials. *Clinical Pharmacology & Therapeutics* 2011; 89: 855 - 866.

<sup>37</sup> McGettigan P, Henry D. Cardiovascular Risk with Non-Steroidal Anti-Inflammatory Drugs: Systematic Review of Population-Based Controlled Observational Studies. *PLoS Med* 2011; 8: e1001098.

<sup>38</sup> Chan FKL et al. Celecoxib versus omeprazole and diclofenac in patients with osteoarthritis and rheumatoid arthritis (CONDOR): a randomised trial. *Lancet* 2010; 376: 173–79.

<sup>39</sup> Kellner HL, Li C, Essex MN. Efficacy and safety of celecoxib versus diclofenac and omeprazole in elderly arthritis patients: a subgroup analysis of the CONDOR trial. *Current Medical Research & Opinion* 2012; 28: 1537–1545.

<sup>40</sup> Mallen SR, Essex MN, Zhang R. Gastrointestinal tolerability of NSAIDs in elderly patients: a pooled analysis of 21 randomized clinical trials with celecoxib and nonselective NSAIDs. *Current Medical Research & Opinion* 2011; 27: 1359–1366.

<sup>41</sup> Castellsague J et al. Individual NSAIDs and Upper Gastrointestinal Complications: A Systematic Review and Meta-Analysis of Observational Studies (the SOS Project). *Drug Saf* 2012; 35: 1127-1146.

<sup>42</sup> Masso Gonzalez EL et al. Variability among Nonsteroidal Antiinflammatory Drugs in Risk of Upper Gastrointestinal Bleeding. *Arthritis & Rheumatism*. 2010; 62: 1592–1601.

<sup>43</sup> Cassina M et al. First trimester diclofenac exposure and pregnancy outcome. *Reproductive Toxicology*. 2010; 30: 401–404.

<sup>44</sup> Gulmez SE et al. Transplantation for Acute Liver Failure in Patients Exposed to NSAIDs or Paracetamol (Acetaminophen). The Multinational Case-Population SALT Study. *Drug Saf*. 2013. 36: 135–144.

<sup>45</sup> Varas-Lorenzo C et al. Myocardial infarction and individual nonsteroidal anti-inflammatory drugs meta-analysis of observational studies. *Pharmacoepidemiology and Drug Safety*. 2013. 22: 559-570.

- French Society for Rheumatology
- European Medicines Agency (EMA)
- ANSM [French National Medicines and Health Products Safety Agency]
- Federal Agency for Medicines and Health Products (Belgium)
- National Institute for Health and Clinical Excellence (NICE) (UK)
- IQWiG [Institute for Quality and Efficiency in Healthcare] (Germany)

## 03 DATA ON CLINICAL EFFICACY

No new clinical efficacy data for systemically administered diclofenac were identified.

## 04 CLINICAL SAFETY DATA

### 04.1 Results of pooled analysis of data from clinical trials conducted using diclofenac potassium

The company NOVARTIS SANTE FAMILIALE (the licence holder for VOLTARENDOLO) performed a pooled analysis of data from clinical trials conducted using systemically administered diclofenac potassium.

A total of 5003 participants (patients and healthy volunteers) were treated with diclofenac potassium in 35 clinical trials.

Twenty studies were carried out using a single dose of diclofenac potassium: 13 with doses  $\leq 25$  mg and 7 with doses  $> 25$  mg. Fifteen studies involved multiple doses of diclofenac potassium: 6 with doses  $\leq 75$  mg/day and 9 with doses  $> 75$  mg/day.

Less than 1% of patients reported a cardiovascular adverse event (AE) on **short-term treatment (< 14 days) with a daily dosage of diclofenac potassium  $\leq 75$  mg/jour**, or indeed on ibuprofen at a dose of  $\leq 1200$  mg/day or on placebo (Table 1). Neither of the 2 events reported with diclofenac potassium resulted in premature withdrawal from the study concerned.

**Table 1: Cardiovascular adverse events in studies involving treatment with diclofenac potassium and its comparators for a duration < 14 days**

	Number of patients, n (%)					
	Diclofenac-K $\leq 75$ mg	Ibuprofen $\leq 1200$ mg	Placebo	Diclofenac-K $> 75$ mg	Ibuprofen $> 1200$ mg	Placebo
Total patients	610	523	599	794	50	423
Total patients with AEs	85 (13.9)	68 (13.0)	63 (10.5)	295 (37.2)	15 (30)	125 (29.6)
Cardiovascular AEs	2 (0.3)	1 (0.2)	2 (0.3)	10 (1.3)	0	2 (0.5)

Less than 1% of patients treated with diclofenac or ibuprofen stopped treatment due to a cardiovascular adverse event in the studies involving multiple doses for a treatment duration  $> 14$  days (Table 2).

Table 2: Cardiovascular adverse events leading to cessation of treatment in studies using multiple doses of diclofenac potassium and ibuprofen for a duration > 14 days

	Number of patients, n (%)			
	Diclofenac-K ≤ 75 mg	Ibuprofen ≤ 1200 mg	Diclofenac-K 150 mg	Ibuprofen 2400 mg
<b>Total patients</b>	687	350	380	197
<b>Total patients with AEs resulting in premature withdrawal from the study</b>	47 (6.8)	23 (6.6)	45 (11.8)	21 (10.7)
<b>Cardiovascular AEs</b>	4 (0.6)	1 (0.3)	0	1 (0.5)

## 04.2 Published data on the cardiovascular risk

### 4.2.1 Literature review on the incidence of cardiovascular events in patients treated with NSAIDs

A literature review<sup>46</sup> which aimed to evaluate coxibs and was published as part of the SOS project included 29 meta-analyses (MAs) of randomised controlled clinical trials versus diclofenac, ibuprofen, piroxicam or naproxen. In these meta-analyses, NSAIDs were used to treat osteoarthritis (23 MAs), rheumatoid arthritis (20 MAs) and chronic lumbar pain (3 MAs). The number of randomised clinical trials included in each meta-analysis ranged from 2 to 72 and the number of patients ranged from 117 to 34,688.

Inasmuch as the objective of this literature review focused on coxibs, the data on diclofenac are probably not exhaustive (data on diclofenac in the literature was not sought systematically as it was for coxibs) and the incidences of cardiovascular events on NSAIDs have been presented separately for information only as a comparison with data on coxibs.

The characteristics of meta-analyses including diclofenac are summarised in Table 3.

Table 3: Characteristics of meta-analyses selected by the SOS project in which diclofenac was administered

	Number of patients	Study medicine evaluated* (number of patients)	Number of trials included in the meta-analysis	Diclofenac dose, mg [min-max]	Duration (weeks) [min-max]	Indications
Cannon et al.	16,483	etoricoxib	3	150	78	Osteoarthritis, RA
Chen et al.	5,420	meloxicam (5152) rofecoxib (298)	5	[100-150]	[4-52]	Osteoarthritis, RA
Chen et al.	11,219	celecoxib (6163) etoricoxib (3518) rofecoxib (823) valdecoxib (715)	13	[100-150]	[6-86]	Osteoarthritis, RA
Chen et al.	11,409	celecoxib (6463) etoricoxib (3518) rofecoxib (713) valdecoxib (715)	12	[100-150]	[4-52]	Chronic lumbar pain, osteoarthritis, RA
Curtis et al.	492	etoricoxib	2	150	[12-174]	Osteoarthritis, RA

<sup>46</sup> Salvo F et al. Cardiovascular and gastrointestinal safety of NSAIDs: a systematic review of meta-analyses of randomized clinical trials. *Clinical Pharmacology & Therapeutics* 2011; 89: 855-66.

	Number of patients	Study medicine evaluated* (number of patients)	Number of trials included in the meta-analysis	Diclofenac dose, mg [min-max]	Duration (weeks) [min-max]	Indications
Goldstein et al.	711	valdecoxib	3	150	[12-26]	Osteoarthritis, RA
Kearney et al.	6913 (patient-years)	celecoxib, etoricoxib, lumiracoxib, rofecoxib, valdecoxib	26	150	[4-190]	Cancer pain, osteoarthritis, RA
Singh et al.	5957	meloxicam	Not stated	[100-150]	> 3	Not stated
Tavakoli et al.	4688	meloxicam	2	100	4	Osteoarthritis

\* It should be noted that rofecoxib (as of 2004), valdecoxib and lumiracoxib are not marketed in France  
RA: rheumatoid arthritis

In these meta-analyses, NSAIDs were often used for very long periods. The dosage for diclofenac ranged between 100 and 150 mg/day (the maximum daily dose).

**The incidences of cardiovascular events (myocardial infarction, ischaemic cerebral vascular accident, cerebral vascular events, thromboembolism) reported in patients treated with diclofenac, ibuprofen, naproxen, celecoxib, rofecoxib, nabumetone or piroxicam are given in Table 4.**

**Table 4: Estimated cumulative incidences of cardiovascular events by NSAID**

NSAID	MI	Ischaemic CVA	CVA	Fatal CVA	Cerebral vascular events	VTE	HF
	Incidence % (min-max) (n)						
Celecoxib	-	-	-	-	-	-	0.19 (1)
Diclofenac	0.20-0.74 (3)	0.20 (1)	-	-	0.29-0.48 (3)	0.22-0.81 (2)	-
Ibuprofen	0.00-0.19 (2)	0.00 (1)	-	-	0.00-0.24 (2)	0.00 (1)	-
Nabumetone	0.39 (1)	-	-	-	0.00 (1)	-	-
Naproxen	0.10-0.33 (6)	0.00-0.20 (2)	0.09-0.24 (3)	0.00-0.04 (2)	0.13-0.28 (4)	0.00-0.91 (4)	-
Piroxicam	-	-	-	-	-	0.08 (1)	-
Rofecoxib*	0.08 (1)	-	-	-	-	-	0.60 (1)

CVA: cerebral vascular accident, HF: heart failure, MI: myocardial infarction, VTE: venous thromboembolism

\* Rofecoxib has not been marketed in France since 2004.

#### 4.2.2 Meta-analysis evaluating the cardiovascular risk (major cardiovascular events, major coronary events, cerebral vascular accidents) with NSAIDs

A meta-analysis<sup>47</sup> was performed on 280 clinical trials evaluating NSAIDs versus placebo (124,513 patients, 68,342 patient-years) and 474 clinical trials evaluating one NSAID versus another NSAID (229,296 patients, 165,456 patient-years). Among these, the results of a comparison between a coxib and an NSAID were available for 113 clinical trials, of which 33 had diclofenac as the comparator (61,572 participants, 90,644 patient-years).

The primary objective of this meta-analysis was to define and quantify the cardiovascular and gastrointestinal risks associated with the use of different NSAIDs. The endpoints evaluated were:

- major vascular events (non-fatal MI, non-fatal CVA or death from vascular causes)
- major coronary events (non-fatal MI, death from coronary causes)
- CVA
- mortality
- heart failure
- upper gastrointestinal complications (perforation, obstruction, bleeding).

The doses administered in the clinical trials were high (**150 mg/day diclofenac**, 2400 mg/day ibuprofen or 1000 mg/day naproxen). **No information was provided on the mean duration of treatment with each NSAID.**

The mean age of the patients on randomisation was 61 years. Two thirds of the patients were female. A small number of patients had a history of atherosclerosis (9%), diabetes (9%) or upper peptic ulcer (7%). On inclusion, one fifth of patients were taking aspirin, 17% were taking a proton pump inhibitor (PPI) and 13% were smokers. In approximately four out of five cases, the NSAID use was associated with the treatment of RA or osteoarthritis.

In comparison with patients given a placebo, a significant increase in relative risk was observed regarding:

- **major vascular events:** RR=1.41, 95% CI [1.12; 1.78], p=0.0036
- **major coronary events:** RR=1.70, 95% CI [1.19; 2.41], p=0.0032
- **hospitalisations for heart failure:** RR=1.85, 95% CI [1.17; 2.94], p=0.0088
- **deaths from vascular causes:** RR=1.65, 99% CI [0.95; 2.85], p=0.0187.

**However, the relative risk of CVA was not significantly increased in patients treated with diclofenac versus placebo: RR=1.18, 95% CI [0.79; 1.78], p=0.42.**

These results in patients taking diclofenac are comparable to those in patients taking a coxib (Table 5).

---

<sup>47</sup> Coxib and traditional NSAID Trialists' (CNT) Collaboration. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *Lancet* 2013; 382: 769-79.

**Tableau 5: Relative risk associated with different events by treatment received (coxib, diclofenac or placebo)**

	<b>Coxib vs. placebo RR [95% CI]</b>	<b>Diclofenac vs. placebo Adjusted RR [95% CI]</b>
Major vascular events	1.37 [1.14; 1.66], p=0.0009	1.41 [1.12; 1.78], p=0.0036
Major coronary events	1.76 [1.31; 2.37], p=0.0001	1.70 [1.19; 2.41], p=0.0032
Hospitalisations for heart failure	2.28 [1.62; 3.20], p<0.0001	1.85 [1.17; 2.94], p=0.0088
Deaths from vascular causes	1.58 [1.11; 2.24], p=0.0103	1.65 [0.95; 2.85], p=0.0187
Upper gastrointestinal tract complications	1.81 [1.17; 2.81], p=0.0070	1.89 [1.16; 3.09], p=0.0106
CVA	1.09 [0.78; 1.52], p=0.64	1.18 [0.79; 1.78], p=0.42

A significant increase in the risk of major coronary events was observed with ibuprofen 2400 mg/day in comparison with placebo (RR=2.22, 95% CI [1.10; 4.48], p=0.0253), as was an increase in the risk of heart failure (RR=2.49, 95% CI [1.19; 5.20], p=0.0155). No significant increase in the relative risk of major vascular events was observed (RR=1.44, 95% CI [0.89; 2.33], p=0.14).

In comparison with placebo, naproxen 1000 mg/day was not associated with an increase in the relative risk of major vascular events (RR=0.93, 95% CI [0.69; 1.27], p=0.66) but was associated with an increase in the risk of heart failure (RR=1.87, 95% CI [1.10; 3.16], p=0.0197).

#### **4.2.3 Systematic literature review of observational studies evaluating the cardiovascular risks associated with NSAIDs**

A systematic literature review<sup>48</sup> of controlled observational studies included 30 case-control studies (184,946 cardiovascular events) and 21 cohort studies (including more than 2.7 million people exposed to NSAIDs). Diclofenac was evaluated in 29 of these studies (16 case-control studies and 13 cohort studies). **No information on the duration of use of each NSAID was given.**

With the exception of piroxicam and valdecoxib, **an increase in the risk of cardiovascular events was observed for all the substances studied and specifically for diclofenac (RR=1.40, 95% CI [1.27; 1.55]) (Table 6).**

<sup>48</sup> McGettigan P, Henry D. Cardiovascular Risk with Non-Steroidal Anti-Inflammatory Drugs: Systematic Review of Population-Based Controlled Observational Studies. PLoS Med. 2011. 8(9): e1001098.



**Tableau 6: Summary of RR for cardiovascular risks associated with each NSAID**

RR [95% CI]	Total number of studies	Cardiovascular event	Heterogeneity I <sup>2</sup> (%)
Etoricoxib	4	2.05 [1.45; 2.88]	0
Etodolac	5	1.55 [1.28; 1.87]	57.70
Rofecoxib*	34	1.45 [1.33; 1.59]	84.20
<b>Diclofenac</b>	<b>29</b>	<b>1.40 [1.27; 1.55]</b>	<b>86.60</b>
Indomethacin	14	1.30 [1.19; 1.41]	32.60
Meloxicam	7	1.20 [1.07; 1.33]	0
Ibuprofen	38	1.18 [1.11; 1.25]	81.90
Celecoxib	35	1.17 [1.08; 1.27]	84.40
Naproxen	41	1.09 [1.02; 1.16]	70.70
Piroxicam	8	1.08 [0.99; 1.30]	18.90
Valdecoxib*	3	1.05 [0.81; 1.36]	77.60

\* Not marketed in France (as of 2004 for rofecoxib)

**This risk was higher when the diclofenac dose was increased (“low” dose RR=1.22, 95% CI [1.12; 1.33] versus “high” dose RR=1.98, 95% CI [1.40; 2.82]).<sup>49</sup>**

Some limitations were disclosed by the authors: this was a review based on observational studies which are not devoid of bias, and some heterogeneities were demonstrated.

#### 4.2.4 Meta-analysis evaluating the risk of myocardial infarction with NSAIDs

A network meta-analysis<sup>50</sup> was performed on 31 randomised clinical trials, representing a total of 116,429 patients (i.e. a follow-up of more than 115,000 patient-years). Patients received naproxen, ibuprofen, diclofenac, celecoxib, etoricoxib, rofecoxib or lumiracoxib, at various dosages and for various conditions, or a placebo.

The primary efficacy endpoint was the occurrence of myocardial infarction (MI). The secondary endpoints evaluated haemorrhagic or ischaemic CVA, death from cardiovascular causes, and death from any cause or unknown causes. Etoricoxib and diclofenac were the NSAIDs with the longest follow-up available, with 26,025 and 27,819 patient-years respectively.

Rofecoxib was the substance resulting in the highest risk of MI compared with placebo (the primary endpoint) (Table 7). **There was no evidence of an increased relative risk of MI with diclofenac compared with placebo** (RR=0.82, 95% CI [0.29; 2.20]). **The relative risk of CVA was significantly increased with diclofenac compared with placebo** (RR 2.86, 95% CI [1.09; 8.36]); ibuprofen was associated with the highest risk (RR 3.36, 95% CI [1.00; 11.60]). For the secondary endpoint **death from cardiovascular causes, diclofenac and etoricoxib were associated with the highest risk**, statistically greater than with placebo (diclofenac RR 3.98, 95% CI [1.48; 12.70], etoricoxib RR 4.07, 95% CI [1.23; 15.70]).

<sup>49</sup> 10 out of 29 studies cited the dose. “Low” dose / “high” dose: six studies ≤ 100 mg / > 100 mg, two studies < 100 mg / ≥ 100 mg, two studies < 150 mg / ≥ 150 mg.

<sup>50</sup> Trelle S et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. BMJ. 2011. 342: c7086.

**Tableau 7: Relative risks of MI, CVA, death from cardiovascular causes and death from any cause by NSAID**

RR [95% CI]	MI (primary endpoint)	CVA	Death from cardiovascular causes	Death from any cause
Non-selective NSAIDs				
<b>Diclofenac</b>	<b>0.82 [0.29; 2.20]</b>	<b>2.86 [1.09; 8.36]</b>	<b>3.98 [1.48; 12.70]</b>	<b>2.31 [1.00; 4.95]</b>
Naproxen	0.82 [0.37; 1.67]	1.76 [0.91; 3.33]	0.98 [0.41; 2.37]	1.23 [0.71; 2.12]
Ibuprofen	1.61 [0.50; 5.77]	3.36 [1.00; 11.60]	2.39 [0.69; 8.64]	1.77 [0.73; 4.30]
Selective NSAIDs				
Celecoxib	1.35 [0.71; 2.72]	1.12 [0.60; 2.06]	2.07 [0.98; 4.55]	1.50 [0.96; 2.54]
Etoricoxib	0.75 [0.23; 2.39]	2.67 [0.82; 8.72]	4.07 [1.23; 15.70]	2.29 [0.94; 5.71]
Rofecoxib*	2.12 [1.26; 3.56]	1.07 [0.60; 1.82]	1.58 [0.88; 2.84]	1.56 [1.04; 2.23]
Lumiracoxib*	2.00 [0.71; 6.21]	2.81 [1.05; 7.48]	1.89 [0.64; 7.09]	1.75 [0.78; 4.17]

\* not marketed in France

It should be noted that in their analysis, the authors did not take into account a number of factors (age, gender, dosages used and mean duration of exposure) which are likely to impact on the evaluation of different risks. In addition, no study included in the meta-analysis compared diclofenac directly with placebo, and the majority of patients receiving placebo did not come from studies conducted in patients with osteoarthritis or RA, diclofenac's main indications. Finally, the low number of events reported in the studies included in the meta-analysis led to a relatively large degree of uncertainty in its estimations.

#### 4.2.5 Meta-analysis of observational studies evaluating the risk of myocardial infarction with NSAIDs

A meta-analysis<sup>51</sup> published as part of the SOS project included 8 cohort studies, 12 case-control studies conducted in Europe, the USA and Canada and 3 observational case-control studies evaluating the risk of myocardial infarction associated with NSAID use and published between 1 January 1990 and 4 May 2011. The NSAIDs evaluated in these studies were naproxen, ibuprofen, diclofenac, celecoxib and rofecoxib. **Diclofenac was associated with an increased risk of myocardial infarction in all patients taken together (RR=1.38, 95% CI [1.26; 1.52]) and in the population of patients with a high cardiovascular risk (RR=1.34, 95% CI [0.91; 1.98]).**

**Tableau 8: Pooled relative risk of MI by NSAID**

NSAID	Number of studies	RR [95% CI]	Heterogeneity
<b>All patients taken together</b>			
Naproxen	17	1.06 [0.94; 1.20]	< 0.00001
Celecoxib	18	1.12 [1.00; 1.24]	< 0.0001
Ibuprofen	13	1.14 [0.98; 1.31]	< 0.00001
Rofecoxib	17	1.34 [1.22; 1.48]	0.0005
<b>Diclofenac</b>	<b>11</b>	<b>1.38 [1.26; 1.52]</b>	<b>&lt; 0.005</b>
<b>Patients with a high cardiovascular risk</b>			
Naproxen	5	1.13 [0.87; 1.46]	0.12
Celecoxib	5	1.28 [0.99; 1.64]	0.0003
Ibuprofen	3	1.32 [1.14; 1.52]	0.28
<b>Diclofenac</b>	<b>4</b>	<b>1.34 [0.91; 1.98]</b>	<b>0.0002</b>
Rofecoxib	5	1.37 [1.06; 1.79]	0.003

<sup>51</sup> Varas-Lorenzo C, Riera-Guardia N, Calingaert B et al. Myocardial infarction and individual nonsteroidal anti-inflammatory drugs meta-analysis of observational studies. *Pharmacoepidemiology and Drug Safety* 2013; 22: 559-570.

#### 4.2.6 Case-control study evaluating the risk of myocardial infarction with and without ST segment elevation with NSAIDs

A case-control study<sup>52</sup> compared patients presenting with a first, non-fatal episode of MI with controls from the same geographical regions. The patients, who were recruited consecutively and prospectively using a French registry comprising 55 cardiology centres, were aged 18 to 75 years and must not have had a history of MI, percutaneous coronary intervention, coronary artery bypass graft or any other history of coronary disease or heart failure. Patients must have been exposed to treatment with NSAIDs in the 2 months preceding the start of the study. No information was provided on the mean dosages and duration of treatment for different NSAIDs. Once a diagnosis of MI had been made, patients were classified according to whether ST segment elevation was present or absent. The recruitment of controls was carried out by generalist physicians selected at random in the regions where the cardiology centres taking part in the study were located.

Between 1 April 2007 and 31 May 2009, 1548 cases presented with a 1<sup>st</sup> non-fatal MI and were recruited into the study. After the inclusion and exclusion criteria were applied, 1125 cases were included in the analysis population. Patients had a mean age of 56.8 years and 78.1% of them were male. 67.3% of cases in the analysis population had ST segment elevation. In addition, a total of 2790 controls were recruited. These had a mean age of 57.7 years and 48.2% of them were male.

No significant increase in the odds ratio for non-fatal MI was demonstrated in pooled analysis with all NSAIDs (adjusted OR=0.96, 95% CI [0.75; 1.23]) or specifically with diclofenac in comparison with the controls (adjusted OR=1.47, 95% CI [0.87; 2.48]). **An increase in the risk of MI without ST segment elevation was observed with diclofenac (adjusted OR=2.82, 95% CI [1.23; 6.48])** (Table 9).

**Table 9: Adjusted OR by NSAID taken and MI characteristics (with or without ST segment elevation)**

Adjusted OR [95% CI]	Myocardial infarction	Myocardial infarction with ST segment elevation	Myocardial infarction without ST segment elevation
	Exposed cases n=1125 Controls n=2790	Exposed cases n=757 Controls n=1884	Exposed cases n=368 Controls n=906
<b>Diclofenac</b>	<b>1.47 [0.87; 2.48]</b>	<b>0.90 [0.43; 1.87]</b>	<b>2.82 [1.23; 6.48]</b>
Ibuprofen	0.91 [0.65; 1.27]	0.98 [0.65; 1.48]	0.75 [0.41; 1.38]
Naproxen and other arylpropionic acid derivatives	0.72 [0.45; 1.16]	0.97 [0.55; 1.68]	0.37 [0.15; 0.91]
Other NSAIDs	1.08 [0.71; 1.66]	1.00 [0.58; 1.73]	1.29 [0.64; 2.60]
All NSAIDs	0.96 [0.75; 1.23]	0.95 [0.70; 1.28]	0.96 [0.63; 1.46]

#### 4.2.7 Meta-analysis of observational studies evaluating the risk of CVA with NSAIDs

A meta-analysis<sup>53</sup> published as part of the SOS project included four cohort studies and two case-control studies conducted in Europe or the USA evaluating the risk of CVA associated with NSAID use and published between 1 January 1990 and 30 November 2008. The NSAIDs most frequently evaluated in these studies were naproxen, ibuprofen, diclofenac, celecoxib and rofecoxib. No information was provided on the mean dosages and durations of use of different treatments.

<sup>52</sup>Grimaldi-Bensouda L, Rossignol M, Danchin N et al. Risk of ST versus non-ST elevation myocardial infarction associated with non-steroidal anti-inflammatory drugs. *Heart* 2011; 97: 1834-1840.

<sup>53</sup>Varas-Lorenzo C, Riera-Guardia N, Calingaert B et al. Stroke risk and NSAIDs: a systematic review of observational studies. *Pharmacoepidemiology and Drug Safety* 2011; 20: 1225–1236.

The risk of CVA was increased in patients treated with rofecoxib (pooled RR=1.64, 95% CI [1.15; 2.33]) and diclofenac (RR=1.27, 95% CI [1.08; 1.48]) compared with patients not taking NSAIDs (Table 10).

**Table 1: Pooled relative risk from studies evaluating CVA by NSAID**

NSAID	Pooled RR [95% CI]	Heterogeneity (p)
Celecoxib	1.04 [0.90; 1.21]	0.85
Ibuprofen	1.10 [0.89; 1.36]	0.05
Naproxen	1.14 [0.76; 1.69]	0.003
<b>Diclofenac</b>	<b>1.27 [1.08; 1.48]</b>	<b>0.37</b>
Rofecoxib*	1.64 [1.15; 2.33]	0.02

\* not marketed in France since 2004

## 04.3 Data on the gastrointestinal risk with NSAIDs

### ➤ Clinical trial (CONDOR)

A randomised, parallel-group, double-blind clinical trial<sup>54</sup> in patients with osteoarthritis or RA was conducted in 196 centres in 32 countries.

Patients included in the study must have needed continuing treatment with NSAIDs for at least 6 months, be aged 60 years or over with or without a history of peptic ulcer or be aged over 18 years with clinical symptoms of peptic ulcer in the 90 days or more preceding the visit, and have had a negative *H. pylori* test.

These patients were randomised to receive treatment with celecoxib 200 mg twice daily (n=2238) or treatment with diclofenac 75 mg twice daily with concomitant omeprazole (n=2246) for 6 months.

The primary endpoint was a composite endpoint allowing gastrointestinal events consisting of the following events to be clinically evaluated:

- gastroduodenal, small bowel or large bowel haemorrhage
- gastric outlet obstruction
- gastroduodenal, small bowel or large bowel perforation
- clinically significant anaemia of gastrointestinal origin
- gastrointestinal haemorrhage of unknown origin

The sociodemographic characteristics were comparable between the two groups. Patients had a mean age of 65 years and 81% to 83% of them were female. The proportion of patients aged 65 years or over was 54.4% in the celecoxib arm and 54.7% in the diclofenac + PPI arm.

Patients in the group receiving diclofenac + omeprazole had more gastrointestinal events than patients receiving treatment with celecoxib (respectively 3.8% vs. 0.9%, difference=2.9%, 95% CI [2.0%; 3.8%],  $p < 0.0001$ ). The hazard ratio favoured the celecoxib group (HR=4.3, 95% CI [2.6; 7.0],  $p < 0.0001$ ).

The proportion of patients who left the study early because of gastrointestinal adverse events was higher in the diclofenac + omeprazole group than in the celecoxib group (respectively 8% vs. 6%,  $p = 0.0006$ ).

An analysis performed in the subgroup of patients aged over 65 years in the CONDOR study and who had a high gastrointestinal risk gave comparable results for the composite primary endpoint (adjusted OR of 6.27 in favour of celecoxib,  $p < 0.0001$ ) and for the proportion of patients who left the study early (adjusted OR of 1.38 in favour of celecoxib,  $p = 0.045$ ).<sup>55</sup>

<sup>54</sup> Chan FKL, Lanas A, Scheiman J et al. Celecoxib versus omeprazole and diclofenac in patients with osteoarthritis and rheumatoid arthritis (CONDOR): a randomised trial. *Lancet* 2010; 376: 173–79.

<sup>55</sup> Kellner HL, Li C, Essex MN. Efficacy and safety of celecoxib versus diclofenac and omeprazole in elderly arthritis patients: a subgroup analysis of the CONDOR trial. *Current Medical Research & Opinion* 2012; 28: 1537–1545.

### ✓ **Meta-analyses evaluating gastrointestinal complications with NSAIDs**

A meta-analysis<sup>56</sup> of 21 parallel-group randomised clinical trials conducted in patients aged over 65 years with osteoarthritis, rheumatoid arthritis or ankylosing spondylitis (n=9461, including 2334 on diclofenac) showed that patients treated with celecoxib reported gastrointestinal adverse events less frequently than patients treated with diclofenac (respectively 16.7% vs. 21.0%,  $p < 0.0001$ ), ibuprofen (26.5%,  $p = 0.0016$ ) or naproxen (29.4%,  $p < 0.0001$ ). The proportion of patients who stopped their treatment due to gastrointestinal adverse events was significantly lower in patients treated with celecoxib (4.0%) compared with those treated with naproxen (8.1%,  $p < 0.0001$ ) and ibuprofen (7.3%,  $p < 0.05$ ). No significant difference was observed with diclofenac (4.2%,  $p = 0.75$ ).

Two meta-analyses<sup>57,58</sup> including 28 and 9 observational studies respectively, showed that the risk of upper gastrointestinal complications<sup>57</sup> and the risk of upper gastrointestinal bleeding<sup>57</sup> were significantly higher in patients treated with selective or non-selective NSAIDs. An increased risk of upper gastrointestinal tract complications was observed specifically with naproxen (RR=4.10, 95% CI [3.22; 5.23]), diclofenac (RR=3.34, 95% CI [2.79; 3.99]), ibuprofen (RR=1.84, 95% CI [1.54; 2.20]) and celecoxib (RR=1.45, 95% CI [1.17; 1.81]).<sup>57</sup> An increased risk of upper gastrointestinal bleeding was observed specifically with naproxen (RR=5.63, 95% CI [3.83; 8.28]), ketoprofen (RR=5.57, 95% CI [3.94; 7.87]) and diclofenac (RR=3.98, 95% CI [3.36; 4.72]).<sup>57</sup> It should be noted that for all non-selective NSAIDs, the RR was estimated to be 4.50, 95% CI [3.82%; 5.31%].<sup>57</sup>

The meta-analysis<sup>59</sup> of 280 clinical trials evaluating NSAIDs versus placebo (124,513 patients, 68,342 patient-years) and 474 clinical trials evaluating an NSAID versus another NSAID (229,296 patients, 165,456 patient-years) demonstrated a significant increase in the relative risk of upper gastrointestinal tract complications (perforation, bleeding, obstruction) in patients treated with diclofenac versus placebo (RR=1.89, 95% CI [1.16; 3.09],  $p = 0.0106$ ). With ibuprofen 2400 mg/day, a significant increase in the risk of upper gastrointestinal complications was demonstrated (RR=3.97, 95% CI [2.22; 7.10],  $p < 0.0001$ ). In comparison with placebo, naproxen 1000 mg/day was associated with a significant increase in the risk of upper gastrointestinal complications (RR=4.22, 95% CI [2.71; 6.56],  $p < 0.0001$ ).

---

<sup>56</sup> Mallen SR, Essex MN, Zhang R. Gastrointestinal tolerability of NSAIDs in elderly patients: a pooled analysis of 21 randomized clinical trials with celecoxib and nonselective NSAIDs. *Current Medical Research & Opinion*. 2011. 27(7): 1359–1366.

<sup>57</sup> Castellsague J, Riera-Guardia N, Calingaert B et al. Individual NSAIDs and Upper Gastrointestinal Complications: A Systematic Review and Meta-Analysis of Observational Studies (the SOS Project). *Drug Saf*. 2012. 35(12): 1127-1146.

<sup>58</sup> Masso Gonzalez EL, Patrignani P, Tacconelli S et al. Variability Among Nonsteroidal Antiinflammatory Drugs in Risk of Upper Gastrointestinal Bleeding. *Arthritis & Rheumatism*. 2010. 62(6): 1592–1601.

<sup>59</sup> Coxib and traditional NSAID Trialists' (CNT) Collaboration. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *Lancet*. May 30, 2013; 382: 769-79. Published online.

## 04.4 Study of the teratogenic risk from diclofenac during the first trimester of pregnancy

An observational, prospective cohort study evaluated the teratogenic risk from diclofenac during the first trimester of pregnancy.<sup>60</sup> Pregnant women were recruited from among those who contacted an information service regarding teratogenic risks between 1988 and 2008. A total of 145 pregnant women who had been exposed to diclofenac between the 5<sup>th</sup> and 14<sup>th</sup> week of pregnancy were recruited. Non-exposed patients (n=501) were selected randomly from among pregnant women who had contacted the same service.

No significant difference in congenital malformations was demonstrated between women who had been exposed to diclofenac and those who had not been (5.6% vs. 2.4% respectively, OR=2.5, 95% CI [0.9; 6.6], p=0.07).

Note that the SPCs for diclofenac-based proprietary medicinal products state that the prescription of NSAIDs during the first 5 months of pregnancy should only be considered if necessary, and that the prescription of NSAIDs is contraindicated from the 6<sup>th</sup> month of pregnancy onwards.

## 05 OTHER DATA

---

### 05.1 French Society of Rheumatology analysis

In October 2013, the French Society of Rheumatology, consulted by HAS, issued the following statement:

*“The cardiovascular risk of diclofenac is well established in the international literature and is similar to that observed with the coxibs when treatment is prescribed over the long term, at the maximum dose, and particularly in patients with cardiovascular risk factors.*

*Analysis of the different published studies and dossiers submitted to the regulatory authorities has not been able to show that diclofenac has superior efficacy to other NSAIDs at comparable dosages... The risk/benefit ratio of diclofenac is poorer than that of other standard NSAIDs in patients with cardiovascular risk factors who require long-term NSAID treatment.”*

### 05.2 SPC data

On 25/10/2011, the SPCs for diclofenac-based proprietary medicinal products were changed following the CHMP recommendations for the use of medicines classed as NSAIDs and systemically administered diclofenac-based proprietary medicinal products in particular. The following additions were made:

- Section 4.2 Posology and method of administration:

“Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms.”

“The maximum daily dose of 150 mg must not be exceeded.”

- Section 4.3 Contraindications:

“History of gastrointestinal haemorrhage or perforation during previous treatment with NSAIDs, active peptic ulcer, history of recurrent peptic ulcer or haemorrhage (two or more separate episodes of documented haemorrhage or ulceration.”

---

<sup>60</sup> Cassina M, De Santis M, Cesari E et al. First trimester diclofenac exposure and pregnancy outcome. *Reproductive Toxicology* 2010; 30: 401–404.

- Section 4.4 Special warnings and precautions for use:

“Patients with uncontrolled hypertension, congestive heart failure, ischaemic heart disease, cerebral peripheral arterial disease, and/or a history of cerebral vascular accident (including transient ischaemic attack) should only be treated with diclofenac after careful consideration.”

- Section 4.8 Undesirable effects:

“Clinical trial and epidemiological data suggest that use of diclofenac, particularly at high dose (150 mg daily) and in long term treatment may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or CVA).”

Following the most recent EMA re-assessment of the risk/benefit ratio of diclofenac-based medicinal products, the SPCs of the products concerned are currently being updated<sup>61</sup> to state the rules for proper use of NSAIDs and to reinforce this information through warnings, as per ANSM’s reminder (Reminder of the rules for proper use of NSAIDs, July 2013). The following additions are planned:

- Section 4.3 Contraindications: “established congestive heart failure (NYHA class II-IV), ischaemic heart disease, peripheral arterial disease and/or cerebral vascular disease”
- Section 4.4 Special warnings and precautions for use: “Patients with significant cardiovascular risk factors (such as hypertension, hyperlipidaemia, diabetes mellitus, tobacco use) should only be treated with diclofenac after careful consideration of these factors. As the cardiovascular risks associated with diclofenac use may increase with the dose and duration of exposure, the lowest effective daily dose should be used for the shortest period possible. The patient’s need for symptom relief and response to treatment should be re-assessed regularly.”
- Section 4.8 Undesirable effects: “Clinical trial and epidemiological data consistently show an increased risk of arterial thrombotic events (such as myocardial infarction and cerebral vascular accident) associated with diclofenac treatment, particularly at high dose (150 mg daily) and during long-term administration.”

For the VOLTARENDOLO and VOLTARENE proprietary medicinal products, following the recommendations of the PRAC, an information letter regarding the cardiovascular safety profile of diclofenac (systemic forms) was sent to healthcare professionals on 19 August 2013.

#### **VOLTARENE:**

Seven requests for amendment of information are currently being assessed:

For all VOLTARENE proprietary medicinal products:

- updating the SPC on the basis of a complete analysis of medicines belonging to the NSAID class and the results of clinical trials relating to the cardiovascular safety of diclofenac
- a more detailed description of the hepatic adverse effects reported
- the addition of new drug interactions
- updating the SPC on the basis of the “Core Safety Profile” produced following the Periodic Safety Update Report work sharing (PSUR WS) procedure for diclofenac-based proprietary medicinal products
- the addition of dosage recommendations for special populations and warnings on cardiovascular risk factors, changes to the wording of adverse effects, etc.

A request for an amendment regarding the presence of excipients with known effect has been filed for VOLTARENE 25 mg, gastro-resistant coated tablet, VOLTARENE 50 mg, gastro-resistant coated tablet and VOLTARENE 75 mg/3 ml, solution for injection.

A request for information to be added regarding use in children is currently being examined for the proprietary medicinal products indicated in children.

---

<sup>61</sup> ANSM. Diclofénac par voie systémique-nouvelles contre-indications et mises en garde après une revue européenne de son profil de sécurité cardiovasculaire. Lettre aux professionnels de santé. August 2013.

## 05.3 Pharmacovigilance data from PSURs

### ✓ **ARTOTEC**

Analysis of the PSUR covering the period from 19 July 2009 to 17 July 2012 did not reveal any new signals.

More than 951,469,746 standard units of diclofenac/misoprostol have been sold throughout the world, corresponding approximately to an exposure of 1,303,383 patient-years in this period. Cardiovascular events accounted for 4.5% of cases reported during the period.

### ✓ **FLECTOR**

Analysis of the PSURs covering the periods from 09/11/1999 to 08/11/2004, 09/11/2004 to 21/08/2009 and 22/08/2009 to 30/09/2012, and the most recent Line Listing covering the period from 01/10/2012 until 30/04/2013, did not reveal any new signals.

### ✓ **VOLTARENDOLO**

About 80.6 million patients throughout the world have been exposed to a low-dose ( $\leq 25$  mg) formulation of diclofenac (sodium or potassium) since it was first marketed in 1983.

In the cumulative review carried out up until 29 February 2012, 12 cardiovascular serious adverse events were reported (3 deaths and 9 serious adverse events).

Analysis of the PSURs covering the periods from 01/10/2006 to 30/09/2009, 01/10/2009 to 30/09/2012 and 01/10/2012 to 30/04/2013 did not reveal any new signals.

### ✓ **VOLTARENE**

Analysis of the PSUR covering the period from 1 October 2009 to 30 September 2012 did not reveal any new signals.

## 05.4 Risk management plan

### ✓ **VOLTARENDOLO**

The European Risk Management Plan (RMP) for diclofenac potassium (12.5 mg and 25 mg) and diclofenac sodium (25 mg) was updated in July 2012. The identified major risks are:

- Allergic reactions
- Cardiovascular diseases
- Gastrointestinal disorders
- Hepatic disorders
- Skin reactions
- Kidney diseases
- Various reactions including: transient haematological effects, psychiatric disorders, nervous system disorders, eye disorders, ear disorders, respiratory disorders, oedema and reversible impaired female fertility.

There are no potential major risks.

The missing information concerns:

- Pregnancy
- Paediatric patients (aged under 14 years).



## 05.5 Usage/prescription data

The prescription and usage data from the IMS panel as a moving annual total for August 2013 are given in the table below.

Proprietary medicinal product	Number of prescriptions (000)	Mean dosage	Duration of treatment (days)
ARTOTEC 50 mg/0.2 mg, tablet (B/30)	149	1.8	25
ARTOTEC 75 mg/0.2 mg, tablet (B/20)	341	1.8	15.9
FLECTOR 50 mg, granules for oral solution in single-dose sachets (B/21)	230	2.8	9.4
VOLTARENDOLO 12.5 mg (formerly VOLTADOL), coated tablet (B/30)	55	3.9	13.3
VOLTARENE 25 mg, gastro-resistant coated tablet (B/30)	64	2.0	7.8
VOLTARENE 50 mg, gastro-resistant coated tablet (B/30)	359	2.5	11.9
VOLTARENE LP 75 mg, prolonged-release coated tablet (B/30)	2467	1.7	13.4
VOLTARENE LP 100 mg, prolonged-release coated tablet (B/15)	274	1.1	24.8
VOLTARENE 25 mg, suppository (B/10)	-	-	-
VOLTARENE 100 mg, suppository (B/10)	34	1.1	20.8
VOLTARENE 75 mg/3 ml, solution for injection (B/2)	82	1.4	6.1

## 06 SUMMARY & DISCUSSION

No new data on the efficacy of systemic forms of diclofenac, particularly comparative data with other NSAIDs, were identified.

The new data, from meta-analyses of clinical trials or observational studies or from literature reviews, relate to:

- cardiovascular safety in patients treated with diclofenac, which show, **in comparison with placebo**:

- a significant increase in the **relative risk of major vascular events** with an RR of 1.41 (95% CI [1.12; 1.78],  $p=0.0036$ ) according to a meta-analysis of clinical trials,<sup>62</sup> and an RR of 1.40 (95% CI [1.27; 1.55]) according to a systematic literature review.<sup>63</sup> This risk appears to increase with the dose of diclofenac (low dose (below 100 or 150 mg depending on the study) RR=1.22, 95% CI [1.12; 1.33] versus high dose (above 100 mg or 150 mg depending on the study) RR=1.98, 95% CI [1.40; 2.82]);<sup>62</sup>

- a significant increase in the risk of a **major coronary event** (RR=1.70, 95% CI [1.19; 2.41],  $p=0.0032$ ) according to a meta-analysis of clinical trials;<sup>62</sup>

<sup>62</sup> Coxib and traditional NSAID Trialists' (CNT) Collaboration. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *Lancet* 2013; 382: 769-79. Published online.

<sup>63</sup> McGettigan P, Henry D. Cardiovascular Risk with Non-Steroidal Anti-Inflammatory Drugs: Systematic Review of Population-Based Controlled Observational Studies. *PLoS Med.* 2011; 8: e1001098.

- a significant increase in the relative risk of **hospitalisation for heart failure** (RR=1.85, 95% CI [1.17; 2.94], p=0.0088) according to a meta-analysis of clinical trials;<sup>62</sup>

- a significant increase in the risk of **death from vascular causes** with an RR of 1.65 (99% CI [0.95; 2.85], p=0.0187) according to a meta-analysis of clinical trials.<sup>62</sup> In a network meta-analysis, diclofenac and etoricoxib were associated with the highest risk, statistically greater than with placebo (diclofenac RR 3.98 [1.48; 12.70], etoricoxib RR 4.07 [1.23; 15.70]).<sup>64</sup>

Regarding the **risk of myocardial infarction**, a meta-analysis<sup>64</sup> identified rofecoxib as the substance exposing patients to the greatest risk of myocardial infarction (MI) in comparison with placebo and did not demonstrate any increased relative risk of MI with diclofenac compared with placebo (RR=0.82, 95% CI [0.29; 2.20]).

According to another meta-analysis of observational studies,<sup>65</sup> diclofenac was associated with an increased risk of myocardial infarction in all patients taken together (RR=1.38, 95% CI [1.26; 1.52]) and in the population of patients with a high cardiovascular risk (RR=1.34, 95% CI [0.91; 1.98]).

According to a case-control study<sup>66</sup> comparing patients presenting with a first, non-fatal MI to controls from the same geographical regions, an increased risk of MI without ST segment elevation was observed with diclofenac (adjusted OR=2.82, 95% CI [1.23; 6.48]).

Regarding the **risk of CVA**, in the meta-analysis by the CNT Collaboration, the risk was not significantly increased in patients treated with diclofenac versus placebo (RR=1.18, 95% CI [0.79; 1.78], p=0.42). According to the network meta-analysis by Trelle et al, the relative risk of CVA was significantly increased with diclofenac compared with placebo (RR 2.86 [1.09; 8.36]); ibuprofen was associated with the highest risk (RR=3.36 [1.00; 11.60]). According to the meta-analysis<sup>67</sup> by Varas-Lorenzo et al, the risk of CVA was increased in patients treated with rofecoxib (pooled RR=1.64, 95% CI [1.15; 2.33]) and diclofenac (RR=1.27, 95% CI [1.08; 1.48]) compared with patients not taking NSAIDs.

It should be noted that data from the different meta-analyses and literature reviews do not always state the dosage of diclofenac used in the studies. Where it is mentioned, it is a high dosage (100 to 150 mg/day). Similarly, in the majority of cases no information is given on the duration of treatment with diclofenac. Where this information is provided, treatment was for several weeks.

- Gastrointestinal safety

In a clinical trial<sup>68</sup>, patients treated with **diclofenac** (75 mg twice daily) combined with **omeprazole** had more gastrointestinal events than patients treated with **celecoxib** (200 mg twice daily) (respectively 3.8% vs. 0.9%, difference=2.9%, 95% CI [2.0%; 3.8%], p < 0.0001). The hazard ratio favoured the celecoxib group (HR=4.3, 95% CI [2.6; 7.0], p < 0.0001). The proportion of patients who left the study early because of gastrointestinal adverse events was higher in the diclofenac + omeprazole group than in the celecoxib group (respectively 8% vs. 6%, p = 0.0006).

---

<sup>64</sup> Trelle S et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. *BMJ*. 2011. 342: c7086.

<sup>65</sup> Varas-Lorenzo C, Riera-Guardia N, Calingaert B et al. Myocardial infarction and individual nonsteroidal anti-inflammatory drugs meta-analysis of observational studies. *Pharmacoepidemiology and Drug Safety*. 2013. 22: 559-570.

<sup>66</sup> Grimaldi-Bensouda L, Rossignol M, Danchin N et al. Risk of ST versus non-ST elevation myocardial infarction associated with non-steroidal anti-inflammatory drugs. *Heart*. 2011. 97: 1834-1840.

<sup>67</sup> Varas-Lorenzo C, Riera-Guardia N, Calingaert B et al. Stroke risk and NSAIDs: a systematic review of observational studies. *Pharmacoepidemiology and Drug Safety*. 2011; 20: 1225-1236.

<sup>68</sup> Chan FKL, Lan A, Scheiman J et al. Celecoxib versus omeprazole and diclofenac in patients with osteoarthritis and rheumatoid arthritis (CONDOR): a randomised trial. *Lancet*. 2010. 376: 173-79.

An analysis performed in the subgroup of patients aged over 65 years in this trial and who had a high gastrointestinal risk gave comparable results.<sup>69</sup>

The meta-analysis by Mallen<sup>70</sup> concerning patients aged over 65 years with osteoarthritis, rheumatoid arthritis or ankylosing spondylitis (n=9461, including 2334 on diclofenac) showed that patients treated with celecoxib reported gastrointestinal adverse events less frequently than patients treated with diclofenac (respectively 16.7% vs. 21.0%,  $p < 0.0001$ ), ibuprofen (26.5%,  $p = 0.0016$ ) or naproxen (29.4%,  $p < 0.0001$ ). The proportion of patients who stopped their treatment due to gastrointestinal adverse events was significantly lower in patients treated with celecoxib (4.0%) compared with those treated with naproxen (8.1%,  $p < 0.0001$ ) and ibuprofen (7.3%,  $p < 0.05$ ). No significant difference was observed with diclofenac (4.2%,  $p = 0.75$ ).

In two meta-analyses<sup>71,72</sup>, an increased risk of upper gastrointestinal tract complications was observed specifically with naproxen (RR=4.10, 95% CI [3.22; 5.23]), diclofenac (RR=3.34, 95% CI [2.79; 3.99]), ibuprofen (RR=1.84, 95% CI [1.54; 2.20]) and celecoxib (RR=1.45, 95% CI [1.17; 1.81]). An increased risk of upper gastrointestinal bleeding was observed specifically with naproxen (RR=5.63, 95% CI [3.83; 8.28]), ketoprofen (RR=5.57, 95% CI [3.94; 7.87]) and diclofenac (RR=3.98, 95% CI [3.36; 4.72]).

A meta-analysis<sup>73</sup> evaluating NSAIDs versus placebo or versus another NSAID demonstrated a significant increase in the relative risk of upper gastrointestinal tract complications (perforation, bleeding, obstruction) in patients treated with diclofenac versus placebo (RR=1.89, 95% CI [1.16; 3.09],  $p=0.0106$ ). With ibuprofen 2400 mg/day, a significant increase in the risk of upper gastrointestinal complications was demonstrated (RR=3.97, 95% CI [2.22; 7.10],  $p < 0.0001$ ). In comparison with placebo, naproxen 1000 mg/day was associated with a significant increase in the risk of upper gastrointestinal complications (RR=4.22, 95% CI [2.71; 6.56],  $p < 0.0001$ ).

No network meta-analysis with correct methodology was identified that could be used to position diclofenac in relation to its clinically relevant comparators.

---

<sup>69</sup> Kellner HL, Li C, Essex MN. Efficacy and safety of celecoxib versus diclofenac and omeprazole in elderly arthritis patients: a subgroup analysis of the CONDOR trial. *Current Medical Research & Opinion* 2012; 28: 1537-1545.

<sup>70</sup> Mallen SR, Essex MN, Zhang R. Gastrointestinal tolerability of NSAIDs in elderly patients: a pooled analysis of 21 randomized clinical trials with celecoxib and nonselective NSAIDs. *Current Medical Research & Opinion* 2011; 27: 1359-1366.

<sup>71</sup> Castellsague J, Riera-Guardia N, Calingaert B et al. Individual NSAIDs and Upper Gastrointestinal Complications: A Systematic Review and Meta-Analysis of Observational Studies (the SOS Project). *Drug Saf* 2012; 35: 1127-1146.

<sup>72</sup> Masso Gonzalez EL, Patrignani P, Tacconelli S et al. Variability among Nonsteroidal Antiinflammatory Drugs in Risk of Upper Gastrointestinal Bleeding. *Arthritis & Rheumatism* 2010; 62: 1592-1601.

<sup>73</sup> Coxib and traditional NSAID Trialists' (CNT) Collaboration. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *Lancet* 2013; 382: 769-79.

## 07 THERAPEUTIC USE

---

The therapeutic indications for systemically administered diclofenac-based proprietary medicinal products vary between proprietary medicinal products depending on the diclofenac dosage unit and the route of administration. Systemically administered proprietary medicinal products containing diclofenac (alone or in combination) are indicated in children and/or adults to relieve pain of varying severity and inflammation in a wide range of conditions, particularly arthritic diseases (such as rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and acute gout), acute musculoskeletal disorders (such as periarthritis, tendonitis, tenosynovitis and bursitis) and other painful disorders resulting from trauma (such as fractures, lumbar pain, sprains, dislocations, and orthopaedic, dental and other minor surgery), as well as in the treatment of primary dysmenorrhoea after an aetiological assessment.

Diclofenac must be prescribed at the lowest effective dose for the shortest duration possible.

### **Taking into account:**

- **new data on the cardiovascular safety of systemically administered diclofenac, which establish that the cardiovascular risk of diclofenac is similar to that observed with coxibs, when treatment is prescribed in the long term, at the maximum dose, and in particular in patients with cardiovascular risk factors;**
- **the existence of other comparators in the same therapeutic category for which no similar cardiovascular safety alerts have emerged;**

**the Committee considers that diclofenac has no role in the therapeutic strategy for diseases treated with NSAIDs in patients with significant risk factors for cardiovascular events (particularly permanent treated or untreated hypertension, dyslipidaemia, treated or untreated diabetes, and current use of tobacco or cessation within the past 3 years).**<sup>74,75</sup>

---

<sup>74</sup> HAS. Management of adult patients with essential hypertension. 2005 update.

<sup>75</sup> AFSSAPS [French Healthcare Product Safety Agency]. Prise en charge thérapeutique du patient dyslipidémique. Recommendations. March 2005.

## 08 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee considers that the conclusions of its previous opinion of 5 January 2011 should be changed.

### 08.1 Actual benefit

✓ **VOLTARENE 25 mg, 50 mg, LP 75 mg, LP 100 mg**

▮Osteoarthritis and chronic inflammatory rheumatic diseases are potentially serious and disabling conditions.

▮Abarticular rheumatism such as scapulohumeral periarthritis, tendonitis and bursitis is painful and/or disabling, but it generally improves spontaneously after a few weeks.

▮Radicular pain is a painful and disabling condition which generally improves under medical treatment.

▮Non-specific acute lumbar pain is a benign condition that resolves spontaneously in most patients. Occasionally it develops into a potentially disabling chronic form.

▮Microcrystalline arthritis is an acute inflammatory form of arthritis associated with the formation of crystals in the joints (sodium urate in gout, calcium pyrophosphate in chondrocalcinosis). Microcrystalline arthritis can be characterised by progression towards disability and/or a marked deterioration in quality of life.

▮Dysmenorrhoea is not usually serious but can impair quality of life.

▮These proprietary medicinal products, used as short courses of treatment, are intended as symptomatic therapy.

▮Their efficacy/adverse effects ratio is modest, due to a possible increased cardiovascular risk in some patients.

▮These medicinal products are first-line or second-line therapies. They have no role in the therapeutic strategy for rheumatic diseases or dysmenorrhoea treated with NSAIDs in patients with significant risk factors for cardiovascular events.

▮There are treatment alternatives.

**Consequently, the actual benefit of these proprietary medicinal products:**

- remains **substantial** in the treatment of:

- chronic inflammatory rheumatic diseases, particularly rheumatoid arthritis, ankylosing spondylitis or related syndromes such as Reiter's syndrome, and psoriatic arthritis;
- severe radicular pain;
- microcrystalline arthritis;
- juvenile inflammatory rheumatic diseases;
- osteoarthritis;
- primary dysmenorrhoea, after aetiological assessment;

- remains **moderate** in abarticular rheumatism and lumbar pain;

- is **insufficient** in the subpopulation of patients who have risk factors for cardiovascular events.

✓ **VOLTARENE ENFANT, suppository**

▮Juvenile inflammatory rheumatic diseases can be serious and disabling.

▮This proprietary medicinal product is intended as a symptomatic therapy.

Local effects related to the rectal route of administration may occur. Local toxicity is more frequent and severe with a longer duration of treatment, more frequent administration or a higher dosage.

Consequently, the oral route of administration should be preferred to the rectal route for long-term treatment.

▶Its efficacy/adverse effects ratio is modest, due to a possible increased cardiovascular risk in some patients.

This medicinal product is a second-line therapy.

▶Paracetamol is the first-line analgesic due to its good safety profile.

NSAIDs should be reserved for painful episodes and be prescribed at the lowest effective dosage for the shortest duration possible. The use of NSAIDs is not recommended in children with chickenpox. This proprietary medicinal product has no role in the therapeutic strategy for juvenile inflammatory rheumatic diseases treated with NSAIDs in patients with significant risk factors for cardiovascular events.

▶There are treatment alternatives.

**Consequently, the actual benefit of this proprietary medicinal product in these indications remains moderate.**

**It is insufficient in the subpopulation of children who could have risk factors for cardiovascular events.**

✓ **VOLTARENE 100 mg, suppository**

▶Osteoarthritis and chronic inflammatory rheumatic diseases are potentially serious and disabling conditions.

Abarticular rheumatism such as scapulohumeral periartthritis, tendonitis and bursitis is painful and/or disabling, but it generally improves spontaneously after a few weeks.

Radicular pain is a painful and disabling condition which generally improves under medical treatment.

Non-specific acute lumbar pain is a benign condition that resolves spontaneously in most patients. Occasionally it develops into a potentially disabling chronic form.

Microcrystalline arthritis is an acute inflammatory form of arthritis associated with the formation of crystals in the joints (sodium urate in gout, calcium pyrophosphate in chondrocalcinosis). Microcrystalline arthritis can be characterised by progression towards disability and/or a marked deterioration in quality of life.

▶This proprietary medicinal product is intended as a symptomatic therapy.

▶NSAIDs should be reserved for painful episodes and be prescribed at the lowest effective dosage for the shortest duration possible. Local effects related to the rectal route of administration may occur. Local toxicity is more frequent and severe with a longer duration of treatment, more frequent administration or a higher dosage. Consequently, the oral route of administration should be preferred to the rectal route for long-term treatment.

This proprietary medicinal product has no role in the therapeutic strategy for rheumatic diseases treated with NSAIDs in patients with significant risk factors for cardiovascular events.

▶Its efficacy/adverse effects ratio is modest, due to a possible increased cardiovascular risk in some patients.

This medicinal product is a second-line therapy.

▶There are treatment alternatives.

**Consequently, the actual benefit of this proprietary medicinal product in these indications remains moderate.**

**It is insufficient in the subpopulation of patients who have risk factors for cardiovascular events.**

✓ **VOLTARENE 75 mg/3 ml, solution for IM injection**

▶Chronic inflammatory rheumatic diseases are potentially serious and disabling conditions.

Radicular pain is a painful and disabling condition which generally improves under medical treatment.

Non-specific acute lumbar pain is a benign condition that resolves spontaneously in most patients. Occasionally it develops into a potentially disabling chronic form.

Renal colic is a painful acute lumbo-abdominal syndrome, associated in 75% to 80% of cases with calculus. It is accompanied by severe pain.

▶ This proprietary medicinal product is intended as symptomatic therapy.

▶ Its efficacy/adverse effects ratio is modest, due to a possible increased cardiovascular risk in some patients.

▶ This medicinal product is a first-line or second-line therapy. It has no role in the therapeutic strategy for rheumatic diseases and renal colic treated with NSAIDs in patients with significant risk factors for cardiovascular events.

**Consequently, the actual benefit of this proprietary medicinal product:**

- remains moderate in episodes of inflammatory rheumatic disease, acute lumbar pain and radicular pain;
- remains substantial in renal colic;
- is insufficient in the subpopulation of patients who have risk factors for cardiovascular event.