HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

20 November 2013

ANTARENE CODEINE 200 mg/30 mg

B/20 film-coated tablets (CIP: 34009 397 555 8)

ANTARENE CODEINE 400 mg/60 mg

B/10 film-coated tablets (CIP: 34009 397 558 7)

Applicant: Elerte

INN	Ibuprofen, codeine phosphate hemihydrate
ATC code (2009)	N02AA59 (analgesic combinations)
Reason for the review	**Inclusion**
List concerned	**National Health Insurance** (French Social Security Code L.162-17) **Hospital use** (French Public Health Code L.5123-2)
Indications concerned	**"Short-term treatment in adults of moderate to severe acute pain or pain that does not respond to a non-opioid analgesic alone."**

Actual Benefit	**Substantial**
Improvement in Actual Benefit	**The proprietary medicinal products ANTARENE CODEINE do not offer any improvement in actual benefit (IAB V, nonexistent) over the available alternatives, particularly combinations of paracetamol with a weak opioid, in the management of moderate to severe acute pain or pain that does not respond to a non-opioid analgesic alone.**
Therapeutic Use	**The proprietary medicinal products ANTARENE CODEINE are a treatment option in the management of moderate to severe acute pain or pain that does not respond to a non-opioid analgesic alone.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	5 October 2009 (national)
Prescribing and dispensing conditions / special status	List I

ATC Classification	2009	
	N:	Nervous system
	N02:	Analgesics
	N02A:	Narcotic analgesic
	N02AA:	Natural opium alkaloids
	N02AA59:	Codeine, combinations

02 BACKGROUND

This fixed combination of an NSAID (ibuprofen) and a weak opioid (codeine) was the subject of an initial application for inclusion on the list of medicines reimbursed in pharmacies and on the list of medicines approved for hospital use in December 2009.
In view of:
- the inadequacies of the dossier, in particular the lack of a study with an adequate level of evidence demonstrating the superiority of ANTARENE CODEINE over ibuprofen alone and
- the absence of comparative data versus other weak opioid analgesics, in particular paracetamol + codeine combinations,
the Transparency Committee had considered that the AB of this medicinal product was insufficient and had not therefore recommended inclusion (Opinion of 31 March 2010).

Since this Opinion, the applicant has carried out a superiority study comparing ANTARENE CODEINE with ibuprofen alone in the treatment of acute pain associated with gonarthrosis. This new application for inclusion on the list of reimbursable proprietary medicinal products is based on the results of this study.

Two ANTARENE CODEINE dosages are proposed, one containing 200 mg of ibuprofen and 30 mg of codeine and the other containing 400 mg of ibuprofen and 60 mg of codeine. The recommended maximum daily dose for these proprietary medicinal products is 1200 mg of ibuprofen and 180 mg of codeine (corresponding to 30 mg of morphine equivalent, taking into account the conversion factor of 1/6).

03 THERAPEUTIC INDICATIONS

“Short-term treatment in adults of moderate to severe acute pain or pain that does not respond to a non-opioid analgesic alone.”

04 DOSAGE

"For use in adults only
ANTARENE CODEINE 200 mg/30 mg:
An initial dose of one or two tablets, depending on the intensity of the pain, followed by one tablet every 4-6 hours, up to a maximum of six tablets per day.

ANTARENE CODEINE 400 mg/60 mg:
An initial dose of one tablet, followed by one tablet every 6-8 hours, up to a maximum of three tablets per day."

05 THERAPEUTIC NEED

The choice of an analgesic depends on the intensity of the pain, on the source of the pain and on whether it is acute or chronic.
There are numerous options for pain management, some involving drug therapy, some not. Analgesic drugs are classically ranked according to their analgesic potency based on a three-step "ladder" established by the World Health Organisation (WHO) for the treatment of cancer pain[1]:

- Level I analgesics are non-opioids (non-morphine-type drugs), represented primarily by paracetamol, acetylsalicylic acid, and low-dose nonsteroidal antiinflammatory drugs (NSAIDs).
- Level II analgesics are weak opioids (weak morphine-type drugs), codeine, tramadol and low-dose opium. These are most often used in combination with Level I analgesics, in particular paracetamol.
- Level III analgesics are strong opioids (strong morphine-type drugs), of which there are three types: pure agonists (morphine, fentanyl, oxycodone, hydromorphone), partial agonists (buprenorphine) and agonist-antagonists (nalbuphine, pentazocine).

Following the withdrawal of paracetamol + dextropropoxyphene ± caffeine combinations (European Commission decision of 14 June 2010), step II[2] treatment options are more limited.

Following this withdrawal, a re-evaluation of the management of moderate to severe pain in adults[3] was carried out by a group of experts at the request of AFSSAPS [French Healthcare Product Safety Agency]:

For postoperative, post-traumatic, nociceptive, acute pain in rheumatology and in gynaecology, paracetamol at the optimum dose is recommended for mild to moderate pain, a short course of an NSAID (unless contraindicated) or a weak opioid for moderate to severe pain, and a weak or strong opioid for very severe pain, depending on the urgency of obtaining relief and on the clinical context.

For acute pain of dental origin, the advice is to refer to the clinical practice guidelines "Prevention and treatment of postoperative pain in oral surgery"[4], which recommend prescription of paracetamol as a first-line drug for mild pain and an NSAID or weak opioid (tramadol ± paracetamol, codeine + paracetamol) for moderate to severe pain.

[1] Perrot S., Quéreux P. *Analgesics* [Analgesics] In: Bouvenot G, Caulin C. *Guide du bon usage du médicament* [Guide to the proper use of medicinal products]. 2nd ed. Médecine Sciences Publications, Paris, 2012, pp. 585-607
[2] Corresponding to weak opioids according to the WHO analgesia ladder for cancer pain. The weak opioids on the market are for the most part formulated in combination with a peripheral analgesic, most commonly paracetamol: codeine in combination with paracetamol and/or acetylsalicylic acid or ibuprofen, tramadol alone or in combination with paracetamol, opium powder in combination with paracetamol, and dihydrocodeine.
[3] Management of moderate to severe pain in adults: Re-evaluation and update, May 2011, AFSSAPS - SFR - SFETD.
[4] Prevention and treatment of postoperative pain in oral surgery, clinical practice guideline, HAS, November 2005.

06 CONTRAINDICATIONS

"This medicinal product is contraindicated in the following situations:

- **children younger than 15 years**,
- after 24 weeks of amenorrhoea (5 months of pregnancy),
- hypersensitivity to ibuprofen or to one of the excipients of the product,
- history of asthma attacks after taking ibuprofen or substances with similar activity, such as other NSAIDs, acetylsalicylic acid,
- history of gastrointestinal haemorrhage or perforation during past treatment with an NSAID,
- ongoing gastrointestinal haemorrhage, cerebrovascular haemorrhage or other haemorrhage,
- progressive peptic ulcer, history of peptic ulcer or recurrent haemorrhage (two or more distinct episodes of diagnosed haemorrhage or ulceration),
- severe hepatic impairment,
- severe renal impairment,
- severe heart failure,
- systemic lupus erythematosus,
- respiratory insufficiency, regardless of severity, due to the depressant action of codeine on the respiratory centres,
- **in nursing mothers, except for one-off doses.**"

07 CLINICALLY RELEVANT COMPARATORS

07.1 Medicinal products

There is no other fixed combination of an NSAID and a weak opioid reimbursed by National Health Insurance.

There are other proprietary medicinal products containing an NSAID and codeine on the market, but these are not reimbursed: NOVACETOL (aspirin + paracetamol + codeine) and SEDASPIR (aspirin + caffeine + codeine).

There is no proprietary medicinal product containing codeine in France that allows separate dosing with ibuprofen and codeine.

In the light of these points, we can consider that the medicinal products comparable to ANTARENE CODEINE are reimbursed combinations of paracetamol and a weak opioid, in particular:

- paracetamol + codeine combinations containing between 600 and 300 mg of paracetamol and between 50 and 20 mg of codeine phosphate, depending on the proprietary medicinal product;
- paracetamol + tramadol combinations (325 mg/37.5 mg);
- paracetamol + opium ± caffeine combination.

The AB of all these proprietary medicinal products is substantial (see table).

INN Dosage Pharmaceutical form	Manufacturer/ Proprietary medicinal product	Indication	Date of TC opinion	AB	IAB
Paracetamol 400 mg/ codeine 20 mg, tablet	Sanofi-Aventis **CODOLIPRANE**	Symptomatic treatment of moderate to severe pain that does not respond to peripheral analgesics alone.	07/12/2011	Substantial	IAB V
Paracetamol 500 mg/ codeine 30 mg, tablet			01/01/2012		
Paracetamol 500 mg/ codeine 30 mg, tablet	Bristol-Myers Squibb **DAFALGAN CODEINE** and generics	Symptomatic treatment of moderate to severe pain or pain that does not respond to peripheral analgesics alone.	04/01/2012		
Paracetamol 600 mg/ codeine 50 mg, tablet Paracetamol 300 mg/ codeine 25 mg, tablet	Pierre Fabre Medicament **KLIPAL CODEINE**	Symptomatic treatment of moderate to severe pain that does not respond to peripheral analgesics alone.	04/11/2009		
Paracetamol 325 mg/ tramadol 37.5 mg, tablet and effervescent tablet	Grunenthal **IXPRIM** and **ZALDIAR**	Symptomatic treatment of moderate to severe pain. Use of Ixprim must be restricted to patients with moderate to severe pain requiring treatment with a combination of paracetamol and tramadol.	05/12/2007		
Paracetamol 300 mg/ opium 10 mg/ caffeine 30 mg, capsule Paracetamol 500 mg/ opium 15 mg/ caffeine 50 mg, suppository Paracetamol 500 mg/ opium 25 mg, capsule	Abbott Products **LAMALINE**	Symptomatic treatment of moderate to severe pain and/or pain that does not respond to peripheral analgesics alone.	23/05/2012		

Conclusion

The comparators listed are all clinically relevant.

08 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Marketing Authorisation in other countries

In Europe, the proprietary medicinal product ANTARENE CODEINE currently has Marketing Authorisation only in France.

Reimbursement in other countries

Not applicable

Ibuprofen + codeine combinations are marketed by other companies in various countries at different dosages (the 200 mg/30 mg dosage is available only in Finland and Sweden). They are reimbursed in three EU countries (Sweden, Finland and Spain).

	Dosages on the market	Brand name	Manufacturer
Australia	Ibuprofen 200 mg/codeine 10 mg	Proven Plus	Actavis
	Ibuprofen 200 mg/codeine 12.8 mg	Nurofen	Reckitt Benckiser
	Ibuprofen 200 mg/codeine 12.8 mg	Panafen	GSK
Finland	**Ibuprofen 200 mg/codeine 30 mg**	**Ardinex**	**Abbott**
Ireland	Ibuprofen 200 mg/codeine 12.5 mg	Nurofen Plus	Reckitt Benckiser
Poland	Ibuprofen 200 mg/codeine 12.5 mg	Nurofen Plus	Reckitt Benckiser
Romania	Ibuprofen 200 mg/codeine 12.5 mg	Nurofen	Reckitt Benckiser
Spain	Ibuprofen 400 mg/codeine 30 mg	Astefor	Farmasierra
	Ibuprofen 400 mg/codeine 30 mg	Neobrufen	Abbott
Sweden	**Ibuprofen 200 mg/codeine 30 mg**	**Ardinex**	**Mundipharma**
UK	Ibuprofen 200 mg/codeine 12.5 mg	Nurofen Plus	Reckitt Benckiser
	Ibuprofen 200 mg/codeine 12.8 mg	Cuprofen Plus	Reckitt Benckiser
	Ibuprofen 300 mg/codeine 20 mg	Codafen continus	Mundipharma

09 SUMMARY OF PREVIOUS ASSESSMENTS

Date of opinion (reason for request)	31 March 2010 (Inclusion)
Indication	"Short-term treatment in adults of moderate to severe acute pain or pain that does not respond to a non-opioid analgesic alone."
AB (wording)	Inadequate
IAB (wording)	Not applicable
Studies requested	Not applicable

010 ANALYSIS OF AVAILABLE DATA

010.1 Efficacy

The efficacy of the proprietary medicinal product ANTARENE CODEINE, a fixed combination of ibuprofen and codeine, in the treatment of moderate to severe pain was evaluated in a study (EVACOD, 47 centres in France and 17 in the Czech Republic) carried out between February 2011 and September 2012.

Objective and method:
This was a controlled, randomised, double-blind study carried out over a period of 19 months. The principal objective was to demonstrate the superiority of ibuprofen + codeine over ibuprofen alone in the treatment of acute episodes of gonarthrosis after 4 days of treatment.

Treatment:
Patients were treated three times daily for seven days with the combination ibuprofen 400 mg + codeine 60 mg (= the maximum recommended dose according to the Marketing Authorisation) or with ibuprofen 400 mg alone.

Efficacy endpoint
The primary efficacy endpoint was the reduction in pain intensity measured according to a visual analogue scale from 0 to 100 mm between day 0 and day 4.
Secondary endpoints included the Lequesne index[5] at day 4 and reduction in pain at day 7.

Statistical analysis
The primary analyses were carried out on all patients who underwent randomisation, received at least one dose of study medication, and underwent evaluation before and after treatment.

Calculation of the number of subjects required
To be able to detect a difference of 8 mm on the VAS between the two treatments, a sample of 143 patients per group was necessary.

Results
The initial study protocol called for the inclusion of 300 patients (150 per group) for 286 analysed patients. However, given the high number of deviations from the protocol, this was amended to include a larger number of patients.

A total of 388 patients were included in the study, of whom 29 did not undergo randomisation and one did not receive treatment.

The primary efficacy analysis was carried out on 348 patients (= 97% of the patients who underwent randomisation); 10 patients were not evaluated for the primary endpoint at day 4 (9 randomised to the ANTARENE CODEINE group and 1 to ibuprofen alone) and 1 patient who did not receive treatment was not included in the analysis.

According to the results of this analysis, the superiority of the combination ANTARENE CODEINE (ibuprofen + codeine) over ibuprofen alone was demonstrated, with a mean difference of 4.76 points on a scale of 100 points, 95% CI [1.28 ; 8.25], see table below.

[5] Composite index on a scale from 0 (best functional state) to 24.

Results for the primary efficacy endpoint (primary analysis, not ITT)

Pain score	ANTARENE CODEINE	Ibuprofen alone
Baseline value N Mean (SD)	**172** **69.7 (10.81)**	**176** **70.1 (9.69)**
Value at day 4 N Mean (SD)	**170*** **41.8 (18.47)**	**176** **46.6 (16.04)**
Change versus baseline value N Mean (SD)	**170*** **28.1 (18.53)**	**176** **23.5 (16.27)**
Adjusted difference versus ibuprofen alone [95% CI], p		**4.76 [1.28; 8.25]. p < 0.0076**

* Data missing for two patients according to study report.

No difference was observed in the secondary endpoints: reduction in pain at day 7 and Lequesne index at day 4.

Results for the two secondary endpoints (primary analysis, not ITT)

Pain score	ANTARENE CODEINE	Ibuprofen alone
Baseline value N Mean (SD)	**172** **69.7 (10.81)**	**176** **70.1 (9.69)**
Value at day 7 N Mean (SD)	**163*** **32.8 (18.87)**	**174*** **35.6 (18.75)**
Change versus baseline value N Mean (SD)	**163*** **37 (19.74)**	**174*** **34.4 (19.69)**
Adjusted difference versus ibuprofen alone [95% CI], p		**2.78 [-1.18; 6.74]. NS**

* Data missing

Lequesne index	ANTARENE CODEINE	Ibuprofen alone
Baseline value N Mean (SD)	**170*** **13.0 (3.78)**	**176** **12.5 (3.43)**
Value at day 4 N Mean (SD)	**165*** **9.9 (3.92)**	**175*** **9.7 (3.62)**
Change versus baseline value N Mean (SD)	**165*** **3.2 (2.89)**	**175*** **2.8 (2.86)**
Adjusted difference versus ibuprofen alone [95% CI], p		**0.35 [-0.27; 0.98] NS**

* Data missing

The applicant carried out a post-hoc analysis on the ITT population including patients with missing data. The observed difference between the two groups was still statistically significant: 3.57, 95% CI [0.06; 7.08], see table below.

Results for the primary efficacy endpoint (post-hoc analysis, ITT population)

Pain score	ANTARENE CODEINE	Ibuprofen alone
Baseline value N Mean (SD)	 **180*** **69.9 (10.82)**	 **178** **70.2 (9.76)**
Value at day 4 N Mean (SD)	 **180*** **43.3 (19.32)**	 **178** **46.9 (16.29)**
Change at day 4 versus baseline value N Mean (SD)	 **181** **26.5 (19.06)**	 **178** **23.3 (16.29)**
Adjusted difference versus ibuprofen alone [95% CI], p		**3.57 [0.06; 7.08]. p = 0.046**

* One patient did not receive treatment.

In this post-hoc analysis carried out on the entire randomised population, the difference was still not statistically significant for the reduction in pain at day 7 and improvement in Lequesne index at day 4.

Other data

The applicant also cites five studies from the older literature published between 1982 and 1993 that evaluated the efficacy of the fixed ibuprofen + codeine combination in the treatment of moderate to severe pain and one literature review published in 1998 that had already been evaluated by the Committee in 2010. The conclusions of the Transparency Committee had been as follows:

"The efficacy and safety of ANTARENE CODEINE, fixed combination of ibuprofen (200 or 400 mg) and codeine (30 or 60 mg), was assessed in five studies carried out in a total of 695 patients with dental pain, arthritis pain or gynaecological pain. ANTARENE CODEINE was compared with codeine alone and with ibuprofen alone. These literature studies published between 1982 and 1993, which are of low methodological quality, do not allow us to quantify the effect of ANTARENE CODEINE, particularly as their results are contradictory.

Indeed, in two studies carried out on dental pain, the pain relief provided by the combination ibuprofen 400 mg + codeine 60 mg was not superior to that of ibuprofen 400 mg alone. The results of a study of pain after episiotomy or caesarean section appear to favour the combination ibuprofen 400 mg + codeine 60 mg over ibuprofen 400 mg alone. This study does, however, contain numerous methodological shortcomings. Finally, in a study of coxarthrosis in a limited number of patients (26), the superiority of the ibuprofen + codeine combination over ibuprofen alone was demonstrated only after six doses of treatment.

All in all, the available data are of low methodological quality and do not allow us to draw any formal conclusions regarding the superiority of the ibuprofen + codeine combination over ibuprofen alone."

010.2 Safety/Adverse effects

In the EVACOD study, the percentage of patients experiencing an adverse event (AE) was 38.1% in the ANTARENE CODEINE group, versus 14.1% in the group treated with ibuprofen alone. The most frequent AEs were gastrointestinal, with constipation, nausea and abdominal pain in particular more frequent in the ANTARENE CODEINE group (26%) than in the group treated with ibuprofen alone (7.3%). Also noteworthy among the more common AEs are drowsiness and dizziness (12.7% in the ANTARENE CODEINE group, versus 4.5% in the group treated with ibuprofen alone).

Eight patients in the ANTARENE CODEINE group discontinued treatment on account of an adverse event, versus none in the group treated with ibuprofen alone. Four serious AEs occurred in two patients in the ANTARENE CODEINE group (one patient experienced severe cardiac decompensation 10 days after treatment, for which the connection with the treatment was assessed as plausible, and another experienced meningioma, depression and epilepsy that were judged to be unconnected to the treatment).

All in all, no new adverse effects over and above those identified for the individual constituents of the fixed combination were reported during this study.

A point to note is that, following a European reassessment of the relative risks and benefits of proprietary medicinal products containing codeine alone or in combination, when used as analgesics in children, the SPCs of the proprietary medicinal products concerned, which include ANTARENE CODEINE[6] are currently being revised by the ANSM [French National Medicines and Health Products Safety Agency]. This reassessment follows an alert from the United States reporting serious cases, some even fatal, of respiratory depression in children who were “fast metabolisers”. The principal changes being made to the SPCs are a restriction on the use of codeine in children, with use now permitted only in patients aged 12 years and over after inadequate response to paracetamol and/or NSAIDs, and a contraindication after surgery (tonsillectomy and adenoidectomy) and in nursing mothers.

010.3 Usage/prescription data

In 2012, 10,030 units of ANTARENE CODEINE 200 mg/30 mg and 20,500 units of ANTARENE CODEINE 400 mg/60 mg were sold in France.

010.4 Summary & discussion

The fixed combination of ibuprofen 400 mg and ibuprofen 60 mg (ANTARENE CODEINE) three times daily has been evaluated in one randomised, double-blind study versus ibuprofen 400 mg three times daily in 359 patients with gonarthrosis treated for 7 days.
The population meeting the criteria for the primary efficacy analysis comprises 348 patients (97% of the randomised population), as 10 patients (9 in the ANTARENE CODEINE group and 1 in the ibuprofen group) were not evaluated for pain at day 4 and 1 patient did not receive the treatment.
The ibuprofen + codeine fixed combination showed superiority over ibuprofen alone of 4.76 points, 95% CI [1.28; 8.25], on a 100-point scale; the clinical relevance of this difference is debatable.
In a post-hoc analysis on the entire randomised population (ITT analysis), the ibuprofen + codeine combination was still superior to ibuprofen alone, but the observed difference (3.57 [0.06; 7.08], p = 0.046) is not so clinically relevant (< 4 points on a 100-point scale).

The ibuprofen + codeine combination did not differ from ibuprofen in relevant secondary endpoints, notably in the reduction in pain at day 7 and in the Lequesne index used to evaluate functional capability at day 4.

No studies have been carried out:
- with the fixed combination of ibuprofen 200 mg and codeine 30 mg of ANTARENE CODEINE
- in pain models other than pain associated with acute episodes of gonarthrosis.

The percentage of patients experiencing an adverse event (AE) was higher with the fixed combination of ibuprofen 400 mg and codeine 60 mg than with ibuprofen 400 mg alone (38.1% vs. 14.1%), the most frequent AEs being gastrointestinal (constipation, nausea, abdominal pain), drowsiness and dizziness. All in all, no new adverse effects over and above those identified for the individual constituents of the fixed combination were reported during this study.

010.5 Planned studies

No studies are currently in progress or planned.

[6] ANSM [French National Medicines and Health Products Safety Agency]

011 THERAPEUTIC USE

The fixed combination of ibuprofen and codeine (ANTARENE CODEINE) is a treatment option in the management of moderate to severe acute pain or pain that does not respond to a non-opioid analgesic alone.

012 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

012.1 Actual benefit

◗ Moderate to severe acute pain can result in a marked deterioration in quality of life.

◗ The medicinal products ANTARENE CODEINE are intended as symptomatic treatment.

◗ There are now fewer drug alternatives since the withdrawal of Marketing Authorisation from dextropropoxyphene-based medicinal products.

◗ Their efficacy/adverse effects ratio in the management of acute pain is high.

◗ These medicinal products are first- or second-line medicines, depending on the source and intensity of the pain.

◗ Public health benefit:
The burden to public health of moderate to severe pain is difficult to quantify but may be considered as moderate, given that such pain is frequent and can affect patients' quality of life.
Improving pain management is a public health need that is one of the objectives of the GTNDO [National Technical Group for the Definition of Public-Health Objectives]. This need is however partly covered by existing analgesics.
Moreover, given the available alternatives and in view of the reported adverse effects, ANTARENE CODEINE is not expected to have any impact on morbidity or quality of life.
The medicinal product ANTARENE CODEINE is not therefore expected to benefit public health.

The Committee therefore considers that the actual benefit of the proprietary medicinal products ANTARENE CODEINE is <u>high</u> in the management of moderate to severe acute pain or pain that does not respond to a non-opioid analgesic alone.

The Committee recommends inclusion of the proprietary medicinal products ANTARENE CODEINE on the list of medicines reimbursed by National Health Insurance and on the list of medicines approved for hospital use in the indication "Short-term treatment in adults of moderate to severe acute pain or pain that does not respond to a non-opioid analgesic alone" and at the dosages in the Marketing Authorisation.

◗ **Proposed reimbursement rate: 65%**

012.2 Improvement in actual benefit (IAB)

The proprietary medicinal products ANTARENE CODEINE do not offer any improvement in actual benefit (IAB V, nonexistent) over the available alternatives, particularly combinations of paracetamol with a weak opioid, in the management of moderate to severe acute pain or pain that does not respond to a non-opioid analgesic alone.

012.3 Target population

According to the wording of the indication in the Marketing Authorization, the target population of the proprietary medicinal products ANTARENE CODEINE tablets consists of patients aged 15 years and over with “moderate to severe acute pain or pain that does not respond to a non-opioid analgesic alone”.
Taking into consideration the contraindications, patients must be excluded from the target population of ANTARENE CODEINE in the following situations:

- pregnancy (after 24 weeks of amenorrhoea, i.e. 5 months of pregnancy),
- nursing mothers (except for one-off doses),
- hypersensitivity to ibuprofen or to one of the excipients of the product.
- history of asthma attacks after taking ibuprofen or substances with similar activity, such as other NSAIDs, acetylsalicylic acid,
- history of gastrointestinal haemorrhage or perforation during past treatment with an NSAID,
- ongoing gastrointestinal haemorrhage, cerebrovascular haemorrhage or other haemorrhage,
- progressive peptic ulcer, history of peptic ulcer or recurrent haemorrhage (two or more distinct episodes of diagnosed haemorrhage or ulceration),
- severe hepatic impairment,
- severe renal impairment,
- severe heart failure,
- systemic lupus erythematosus,
- respiratory insufficiency, regardless of severity, due to the depressant action of codeine on the respiratory centres.

In the absence of accurate epidemiological data on acute pain, this target population cannot be quantified accurately.

Conclusion
In the absence of accurate epidemiological data on acute pain, the target population of ANTARENE CODEINE cannot be identified.

013 TRANSPARENCY COMMITTEE RECOMMENDATIONS

◗ Packaging
Appropriate for the prescription conditions according to the indication, dosage and duration of treatment.