HAUTE AUTORITÉ DE SANTÉ

**The legally binding text is the original French version**

**TRANSPARENCY COMMITTEE**

OPINION

29 April 2009

**ARCOXIA 120 mg, film-coated tablet**
**Box of 7 (CIP: 387 964-2)**
**Box of 50 (CIP: 573 527-8)**

**Applicant: MSD - CHIBRET**

Etoricoxib
ATC code: M01AH05

List I

Date of Marketing Authorisation: 28 August 2008 (mutual recognition procedure)

Reason for request: Inclusion on the list of medicines reimbursed by National Health Insurance (box of 7) and approved for use by hospitals (box of 50).

Medical, Economic and Public Health Assessment Division

# 1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

## 1.1. Active ingredient

etoricoxib, selective cyclooxygenase-2 inhibitor NSAID

## 1.2. Novel aspects

None. ARCOXIA is an additional NSAID from the class of selective cyclooxygenase-2 inhibitors or coxibs.

## 1.3. Indication

“Relief of the pain and signs of inflammation associated with acute gouty arthritis.
The decision to prescribe a selective COX-2 inhibitor should be based on an assessment of the individual patient's risks.”

## 1.4. Dosage

“ARCOXIA is administered orally and may be taken with or without food. When rapid relief is needed, it should be noted that the medicinal product takes effect more quickly if etoricoxib is administered without food. As the cardiovascular risks of etoricoxib may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically.

The recommended dose is 120 mg once daily. Etoricoxib 120 mg should be used only for the acute symptomatic period. In clinical trials for acute gouty arthritis, etoricoxib was given at a dose of 120 mg for 8 days.

Doses greater than those recommended have either not demonstrated additional efficacy or have not been studied. Therefore: The dose for acute gout should not exceed 120 mg daily, limited to a maximum of 8 days treatment.”

Elderly: no dosage adjustment is necessary for elderly patients. As with other drugs, caution should be exercised in elderly patients.

Hepatic insufficiency: in patients with mild hepatic dysfunction (Child-Pugh score 5-6) a dose of 60 mg once daily should not be exceeded. In patients with moderate hepatic dysfunction (Child-Pugh score 7-9), the dose of 60 mg every other day should not be exceeded; administration of 30 mg once daily can also be considered.

Clinical experience is limited particularly in patients with moderate hepatic dysfunction and caution is advised.. There is no clinical experience in patients with severe hepatic dysfunction (Child-Pugh score ≥10); therefore, its use is contra-indicated in these patients.

Renal insufficiency: no dosage adjustment is necessary for patients with creatinine clearance ≥30 ml/min. The use of etoricoxib in patients with creatinine clearance <30 ml/min is contra-indicated.

Paediatric patients: etoricoxib is contra-indicated in children and adolescents under 16 years of age.

## 2 SIMILAR MEDICINAL PRODUCTS

### 2.1. ATC Classification (2008)

| | |
|---|---|
| M | : Musculo-skeletal system |
| M01 | : Anti-inflammatory and antirheumatic products |
| M01A | : Anti-inflammatory and antirheumatic products, non-steroids |
| M01AH | : Coxibs |
| M01AH05 | : Etoricoxib |

### 2.2. Medicines in the same therapeutic category

2.2.1. Comparator medicines

All the NSAIDs indicated for gout.

### 2.3. Medicines with a similar therapeutic aim

Colchicine.

## 3 ANALYSIS OF AVAILABLE DATA

### 3.1. Efficacy

The clinical development programme for etoricoxib in acute gout is based on 2 phase III studies of non-inferiority versus an active comparator (indomethacin 150 mg/day): study 040[1] and study 049[2].

The aim of these two controlled, randomised, double-blind studies was to demonstrate non-inferiority of etoricoxib (120 mg/day) to indomethacin (150 mg/day) in the treatment of acute gout in 150 patients (study 040) and in 189 patients (study 049).

Primary endpoint: assessment of pain by the patient on the Likert scale running from 0 (no pain) to 4 points (extreme pain). The initial value was ascertained on day 1 before administration of the medicine. The pain was assessed daily from day 2 to day 4, 4 h after administration of the medicine.

The hypothesis made was that etoricoxib would be considered non-inferior to indomethacin if the upper limit of the 95% confidence interval of the difference in the pain assessed by the patient between day 2 and day 5 was below 0.5 points on the Likert scale (primary analysis).

Results:
The company did not provide a PP analysis of the results. In study 040, 4% of the patients in the etorixocib group and 2.6% of the patients in the indomethacin group discontinued the treatment on account of a lack of efficacy. In study 049, 4.9% of the patients in the etorixocib group and 8.1% of the patients in the indomethacin group discontinued the treatment because of a lack of efficacy.

Table 1: Evaluation of pain by the patient on the Likert scale – primary analysis – ITT population

| Mean values (studies vs. placebo) | | Etoricoxib 120 mg/day | | Indomethacin 150 mg/day. | | Difference in LS mean change, between the treatment groups |
|---|---|---|---|---|---|---|
| | | Baseline value | Value at end of study | Baseline value | Value at end of study | Etoricoxib 120 mg/day vs indomethacin 150 mg/day |
| 040 | Assessment of pain by the patient – change in the score on the Likert scale (0-4) - Primary analysis (day 2 and 5) | 2.88 | 1.13 | 2.99 | 1.03 | 0.11 (0.14, 0.35) |
| | Mean of LS of cha. vs. initial value (95% CI) | -1.72 (-1.90, -1.55) | | -1.83 (-2.01, -1.65) | | |
| 049 | Assessment of pain by the patient – change in the score on the Likert scale (0-4) - Primary analysis (day 2 and 5) | 2.88 | 1.06 | 3.01 | 1.18 | -0.08 (-0.29, 0.13) |
| | Mean of LS of cha. vs. initial value (95% CI) | -1.79 (-1.95, -1.63) | | -1.71 (-1.88, -1.54) | | |

LS: least squares - vs.: versus - cha.: change

However, the results of these non-inferiority studies must be interpreted with caution, for the following reasons:

- The primary analysis of the results was carried out on an ITT basis and not on a PP basis even though this was a non-inferiority trial. PP analysis results are not available.

1 H R Schumacher et al. Randomised double blind trial of etoricoxib and indomethacin in treatment of acute gouty arthritis. BMJ 2002;324:1488–92.
2 B R. Rubin, R Burton, S Navarra et al. Efficacy and tolerance profile of treatment with etoricoxib 120 mg once daily compared with indomethacin 50 mg three times daily in acute gout. Arthritis Rheum 2004; 50: 598–606.

- Furthermore, as the study did not have a placebo arm, the internal validity of the trial is not guaranteed.

In addition, the Transparency Committee stresses that the comparison with indomethacin is not relevant as this NSAID is no longer used in practice, notably because of its poor tolerability.

### 3.2. Adverse effects

The following were taken into account in the analysis of the tolerance of ARCOXIA:
- the results of the European reassessments (2002, 2004, and 2008) which concluded that etoricoxib has a favourable risk-benefit ratio,
- the relevant data from the clinical trials, including the MEDAL programme,
- the pharmacovigilance data.

3.2.1. Adverse-effects data from the clinical trials

The tolerance of etoricoxib (ARCOXIA) was evaluated in 7152 patients in clinical trials. The adverse effects that were most commonly encountered and attributable to etoricoxib were:
- gastrointestinal: digestive-tract disturbances (abdominal pain, flatulence, epigastric burning sensation), diarrhoea, dyspepsia, epigastric discomfort, nausea,
- cardiovascular: hypertension, peripheral oedema, lower-limb oedema, palpitations,
- neurological: dizziness, headaches,
- other: ecchymoses, asthenia, flu-like symptoms.

These principal adverse effects are described in the SPC and are similar to those of coxibs in general. Special warnings and precautions for use regarding the gastrointestinal, thrombotic cardiovascular, cardiorenal, and cutaneous effects associated with the use of etoricoxib were included in the SPC (summary of product characteristics). It is stated, among other things, that "etoricoxib may be associated with more frequent and severe hypertension than some other NSAIDs and selective COX-2 inhibitors, particularly at high doses".

Gastrointestinal, cardiovascular, and renal tolerance was the subject of specific assessments, which are presented below:

- Cardiovascular tolerance

A combined analysis of cardiovascular tolerance in 12 studies was submitted by the company, but was not taken into account as it was only available in the form of an abstract.

Another combined analysis of renovascular-type events in 8 phase II and III studies including a total of 4770 patients was submitted[3]. The incidence of adverse events of the following kind, and discontinuations of treatment because of them, were analysed: elevated blood pressure, lower-limb oedema, increase in bood creatinine levels, occurrence of congestive heart failure. A significant difference (p=0.001) between the etoricoxib 90 mg group and the placebo group was demonstrated in regard to the incidence of hypertension: 2% (30/1491) with placebo versus 3.4% (30/889) with etoricoxib 90 mg. No statistically significant difference was demonstrated in regard to the incidence of other renovascular events. Discontinuation of treatment because of renovascular adverse effects was rare.

3 Curtis SP, Jennifer Ng et al. Renal effects and comparator nonsteroidal anti-inflammatory drugs in controlled clinical trials. Clin. Ther, 2004, 26 :70-83.

Cardiovascular tolerance data from the MEDAL programme[4]

The primary aim of the MEDAL programme was to evaluate the non-inferiority of etoricoxib (60 mg and 90 mg combined) in comparison with difclofenac 150 mg in regard to the risk of serious thrombotic cardiovascular events on the basis of the combined results of the three studies EDGE I & II and MEDAL. These 3 studies are presented in the following table.

Table 2: Summary and description of the 3 clinical trials that make up the MEDAL programme

| | EDGE I | EDGE II | MEDAL |
|---|---|---|---|
| Primary aim | To compare the gastrointestinal tolerance of etorixocib with that of diclofenac in osteoarthritis patients | To compare the gastrointestinal tolerance of etorixocib with that of diclofenac in RA patients | To compare the cardiovascular events with etoricoxib and diclofenac |
| Numbers and disease | 7111 osteoarthritis | 4086 RA | 23,504 patients<br>- 17,804 (76%) osteoarthritis<br>- 5700 (24%) RA |
| Treatment investigated | Etoricoxib 90 mg x 1/day *vs* diclofenac 50 mg x 3/day (1:1) | Etoricoxib 90 mg x 1/day *vs* diclofenac 75 mg x 2/day (1:1) | Etoricoxib (60 mg or 90 mg x 1/day in osteoarthritis 90 mg in RA) *vs* diclofenac 75 mg x 2/day (1:1)* |
| Duration of treatment [ mean (max) in months] | 9 (16) | 19 (34)** | 20.4 (12.3) |

*In the MEDAL study, the first 4000 osteoarthritis patients were randomised to etoricoxib 90 mg or diclofenac 75 mg x 2/day. The other osteoarthritis patients were randomised to etoricoxib 60 mg or diclofenac 75 mg x 2/day.

**The duration of the EDGE II study was specified as being 2 years from the last patient randomised.

A total of 34,701 patients, 72% of whom had osteoarthritis and 28% had RA, were treated for a mean duration of 18 months (approximately 13,000 patients were treated for over 24 months).

It is strongly recommended to prescibe low-dose aspirin be prescribed to all patients at cardiovascular risk and a gastroprotective agent (PPI, misoprostol) be prescribed to all patients at gastrointestinal risk.

The primary endpoint was the incidence of confirmed arterial or venous thrombotic cardiovascular serious adverse events during treatment and up to 14 days after the last administration of the medicine.

This composite enpdoint consisted of the the following events: myocardial infarction (including silent MI), unstable angina, intracardiac thrombus, resuscitated cardiac arrest, thrombotic cerebrovascular accident, cerebrovascular thrombosis, transient ischaemic attack, peripheral venous thrombosis, pulmonary embolism, peripheral arterial thrombosis, and sudden and/or unexplained death.

The protocol specified that etoricoxib would be considered non-inferior to diclofenac if the upper limit of the 95% confidence interval of the relative risk of occurrence of confirmed thrombotic cardiovascuar serious adverse events was below 1.3.

Results: PP and ITT analysis

Treatment was discontinued in 52.2% of the patients receiving etoricoxib and 54.4% of the patients receiving diclofenac. Discontinuation of treatment on account of clinical adverse events occurred in 19.2% of the patients treated with etoricoxib versus 19.4% of the patients treated with diclofenac.

The patients included had numerous cardiovascular and gastrointestinal risk factors (see Table 3).

4 Cannon et al. Cardiovacular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in MEDAL program : a randomised comparison. Lancet 2006 ;368 :1771-81

Table 3: MEDAL programme: characteristics of the patients on inclusion

| **Demographic data** | **Etoricoxib (n=17,412)**<br>*Etoricoxib 60 mg: n=6769;*<br>*Etoricoxib 90 mg: n=10,643* | **Diclofenac (n=17,289)**<br>*Diclofenac 50 mg x 3: n=3518*<br>*Diclofenac 75 mg x 2: n=13,771* |
|---|---|---|
| Age (years), mean (SD) | 63.2 (8.5) | 63.2 (8.5) |
| < 65 years, n (%) | 10,178 (58.5) | 10,127 (58.6) |
| ≥ 65 to < 75 years, n (%) | 5201 (29.9) | 5261 (30.4) |
| ≥ 75 years, n (%) | 2033 (11.7) | 1901 (11.0) |
| Osteoarthritis, n (%) | 12,533 (72.0) | 12,380 (71.6) |
| Rheumatoid arthritis, n (%) | 4878 (28.0) | 4909 (28.4) |
| Weight (kg), mean (SD) | 78.9 (18.6) | 78.9 (18.5) |
| BMI (kg/m$^2$), mean (SD) | 29.5 (6.1) | 29.5 (6.0) |
| Diabetes, n (%) | 1810 (10.4) | 1855 (10.7) |
| Hypertension[2], n (%) | 8109 (46.6) | 8221 (47.6) |
| Dyslipidaemia[2], n (%) | 5097 (29.3) | 5034 (29.1) |
| Smoker, n (%) | 2034 (11.7) | 2037 (11.8) |
| Confirmed atherosclerotric CV disease[§], n (%) | 2014 (11.6) | 2010 (11.6) |
| ≥ 2 CV risk factors[¶] or confirmed atherosclerotic CV disease, n (%) | 6586 (37.8) | 6639 (38.4) |
| Use of low-dose aspirin, n (%) | 6030 (34.6) | 5976 (34.6) |
| Medicines for cardiac purposes, n (%) | | |
| β-blocker | 2806 (16.1) | 2837 (16.4) |
| ACE inhibitor or ARB | 4571 (26.3) | 4535 (26.2) |
| Calcium inhibitor | 2096 (12.0) | 2149 (12.4) |
| Statin | 2859 (16.4) | 2890 (16.7) |
| Diuretic | 3129 (18.0) | 3147 (18.2) |
| Medicines n (%) | | |
| Selective COX-2 NSAID | 4873 (28.0) | 4939 (28.6) |
| Non-selective NSAID | 14,209 (81.6) | 14,174 (82.0) |
| Paracetamol | 10,852 (62.3) | 10,765 (62.3) |
| High-dose aspirin | 173 (1.0) | 185 (1.1) |
| Glucocorticosteroid | 2758 (15.8) | 2762 (16.0) |
| DMARD[**] | 2246 (12.9) | 2208 (12.8) |

[2]Clinical history at time of selection
[§]From: clinical history of myocardial infarction, angina, cerebrovacular accident, transient ischaemic attack, angioplasty, carotid artery disease, peripheral vascular disease, or aortocoronary bypass.
[¶]At least 2 of the following risk factors: history of hypertension, diabetes, dyslipidaemia, familial history of CV disease, smoking.
[**]Disease-modifying antirheumatic drug.

No significant difference was observed between etoricoxib and diclofenac in regard to thrombotic cardiovascular adverse events (primary endpoint). In total, 643 patients in the PP population had a cardiovascular event; 320 (1.24%) were receiving etoricoxib and 323 (1.30%) were receiving diclofenac: RR = 0.95, 95% CI [0.81; 1.11]; this suggests that etoricoxib is non-inferior to diclofenac in terms of thrombotic cardiovascular risk.

Comparable results were observed in regard to arterial thrombotic events on their own and in regard to the APTC composite endpoint[5].

However, this study has methodological limitations which make difficult results interpretation, namely:

- the absence of a placebo arm, given the “non-inferiority” approach,
- the absence of arguments concerning the choice of non-inferiority threshold,
- the absence of discussion of the relative disparity of the trials included, particularly in terms of their aims,
- the comparison of two doses of etoricoxib (mean - 60 mg and high dose - 90 mg) with diclofenac 150 mg (maximum authorised dose) is not relevant in that, in osteoarthritis, it is recommended that NSAIDs be used at their minimum effective dosage.

Cardiorenal effects related to the dose - SPC data

“In the MEDAL study, the incidence of congestive heart failure adverse events (discontinuations and serious events) occurred at similar rates on etoricoxib 60 mg compared to diclofenac 150 mg but was higher for etoricoxib 90 mg compared to diclofenac 150 mg (statistically significant for 90 mg etoricoxib vs. 150 mg diclofenac in

5 Antiplatelet Trialists' Collaboration, defined as the combined incidence of deaths of CV, haemorrhagic, and unknown origin, myocardial infarction, and CVA.

MEDAL OA cohort). The incidence of confirmed congestive heart failure adverse events (events that were serious and resulted in hospitalisation or a visit to an emergency department) was non-significantly higher with etoricoxib than diclofenac 150 mg, and this effect was dose-dependent. The incidence of discontinuations due to edema-related adverse events was higher for etoricoxib than diclofenac 150 mg, and this effect was dose-dependent (statistically significant for etoricoxib 90 mg, but not for etoricoxib 60 mg).
The cardiorenal results for EDGE and EDGE II were consistent with those described for the MEDAL Study.
In the individual MEDAL Programme studies, for etoricoxib (60 mg or 90 mg), the absolute incidence of discontinuation in any treatment group was up to 2.6% for hypertension, up to 1.9% for edema, and up to 1.1% for congestive heart failure, with higher rates of discontinuation observed with etoricoxib 90 mg than etoricoxib 60 mg."

- Gastrointestinal tolerance:

A combined analysis of the tolerance data from 10 phase IIb and IV[6] studies (ended in June 2003 and including 2 gastrointestinal endoscopy studies 026 and 029) carried out with etoricoxib was submitted by the company. It compared the incidence of gastrointestinal events of the PUH type (perforation, symptomatic gastroduodenal ulcers, and haemorrhage) under etoricoxib (5,10, 30, 60, 90, or 120 mg) - mean dose of 87.3 mg/day) with that under conventional NSAIDs (diclofenac 150 mg, naproxen 1000 mg, or ibuprofen 2400 mg). In total, 5441 patients were included, 3226 of whom were treated with etoricoxib and 2215 with conventional NSAIDs. The median duration of exposure to the treatment was 12.4 months in the etoricoxib group vs. 6.3 months in the conventional-NSAIDs group. The patients' mean age was 56.7 years (29% were over 65 years of age). The incidence of PUH was significantly lower with etoricoxib than with conventional NSAIDs: 1.24% vs. 2.48%, $p<0.001$. However, the overall incidence of discontinuation due to adverse effects was similar in the two groups. The results of this combined analysis must be interpreted with caution, for the following reasons:

- because of the small number of events per dose and the heterogeneity of the doses, the diseases, and the methodology of the studies included, it is not possible to evaluate the differences between the etoricoxib doses on the basis of this analysis,
- as the numbers in the diclofenac and ibuprofen arms were very small, these results are due principally to naproxen and do not permit conclusions to be drawn for all the NSAIDs,
- no information is available on the homogeneity of the results of the studies included.

Gastrointestinal tolerance results from the MEDAL programme

No definite conclusion can be drawn from these data, firstly because the evaluation of gastrointestinal tolerance was of an exploratory nature only and secondly because a substantial percentage of patients in the 2 groups (etoricoxib and diclofenac) received PPIs. The percentage of patients taking a PPI was 39% at the start in the 2 arms, and 82% of the subjects treated with etoricoxib and with diclofenac took a PPI for a period ≥75% of the duration of the trial.[7] As a rough guide, the rate of confirmed upper gastrointestinal clinical events (perforation, ulcers, haemorrhage or PUH) was significantly lower with etoricoxib (1.01%) than with diclofenac (1.42%), RR = 0.69, 95% CI [0.57-0.83]. However, no difference between etoricoxib and diclofenac was shown in regard to the rate of upper gastrointestinal events deemed to be "*complicated*"* (complicated bleeding, obstruction, and perforation): 0.45% with etoricoxib versus 0.47% with diclofenac, p=NS.

In addition, no difference between etoricoxib and diclofenac was shown in regard to the rate of confirmed lower gastrointestinal clinical events (perforation, obstruction, haemorrhage or PUH): 0.48% with etoricoxib versus 0.56% with diclofenac, RR =0.84,

6 Ramey DR et al. The incidence of upper gastrointestinal adverse events in clinical trials of etoricoxib versus non-selective NSAIDs: an updated combined analysis. CMRO. 2005; 21: 715-722.
7 The mean duration of the trial was 18 months.
* term not defined in the company's dossier

95% CI [0.63-1.13]. Finally, no difference between etoricoxib and diclofenac was demonstrated in regard to upper gastrointestinal events in patients taking concomitant low-dose aspirin (approximately 33% of patients) - SPC data.

3.2.2. Pharmacovigilance data

ARCOXIA has been granted Marketing Authorisation in 70 countries. Since the first MA, which was issued in October 2001 (Mexico), there have been 13 pharmacovigilance reports, analysing a total of 3.4 million patient-years (last report - 31 March 2008). No significant signal, including from the viewpoint of possible cardiovascular adverse effects, has been demonstrated.

The marketing of ARCOXIA in France is subject to a risk management plan which includes national pharmacovigilance monitoring and a study of use in order to assess its conformity to correct practice and compliance with the Marketing Authorisation recommendations.

## 3.3. Conclusion

3.3.1 Efficacy

The efficacy of ARCOXIA (etoricoxib) 120 mg in gout was assessed in 2 phase III clinical studies. ARCOXIA administered at a dosage of 120 mg/day for 8 days was non-inferior to indomethacin 150 mg/day in regard to pain and inflammation. However, the comparison with indomethacin is not relevant as this NSAID is no longer used in practice because of its poor tolerability.

3.3.2 Adverse effects

Gastrointestinal tolerance: upper gastrointestinal complications (perforation, ulcer, or haemorrhage), some of them fatal, were observed with etoricoxib. Although the available data suggest better gastrointestinal tolerability with etoricoxib than with non-selective NSAIDs taken at their maximum dosage and without a gastroprotective agent, it should be noted that no difference was demonstrated in respect of complicated events in the MEDAL programme. Consequently, the utmost caution is recommended in populations at risk of gastrointestinal complications (the elderly, persons with a history of ulcer or haemorrhage, persons receiving concomitant treatment with aspirin, clopidogrel, an anticoagulant, or a corticosteroid).

Cardiovascular tolerance: the available data suggest that ARCOXIA brings an increased cardiovascular risk in comparison with other NSAIDs already on the market. In the MEDAL programme, renovascular effects (hypertension, oedema, congestive heart failure) were more common with etoricoxib than with diclofenac, and these effects were dose-dependent (statistically significant for etoricoxib 90 mg, but not for etoricoxib 60 mg). The SPC states that: “etoricoxib may be associated with more frequent and severe hypertension than some other NSAIDs and selective COX-2 inhibitors, particularly at high doses.”

Cutaneous tolerance: a risk of severe skin reactions cannot be excluded with etoricoxib.

In general, the data submitted in the dossier show that ARCOXIA has efficacy comparable to that of the other NSAIDs, though poses a higher risk of hypertension.

# 4 TRANSPARENCY COMMITTEE CONCLUSIONS

### 4.1 Actual benefit

Without treatment, gout can lead to disability and/or marked impairment of quality of life, connected with joint problems and/or kidney problems (lithiasis, nephropathy).

ARCOXIA 120 mg/day was non-inferior to indomethacin 150 mg/day in the treatment of acute gout. However, the available data suggest that etoricoxib may be associated with more frequent and severe hypertension than some other NSAIDs and selective COX-2 inhibitors, particularly at high doses.
There are numerous alternative treatments.

Consequently, in view of continuing uncertainties over the cardiovascular tolerance of high-dose etoricoxib, the Transparency Committee is of the opinion that the actual benefit of ARCOXIA 120 mg is at present insufficient, relative to that of other treatments available for gout, to warrant its being paid for by National Insurance.

### 4.3. Transparency Committee recommendations

The Transparency Committee does not recommend inclusion on the list of medicines reimbursed by National Health Insurance and on the list of medicines approved for use by hospitals and various public services in the indication and at the dosage in the Marketing Authorisation.