ADENURIC 80 mg, film-coated tablets  
B/28 (CIP code: 385 724-4)  
B/84 (CIP code: 572 820-3)

ADENURIC 120 mg, film-coated tablets  
B/28 (CIP code: 385 725-0)  
B/84 (CIP code: 572 822-6)

Applicant: BEAUFOR IPSEN

febuxostat  
ATC code: M04AA03

Date of Marketing Authorisation: 21 April 2008 (centralised procedure)

Reason for request: Inclusion on the list of medicines reimbursed by National Health Insurance and approved for hospital use.
1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
febuxostat

1.2. Background
Non-purine, selective inhibitor of xanthine oxidase.

1.3. Indication
“Treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred (including a history, or presence of, tophus and/or gouty arthritis)”

1.4. Dosage
“The recommended oral dose of ADENURIC is 80 mg once daily without regard to food. If serum uric acid is > 60 mg/l (360 µmol/l) after 2-4 weeks, ADENURIC 120 mg once daily may be considered.
ADENURIC works sufficiently quickly to allow retesting of the serum uric acid after 2 weeks. The therapeutic target is to decrease and maintain serum uric acid below 60 mg/l (360µmol/l).
Gout flare prophylaxis of at least 6 months is recommended”.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2009)
M : Musculo-skeletal system
M04 : Antigout preparations
M04A : Antigout preparations
M04AA : Preparations inhibiting uric acid production
M04AA 03 : febuxostat

2.2. Medicines in the same therapeutic category
A Marketing Authorisation has been issued in France for only one other xanthine oxidase inhibitor: allopurinol - ZYLORIC and generics.

As a reminder, its indications are as follows:
- “treatment of symptomatic primary or secondary hyperuricaemia (blood disorders, nephropathy, iatrogenic hyperuricaemia),
- treatment of gout: tophaceous gout, recurrent gout, urate crystal arthropathy even when accompanied by hyperuraturia, uric lithiasis or renal insufficiency,
- treatment of hyperuricosuria and hyperuraturia,
- treatment and prevention of uric lithiasis,
- prevention of recurrent of calcic lithiasis in patients with hyperuricaemia or hyperuricosuria, in addition to the usual dietary measures, in particular the restriction of protein and calcium intake.”
2.3. Medicines with a similar therapeutic aim

Medicines for which a Marketing Authorisation has been granted for chronic hyperuricaemia/gout:

- Probenecid (BENEMID, uricosuric) indicated in “gout, whether or not tophaceous, in the absence of hyperuraturia, in symptomatic primary or secondary hyperuricaemia not associated with renal impairment and as an adjunct to penicillin therapy.”

In practice, this medicine is usually reserved for cases in which allopurinol cannot be tolerated, particularly in the absence of hyperuraturia, a history of lithiasis and renal impairment, but its efficacy is limited.

Medicines used outside the Marketing Authorisation in hyperuricaemia and gout:

➢ Another uricosuric agent, benzbromarone (DESURIC) was withdrawn in 2003 because of hepatic adverse effects but is available under nominative compassionate use. Use of this product is restricted to certain specific situations on account of its poor hepatic tolerability.
3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy
Account has been taken only of phase III studies conducted at the dosage and in the indication set out in the Marketing Authorisation.
The plan for the development of febuxostat (ADENURIC) in symptomatic chronic hyperuricaemia is based primarily on three phase III studies, lasting 6 months to 1 year, conducted in the United States (APEX, FACT and CONFIRMS studies).
APEX and FACT were pivotal studies for the European Marketing Authorisation. The CONFIRMS study was conducted at the request of the FDA and was underway at the time the application was submitted for a European Marketing Authorisation. The results have been sent to the EMEA purely for information, and no amendments are requested to the SPC. The results of 2 and 5-year open-label extensions to these studies have been included in the file.

3.1.1. Pivotal studies for the Marketing Authorisation: APEX and FACT studies conducted between 2003 and 2004

Methodology:
Randomised, double-blind, controlled studies to compare febuxostat (80, 120, 240 mg) to allopurinol (100 and 300 mg) in the treatment of hyperuricaemia and/or gout. The aim of these studies was to demonstrate the non-inferiority and then the superiority of febuxostat compared to allopurinol.

Inclusion criteria
- men and women from 18 to 85 years of age,
- hyperuricaemia, defined as serum uric acid ≥ 80 mg/l or 480 µmol/l,
- history or signs of gout as defined by the presence of one or more of the criteria issued by the American Rheumatism Association (ARA) for the diagnosis of primary gout,
- renal function, defined at the pre-screening visit, by serum creatinine ≤ 177 µmol/l (APEX study) or ≤ 133 µmol/l (FACT) and creatinine clearance ≥ 30 ml/minute (APEX) or ≥ 50 ml/minute (FACT).

Non-inclusion criteria
- history of xanthinuria, renal calculi, inability to tolerate allopurinol,
- certain associated medicines, including thiazide diuretics and treatments that lower levels of serum uric acid,
- various disorders such as active ulcerative disease or rheumatoid polyarthritis requiring pharmacological treatment,
- secondary hyperuricaemia,
- excessive alcohol consumption or history of alcoholism in the last 5 years,
- ALAT and ASAT liver enzymes more than 1.5 times the upper normal limit or active liver disease,
- history of myocardial infarction or cerebrovascular accident in the last 6 months or a history of cancer in the last 5 years.

Treatments
In order to limit gout flares when starting uric acid lowering treatment, patients were given naproxen (250 mg twice daily) or colchicine (0.6 mg once daily) up to the eighth week of the study.
Note: the dosage of colchicine used in the United States was lower than that recommended in France (1 mg daily) in the prophylaxis of acute gout attacks in patients with chronic gout particularly when starting uric acid lowering treatment.

In the APEX study, the 1072 patients included were randomised and divided into 5 groups and allocated for 28 weeks either:
- placebo (n =134),
- febuxostat 80 mg x 1/d (n = 267), 120 mg x 1/d (n = 269), 240 mg x 1/d (n = 134),
- allopurinol at a dose adjusted according to serum creatinine (300 mg x1/d [n = 258] if the initial level was ≤ 133 µmol/l or 100 mg x1/d [n=10] if it was > 133 µmol/l and ≤ 177 µmol/l).

In the FACT study, the 760 patients included were randomised and divided into 3 groups and allocated for one year either:
- febuxostat 80 mg x 1/d (n = 256)
- febuxostat 120 mg x 1/d (n = 251)
- allopurinol 300 mg x 1/d (n=253)

Primary efficacy endpoint
The primary efficacy endpoint was a biological criterion: the proportion of patients with a uric acid level < 60 mg/l (360 µmol/l) in the last three monthly serum determinations.

Note: this criterion corresponds to the therapeutic target to be achieved for the treatment of symptomatic hyperuricaemia namely the reduction and maintenance of serum uric acid below the threshold of 60 mg/l.

Secondary efficacy endpoints included the clinical criteria
- incidence of gout flares,
- reduction in the number and size of tophi.

Statistical analysis
The statistical analysis was based on a hypothesis of the non-inferiority of febuxostat compared to allopurinol (300/100 mg) in the case of a lower limit of the confidence interval (97.5%) for the difference of less than 10%. If non-inferiority was demonstrated, a superiority test was carried out.

Results

Demonstration of non-inferiority
The results of the per protocol (PP) analysis of non-inferiority were not included in the clinical study reports. The study reports included only the results of the intention to treat (ITT) analysis of superiority.

28-week study – APEX (C02-009)

- Patient characteristics
In the APEX study, the average age was 52 years, and patients had suffered from gout for an average of 11 years. 40% of patients had a uric acid level of ≥ 100 mg/l. Over 87% of patients had had an episode of gout during the year prior to inclusion in the study and 28% of patients had tophi or a history of tophi at inclusion. In addition to manifestations of hyperuricaemia, these patients had arterial hypertension (47%) and hyperlipidaemia (33%), obesity defined by a BMI ≥ 30 (62%). Forty (40) patients with moderate renal impairment (serum creatinine between 133 and 177 µmol/l) were included.
Analysis of superiority (ITT analysis) based on the primary endpoint
The ITT population was defined as the population which received at least one dose of treatment (n = 1072). However, 5 patients in the febuxostat 80 mg group were excluded from the analysis on account of serum uric acid at inclusion of < 80 mg/l.
The proportion of patients achieving the therapeutic target of a reduction in serum uric acid below 60 mg/l was higher with febuxostat 80 mg and 120 mg and 240 mg than with allopurinol 300/100 mg (see Table 1).

Note: The Marketing Authorisation issued for France includes only 80 mg and 120 mg. The dose of 240 mg/day was included in this study in order to evaluate the tolerance of a dose twice the maximum dose recommended by the SPC.

Table 1. Proportion of patients in whom the 3 determinations of serum uric acid for the last 3 months of treatment were < 60 mg/l (ITT population) – APEX study (n/N, %)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Febuxostat 80 mg</th>
<th>Febuxostat 120 mg</th>
<th>Febuxostat 240 mg</th>
<th>Allopurinol 300/100 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>APEX Study</td>
<td>0/134 (0%)</td>
<td>126/262 (48%)*</td>
<td>175/269 (65%)*</td>
<td>92/134 (69%)*</td>
<td>60/268 (22%)</td>
</tr>
</tbody>
</table>

* p<0.001 vs. allopurinol

Table 2 below shows the mean variation in serum uric acid in each group.

Table 2. Mean reduction in levels of serum uric acid between inclusion and week 28 – APEX study

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Febuxostat 80 mg</th>
<th>Febuxostat 120 mg</th>
<th>Febuxostat 240 mg</th>
<th>Allopurinol 300/100 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>134</td>
<td>262</td>
<td>269</td>
<td>268</td>
<td></td>
</tr>
<tr>
<td>Serum uric acid at inclusion (mg/l)</td>
<td>98.0</td>
<td>99.6</td>
<td>98.8</td>
<td>97.8</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>99</td>
<td>161</td>
<td>188</td>
<td>208</td>
<td></td>
</tr>
<tr>
<td>Serum uric acid at 28 weeks (mg/l)</td>
<td>92.5</td>
<td>51.5</td>
<td>44.1</td>
<td>63.5</td>
<td></td>
</tr>
<tr>
<td>Absolute reduction in serum uric acid between inclusion and W 28 (mg/l) (%)</td>
<td>-5.5 (-3.58%)</td>
<td>-48.1 (-47.58%)*</td>
<td>-54.7 (-54.88%)*</td>
<td>-34.3 (-34.35 %)</td>
<td></td>
</tr>
</tbody>
</table>

* p<0.05 vs. allopurinol

Of the patients with moderate renal impairment, serum uric acid was < 60 mg/l in 4 of the 9 patients treated with febuxostat 80 mg as well as in 5 of the 11 patients treated with 120 mg. None of the patients treated with allopurinol or placebo achieved this therapeutic target.

Results on the clinical secondary endpoints
In the APEX study, for the first 8 weeks of treatment, during which prophylaxis for gout attacks with naproxen or colchicine was obligatory, the incidence of gout flares was higher with febuxostat 80, 120 mg/d than with allopurinol (see Table 3). Interpretation of this criterion is however difficult.
No difference was observed in the size of tophi between patients treated with febuxostat and allopurinol.
Table 3. Results for secondary endpoints – APEX Study

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Febuxostat 80 mg</th>
<th>Febuxostat 120 mg</th>
<th>Allopurinol 100 / 300 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of subjects requiring treatment for a gout flare</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At inclusion</td>
<td>12/134 (9%)</td>
<td>21/262 (8%)</td>
<td>28/269 (10%)</td>
<td>20/268 (7%)</td>
</tr>
<tr>
<td>D 1 to W 8 (prophylaxis)</td>
<td>27/134 (20%)</td>
<td>73/262 (28%)</td>
<td>97/269 (36%)*</td>
<td>61/268 (23%)</td>
</tr>
<tr>
<td>During the 28-week period</td>
<td>74/137 (55%)</td>
<td>149/262 (57%)</td>
<td>168/269 (62%)*</td>
<td>136/268 (51%)</td>
</tr>
<tr>
<td>Median reduction in the size of tophi between inclusion and W 28 (%)</td>
<td>-52</td>
<td>-45.6</td>
<td>-54.2</td>
<td>-31.5%</td>
</tr>
<tr>
<td>Mean reduction in the number of tophi between inclusion and W 28 (%)</td>
<td>-0.3</td>
<td>-0.3</td>
<td>-1.2</td>
<td>-0.4</td>
</tr>
</tbody>
</table>

* difference statistically significant versus allopurinol, p<0.05

Conclusion:
Febuxostat 80 mg or 120 mg/d was superior to a fixed dose of allopurinol (100-300 mg) in reducing serum uric acid and maintaining it below 60 mg/l. Furthermore, no statistically significant difference was reported between febuxostat 80 mg and allopurinol using clinical parameters: reduction in the number of tophi, or their size, and the proportion of patients requiring treatment for a gout flare.
However, the proportion of patients requiring treatment for a gout flare was statistically higher with febuxostat 120 mg than with allopurinol.

Study after 52 weeks – FACT (C02-010)

- Patient characteristics
In the FACT study, the average age was 52 years and patients had suffered from gout for an average of approximately 12 years. In 41% of patients, serum uric acid was ≥ 100 mg/l at inclusion. Over 85% of patients had a gout flare during the year prior to inclusion in the study and an average of 24% of patients had tophi or a history of tophi at inclusion. Almost half the patients (42-45%) had already been treated with a uric acid lowering agent. In addition to manifestations of hyperuricaemia, these patients had arterial hypertension (44%), hyperlipidaemia (34%), obesity defined by a BMI ≥ 30 (62%).

- Results for the primary endpoint
The proportion of patients achieving the therapeutic target of reducing serum uric acid to less than 60 mg/l was higher with febuxostat 80 mg and 120 mg than with allopurinol 300 mg (see Table 4).

Table 4. Proportion of patients in whom the last 3 determinations of serum uric acid were < 60 mg/l (ITT population) – FACT study (n/N, %)

<table>
<thead>
<tr>
<th></th>
<th>Febuxostat 80 mg</th>
<th>Febuxostat 120 mg</th>
<th>Allopurinol 300 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>136/255 (53%)*</td>
<td>154/250 (62%)*</td>
<td>53/251 (21%)</td>
</tr>
</tbody>
</table>

*p<0.001 vs. allopurinol
Table 5 below shows the mean variation in serum uric acid in each group.

Table 5. Mean reduction in levels of serum uric acid between inclusion and week 52 in the FACT study

<table>
<thead>
<tr>
<th></th>
<th>Febuxostat 80 mg</th>
<th>Febuxostat 120 mg</th>
<th>Allopurinol 300 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>255</td>
<td>250</td>
<td>251</td>
</tr>
<tr>
<td>Serum uric acid at inclusion (mg/l)</td>
<td>98.0</td>
<td>98.4</td>
<td>99.0</td>
</tr>
<tr>
<td>N</td>
<td>159</td>
<td>145</td>
<td>178</td>
</tr>
<tr>
<td>Serum uric acid at 52 weeks (mg/l)</td>
<td>50.7</td>
<td>46.4</td>
<td>63.7</td>
</tr>
<tr>
<td>Absolute reduction in serum uric acid between inclusion and W 52 (mg/l) (%)</td>
<td>-47.3 (-47.74%)*</td>
<td>-52 (-53.02%)*</td>
<td>-35.3 (-34.75%)</td>
</tr>
</tbody>
</table>

* p<0.05 vs. allopurinol

Results on secondary endpoints (see Table 6)

In the FACT study, during the first eight weeks of treatment, the incidence of gout flares was higher with febuxostat 120 mg/d (36%) than with allopurinol 300 mg (21%). For this criterion over the rest of the study, no difference was reported between the three groups. Furthermore, no difference was reported for the reduction in the number of tophi or their size.

Table 6. Results on the secondary endpoints -FACT Study

<table>
<thead>
<tr>
<th></th>
<th>Febuxostat 80 mg</th>
<th>Febuxostat 120 mg</th>
<th>Allopurinol 300 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of subjects requiring treatment for a gout flare</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At inclusion</td>
<td>20/255 (8%)</td>
<td>28/250 (11%)</td>
<td>20/251 (8%)</td>
</tr>
<tr>
<td>D 1 to W 8 (prophylaxis)</td>
<td>55/255 (22%)</td>
<td>90/250 (36%)*</td>
<td>52/251 (21%)</td>
</tr>
<tr>
<td>During the 52-week period</td>
<td>163/255 (64%)</td>
<td>179/250 (72%)</td>
<td>163/251 (65%)</td>
</tr>
<tr>
<td>Median reduction in the size of tophi between inclusion and W 52 (%)</td>
<td>-83.4</td>
<td>-66</td>
<td>-50</td>
</tr>
<tr>
<td>Mean reduction in the number of tophi between inclusion and W 52 (%)</td>
<td>-0.4</td>
<td>-1</td>
<td>-0.7</td>
</tr>
</tbody>
</table>

* p<0.05 vs. allopurinol 300 mg

Conclusion of the FACT study

Febuxostat at a daily dose of 80 or 120 mg proved to be more efficacious than allopurinol at a fixed daily dose of 300 mg in reducing serum uric acid below 60 mg/l. No difference between febuxostat 80 mg and allopurinol was reported for clinical criteria: reduction in the number of tophi and their size and the proportion of patients requiring treatment for a gout flare. The proportion of patients requiring treatment for a gout flare was however statistically higher with febuxostat 120 mg than with allopurinol between W1 and W8.
3.1.2. Additional study after 6 months: CONFIRMS F-GT06-153

The methodology, inclusion and non-inclusion criteria were similar to those for the two previous studies. The objective of this randomised, double-blind, controlled study was to evaluate the efficacy and tolerance of febuxostat 40 and 80 mg compared to allopurinol 200 mg/300 mg (dose according to renal function) in the treatment of hyperuricaemia and/or gout.

The 2269 patients included were randomised and divided into 3 groups for treatment for 6 months with:
- Febuxostat 40 mg x 1/d (n = 757)
- Febuxostat 80 mg x 1/d (n = 756)
- Allopurinol 300/200 mg x 1/d (n=756) including 145 patients treated with 200 mg.

Patients with normal renal function (creatinine clearance \( \geq 90 \text{ ml/min} \)) or mild renal impairment (creatinine clearance between 60 and 89 ml/min) received 300 mg allopurinol and those with moderate renal impairment (creatinine clearance between 30 and 59 ml/min) received 200 mg allopurinol daily.

Patients received colchicine or naproxen for a period of 6 months.

The primary evaluation endpoint was the proportion of patients with serum uric acid < 60 mg/l (360 µmol/l) at the last visit.

The hypothesis had been put forward that febuxostat would be considered as not inferior to allopurinol if the lower limit of the 95% confidence interval for the difference was less than 10%. If non-inferiority was demonstrated, a superiority test was carried out.

Results:
Characteristics of patients included
In the CONFIRMS study, the mean age was 52.8 years. Patients had suffered from gout for an average of 11.6 years, and in 32.3% of patients serum uric acid was \( \geq 100 \text{ mg/l} \). The majority of the patients were obese (63.6 %, BMI \( \geq 30 \)), 52.8% had arterial hypertension and 41.5% had hyperlipidaemia. Furthermore, mild to moderate renal impairment was reported in 65.4% of patients (i.e. 1483/2269): renal impairment was moderate in 17.7% and mild in 47.7%.

The non-inferiority of febuxostat 40 mg compared to allopurinol (300/200 mg) was demonstrated: difference of 3.1% with a lower limit for the 95% confidence interval (-1.9%). The 80 mg dose was superior to allopurinol.

Table 7. Proportion of patients in whom serum uric acid at the final visit was < 60 mg/l (n/N, %)

<table>
<thead>
<tr>
<th></th>
<th>Febuxostat 40 mg</th>
<th>Febuxostat 80 mg</th>
<th>Allopurinol 300/200 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>342/757</td>
<td>507/756</td>
<td>318/755</td>
</tr>
<tr>
<td></td>
<td>45.2%</td>
<td>67.1%*</td>
<td>42.1%</td>
</tr>
</tbody>
</table>

*p<0.001 vs. allopurinol
Table 8. Mean reduction in serum uric acid levels between inclusion and the final visit of the CONFIRMS study

<table>
<thead>
<tr>
<th></th>
<th>Febuxostat 40 mg</th>
<th>Febuxostat 80 mg</th>
<th>Allopurinol 300/200 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>N = 757</td>
<td>N = 756</td>
<td>N = 755</td>
</tr>
<tr>
<td>Serum uric acid at inclusion (mg/l)</td>
<td>95.6</td>
<td>95.6</td>
<td>95.5</td>
</tr>
<tr>
<td>N</td>
<td>N = 757</td>
<td>N = 756</td>
<td>N = 755</td>
</tr>
<tr>
<td>Serum uric acid at the final visit (mg/l)</td>
<td>63.7</td>
<td>56.7</td>
<td>65.2</td>
</tr>
<tr>
<td>Absolute reduction in serum uric acid between inclusion and final visit</td>
<td>-31.9 (-33.06%)*</td>
<td>-38.9 (-40.63%)*</td>
<td>-30.3 (-31.32%)</td>
</tr>
</tbody>
</table>

* p<0.05 vs. allopurinol

Thirty-one percent of patients required treatment for a gout attack in the febuxostat 40 and 80 mg groups and 25% in the allopurinol group.

Efficacy data for the subpopulation of patients with impaired renal function – per protocol analysis
In this study, renal function was impaired in 65.4% (1483/2269) of patients. In these patients, febuxostat 80 mg/d proved to be superior to allopurinol.

Table 9. Proportion of patients with impaired renal function with final serum uric acid < 60 mg/l (CONFIRMS Study – 6-month follow-up)

<table>
<thead>
<tr>
<th>Renal functiona</th>
<th>Febuxostat 40 mg (N = 479)</th>
<th>Febuxostat 80 mg (N = 503)</th>
<th>Allopurinol 300/200 mgb (N = 501)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild to moderate renal impairmentc</td>
<td>49.7 (238/479)</td>
<td>71.6 (360/503) *</td>
<td>42.3 (212/501)</td>
</tr>
</tbody>
</table>

a moderate renal impairment: 30 ml/min ≤ Cl creatinine ≤ 59 ml/min
b mild renal impairment: 60 ml/min ≤ Cl creatinine ≤ 89 ml/min
c Allopurinol 200 mg (N = 145; allopurinol 300 mg N = 356)
d Includes 2 patients with Cl creatinine < 30 ml/min
* Statistically significant versus allopurinol (p ≤ 0.05)

Conclusion
This CONFIRMS study demonstrated the non-inferiority of a lower dose of febuxostat (40 mg/d) compared to allopurinol (300/200 mg/d). Furthermore, the superiority of febuxostat 80 mg in terms of efficacy compared to allopurinol was demonstrated in patients with mild to moderate renal impairment.

3.1.3. Long-term results – C02-021 - EXCEL
In open-label study C02-021 including patients who took part in the FACT and APEX studies, certain patients were followed up for 40 months. The therapeutic results were maintained, with less than 3% of patients requiring treatment for a gout flare after 16 to 24 months of treatment and the disappearance of tophi in 54% of subjects after 24 months of treatment. However, these results should be interpreted with caution on account of the open-label methodology of this study.

3.2. Adverse effects
The tolerance analysis for febuxostat (ADENURIC) took account of data from:

- two phase III studies included in the Marketing Authorisation application, and the open-label extension phase for these studies (C02-021) and,
- the complementary CONFIRMS study (not examined by the EMEA)·

### 3.2.1 Data from the APEX and FACT studies and the open-label extension phase

During these two studies, over 1000 patients were treated at the dose of 80 mg or 120 mg recommended in France. The incidence of adverse events associated with treatment (in the investigator’s opinion) was 23% with febuxostat 80 mg, 21% with febuxostat 120 mg and 19% with allopurinol. The most commonly-reported treatment-related adverse events were liver function abnormalities such as transaminase elevation (3.5%), diarrhoea (2.7%), headaches (1.8%), nausea (1.7%) and rashes (1.5%) - source SPC.

#### Discontinuation of treatment:

In the APEX study, cases of discontinuation of treatment were frequent:

- “all causes together” - 35% with febuxostat 80 mg, 26% with febuxostat 120 mg as compared to 21% with allopurinol.
- “due to gout attacks” - 14% with febuxostat 80 mg, 9% with febuxostat 120 mg as compared to 2% with allopurinol.
- “due to adverse effects” - 23% with febuxostat 120 mg, 19% with febuxostat 80 mg as compared to 32% with allopurinol.

In the FACT study, cases of discontinuation of treatment were also frequent:

- “all causes together” - 34% with febuxostat 80 mg, 39% with febuxostat 120 mg as compared to 26% with allopurinol.
- “due to gout flares” - 11% with febuxostat 80 mg, 29% with febuxostat 120 mg as compared to 14% with allopurinol.
- “due to adverse effects” - 18% with febuxostat 80 mg, 23% with febuxostat 120 mg as compared to 12% with allopurinol.

During the open-label extension phase, the incidence of adverse events associated with treatment was higher in the febuxostat 80 mg group (14.7%) and febuxostat 120 mg group (12.6%) than in the allopurinol group (8.4%). The most common adverse effects (in the investigator’s opinion) were liver function abnormalities, diarrhoea, headaches, rashes and hypertension – source SPC.

#### Deaths

In the FACT study, 4 patients died in the febuxostat group and no patients died in the allopurinol group. In the open-label study (C02-021), 8 patients died in the febuxostat group as compared to none in the allopurinol group. None of these deaths were considered by the investigator to be treatment-related. Nine of these deaths were considered by the investigator as being potentially of cardiovascular origin.

- **Cardiovascular tolerance**

Compared to the allopurinol group, a higher incidence of cardiovascular events was reported by investigators in the febuxostat group during the APEX and FACT studies (1.3 events per 100 patient-years as compared to 0.3) and the open-label extension phase (1.4 versus 0.7 events per 100 patient-years). However, no casual relationship with febuxostat was established. In these patients, the risk factors identified were a history of atherosclerosis and/or myocardial infarction or congestive heart failure.

The SPC includes a special warning not to use ADENURIC in cases of ischaemic heart disease or congestive heart failure.

Furthermore, the risk management plan includes the conducting of a prospective, randomised, open-label study versus allopurinol, with blind evaluation of the primary endpoint, intended to study the cardiovascular risk in current practice. It allows for the

· but analysed by the FDA and leading to the granting of the Marketing Authorisation for 40 mg and 80 mg doses.
inclusion of over 4000 patients in at least two European countries who will be monitored for 3 years. The primary efficacy endpoint is the time to onset of the first event involving hospitalisation or death due to an APTC event (Anti-platelet Trialists’ Collaboration composite endpoint), i.e. non-fatal myocardial infarction, non-fatal cerebrovascular accident or cardiovascular death. These events are to be analysed on a blind basis, by an independent committee.

- **Hepatic tolerance**
  The percentage of liver function abnormalities was similar (3.5%) to that reported with allopurinol. The SPC recommends a liver function test before starting treatment with febuxostat and monitoring of liver function.

- **Skin rash**
  In the FACT and APEX studies, 14 patients in the febuxostat group as compared to 2 patients in the allopurinol group discontinued treatment on account of a skin rash.

3.2.2 **CONFIRMS study not examined by the EMEA**
During this study, the incidence of adverse events related to the treatment (in the investigator’s opinion) was 18.2% with febuxostat 40 mg, 18.1% with febuxostat 80 mg and 20% with allopurinol. The most common adverse events (in the investigator’s opinion) were liver function abnormalities and diarrhoea.

The incidence of liver enzyme elevation considered to be treatment-related was 6.6% in the febuxostat 40 mg group, 5.4% in the febuxostat 80 mg group and 4.6% in the allopurinol group.

Considering all causes together, 16.5% of patients discontinued treatment with febuxostat 40 mg, 20.9% with febuxostat 80 mg and 17.9% with allopurinol.

The incidence of discontinuation of treatment due to adverse effects was 6.5% with febuxostat 40 mg, 8.1% with febuxostat 80 mg and 8.5% with allopurinol.

The incidence of discontinuation of treatment due to gout flares was 0.4% with febuxostat 40 mg, 0.9% with febuxostat 80 mg and 0.3% with allopurinol.

Five deaths occurred during the study, 2 in patients treated with febuxostat and 3 in patients treated with allopurinol. None of the three deaths in the allopurinol group was considered by the investigator to be treatment-related. Two were considered to be of cardiovascular origin and the 3rd was reported in a patient with lymphoid leukaemia who within 60 days after starting treatment had an adenocarcinoma of the lung then 25 days later necrotic lung disease and post-operative septicaemia.

In the febuxostat 40 mg group, the death was due to anaphylactic shock occurring 117 days after the start of treatment. The investigator considered that a causal link to treatment was unlikely.

Sub-arachnoid bleeding was reported in a patient in the febuxostat 80 mg group with chronic obstructive pulmonary disease associated with type 2 diabetes and hypertension. The investigator considered that the death was not treatment-related.

Differences in cardiovascular adverse effects and mortality of cardiovascular origin to the detriment of febuxostat, observed in the phase III APEX and FACT studies and in their open-label extensions, were not reported in this study.

The rate of cardiovascular events was low and similar in all treatment groups: 5.2% with febuxostat 40 mg, 5.4% with febuxostat 80 mg as compared to 5.8% with allopurinol.
3.3. Conclusion

In three clinical studies, febuxostat (ADENURIC) administered at doses of 80 mg and 120 mg/day demonstrated its superiority over a fixed dose of allopurinol (300, 200 or 100 mg/day) in reducing serum uric acid and maintaining it below the threshold of 60 mg/l, corresponding to the therapeutic target to be achieved in the treatment of symptomatic chronic hyperuricaemia.

In the APEX study, the absolute reduction in serum uric acid compared to baseline was -47.58% in the febuxostat 80 mg group, -54.88% in the febuxostat 120 mg group as compared to -34.35% in the allopurinol group, p<0.05 in favour of febuxostat.

In the FACT study, the absolute reduction in serum uric acid was -47.74% in the febuxostat 80 mg group, -53.02% in the febuxostat 120 mg group as compared to -34.75% with allopurinol, p<0.05 in favour of febuxostat.

In the CONFIRMS study in which 2269 patients were included, the efficacy of febuxostat was evaluated in patients with mild renal impairment (48% of the study population) or moderate renal impairment (18% of the study population). Moderate renal impairment had been defined as creatinine clearance between 30 and 59 ml/min; and mild renal impairment as creatinine clearance between 60 ml/min and 89 ml/min.

In this sub-group of patients with impaired renal function, the proportion of patients achieving the therapeutic target (serum uric acid < 60 mg/l) was higher with febuxostat 40 mg (49.7%) and 80 mg (71.6%) than with allopurinol 300/200 mg (42.3%), p<0.05.

However, the superiority of febuxostat over allopurinol in terms of the improvement in clinical parameters (gout attacks, reduction in the number of tophi and their size, prevention of joint and renal damage) was not demonstrated.

No randomised studies looked at the efficacy of febuxostat in patients unable to tolerate allopurinol.

Tolerance was relatively satisfactory. The most frequent adverse events were hepatic function abnormalities, diarrhoea, headaches, nausea and skin rashes. Serious adverse events were reported during the studies, particularly of cardiovascular origin, without any causal relationship being demonstrated.

Although no causal relationship has been established, a higher number of deaths of cardiovascular origin and cardiovascular adverse effects (non-fatal infarction and non-fatal CVA) was reported in patients treated with febuxostat compared to those treated with allopurinol in the phase III APEX and FACT studies and in the open-label extension to these studies. These differences were not reported in the CONFIRMS study in which more than 2200 patients were included. However, the SPC includes a special warning that ADENURIC should not be used in cases of ischaemic heart disease or congestive heart failure.

Furthermore, the risk management plan includes the conducting of a study (PROBE) to examine the cardiovascular risk of febuxostat versus allopurinol in current practice. It is proposed to include 6000 patients in this study with a follow-up period of 3 years.
4.1. Actual benefit

In the absence of treatment, symptomatic chronic hyperuricaemia is likely to cause disability and/or severely reduce the patient’s quality of life, due to effects on the joints and/or kidneys (lithiasis, nephropathy).

ADENURIC is a curative treatment for chronic hyperuricaemia in patients who have, or who have a history of, tophus and/or gouty arthritis. Its uric acid lowering effect is superior to that of allopurinol.

The efficacy/adverse effects ratio is high.

Public health benefit:

The public health burden of chronic hyperuricaemia, a disabling disease, is moderate. The burden of the disease associated with the population for which treatment with ADENURIC is indicated (chronic hyperuricaemia in patients with, or with a history of, tophus and/or gouty arthritis) is moderate.

Improving the management of chronic hyperuricaemia is a public health need according to priorities defined (Pain Management Improvement Plan 2006 – 2010, Quality of Life Improvement Plan for Patients with Chronic Disorders 2007-2011).

On the basis of clinical data available and current therapeutic strategies, a limited impact in terms of morbidity is expected for the proprietary medicinal product ADENURIC. Furthermore, the impact on quality of life has not yet been documented.

Thus, the proprietary product ADENURIC should be able to provide a partial response to the public health need identified, particularly in patients with mild to moderate renal impairment and in patients unable to tolerate allopurinol.

Finally, the proprietary product ADENURIC is not expected to have any impact on the use of the health system.

As a result, it is expected that for this indication, ADENURIC will benefit public health. This benefit is limited.

There are few therapeutic alternatives.

The actual benefit of ADENUIRC is substantial.

4.2. Improvement in actual benefit (IAB)

The superiority of ADENURIC over allopurinol has been demonstrated in terms of normalisation of serum uric acid below the threshold of 60 mg/l. This efficacy has also been demonstrated in patients with mild renal impairment (creatinine clearance between 60 and 89 ml/min) to moderate renal impairment (creatinine clearance between 30 and 59 ml/min).

As a result, the Transparency Committee considers that ADENURIC provides a minor improvement in actual benefit (level IV) in the management of symptomatic chronic hyperuricaemia compared to the current therapeutic strategy based on allopurinol.

* Law of 9 August 2004 on public health policy
4.3. Therapeutic use

Hyperuricaemia is defined as serum uric acid > 420 µmol/l or 70 mg/l, and is symptomatic when it leads to gout, uric lithiasis or nephropathy.

Uric acid lowering treatment is indicated in patients who have repeated gout attacks, arthropathy, tophus, radiography lesions, uric lithiasis, or nephropathy.

First of all, measures relating to diet and exercise should be proposed: reduce alcohol consumption, calorie intake and purine intake (cooked meats, offal...).

If diet and exercise are unsuccessful in reducing serum uric acid to below the saturation threshold for sodium urate, i.e. less than or equal to 360 µmol/l or 60 mg/l, uric acid lowering can be prescribed.

The correction of associated comorbidities and the management of cardiovascular risk factors such as hyperlipidaemia, hypertension, hyperglycaemia, obesity and smoking play an important role in the management of this condition.

There may be flares during the early months after starting uric acid lowering treatment. They can be prevented by associated prophylaxis (3 to 6 months, or even longer in the case of tophus) with NSAIDs or colchicine.

Allopurinol is the reference treatment for chronic hyperuricaemia. The dose should be adjusted according to target serum uric acid (<360 µmol/l or 60 mg/l) according to age, renal function and adverse effects. The dose must be carefully adjusted according to creatinine clearance in order to limit accumulation of the drug and its metabolite, oxypurinol, and thus prevent the onset of a rare but very serious adverse effect, allopurinol hypersensitivity syndrome.

Uricosuric agents (probenecid, benzbromarone) are alternatives in the event of failure or adverse effects with allopurinol, having verified that urinary uric acid levels are normal and there is no history of urinary lithiasis. The maximum dose of probenecid is limited on account of the risk of convulsions at a dose of more than 2 g/day. Its use is not recommended in cases of renal impairment. Benzbromarone is available only with nominative compassionate use [ATU nominative in French] on account of its poor hepatic tolerance.

Febuxostat is a xanthine oxidase inhibitor, the efficacy of which is superior to that of allopurinol in reducing serum uric acid. In clinical studies, febuxostat was superior to a fixed allopurinol dose of 300 mg/day in reducing serum uric acid to below the threshold of 60 mg/l, which is the therapeutic target. When starting treatment with ADENURIC, the SPC recommends treatment to prevent gout flares using NSAIDs or colchicine for at least 6 months. ADENURIC is not recommended in cases of ischaemic heart disease or congestive heart failure.

ADENURIC may be a beneficial alternative to allopurinol particularly:

- in patients with mild renal impairment (creatinine clearance between 60 and 89 ml/min) to moderate renal impairment (creatinine clearance between 30 and 59 ml/min). In fact, unlike allopurinol, no adjustment of the dose is necessary in such patients. The CONFIRMS study conducted in more than 1000 patients with mild to moderate renal impairment demonstrated the superiority of febuxostat 80 mg compared to allopurinol 300/200 mg/day. Similar results were reported in a sub-group in the APEX study. However, the efficacy and tolerance of febuxostat have not been evaluated in cases of severe renal impairment.

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- in patients not able to tolerate allopurinol. Its efficacy has not however been evaluated in this population.

No data are available for patients who have undergone an organ transplant or those with uric lithiasis.

### 4.4. Target population

Precise epidemiological data on the prevalence of gout in Europe are very limited. As a result, it is not possible to estimate precisely the target population for ADENURIC for the indication in the Marketing Authorisation, i.e. “chronic hyperuricaemia in conditions where urate deposition has already occurred (including a history, or presence of, tophus and/or gouty arthritis).”

Recent studies conducted in the United Kingdom and Germany produced similar results in terms of prevalence. Thus, Mikuls\(^3\) reported a prevalence of gout of 1.4% in 1999 in the United Kingdom, and approximately 7% in men over 65 years of age. These figures were confirmed by another study conducted between 2000 and 2005 in the United Kingdom and Germany\(^4\) which reported a prevalence of 1.4%.

A French observational study dating back to 1981, conducted in 4663 men employed in a public organisation in Paris\(^5\), reported a prevalence of gout of 1.2% (0.4% in men between 20 and 34, 1.1% between 35 and 39, 2% between 40 and 44 years of age). The incidence after 5 years for the 40-44 age group was 1.6%.

More recently (September 2006), a Disease Analyser study conducted by IMS at the request of IPSEN (not published) and analysing the population with gout in the United Kingdom and France, identified a prevalence ratio of 72% between the two countries.

On these bases, it can be estimated that the population with gout in France is approximately 604,800 patients.

The population that could benefit from ADENURIC comprises patients with gout, with the exception of patients with coronary disease, as its use in this group is not recommended.

According to data from the Mikuls study, 25% of gout patients have coronary disease, i.e. 151,200 patients on the basis of the gout population in France.

The target population for ADENURIC, according to its Marketing Authorisation, can be estimated at 453,600 patients. This is certainly an overestimate but no data are available to refine the figure.

### 4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Health Insurance and on the list of medicines approved for hospital use and various public services in the indications and at the dosage in the Marketing Authorisation. The Transparency Committee is to re-evaluate ADENURIC as soon as the results of the study to evaluate its cardiovascular safety in current practice are available, as requested by the EMEA.

4.5.1. Packaging: appropriate for the prescription conditions

4.5.2. Reimbursement rate: 65%