HAUTE AUTORITÉ DE SANTÉ

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

**TRANSPARENCY COMMITTEE**

OPINION
6 September 2006

**RAFTON 3 mg, gastroresistant capsule, B/50**
**CIP 356 926-1**

**Applicant : FERRING SAS**

Budesonide
List I

Marketing Authorisation date: 31st May, 2001 (mutual recognition procedure)

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals

Health Technology Assessment Division

# 1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

## 1.1. Active ingredient

Budesonide

## 1.2. Indications

- Induction of remission in patients with mild to moderate active Crohn's disease, affecting the ileum and/or the ascending colon.

- Symptomatic treatment of chronic diarrhoea due to collagenous colitis.

## 1.3. Dosage

Adults aged more than 18 years:
The recommended daily dose is one capsule (containing 3 mg budesonide) three times daily (morning midday and evening) approximately half an hour before meals.

Children:
RAFTON 3 mg should not be administered to children due to insufficient experience in this age group.

The duration of treatment to induce remission in Crohn's disease and for symptomatic treatment of chronic diarrhoea caused by the collagenous colitis should be limited to 8 weeks.

Treatment with RAFTON 3 mg should not be stopped abruptly, but withdrawn gradually by tapering doses. During the first week, the dosage should be reduced to two capsules a day, one in the morning, one in the evening. During the second week, only one capsule should be taken in the morning. Treatment may then be stopped.

# 2 SIMILAR MEDICINAL PRODUCTS

## 2.1. ATC Classification

A : Gastrointestinal tract and metabolism
A07 : Antidiarrheals, intestinal anti-inflammatory and anti-infective agents
A07E : Intestinal anti-inflammatory agents
A07EA : Local corticosteroids
A07E06 : Budesonide

## 2.2. Medicines in the same therapeutic category

Crohn's disease
ENTOCORT (budesonide)

Collagenous colitis
RAFTON is the only medicinal product indicated for the management of chronic diarrhoea due to collagenous colitis.

### 2.3. Medicines with a similar therapeutic aim

Medicinal products used for the induction of remission in patients with mild to moderate Crohn's disease.

*Aminosalicylate derivatives:*

SALAZOPYRINE (sulfasalazine)
PENTASA (mesalazine)

*Oral glucocorticoids*
SOLUPRED, HYDROCORTANCYL (prednisolone)
CORTANCYL (prednisone)
MEDROL (methylprednisolone)
DECTANCYL (dexamethasone)
BETNESOL, CELESTENE (betamethasone)

## 3 ANALYSIS OF AVAILABLE DATA

### 3.1. Efficacy

**Induction of remission in Crohn's disease**

Clinical data presented by the company:

- One randomised, double-blind, pivotal study BUC-23[1] enrolled 201 patients and compared the efficacy and safety of RAFTON (3 mg three times daily) with those of prednisone (40 mg/day for 2 weeks, then a progressive reduction in the doses up to 8 weeks) in patients with active Crohn's disease.
- Literature data: THOMSEN study [2] (comparative study budesonide vs mesalazine), review in the *Cochrane Library*[3].

BUC-23 Pivotal Study:

Randomised, double-blind, parallel-group study comparing RAFTON (modified-release form) with prednisone for 8 weeks.
100 patients were treated by budesonide at the dosage of 3 mg three times daily.
101 patients were treated by prednisone at the dosage of 40 mg/day for the first two weeks, followed by 30mg/day of prednisone the 3rd week, and then from the 4th week a progressive reduction of the dosage by 5 mg/week until the end of the study.

[1] BAR-MEIR S. et al. Budesonide versus prednisone in the treatment of active Crohn's disease. Gastroenterology 1998; 115: 835-840
[2] THOMSEN O.Ø et al. A comparison of budesonide and mesalazine for active Crohn's disease. *N Engl J Med* 1998; 339: 370-374
[3] OTLEY A. & al. Budesonide for induction of remission in Crohn's disease. The Cochrane Database of Systematic Reviews 2005 issue 4

Baseline patient characteristics were as follows:

| Variable | Budesonide | Prednisone |
|---|---|---|
| N | 100 | 101 |
| Mean age (years) | 32.7 | 32.8 |
| Sex ratio (M/F) | 53/47 | 51/50 |
| Smokers (%) | 30 | 31 |
| CDAI Score | 264 | 265 |
| Duration of disease (years) | 5 | 5 |

The clinical response was considered to be relevant when the CDAI score[4] was less than 150.

The primary endpoint R1 corresponded to the percentage of responder patients not presenting adverse effects caused by corticosteroids (12 adverse effects that may be related to corticosteroid therapy were predefined).

Among the secondary endpoints efficacy evaluated, the endpoint R0 was the percentage of responders, whatever the tolerance of the product.

The main results for the ITT population were as follows:

| **Responder rate** | **Budesonide (n = 100)** | **Prednisone (n = 101)** | **p** |
|---|---|---|---|
| **R1** | 30 (30%) | 14 (13.9%) | 0,006 |
| **R0** | 51 (51%) | 53 (52.5%) | NS |

The percentage of patients presenting a clinical response without an adverse effect due to corticosteroids was significantly higher in the RAFTON group than in the Prednisone group (30% versus 13.9%, p=0.006).

Regardless of the safety data, the percentage of patients presenting a clinical response was not significantly different between the two groups (51% versus 52.5%, non-significant).

Literature data

- THOMSEN 1998 Study

A randomised, double-blind, study in 182 patients with mild to moderate exacerbations of Crohn's disease, compared the efficacy and safety of budesonide (9 mg/day, 93 patients) versus mesalazine (4g/day, 89 patients) for 16 weeks.
Results:
At week 16, a greater number of patients had prematurely stopped the study in the mesalazine group (44%) than in the budesonide group (17%) (p<0.001). The main reasons for these premature trial discontinuations were:

- Lack of efficacy (10 patients in the budesonide group, 27 patients in the mesalazine group);

[4] CDAI score: Crohn's Disease Activity Index.
This evaluates 8 clinical and laboratory values: number of stools, abdominal pain, well-being, occurrence of complications, use of antidiarrheal agents, detection of an abdominal mass, body weight and haematocrit.

| | | |
|---|---|---|
| A score | < 150: | Clinical remission |
| | 150-220: | Mild exacerbation |
| | 220-450: | Moderate exacerbation |
| | > 450: | Severe exacerbation |

- effects (3 patients in the budesonide group, 8 patients in the mesalazine group);
- Other reasons (3 patients in the budesonide group, 4 patients in the mesalazine group).

In terms of efficacy, the clinical remission rate (CDAI<150) was significantly higher in the budesonide group (69%) than in the mesalazine group (45%) (p=0.001) at week 8 and was significantly higher in the budesonide group (62%) than in the mesalazine group (36%) (p<0.001) at week 16.

- Cochrane Review

A review of the *Cochrane Library*, published in 2005, confirmed the efficacy of budesonide in the treatment of mild to moderate flare up of Crohn's disease.
The efficacy on the clinical remission rate of budesonide (9 mg/day) was:

- Superior than that of placebo for the induction of a remission at week 8 (2 studies analyzed, 324 patients): odds ratio of 2.85 (95% CI: 1.67 – 4.87; NNT = 5);
- Superior than that of mesalazine (1 study analyzed, 174 patients): odds ratio of 2.80 (95% CI: 1.50 – 5.20; NNT=4);
- Lower than that of conventional corticosteroids (prednisone, prednisolone, 6-methylprednisolone) (5 studies including study BUC-23, 667 patients): odds ratio of 0.69 (95% CI: 0.51 – 095; NNT = 12).

In terms of safety, five trials comparing budesonide with conventional corticosteroids were analyzed. The results showed that corticoid therapy caused significantly fewer adverse effects in the budesonide group than in the conventional corticosteroid group: odds ratio 0.38 (95% CI: 0.28 – 0.53).

Hence, in the treatment of mild to moderate flare up of Crohn's disease, the superiority of budesonide in terms of efficacy compared to placebo on the one hand, and mesalazine on the other hand, was demonstrated (Cochrane review).

However, budesonide (9 mg/day for 8 to 10 weeks) appeared to be inferior to conventional corticosteroids in inducing a clinical remission (Cochrane review) but superior in terms of safety (Cochrane review + study BUC23).

**Treatment of collagenous colitis**

Collagenous colitis is characterised by chronic liquid diarrhoea, microscopic abnormalities of the colon and normal radiological and endoscopic findings. The specific histopathological feature is the presence of a subepithelial band (10 µm or more) of collagen next to the basal membrane, accompanied by epithelial infiltration of lymphocytes and chronic inflammation in the lamina propria[5].

Clinical data presented by the company:

- 3 comparative clinical studies
- A *Cochrane Library review*

BAERT 2002 Study[6]

[5] Fernandez-Banares F. Collagenous colitis, Orphanet encyclopedia, February 2005

[6] BAERT P. et al. Budesonide in collagenous colitis: a double-blind placebo-controlled trial with histologic follow-up. Gastroenterology 2002; 122: 20-25

Randomised, double-blind study comparing the efficacy and safety of budesonide (9 mg/day) with those of placebo for 8 weeks in 28 patients (14 in each group) presenting liquid stools for at least 2 months characterised by at least 3 liquid or semi-liquid stools per day (or 21 stools/weeks on Day 0) and inflammation of the lamina propria and/or a collagen band of at least 10 µm on histological examination of a biopsy (8 biopsies were carried out at fixed intervals, 4 at the start and 4 at the end of treatment at week 8 and at the same sites, 2 in the sigmoid and 2 in the rectosigmoid colon).

The primary endpoint was a composite endpoint associating:

- AA clinical response defined by a 50% reduction in stool frequency between the start and end of treatment (Day 0 to week 8);
- A histological response defined by a significant reduction in the infiltration of the lamina propria by inflammatory cells and/or by a significant reduction in the thickness of the collagen band.

3 patients (1 in the budesonide group and 2 in the placebo group) prematurely stopped the study because of the lack of treatment efficacy or because of poor compliance.

Clinical result:
The number of patients presenting a clinical response was 8/14 with budesonide and 3/14 with placebo (ITT population; p = 0.05).

Histological results:
No statistically significant difference was observed between the groups for the thickness of the collagen band. However, the histological response assessed from the infiltration of the lamina propria by inflammatory cells was significantly higher in the budesonide group than in the placebo group.

| Histological results for lamina propria infiltration | | | |
|---|---|---|---|
| | Placebo | Budesonide | Value of p |
| Total response (No infiltration) | 4 | 9 | p<0.001 |
| Partial response (remaining infiltrate) | 0 | 4 | |
| No response | 8 | 0 | |

<u>BONDERUP 2003 Study</u>[7]
Randomised, double-blind study comparing the efficacy and safety of budesonide (9 mg/day) to placebo for 8 weeks in 20 patients (10 in each group) presenting at least 4 stools per day or a stool weight > 200 g/day and inflammation of the lamina propria and/or a collagen band of at least 10 µm on histological examination of a biopsy (12 biopsies were carried out at fixed time intervals, 6 at the start and 6 at the end of treatment, including 4 in the sigmoid colon and 2 in the rectum).

A composite primary endpoint was used associating the following outcome variables:

- A clinical response defined by a 50% reduction in stool frequency or stool weight between the start and end of treatment (day 0 to week 8);
- A histological response defined by a significant reduction in the infiltration of the lamina propria by inflammatory cells and/or a significant reduction in the thickness of the collagen band.

[7] BONDERUP O.K. et al. Budenoside treatment of collagenous colitis: a randomised, double blind, placebo controlled trial with morphometric analysis. Gut 2003; 52: 248-251

Clinical result:
The number of patients with a clinical response was 10/10 on budesonide and 2/10 on placebo ($p < 0.001$). In the budesonide group, the stool weight fell from 574 g/day to 200 g/day and the stool frequency fell from 6.2/day to 1.9/day ($p<0.01$).

During the 8 weeks of follow-up after discontinuation of treatment, 8/10 patients again presented clinical symptoms of the disease.

Histological results:
For the histological criteria, the results varied according to the rectal or sigmoidal site of the inflammatory lesions.

In the sigmoid, the histological response assessed from the infiltration of the lamina propria by inflammatory cells was significantly higher in the budesonide group than in the placebo group ($p<0.01$). The same was shown for the reduction in the thickness of the collagen band ($p<0.02$).

In the rectum, no statistically significant difference was noted for the histological criteria evaluated.

MIEHLKE 2002 Study[8]
Randomised, double-blind study comparing the efficacy and safety of budesonide (9 mg/day) with those of placebo for 6 weeks in 51 patients (26 in the budesonide group, 25 in the placebo group) with liquid stools characterised by at least 5 stools per day (or at least 35 stools/week) and histological lesions confirmed by biopsy (collagen band > 10 µm; 24 biopsies were carried out at fixed intervals, 12 at the start and 12 at the end of treatment including 10 in the sigmoid colon and 2 from the rectum. At the end of the study, 16 symptomatic patients in the placebo group were treated open-label by budesonide for 6 weeks.

A composite primary endpoint was used associating the following outcome variables:

- A clinical response defined by a daily number of stools ≤ 3 between the start and end of treatment (D0 to week 6);
- A histological response considered to be significant when two of the three following criteria were improved:
    - Reduction of at least 50% compared to baseline of infiltration of the lamina propria by inflammatory cells (semi-quantitative method);
    - Reduction in the thickness of the collagen band (thickness ≤ 10µm);
    - Breakdown of the epithelial surface (present/absent).

Clinical results:
6 patients (3 in each group) prematurely stopped the study for lack of efficacy of treatment or because of poor tolerance.

The number of clinical responder patients was 20/26 in the budesonide group and 3/25 in the placebo group (ITT population; $p<0.001$).

Histological results:

[8] MIEHLKE S. & al. Budesonide treatment for collagenous colitis: a randomised double-blind, placebo-controlled, multicenter trial. Gastroenterology 2002; 123: 978-984

The histological response was significantly better in the budesonide group (14/23 patients) than in the placebo group (1/22 patients) ($p<0.001$).
This improvement was mainly related to a considerable reduction in inflammation of the lamina propria.

In addition a quality-of-life study was also carried out. This could not be taken into account by the Committee for methodological reasons (before-after comparison).

Maintenance of long-term efficacy:
The MIEHLKE study was extended by an open-label, follow-on study in 33 patients who either presented a clinical improvement after the initial treatment or crossed over to budesonide. The mean duration of patient follow-up was 16 months. A clinical relapse, defined by the occurrence of at least 5 soft or liquid stools per day, was observed in 20 patients (60.6%) on average 2 weeks after the discontinuation of treatment.

Conclusion of the 3 clinical studies:
Although the sample sizes of the studies were low, the clinical efficacy of budesonide in patients with chronic diarrhoea related to collagenous colitis was established. From an histological point of view, budesonide seemed to reduce infiltration of the lamina propria by inflammatory cells more effectively than the thickness of the collagen band.

However, the relapse rate observed on discontinuation of treatment was high.

Additional data
A *Cochrane Library* review published in 2005[9], evaluated the efficacy of budesonide in the treatment of collagenous colitis.

The efficacy of budesonide (9 mg per day for 6 to 8 weeks) was superior to that of placebo for the induction of a clinical response (3 analyzed studies, 94 patients): pooled odds ratio of 12.32 (95% CI: 5.53 – 27.46; NNT = 2). A significant histological improvement was observed in all the studies analyzed. In addition, budesonide seemed to improve patient quality of life. However, the long-term efficacy with maintenance of the clinical improvement and prevention of recurrences has not yet been defined.

### 3.2. Adverse effects

According to the SPC, the following adverse effects were very rarely reported:

- Oedema of the lower limbs
- Benign intracranial hypertension syndrome (including papillary oedema) in adolescents
- Diffuse pain and muscular weakness
- Tiredness, malaise.

Typical adverse effects of systemic glucocorticoids may sometimes occur. These adverse effects depend on the dosage, treatment period, concomitant or previous administration of other glucocorticoids and individual sensitivity.

Moreover, the *Cochrane Library* review[10] showed that the incidence of adverse effects associated with glucocorticoids was less with budesonide than with oral prednisolone treatment at equivalent doses: 5 analyzed studies, pooled odds ratio of 0.38 (95% CI: 0.28 – 0.53).

[9] CHANDE N. & al. Interventions for treating collagenous colitis. The Cochrane Database of Systematic Reviews 2005, Issue 4.
[10] OTLEY A. & al. Budesonide for induction of remission in Crohn's disease. The Cochrane Database of Systematic Reviews 2005 issue 4

## 4 TRANSPARENCY COMMITTEE CONCLUSIONS

### 4.1. Actual Benefit

Crohn's disease

The disorder concerned by this drug is life-threatening either in the immediate term or because of complications. Crohn's disease is a recurrent chronic inflammatory bowel disease (CIBD) recurrent and that progresses by flare up. It is invalidating and reduces quality of life.

This product is intended for symptomatic treatment.
The efficacy/ adverse effects ratio of this product in this indication is high.
This product is intended for first-line therapy.
There are alternative medications to this product.

> The public health burden represented by Crohn's disease is moderate. The target population, as defined by the indication (induction of remission in patients with a mild to moderate, ileocolonic form of the disease) is low.
> The availability of an effective treatment for the induction of remission in Crohn's disease is a public health need. Budesonide provides a partial response to this need, but as it is already available in this indication in the proprietary drug ENTOCORT, RAFTON is not expected to provide an additional answer to this need or have an additional impact on quality of life or morbidity.
> Consequently, RAFTON is not expected to have an impact on public health in this indication.

The actual benefit of this drug is substantial.

Collagenous colitis

Collagenous colitis is a microscopic colitis defined by the association of chronic diarrhoea, normal colonoscopy findings and histological examination showing chronic inflammation of the colonic mucosa. It is incapacitating and reduces quality of life. The global prognosis of this disease is good. In fact, it regresses in all patients either spontaneously (in approximately 20% of the cases) or with appropriate treatment.

This drug provides symptomatic treatment.
The efficacy/adverse effects ratio of this product is high in this indication.
This drug is intended for first or second-line therapy.
There is no alternative treatment in this indication.

> Chronic diarrhoea caused by collagenous colitis represents a non-quantifiable public health burden.
>
> The improved management of rare diseases is an established priority. However, chronic diarrhoea caused by collagenous colitis is not sufficiently serious to be considered as a public health need.
>
> The available data do not permit quantification of the impact of budesonide on the quality of life of patients, although an improvement is expected. Its impact compared to non-specific anti-diarrhoeal treatments is not known, and there are insufficient data on the maintenance of the clinical improvement and prevention of recurrence. Taking

into account these considerations and the small number of patients concerned, budesonide is not expected to have an impact on the improvement in quality of life at population level.

Consequently, RAFTON is not expected to have an impact on public health in this indication.

The actual benefit of RAFTON in this indication is substantial.

### 4.2. Improvement in actual benefit

Crohn's disease
For the induction of remission in Crohn's disease, RAFTON does not provide an improvement in actual benefit (IAB V) compared to ENTOCORT.

Collagenous colitis
RAFTON provides a level IV improvement in actual benefit in the management strategy of patients with chronic diarrhoea due to collagenous colitis.

### 4.3. Therapeutic use

Crohn's disease
The first objective during management of active Crohn's disease is to control symptoms (induce remission). The second objective is to maintain remission by reducing the risk of recurrence (maintenance treatment).

Symptomatic medication mainly comprises aminosalicylates, corticosteroids, immunosuppressive agents and biotherapies with various treatment regimens that are chosen according to the severity and topography of the intestinal lesions.

RAFTON is a proprietary drug containing an oral corticosteroid which may be used as first-line treatment for mild to moderate flare up of Crohn's disease affecting the ileum and/or ascending colon.

Collagenous colitis
Collagenous colitis is a microscopic colitis defined by the association of chronic diarrhoea, an endoscopically normal mucosa during colonoscopy and chronic inflammation of the colonic mucosa on histological examination. The aetiology of this disease is unknown. However, administration of certain medicinal products may have a role in its pathogenesis (NSAIDS [non steroidal anti-inflammatory drug], ranitidine, lansoprazole, venotonic, ticlopidine, flutamide)[11]. The global prognosis of this disease is good. It regresses in all patients either spontaneously (in approximately 20% of cases) or with appropriate treatment.

For first-line treatment, the management of symptoms of patients with chronic diarrhoea due to collagenous colitis is based on discontinuation of drugs that may have caused the collagenous colitis and symptomatic management of the diarrhoea by non-specific and well-tolerated antidiarrheal agents (loperamide for example)[12]. If these measures fail, RAFTON, the only medicinal product with a specific Marketing Authorisation in the symptomatic management of this disorder, is the treatment with the highest level of evidence in this indication (COCHRANE 2005).

[11] CAPPELL MS. Colonic toxicity of administered drugs and chemicals. Am J Gastroenterol 2004; 99:1175-90
[12] FERNANDEZ-BANARES F. Collagenous colitis, Orphanet encyclopedia, February 2005

### 4.4. Target population

Crohn's disease
The target population of RAFTON is represented by patients with mild to moderate exacerbations of Crohn's disease affecting the ileum and/or ascending colon.

The population may be estimated from the following data:
In France, 60,000 patients would be affected by Crohn's disease[13].
Ileocolonic and/or iliac sites account for 65% of cases[14], i.e. 39,000 patients.
Available epidemiologic data do not make it possible to determine the percentage of patients with mild to moderate exacerbations. According to the experts, 2/3 to 3/4 of the ileocolonic forms are mild to moderate, representing between **26,000 and 30,000 patients**.

Collagenous colitis
The target population of RAFTON is represented by patients with chronic diarrhoea caused by collagenous colitis.

The prevalence of collagenous colitis in France is not known.

A prevalence of 15.7 cases per 100,000 inhabitants was observed in a study carried out in Sweden[15]. If these values are applied to the whole French population aged over 20 years, approximately 7,400 patients would be affected by collagenous colitis.

However, as this disorder regresses spontaneously in 20% of cases[16], approximately **6,000 patients** may benefit from this treatment.

### 4.5. Transparency Committee recommendations

The Transparency Committee recommendes inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals and various public services for indications and posology in the Marketing Authorisation.

4.5.1. Packaging: Appropriate for the prescription conditions
4.5.2. Reimbursement rate: 65 %

[13] DGS/GTNDO, Chronic Inflammatory Bowel Disease, available on http://www.sante.gouv.fr/htm/dossiers/losp/52maladies_intestin.pdf, updated on 13/06/03
[14] CORTOT A. Crohn's disease. Orphanet Encyclopedia, June 2003
[15] FLÉJOU JF. et al. Les colites microscopiques. Hepato-Gastro 1998; 5 (2): 101-108
[16] FERNANDEZ-BANARES F. Collagenous colitis, Orphanet encyclopedia, February 2005