HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

26 April 2006

ENTOCORT 3 mg, gastro-resistant capsule containing microgranules
Bottle of 45 capsules (CIP code: 341 477-1)

AstraZeneca

budesonide

List I

Date of Marketing Authorisation: 31 July 1996

Reason for request:

- Inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals in the extensions of indications

Health Technology Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Budesonide

1.2. Indications

- Acute therapy in mild to moderate Crohn's disease affecting the ileum and/or or the ascending colon.

- **Maintenance therapy in Crohn's disease (maximum duration 9 months): while waiting for immunosuppressant therapy to reach efficacy, as a replacement for prednisolone in corticosteroid-dependent patients at doses of $\leq$ 30 mg/day prednisolone or equivalent.**

- **Maintenance of remission of Crohn's disease after acute therapy.**

1.3. Dosage

For use in adults only

Capsules should be swallowed with a glass of water. They should not be bitten or chewed.

Treatment should always be withdrawn gradually by reducing the dose.

Acute therapy

The recommended dose is 3 capsules (i.e. 9 mg of budesonide) taken as a single morning dose, for 8 weeks.

Optimum response to treatment is generally obtained in 2–4 weeks.

Maintenance therapy in corticosteroid-dependent patients

The recommended dose is 2 capsules (i.e. 6 mg of budesonide) taken as a single morning dose. If necessary, treatment may be continued for up to 9 months, with a gradual reduction in the dose.

Maintenance of remission in Crohn's disease after acute therapy

The recommended dose is 2 capsules (i.e. 6 mg of budesonide) taken as a single morning dose.

If necessary, treatment may be continued for up to 9 months, with a gradual reduction in the dose.

2 SIMILAR MEDICINAL PRODUCTS

2.1. 2005 ATC Classification

A : ALIMENTARY TRACT AND METABOLISM
A07 : ANTIDIARRHOEALS, INTESTINAL ANTI-INFLAMMATORY / ANTI-INFECTIVE AGENTS
A07E : INTESTINAL ANTI-INFLAMMATORY AGENTS
A07EA : CORTICOSTEROIDS ACTING LOCALLY
A07EA06 : Budesonide

2.2. Medicinal products in the same therapeutic category

There are no other medicinal products in the same therapeutic category with these indications.

2.3. Medicinal products with a similar therapeutic aim

- *5-aminosalicylic acid derivatives:*

  Salazopyrin (sulfasalazine)
  Fivasa, Pentasa, Rowasa (mesalazine)
- Imurel (azathioprine) (Imurel is indicated in severe forms of Crohn's disease, in corticosteroid-intolerant or corticosteroid-dependent patients, or in patients with insufficient therapeutic response despite high doses of corticosteroids.)

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

3.1.1. Placebo-controlled trials

- ***Pooled analysis in the indication "Maintenance of remission in Crohn's disease after acute therapy" (Pooled analysis, 08-CR-S007[1])***

This was a pooled analysis of 4 randomised double-blind trials carried out between April 1991 and August 1998.

The trials compared budesonide 6mg/day to budesonide 3mg/day and to placebo.

Three hundred and eighty-four (384) patients were randomised to receive maintenance therapy for 52 weeks:

- Budesonide 6 mg group: 145 patients
- Budesonide 3 mg group: 90 patients
- Placebo group: 145 patients

[1] William J. Sandborn, Robert Löfberg, Brian G. Feagan, Stephen B. Hanauer et al. Budesonide for maintenance of remission in patients with Crohn's disease in medically induced remission: a predetermined pooled analysis of four randomized, double-blind, placebo-controlled trials. Am J Gastroenterol 2005;100:1780-1787.

All patients had:

- Crohn's disease affecting the ileum and/or right colon.
- a mild to moderate attack (CDAI[*] <450 before treatment) with remission (CDAI score <150) previously achieved by acute therapy with budesonide, prednisolone or placebo.

Primary endpoint was median time to recurrence.
Recurrence was defined as CDAI score >150 with an increase of at least 60 points from baseline score, or withdrawal from the trial because of disease exacerbation.

Results

NB: As the dose recommended in the Marketing Authorisation is budesonide 6 mg/day, data in the group given budesonide 3 mg/day were not taken into account.

Patient characteristics

Variable	Budesonide 6 mg/day	Placebo
Population	145	145
Mean age (yrs)	35	36
Sex ratio (M/F)	59/86	60/85
CDAI score	101	104
Duration of disease (yrs)	6.2	6.6

Primary endpoint results

	Budesonide 6 mg/day	Placebo	p
Median time to recurrence (days)	268	154	0.0024

Secondary endpoint results:

Percentage recurrence was significantly lower in the budesonide 6 mg group compared toplacebo:

- 25% recurrence *vs* 51% ($p<0.001$) at 3 months
- 37% *vs* 50% ($p<0.05$) at 6 months.

The trial did not demonstrate any significant difference in this endpoint after 6 months.

Mean CDAI was significantly lower in the budesonide 6 mg/day group compared to placebo, at 3 months ($p<0.01$), 6 months ($p<0.05$), 9 months ($p<0.05$) and 12 months ($p<0.05$).

- ***Pivotal trial in the indication "Maintenance therapy for Crohn's disease in corticosteroid-dependent patients" (Trial 08-CR-3038[2])***

This was a comparative, randomised, double-blind trial comparing the efficacy of budesonide 6 mg/day to placebo, by replacing prednisolone in patients with corticosteroid-dependent Crohn's disease involving the ileum and/or right colon.

The 120 patients in the trial were taking prednisolone 1-30 mg/day during the 6 months preceding inclusion.

[*] CDAI score: Crohn's Disease Activity Index: Composite score measuring 8 clinical and laboratory variables, i.e. stools number , severity of abdominal pain, general well-being, complications, use of antidiarrhoeal drugs, presence of an abdominal mass, body weight and haematocrit value.
CDAI score <150: clinical remission; 150-220: mild attack; 200-450: moderate attack; >450: severe attack.

[2] A Cortot, J-F Colombel, P. Rutgeerts, K. Lauritsen et al. Switch from systemic steroids to budesonide in steroid dependent patients with inactive Crohn's disease. Gut 2001;48;186-190

After randomisation, prednisolone was gradually reduced (at a rate of 5 mg/week down to 20 mg, followed by reduction of 2.5 mg a week down to 0 mg) over a period of 4-10 weeks depending on prednisolone dose at inclusion. The primary endpoint was percentage recurrence 1 week and 13 weeks after withdrawal of prednisolone.
Recurrence was defined as CDAI score >200 with an increase of at least 60 points from baseline score, or withdrawal from the trial because of disease exacerbation.

Results

Patient characteristics

	Budesonide 6 mg/day (n = 59)	**Placebo** (n=58**)**
Sex (M/F)	47/53	34/66
Mean age (yrs)	35	32
CDAI	103	109
Duration of disease (yrs) (mean number of yrs)	8.9	8.1
Involvement (ileum/colon) (n)	97/3	100 /0
Current 5 ASA therapy (% / mean dose as g/day)	49/2.8	48/2.7
Current azathioprine therapy (% / mean dose as mg/day)	15/139	8/115
Prednisolone therapy (initial dose in mg)	16.5	15.7

Recurrence

	Budesonide 6 mg/day	**Placebo**	***p***
Recurrence - 1 week after withdrawal of prednisolone - 13 weeks after withdrawal of prednisolone	 17% 32%	 41% 65%	 0.004 < 0.001
Median time to recurrence (days)	> 160	75	< 0.001

Dose of prednisolone at inclusion, history of intestinal resection and treatment with 5-ASA or azathioprine had no effect on time to recurrence.

Trial BU-008-CR-005[3]

This randomised, double-blind trial assessed the efficacy of a flexible dose compared with a fixed dose of budesonide in preventing and managing recurrence of Crohn's disease.

One hundred and forty-three (143) patients were randomised to therapy for a period of 12 months.

Patients had Crohn's disease of the ileum or right colon, in remission, and took either a fixed dose of budesonide 6 mg, or a flexible dose of budesonide 3, 6 or 9 mg depending on Crohn's disease activity, for 1 year.

The primary endpoint was percentage of treatment failures.

Failure was defined as the presence of moderate to severe symptoms at a "level 3" dose (budesonide 9 mg for the flexible dose regimen and budesonide 6 mg for the fixed dose regimen) after 8 weeks of treatment, or CDAI score >200 after 12 weeks of treatment.

Results: There was no significant difference between the two groups.

[3] J.R.B. Green, A.J. Lobo, M. Giaffer, S. Travis et al. Maintenance of Crohn's disease over 12 months: fixed versus flexible dosing regimen using budesonide controlled ileal release capsules. Aliment Pharmacol Ther 2001; 15: 1331-1341.

3.1.2 Trials versus active comparator

- ***Trial of budesonide versus mesalamine (mesalazine)***[4]

The aim of the trial was to compare the efficacy of budesonide (6 mg/day) with that of mesalamine (1g x 3/day) in maintaining remission and improving quality of life in corticosteroid-dependent patients.

The trial was a randomised, controlled trial, carried out single-blind (investigator).

Qualifying patients had Crohn's disease in remission (CDAI score <150) and were corticosteroid-dependent (corticosteroid dependence was defined as clinical recurrence after withdrawal of corticosteroid therapy, on at least two occasions in the year preceding the trial).

All patients had to have taken prednisolone for at least 4 months before the trial. The dose had to be reduced in 5 mg steps until the minimum effective dose was reached.

Patients who had been treated with azathioprine, but who had stopped taking the drug because of side effects at least 3 months before the trial started, could nevertheless be included.

At randomisation, patients in the budesonide group had to stop prednisolone. Patients in the mesalamine group had to continue to reduce prednisolone in 5mg steps. Prednisolone had to be withdrawn within 3 weeks of inclusion.

Primary endpoint was percentage recurrence after one year of treatment. Recurrence was defined as CDAI score >150 or an increase of more than 100 points from baseline value.

Results

Patient characteristics

	Budesonide 6 mg/day (n=29)	**Mesalamine 3g/day (n=28)**
Sex ratio (M/F)	13/16	12/16
Mean age (yrs)	34.1	31.8
Mean CDAI score at inclusion	139 ± 5.1	138 ± 5.0
Duration of disease (mean number of yrs)	3.5 ± 1.0	3.2 ± 0.8
Mean time in remission (wks)	6.14	5.91
Remission obtained by - steroids (%) - steroids + azathioprine (%)	 59 41	 57 43
Mean time on steroids (wks)	13.7±1.2	13.5±1.6
Mean steroid dose at inclusion (mg)	8.62 (5-15)	7.95 (5-12.5)
Disease involvement (%): ileum and colon colon	 90 10	 82 18

Fifty-seven (57) patients were included in the trial: 29 in the budesonide group and 28 in the mesalamine group. Twenty-three patients (23) in the mesalamine group withdrew because of treatment failure compared with 16 in the budesonide group.

[4] Gerassimos J. Mantzaris, Kalliopi Petraki, Michael Sfakianakis, Emmanuel Archavlis et al. Budesonide versus mesalamine for maintaining remission in patients refusing other immunomodulators for steroid-dependent Crohn's disease. Clin Gastroenterol Hepatol 2003;1:122-128.

Percentage recurrence in the budesonide group at 1 year was significantly lower than in the mesalamine group (55% vs 82%, CI $_{95}$[12.4%-41%], p=0.045).
Remission lasted significantly longer in the budesonide group than in the mesalamine group (241 $\pm$ 114 days vs 147 $\pm$ 117 days, CI $_{95}$[32.7-155.3] p=0.003).

- ***Trial 08-CR-3039[5]***

This was an open, randomised trial comparing the effects of prednisolone and budesonide on bone mineral density in patients with Crohn's disease affecting the ileum and/or right colon, whether or not they were corticosteroid dependent.

In view of the endpoint, this trial was not included in this assessment.

3.2. Undesirable effects

- ***Pooled analysis 08-CR-S007 [6]***

At each visit, the following corticosteroid-induced effects were assessed in each patient: ecchymosis, acne, puffiness of the face ("moon face"), hirsutism, cushingoid features, depression, etc.).

The majority of side effects were of average or moderate severity.

The global incidence of corticosteroid-induced effects was slightly higher in the budesonide group than in the placebo group; however, only acne and puffiness of the face were reported significantly more often ($p<0.05$).

- ***Trial 08-CR-3038[2]***

The secondary aim of the trial was to assess the safety profile of budesonide by measuring corticosteroid-related side effects and effects on corticotropic function. All side effects were reported and assessed at every visit.

The number of corticosteroid-induced side effects gradually reduced during the trial in both groups (placebo and budesonide) compared with the number at the start of the trial (prednisolone).

3.3. Conclusion

- ***Placebo-controlled trials***

Pooled analysis 08-CR-S007[6], demonstrated a significant difference in favour of the budesonide group for time to recurrence. However, there was no significant difference in recurrence level after 6 months of treatment.

Trial 08-CR-3038[2] demonstrated a significant difference in recurrence level, in favour of the budesonide group.

- ***Trials versus active comparator***

A trial of budesonide versus mesalamine[7] demonstrated a significant difference between both treatment groups in terms of length of remission and percentage recurrence at 1 year.

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[5] Erik J. Schoon, Simona Bollani, Peter R. Mills, Eran Israeli et al. Bone mineral density in relation to efficacy and side effects of budesonide and prednisolone in Crohn's disease. Clin Gastroenterol Hepatol 2005;3:113-121.

[6] William J. Sandborn, Robert Löfberg, Brian G. Feagan, Stephen B. Hanauer et al. Budesonide for maintenance of remission in patients with Crohn's disease in medically induced remission: a predetermined pooled analysis of four randomized, double-blind, placebo-controlled trials. Am J Gastroenterol 2005;100:1780-1787.

[7] Gerassimos J. Gerassimos J.Mantzaris, Kalliopi Petraki, Michael Sfakianakis, Emmanuel Archavlis et al. Budesonide versus mesalamine for maintaining remission in patients refusing other

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

The disease treated by this product carries a life-threatening prognosis for the patient, either immediately or following complications. Crohn's disease is a chronic inflammatory intestinal disease with a pattern of recurrent attacks. It is incapacitating and adversely affects quality of life.

Maintenance therapy in Crohn's disease (maximum duration 9 months): while waiting for immunosuppressant therapy to be effective, replacement for prednisolone in corticosteroid-dependent patients at doses of ≤ 30 mg/day prednisolone or equivalent

- The drug is given as preventive therapy.
- The efficacy/side effects ratio for the drug is substantial in this indication.
- The product is a first-line drug.
- There are no alternative drug or non-drug therapies to this drug
- Public health burden
  - The public health burden from Crohn's disease is moderate. The public health burden among the population defined by the indication (maintenance therapy in corticosteroid-dependent patients with disease affecting the ileum and/or colon) is low.
  - Providing access to effective maintenance therapy in Crohn's disease is a public health need to which Entocort is likely to offer a partial response.
  - The available data suggests that Entocort may be expected to have some impact on quality of life or morbidity, but the impact cannot be quantified.
  - In view of the possible response to a public health need, it is anticipated that Entocort will be of benefit to public health. This benefit is minor.

The actual benefit of this medicinal product is substantial.

Maintenance of remission of Crohn's disease after acute therapy

- The drug is given as preventive therapy.
- The efficacy/side effects ratio for the drug is substantial in this indication.
- The product is a first-line drug.
- There are alternative drug or non-drug therapies to this drug.
- Public health burden
  - The public health burden from Crohn's disease is moderate.
  - The public health burden to the population defined by the indication (maintenance of remission of Crohn's disease after acute therapy in patients with a mild to moderate form of disease, affecting the ileum and/or colon) is low.
  - Providing access to effective maintenance therapy in Crohn's disease is a public health need to which Entocort is likely to offer a partial response.
  - The available data suggests that Entocort may be expected to have some impact on quality of life or morbidity, but the impact cannot be quantified.

immunomodulators for steroid-dependent Crohn's disease. Clin Gastroenterol Hepatol 2003;1:122-128.

– In view of the possible response to a public health need, it is anticipated that Entocort will be of benefit to public health. This benefit is minor.

The actual clinical benefit of this medicinal product is substantial.

4.2. Improvement in actual benefit

For both new indications, this medicinal product contributes minor IAB (level IV) to the management of Crohn's disease involving the ileum and/or ascending colon.

4.3. Therapeutic use

The main aim of management of symptomatic Crohn's disease is to control symptoms (acute therapy). The secondary aim is to maintain remission by reducing risk of recurrence (maintenance therapy).

Drug therapy to control symptoms mainly consists of 5 ASA, corticosteroids and immunosuppressants, chosen according to decision-making criteria and prescription procedures governed mainly by the severity and location of intestinal lesions.

In maintenance therapy, and to reduce the risk of complications, preventing recurrence is an important aim of disease management.

Only 5-ASA and budesonide have a marketing authorisation for maintaining remission of mild to moderate Crohn's disease, in non-corticosteroid-dependent patients with disease involving the ileum and/or ascending colon,.

In maintenance therapy for Crohn's disease in corticosteroid-dependent patients (≤ 30 mg/day prednisone equivalent), with disease involving the ileum and/or ascending colon, budesonide is the drug with the best efficacy/safety profile while waiting for the reference therapy, azathioprine, to reach efficacy. At present there is no alternative to this strategy, other than continuing systemic-acting corticosteroids until azathioprine begins to be effective. Immune modulator is currently only indicated in the event of immunosuppressant failure.

4.4. Target population

According to the GTNDO[8] (2003), the incidence of Crohn's disease is 5.7 per 100 000 per year and the disease affects 60 000 people in France (80 – 100 000 in 10 years).

In addition, the EPIMAD[9] registry shows that intestinal lesions predominantly occur in the ileum and/or colon, accounting for 66% of locations (65% according to expert opinion).

Using a base of 60 000 patients, the estimated number of patients with Crohn's disease involving the ileum or colon is 39 600.

Expert opinion considers that severe ileal or colonic forms of the disease account for 25% of cases.

As maintenance therapy for Crohn's disease while waiting for an immunosuppressant to reach efficacy is reserved for severe forms, the estimated number of patients involved is 9 900, 3 300 of whom would be corticosteroid-dependent (assuming corticosteroid dependent forms account for 1/3 of patients treated with corticosteroids for 1 year).

[8] DGS/GTNDO Chronic Inflammatory Intestinal disease, 13 June 2003

[9] EPIMAD registry. Change in incidence of Crohn's disease and irritable bowel syndrome (1988-1990) in the north of France. Unpublished results.

4.5. Transparency Committee recommendations

The Transparency Committee recommended inclusion on the list of medicines approved for use by hospitals and various public services in both the new indications and at the posology in the marketing authorisation.

4.5.1. Packaging: The packaging is appropriate for acute therapy. It is not appropriate for other situations.

4.5.2. Reimbursement rate: 65%