

discontinuation. No marked differences are seen among the three treatment arms.

**Table 35: Reasons for Discontinuation in Study 08-3013**

|                     | Bud 9 mg QD<br>n = 58 | Bud 4.5 mg BID<br>n = 61 | Prednisolone<br>n = 59 |
|---------------------|-----------------------|--------------------------|------------------------|
| AE                  |                       | 1                        | 2                      |
| Lost to follow-up   |                       | 3                        |                        |
| Therapeutic failure | 9                     | 10                       | 7                      |
| Non-compliance      |                       |                          | 1                      |
| Other reasons       |                       | 1                        | 3                      |
| Completed study     | 49                    | 46                       | 46                     |

AE=Adverse event

Reviewer's table, modified from table 3, Vol. 70, page 153

### Compliance

Compliance with the study regimen was similar in all treatment groups. Visits excluded from the per protocol analyses due to non-compliance were 3 in the budesonide bid. group and 4 in the prednisolone group.

### Protocol Violations

Major protocol violations occurred in 34 patients, resulted in the exclusion of these patients from the per protocol analysis. Table 36 summarizes the protocol violations by treatment group.

**Table 36: Summary of Protocol Violations by Treatment Groups**

|   | Bud 9mg QD<br>n = 58 | Bud 4.5mg BID<br>n = 61 | Prednisolone<br>n = 59 |
|---|----------------------|-------------------------|------------------------|
| CDAI < 200                                      | 2                    | 6                       |                        |
| No valid CDAI                                   | 1                    | 5                       |                        |
| Use of non-allowed medication                   | 6                    | 1                       | 2                      |
| Age >65   |                      | 1                       | 1                      |
| non-compliance                                  |                      | 2                       |                        |
| violated other inclusion/<br>exclusion Criteria | 1                    | 3                       | 3                      |
| Total   | 10                   | 18                      | 6                      |

Reviewer's table summarized from Vol. 70, page 155 – 157

Significantly more patients with CDAI < 200 or no valid CDAI value at baseline in budesonide groups (11 in the BID group and 3 in the QD group) were enrolled than in the prednisolone group (none). Six patients in the budesonide QD group used non-allowed medications during the study compared to 2 in the prednisolone group. These two imbalances may influence the final results and favor the budesonide groups for all patients treated analysis.

### 6.2.5 Efficacy Results

#### Primary efficacy endpoint

Primary efficacy endpoint was defined as remission rate (CDAI ≤ 150) for all patients who have received at least one dose of the drug. The last value extended principle was applied (from 2 weeks treatment onwards).

After two weeks of treatment the highest remission rate, 48%, was observed in the budesonide QD group, compared with 37% in the prednisolone group and 27% in the budesonide BID group. This difference in remission rates was not significant (p=0.052). After eight weeks of treatment, equal remission rates of 60% were found in the budesonide QD and prednisolone groups, compared with 42% in the budesonide BID group. The difference between the groups was not statistically significant (p=0.062). Table 37 summarizes remission rates by treatment groups during the treatment period. Using this parameter of evaluation, small and not statistically significant differences were seen between the budesonide 9 mg per day group and the prednisolone 40 mg per day tap group.

**Table 37: Summary of Remission Rates by Treatment groups**

|                           | Bud QD, n=58<br>Remission % | Bud BID, n=60<br>Remission % | Prednisolone, n=58<br>Remission % | p-value |
|---------------------------|-----------------------------|------------------------------|-----------------------------------|---------|
| 2 weeks therapeutic gain  | 28 48<br>11%                | 16 27<br>None                | 21 37                             | N.S.    |
| 4 weeks therapeutic gain  | 31 53<br>None               | 27 45<br>None                | 36 62                             | N.S.    |
| 8 weeks therapeutic gain  | 35 60<br>None               | 25 42<br>None                | 35 60                             | N.S.    |
| 12 weeks therapeutic gain | 34 59<br>6%                 | 31 52<br>None                | 31 53                             | N.S.    |

Therapeutic gain (%) = remission rate in the Entocort group – remission rate in the prednisolone group

N.S.=No statistically significant difference

Reviewer's table summarized from Vol. 70, page 185

**Secondary efficacy endpoint**

• **The quantitative Changes of CDAI**

The mean initial CDAI score was very similar among the treatment arms: 277 in the budesonide QD group, 274 in the budesonide BID group and 279 in the prednisolone group. The most pronounced decrease in CDAI score in all three groups was observed during the first two treatment weeks. The mean CDAI scores decreased more in the budesonide QD and prednisolone groups than in the budesonide BID group. The difference in reduction of CDAI score was not statistically significant after eight weeks (p=0.093). Table 38 summarizes quantitative CDAI scores by treatment groups during treatment period. Once again, using this parameter of evaluation, the efficacy of the 9 mg qd budesonide dose appeared to be similar to that seen in the prednisolone 40 mg group.

**Table 38: Summary of quantitative CDAI Scores by Treatment Groups**

|                  | Bud QD, n=58 |    | Bud BID, n=60 |     | Prednisolone n=58 |    |
|------------------|--------------|----|---------------|-----|-------------------|----|
|                  | CDAI         | SD | CDAI          | SD  | CDAI              | SD |
| Baseline         | 277          | 71 | 274           | 66  | 279               | 58 |
| 2 weeks          | 164          | 85 | 193           | 85  | 175               | 92 |
| 4 weeks          | 157          | 95 | 166           | 98  | 141               | 80 |
| 8 weeks          | 139          | 88 | 161           | 101 | 131               | 95 |
| average decrease | 138          |    | 113           |     | 148               |    |
| 12 weeks         | 140          | 90 | 165           | 102 | 140               | 84 |

Reviewer's table summarized from Vol. 70, page 185

• **Per Protocol Analysis of Remission Rate (Table 39)**

After two weeks, the highest remission rate, 49%, was found in the budesonide QD group, compared with 43% in the prednisolone group and 20% in the budesonide BID group. After eight weeks equal proportions, 68% of the patients in the budesonide QD and in the prednisolone group were in remission, compared with 39% in the budesonide bid- group. The differences in remission rates were statistically significant regarding budesonide QD versus budesonide BID (P=0.026). This finding constitutes an additional demonstration that budesonide 9 mg QD is active since an effect is being demonstrated against the 4.5 mg BID regimen in a dose-response fashion. This regimen (budesonide 4.5 mg BID) is also inferior to prednisolone 40 mg per day (p=0.033). On the other hand, in this study, the budesonide 9 mg QD regimen was not less efficacious than the prednisolone regimen.

**Table 39: Summary of Remission Rates by Treatment groups Per Protocol Analysis**

|               | Bud QD                   |           |    | Bud BID |           |    | Prednisolone |           |    |
|---------------|--------------------------|-----------|----|---------|-----------|----|--------------|-----------|----|
|               | Total                    | Remission | %  | Total   | Remission | %  | Total        | Remission | %  |
| 2 weeks       | 47                       | 23        | 49 | 40      | 8         | 20 | 47           | 20        | 43 |
| 4 weeks       | 43                       | 25        | 58 | 37      | 14        | 38 | 42           | 28        | 67 |
| 8 weeks       | 38                       | 26        | 68 | 31      | 12        | 39 | 37           | 25        | 68 |
| 12 weeks      | 39                       | 25        | 64 | 31      | 18        | 58 | 36           | 22        | 61 |
| p value       | Bud QD vs. Bud BID       |           |    | 0.026   |           |    |              |           |    |
| After 8 weeks | Bud QD vs. Prednisolone  |           |    | N.S.    |           |    |              |           |    |
|               | Bud BID vs. Prednisolone |           |    | 0.033   |           |    |              |           |    |

N.S.=No statistically significant difference  
Reviewer's table summarized from Vol. 70, page 186

#### 6.2.6 Reviewer's Efficacy Summary and Comments for Study 08-3013

A total of 177 patients were randomized and treated in this randomized, double-blind with 3 parallel groups study. The demography and disease history for all patients treated were well matched, although duration of current exacerbation was slightly longer in the budesonide BID group. Less male patients were enrolled in the study across the treatment groups.

Significantly more patients with CDAI < 200 or no valid CDAI value at baseline were enrolled in the budesonide groups (11 in the BID group and 3 in the QD group) than in the prednisolone group (none). Six patients in the budesonide QD group used non-allowed medications during the study and only 2 patients did in the prednisolone group.

The comparison of most interest is that after eight weeks of treatment. At this time, equal remission rates (primary efficacy end-point) of 60% were found in the budesonide QD and prednisolone groups, compared with only 42% in the budesonide BID group. However, the difference between the groups was not statistically significant (p=0.062).

For the secondary efficacy end-point analyses, the difference in reduction of CDAI score was not statistically significant after eight weeks (p=0.093) between budesonide and prednisolone group. For the per protocol analysis of remission rate, the differences in remission rates were statistically significant regarding budesonide QD versus budesonide BID (P=0.026). This finding constitutes an additional demonstration that budesonide 9mg QD is active since an effect is being demonstrated against the 4.5 mg BID regimen in a dose-response fashion. This regimen (budesonide 4.5 mg BID) is also inferior to prednisolone 40 mg per day (p=0.033). On the other hand, in this study, the budesonide 9mg QD regimen was not less efficacious than the prednisolone regimen.

#### D. Efficacy Conclusions

Five randomized, double-blind and controlled clinical studies demonstrated that administration of ENTOCORT at a dose of 9 mg once daily is effective in the treatment of mild to moderate active CD involving the ileum and/or ascending colon.

The numbers of patients treated with Entocort and comparative agents in these 5 clinical trials are summarized in Table 40.

**Table 40: Numbers of Patients Treated with Entocort and Comparative Agents**

| Study # | Entocort 9mg/day |     |     | Placebo | Prednisolone | Mesalamine |
|---------|------------------|-----|-----|---------|--------------|------------|
|         | Total            | QD  | BID |         |              |            |
| 08-3027 | 93               | 93  |     |         |              | 89         |
| 08-3001 | 192*             |     | 61  | 66      |              |            |
| 08-3025 | 159              | 80  | 79  | 41      |              |            |
| 08-3002 | 88               | 88  |     |         | 88           |            |
| 08-3013 | 119              | 58  | 61  |         | 58           |            |
| Total   | 651              | 319 | 201 | 107     | 146          | 89         |

\*Included Entocort 3 and 15mg/day groups

Reviewer's table summarized from Vol. 35, page 250 – 251

A total of 651 adult patients were treated with Entocort which included 319 patients with 9mg once daily and 201 patients with 4.5mg twice daily. A total of 342 patients were treated with comparative agents which included 107 with placebo, 146 with prednisolone and 89 with mesalamine. Patient populations were relatively homogeneous across the trials. However, only approximately one-third of randomized patients were male, and this female predominant ratio is different from most studies reports which show, regardless of geographic location, relatively equal incidence of Crohn's disease in both sexes (Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 6th Edition, page 1710).

Only 30 of 991 patients in the controlled studies in active CD were of a racial origin other than Caucasian. Six patients were black, 3 oriental and 21 patients were characterized as of "other" racial origin. Thus, experience in patients other than Caucasian is very limited.

The efficacy analyses for the primary clinical trials were based on all patients treated. The clinical improvement response rate (remission rate) was defined as a CDAI score of  $\leq 150$  after 8 weeks treatment. Entocort 9 mg once daily is the regimen that the sponsor proposed in the labeling for this application. The five clinical trials are identified as a comparison to mesalamine (08-3027), two placebo-controlled (08-3001 and 08-3025) and two comparisons to prednisolone (08-3013 and 08-3002). Table 41 summarizes the remission rates by clinical studies.

**Table 41: Percentage of Remission Rates (CDAI<sub>≤</sub>150) and Therapeutic Gain\* After 8 weeks Treatment by Clinical Studies**

| Study # | Entocort   |            | Placebo | Prednisolone | Mesalamine | p-value |
|---------|------------|------------|---------|--------------|------------|---------|
|         | 9mg QD     | 4.5mg BID  |         |              |            |         |
| 08-3027 | 69% (25%)* |            |         |              | 45%        | 0.001   |
| 08-3001 |            | 51% (31%)  | 20%     |              |            | 0.0004  |
| 08-3025 | 48% (15%)  | 53% (20%)  | 33%     |              |            | N.S.    |
| 08-3002 | 52% (-13%) |            |         | 65%          |            | N.S.    |
| 08-3013 | 60% (0)    | 42% (-18%) |         | 60%          |            | N.S.    |

\* The number in ( ) is therapeutic gain.

Therapeutic gain (%) = remission rate in the Entocort group – remission rate in the control group  
N.S.=No statistically significant difference

Reviewer's summary table.

- Study 08-3027 demonstrated that Entocort 9 mg once daily in the morning was significantly better in inducing remission of CD than mesalamine (69% vs. 45%, p=0.001) with 24% therapeutic gain. Mesalamine is considered as active comparator because although this drug is not approved for the treatment of CD in the US, it is widely used in this country to treat active CD in clinical practice.
- One of the 2 placebo-control studies (08-3001), showed that Entocort 4.5 mg bid was statistically significantly better in inducing remission of active CD (p=0.0004) with 31% therapeutic gain. Although the Entocort 4.5 mg bid regimen is different from 9 mg qd, from a clinical perspective there is no apparent difference in the efficacy, pharmacodynamics or safety of ENTOCORT 9 mg/day when given as a once-a-day or two divided dosing regimen. Therefore, study 08-3001 is considered supportive. The other placebo-control study (08-3025) showed that Entocort 9 mg once daily in the morning was numerically better in inducing remission of CD with 15% therapeutic gain. The lack of statistically significant difference in this study might be the consequence of less patients enrolled in the placebo group (2:1 enrollment, n=41) and more patients with mild disease enrolled (median CDAI=253, 71% < 300) in comparison with in the first placebo study (median CDAI=287, 62% < 300). These imbalances might have resulted in a higher placebo response rate (33% vs. 20%) and lower dropout rate.
- In comparison with prednisolone, equal remission rates (60%) were found in the Entocort 9 mg qd group and the prednisolone group in Study 08-3013, whereas there was a 13% less remission rate (52%) in the Entocort than in the prednisolone group (65%) in Study 08-3002. In the latter study, however, the difference between the two arms was not statistically significant with p=0.12. Owing to inconsistent results, no firm conclusion can be drawn, although Entocort might be less effective than prednisolone.

## VII. INTEGRATED REVIEW OF SAFETY

### A. Brief Statement of Conclusions

Short-term treatment of patients with active CD with ENTOCORT (9 mg) for up to 8-10 weeks was well tolerated. The overall AE incidence and AE profile were similar to those of placebo treatment except for those side effects that are the consequence of corticosteroid treatment. It is therefore concluded that ENTOCORT does have glucocorticosteroid (GCS) effect. Almost half (48%) of the patients on prednisolone reported at least one GCS side effect which was significantly higher than those in the ENTOCORT 9 mg group (34%,  $p < 0.01$ ) or placebo group (27%) respectively. Two specific CCS side effects, acne and moon face, were higher in the prednisolone group 23% and 37% in comparison with 15% and 11% in the ENTOCORT 9 mg group ( $p < 0.05$  and  $p < 0.001$ ). Acne and moon face were reported in 13% and 4% of the patients in the placebo group. In comparison with prednisolone, ENTOCORT had statistically significant less AEs in endocrine, gastro-intestinal, skin & appendages ( $p < 0.05$ ) and psychiatric ( $p < 0.01$ ) systems. After 8 weeks treatment, 60-66% of patients in the ENTOCORT group and 26-28% of patients in the prednisolone group had normal cortisol levels ( $\geq 150$  nmol/L). This finding indicated that ENTOCORT had statistically significant less suppressing effect on plasma cortisol level and adrenal function at clinical equivalent doses ( $p < 0.0001$ ). There were no trends or patterns of AE that would not be expected with a corticosteroid in the treatment of patients with CD.

No deaths occurred during the course of the trial among the patients in the controlled studies in active CD. The incidence rate of SAE was 10% in the ENTOCORT 9 mg group, 13% in the Prednisolone 40 mg taper group, 19% in the mesalamine 4 g group and 6% in the placebo group.

A total of 208 patients were treated with ENTOCORT 3-6 mg/day and evaluable for AE in these five controlled one-year studies. Of the most commonly reported AEs, the symptoms of Cushing Syndrome were reported in 38% of the patients in the ENTOCORT 6 mg group and 24% in the placebo group. Acne was the most frequently reported glucocorticosteroid side effect, with 15% of patients in the ENTOCORT 6 mg group and 9% in the placebo group. Bruising easily (11%), moon face (11%) and hirsutism (6%) were more common in the ENTOCORT 6 mg group than the placebo group (1%, 6% and 2% respectively). No death was reported in the long-term controlled studies. Eight percent (8%) of the ENTOCORT 6 mg patients, 5% of the ENTOCORT 3 mg patients and 10% of the placebo patients were withdrawn due to AE in the five one-year studies.

Due to small numbers of geriatric, pediatric and racial origin other than Caucasian patients no conclusions can be drawn about the safety of ENTOCORT in these populations. The safety of ENTOCORT in pregnancies has not been actively evaluated.

As of 01 June 2000, 182 AE reports, comprised of 383 symptoms from the marketed use of ENTOCORT have been reported to the sponsor which included 23 SAEs and one

death. The number of units of ENTOCORT that have been sold through 30 June, 2000 corresponds \_\_\_\_\_

## **B. Description of Patient Exposure**

The clinical Phase I-III program for ENTOCORT capsules included a total of 2076 patients and subjects who received at least one dose of study drug or comparators and were evaluable for safety. Of these patients and subjects 1400 received at least one dose of 3mg ENTOCORT capsules. A total of 651 adult patients with active CD were treated with ENTOCORT which included 319 patients who received 9 mg once daily and 201 patients who received 4.5 mg twice daily. In addition, 11 patients in a study in chronic active hepatitis received Entocort capsules and were evaluable for safety.

ENTOCORT 3 mg capsules were first approved for prescription use in March 1995 in Sweden. As of 1 June 2000, ENTOCORT capsules have been approved for marketing for the induction of remission of CD localized to the ileum and ascending colon in 42 countries and the number of units of ENTOCORT that have been sold through 30 June, 2000 corresponds to \_\_\_\_\_

There were 5 controlled short-term studies in active CD, 6 controlled long-term studies in CD, 7 open label studies and 21 pharmacokinetic /pharmacodynamic studies in subjects and patients. \_\_\_\_\_; 7 in CD and 3 in other indications. In the next section of this review, the safety data from 5 controlled studies in patients with active CD will be presented and discussed first. This is followed by an evaluation of the safety data from other studies.

## **C. Methods and Specific Findings of Safety Review**

### **1. Controlled Studies in Patients with Active CD**

#### **1.1 Methodology for Evaluation of Safety**

Safety assessments which were evaluated in all of 5 controlled studies in patients with active CD at both baseline and 8-10 weeks follow-up included AEs, checklist for glucocorticosteroid side-effects, clinical laboratory tests and vital sign. P-Cortisol was evaluated in 4 of 5 studies and ACTH/Cortisyn tests was tested in 3 of 5 studies at baseline and 8-10 weeks follow-up. Comprehensive physical examination was only done in study 08-3025. Glucocorticosteroid side effects in the Case Report Form included a checklist for the following signs: moon face, acne, swelling of ankles, bruising easily, hirsutism, buffalo hump, purple skin striae, and other. Safety assessments and time points for the assessment in the controlled studies in active CD are summarized in Table 42.

**Table 42: Safety Assessments in the Controlled Studies in Active Crohn's Disease**

| Procedure  | Baseline <sup>a</sup><br>(week -1 or<br>week 0) | Week 2                | Week 4                | Week 8                | Week 10 <sup>b</sup>  | Week 12 <sup>c</sup>  | Week 16 <sup>d</sup>  |
|--|---|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Comprehensive<br>Physical<br>examination<br>08-3025  | X   |                       |                       |                       | X                     |                       |                       |
| Weight   | X   | X                     | X                     | X                     | X                     | X                     | X                     |
| Laboratory<br>samples for<br>clinical<br>chemistry/<br>hematology<br>08-3001<br>08-3002<br>08-3013<br>08-3025<br>08-3027 | X<br>X<br>X<br>X<br>X                           | X<br>X<br>X<br>X<br>X | X<br>X<br>X<br>X<br>X | X<br>X<br>X<br>X<br>X | X<br>X<br>X<br>X<br>X | X<br>X<br>X<br>X<br>X | X<br>X<br>X<br>X<br>X |
| P-Cortisol<br>08-3001<br>08-3002<br>08-3013<br>08-3025<br>08-3027  | X<br>X<br>X<br>X<br>X                           | X<br>X<br>X<br>X<br>X | X<br>X<br>X<br>X<br>X | X<br>X<br>X<br>X<br>X | X<br>X<br>X<br>X<br>X | X<br>X<br>X<br>X<br>X | X<br>X<br>X<br>X<br>X |
| Short ACTH/<br>Cortisyn test<br>08-3001<br>08-3002<br>08-3013<br>08-3025<br>08-3027                                      | X<br>X<br>X<br>X<br>X                           |                       |                       | X<br>X<br>X<br>X<br>X |                       | X<br>X<br>X<br>X<br>X | X<br>X<br>X<br>X<br>X |
| Pregnancy test<br>08-3001<br>08-3002<br>08-3013<br>08-3025<br>08-3027  | X<br>X<br>X<br>X<br>X                           |                       |                       | X<br>X<br>X<br>X<br>X |                       |                       |                       |
| Adverse events<br>assessment   | X <sup>f</sup>                                  | X                     | X                     | X                     | X                     | X                     | X                     |
| GCS side<br>effects <sup>e</sup>   | X <sup>f</sup>                                  | X                     | X                     | X                     | X                     | X                     | X                     |
| Pulse and blood<br>pressure<br>08-3001<br>08-3002<br>08-3013<br>08-3025<br>08-3027                                       | X<br>X<br>X<br>X<br>X                           | X<br>X<br>X<br>X<br>X | X<br>X<br>X<br>X<br>X | X<br>X<br>X<br>X<br>X | X<br>X<br>X<br>X<br>X | X<br>X<br>X<br>X<br>X | X<br>X<br>X<br>X<br>X |

<sup>a</sup> Baseline measurements were generally obtained Week -1 (or -2) in study 08-3001, 08-3013 and 08-3025. In study 08-3002 and 08-3027 all baseline measurements were obtained at Week 0.

<sup>b</sup> Week 10 visit not performed in study 08-3013 and 08-3027

<sup>c</sup> Week 12 visit not performed in study 08-3002 and 08-3025

<sup>d</sup> Week 16 week only performed in study 08-3027

<sup>e</sup> Evaluation of Glucocorticosteroid (GCS) side effects was not performed in study 08-3027

<sup>f</sup> 'Adverse events' and 'GCS side effects' were evaluated pre-treatment to provide a baseline of adverse signs/ symptoms the patient may have had before starting the study drug.

## 1.2 Extent of Exposure

Across these 5 controlled trials in active CD, a total of 993 patients were treated. A total of 651 patients with active CD were treated in the ENTOCORT groups which included 3 different daily dose levels (3, 9 or 15 mg) and 2 different regimens (qd or bid). A total of 107, 146 and 89 patients with active CD were treated by either placebo, prednisolone or mesalamine separately in those 5 clinical studies.

In the controlled studies in active CD between 57% and 88% of the patients were exposed to study drug 8 weeks or more. In the 9 mg group and prednisolone group, 84% and 88% of the patients were exposed 8 weeks or more. The corresponding figures for the placebo and mesalamine groups were 57% and 69%. The lower % of patients exposed to treatment drugs in the mesalamine and placebo groups might result from therapeutic failure (more patients withdrawn). Across all treatment groups only 3% or less of the patients received less than one week of treatment. The cumulative exposure and duration of exposure to treatment are summarized in Table 43.

**Table 43: Summary of The cumulative Exposure and Duration of Exposure to Treatment**

|                                     | Entocort<br>total<br>N=651 | Entocort<br>15 mg<br>N=64 | Entocort<br>9 mg<br>N=520 | Entocort<br>3 mg<br>N=67 | Prednisolone<br>40 mg taper<br>N=145 | Mesalamine<br>4 g<br>N=88 | Placebo<br>N=107 |
|-------------------------------------|----------------------------|---------------------------|---------------------------|--------------------------|--------------------------------------|---------------------------|------------------|
| <b>Cumulative Exposure. n (%)</b>   |                            |                           |                           |                          |                                      |                           |                  |
| >= 1 Week                           | 641 (98%)                  | 63 (98%)                  | 512 (98%)                 | 66 (99%)                 | 145 (100%)                           | 85 (97%)                  | 105 (98%)        |
| >= 2 Weeks                          | 628 (96%)                  | 61 (95%)                  | 505 (97%)                 | 62 (93%)                 | 144 (99%)                            | 81 (92%)                  | 98 (92%)         |
| >= 4 Weeks                          | 596 (92%)                  | 54 (84%)                  | 486 (93%)                 | 56 (84%)                 | 134 (92%)                            | 72 (82%)                  | 81 (76%)         |
| >= 6 Weeks                          | 546 (84%)                  | 45 (70%)                  | 460 (88%)                 | 41 (61%)                 | 132 (91%)                            | 67 (76%)                  | 66 (62%)         |
| >= 8 Weeks                          | 522 (80%)                  | 44 (69%)                  | 439 (84%)                 | 39 (58%)                 | 128 (88%)                            | 61 (69%)                  | 61 (57%)         |
| <b>Descriptive Statistics. Days</b> |                            |                           |                           |                          |                                      |                           |                  |
| Mean (SD)                           | 69.2 (26.3)                | 55.5 (22.2)               | 73.4 (25.5)               | 49.9 (22.5)              | 69.2 (17.9)                          | 80.9 (42.1)               | 50.4 (24.4)      |
| Median                              | 71                         | 69                        | 72                        | 58                       | 71                                   | 110                       | 68               |
| Range                               | 0-125                      | 5-82                      | 0-125                     | 0-77                     | 11-103                               | 0-128                     | 6-78             |

† Exposure time based on time from Visit 2 (Visit 1 in 08-3002 and 08-3027) to patient's last visit in the study.  
(Source: Data on file)

The median time of exposure was similar in the ENTOCORT 9 mg group, the placebo group and the Prednisolone group (68-72 days). In the mesalamine 4 g group the median exposure time was higher (110 days) which might be explained by the treatment duration of 16 weeks instead of 10-12 weeks as in the other four studies.

## 1.3 Frequent Adverse Events

Gastrointestinal symptoms were reported in all groups (ENTOCORT, placebo and

reference drug) at similar rates, mostly reflecting the underlying CD rather than expressing side effects. Table 44 summarizes the most frequently occurring body system disorders in the AE reporting ( $\geq 10\%$ ) in controlled studies in active CD.

**Table 44: Summary of the Most Frequently Occurring Body System Disorders in the AE Reporting ( $\geq 10\%$ ) in Controlled Studies in Active CD**

| Disorders by body system n (%) | Entocort 9mg n=520 | Placebo n=107 | Prednisolone n=145 | Mesalamine n=88 | Difference Pred. Vs. Ent. |
|--------------------------------|--------------------|---------------|--------------------|-----------------|---------------------------|
| Gastro-intestinal              | 218 (42)           | 47 (44)       | 77 (53)            | 37 (42)         | 11%*                      |
| Endocrine                      | 186 (36)           | 40 (37)       | 69 (48)            | 0               | 12%*                      |
| Body as whole                  | 156 (30)           | 41 (38)       | 53 (37)            | 21 (24)         | 7%                        |
| Nervous                        | 146 (28)           | 24 (22)       | 51 (35)            | 17 (19)         | 7%                        |
| Respiratory                    | 108 (21)           | 21 (20)       | 29 (20)            | 8 (9)           | -1%                       |
| Psychiatric                    | 80 (15)            | 11 (10)       | 38 (26)            | 8 (9)           | 11%**                     |
| Skin & appendages              | 75 (14)            | 17 (16)       | 35 (24)            | 7 (8)           | 10%*                      |
| Musculo-skeletal               | 61 (12)            | 10 (9)        | 22 (15)            | 6 (7)           | 3%                        |

\* = statistically significantly different from Entocort 9mg,  $p < 0.05$

\*\* = statistically significantly different from Entocort 9mg,  $p < 0.01$

p-values were calculated by FDA statistician.

Reviewer's table, summarized from Vol. 36, page 71

The incidences of most body system disorders were similar between the ENTOCORT group and placebo group except nervous system and psychiatric disorders that were 6% and 5% more frequent in the ENTOCORT 9mg group than in the placebo group. More frequent disorders were observed in the prednisolone 40 mg taper group than in the Entocort group. Statistically significant differences were noted for endocrine, psychiatric, gastro-intestinal and skin & appendages systems disorders between treatment with prednisolone and ENTOCORT (Table 44).

#### 1.4 Glucocorticosteroid (GCS) side effects

Almost half (48%) of the patients in the prednisolone group reported at least one GCS side effect. The corresponding figures for the ENTOCORT 9 mg group and the placebo group were 34% and 27%; it was statistically significant different between the ENTOCORT group and the prednisolone group ( $p < 0.01$ ). Two specific CCS side effects, acne and moon face, were reported in the prednisolone group 23% and 37% in comparison with 15% and 11% in the Entocort 9 mg group ( $p < 0.05$  and  $p < 0.001$ ). Acne and moon face were reported in 13% and 4% of the patients in the placebo group. There were no trends or patterns of AE that would not be expected with a corticosteroid in the treatment of patients with CD. Other CCS side effects occurred at similar rates between

two groups. The incidences of GCS side effects are summarized in Table 45.

**Table 45: The Incidences of GCS Side Effects in Clinical Studies in Active CD**

|   | Entocort total<br>n=558 (%) | Entocort 9 mg<br>n=427 (%) | Placebo<br>n=107 (%) | Prednisolone 40mg<br>taper n=145 (%) |
|---|-----------------------------|----------------------------|----------------------|--------------------------------------|
| Any GCS side effect                                 | 175 (31)                    | 145 (34)                   | 29 (27)              | 69 (48)**                            |
| Acne  | 79 (14)                     | 63 (15)                    | 14 (13)              | 33 (23)*                             |
| Bruising easily                                     | 70 (13)                     | 63 (15)                    | 12 (11)              | 13 (9)                               |
| Moon face   | 54 (10)                     | 46 (11)                    | 4 (4)                | 53 (37)***                           |
| Swollen ankles                                      | 41 (7)                      | 32 (7)                     | 6 (6)                | 13 (9)                               |
| Hirsutism   | 22 (4)                      | 22 (5)                     | 2 (2)                | 5 (3)                                |
| Buffalo hump  | 6 (1)                       | 6 (1)                      | 2 (2)                | 5 (3)                                |
| Skin striae   | 4 (1)                       | 4 (1)                      | 2 (2)                | 0                                    |
| Evaluable patients for<br>following AE <sup>a</sup> |                             | 159                        | 41                   |                                      |
| Any of below listed AE                              |                             | 86 (54)                    | 23 (56)              |                                      |
| Insomnia  |                             | 57 (36)                    | 16 (39)              |                                      |
| Mood swings   |                             | 54 (34)                    | 15 (37)              |                                      |
| Depression  |                             | 43 (27)                    | 9 (22)               |                                      |
| Hair loss   |                             | 13 (8)                     | 2 (5)                |                                      |

<sup>a</sup> only evaluated in study 08-3025

\* = statistically significantly different from Entocort 9 mg, p<0.05

\*\* = statistically significantly different from Entocort 9 mg, p<0.01

\*\*\* = statistically significantly different from Entocort 9 mg, p<0.001

reviewer's Table summarized from Vol. 36, page 79

As expected, the incidence of most GCS side effects was lower in the placebo group. The greatest differences in comparison to placebo were seen in moon face and bruising easily, with a more than 7% and 4% higher incidences in the ENTOCORT 9 mg group than the placebo group respectively\*. The incidence of mood swings, depression and insomnia (only evaluated in study 08-3025) were similar in the ENTOCORT 9 mg group and the placebo group.

### 1.5 Summary of Deaths

No deaths occurred during the course of the trial among the patients in active CD. One patient (No. 288; a female, age 37), who had received Entocort 9 mg for 10 weeks in study 08-3025 was hospitalized 4.5 months after the study was completed due to a severe flare up of CD (enteritis) and subsequently died 2 weeks later due to post-surgical shock. The Investigator did not consider the event to be causally related. The reviewer agrees with this assessment.

### 1.6 Summary of Nonfatal Serious Adverse Events (SAEs)

In these 5 controlled studies in active CD, 103 patients experienced a total of 113 SAEs. The incidence of SAE was 10% in the Entocort 9 mg group, 13% in the prednisolone 40 mg taper group, 19% in the mesalamine 4 g group and 6% in the placebo group. Table 46 summarizes nonfatal SAEs in controlled studies in active CD.

**Table 46: Summary of nonfatal SAEs in controlled studies in active CD**

|                          | Entocort 9 mg/day<br>n=520   | Placebo<br>n=107          | Prednisolone<br>n=145        | Mesalamine<br>n=88           |
|--------------------------|------------------------------|---------------------------|------------------------------|------------------------------|
| Total                    | 55 SAEs in 51 patients (10%) | 6 SAEs in 6 patients (6%) | 22 SAEs in 19 patients (13%) | 19 SAEs in 17 patients (19%) |
| Enteritis                | 12                           |                           |                              | 6                            |
| Intestinal Obstruction   | 10                           | 1                         | 1                            | 6                            |
| CD Aggravated            | 10                           | 1                         | 4                            |                              |
| Gastrointestinal Fistula | 5                            |                           | 2                            |                              |
| Intraabdominal Abscess   | 1                            |                           |                              |                              |
| Abdominal Pain           | 2                            | 2                         | 1                            | 3                            |
| Fever                    | 2                            |                           |                              | 1                            |
| Ileus                    | 2                            | 1                         | 6                            | 1                            |
| Aggressive Reaction      | 1                            |                           |                              |                              |
| Anemia                   | 1                            |                           |                              |                              |
| Arthritis                | 1                            |                           |                              |                              |
| Arthritis Aggravated     | 1                            |                           |                              |                              |
| Chest Pain               | 1                            |                           |                              |                              |
| Diarrhea                 | 1                            |                           |                              |                              |
| Intestinal Perforation   | 1                            |                           | 1                            |                              |
| Pneumonia                | 1                            |                           |                              |                              |
| Renal Calculus           | 1                            |                           |                              |                              |
| Testis Disorder          | 1                            |                           |                              |                              |
| Vomiting                 | 1                            |                           |                              | 2                            |
| Accident And/or injury   |                              | 1                         |                              |                              |
| Abortion                 |                              |                           | 1                            |                              |
| Embolism Arterial        |                              |                           | 1                            |                              |
| Hyperglycemia            |                              |                           | 1                            |                              |
| Hyperpyrexia             |                              |                           | 1                            |                              |
| Esophagitis              |                              |                           | 1                            |                              |
| Phlegmon                 |                              |                           | 1                            |                              |
| Thrombophlebitis leg     |                              |                           | 1                            |                              |

Reviewer's table modified from Vol.36, page 101 - 102

A significantly higher incidence of nonfatal SAE was reported in the mesalamine group (19%) in comparison with 10% in the Entocort group ( $p=0.0309$ , calculated by FDA statistician). However, the medium exposure time was 110 days for mesalamine in comparison with 68-72 days for Entocort.

The majority of the SAEs reported in the Entocort patient groups (50 out of 66) were gastrointestinal symptoms associated with deterioration of CD demanding in-patient hospitalization. Of the 103 patients who reported a SAE, 69 were withdrawn from the study as a consequence of the SAEs (40 of the Entocort patients, 9 of the Prednisolone patients, 16 of the Mesalamine patients and 4 of the Placebo patients).

In patients treated with prednisolone, 5 SAEs were considered causally related which included 2 ileuses, 1 hyperglycemia, 1 thrombophlebitis leg and 1 esophagitis. Three patients in the mesalamine group (2 with vomiting and 1 with fever) and one patient with ileus in the placebo group were judged by the investigator to be probably or possibly related to the study drug. Only two (3%) of the 66 SAEs reported in Entocort patients were judged by the investigator to be probably or possibly related to the study drug. One female patient (No. 1811, age 21) who was treated with Entocort 15 mg in study 08-3001 was hospitalized after 3 weeks of treatment due to an intra-abdominal abscess which did not respond to medical treatment. The patient underwent surgery and recovered completely. The second SAE that was judged as causally related was a male patient (No. 2103, age 29) treated with Entocort 9 mg in study 08-3027 who experienced an aggressive reaction (mood disturbance) after 50 days of treatment. The patient discontinued the study drug and recovered completely within a few days.

### **1.7 Discontinuations Due to AE from Controlled Active CD Studies**

In the Entocort 9 mg group 22 patients (4%) were withdrawn from the study prematurely due to AE(s) (a total of 35 AE by preferred term). The corresponding number of patients (incidence) in the placebo group was 6 (6%), in the Prednisolone group 5 (3%) and in the mesalamine group 8 (9%).

For the Entocort 9 mg group, 18 of the 35 AEs leading to withdrawal were gastrointestinal symptoms most likely reflecting symptoms of the underlying condition of CD. Non-gastrointestinal adverse events leading to withdrawal in the Entocort 9 mg group included fever, allergic reaction, cold sweats, ESR increased, edema generalized, rigors (chills), leukocytosis, neutrophils atypical, lymphopenia, rash and aggressive reaction. However, most of these reasons for discontinuation occurred as singular cases. Of these AEs edema generalized, leukocytosis, lymphopenia, rash and aggressive reaction could be classified as glucocorticosteroid side effects. Table 47 summarizes AE discontinuations by study group in the controlled studies in active CD.

**Table 47: Summary of AE Discontinuations by Study Group in the Controlled Studies in Active CD.**

|                          | Entocort 9 mg<br>n=520            | Placebo<br>n=107                 | Prednisolone<br>n=145            | Mesalamine<br>n=88               |
|--------------------------|-----------------------------------|----------------------------------|----------------------------------|----------------------------------|
| <b>Total</b>             | <b>35 AEs in 22 patients (4%)</b> | <b>11 AEs in 6 patients (6%)</b> | <b>11 AEs in 5 patients (3%)</b> | <b>10 AEs in 8 patients (9%)</b> |
| Enteritiis               | 6                                 |                                  |                                  | 1                                |
| Abdominal Pain           | 3                                 | 3                                |                                  | 1                                |
| Intestinal obstruction   | 3                                 | 1                                |                                  |                                  |
| Diarrhea                 | 2                                 |                                  |                                  |                                  |
| Nausea                   | 2                                 | 1                                |                                  | 1                                |
| Intestinal Perforation   | 1                                 |                                  | 1                                |                                  |
| Vomiting                 | 1                                 | 1                                |                                  | 2                                |
| Diarrhea With Blood      |                                   | 1                                |                                  |                                  |
| Gastrointestinal Fistula |                                   |                                  | 1                                |                                  |
| Fever                    | 2                                 | 2                                |                                  | 1                                |
| Allergic Reaction        | 1                                 |                                  |                                  |                                  |
| Cold Sweats              | 1                                 |                                  |                                  |                                  |
| ESR Increased            | 1                                 |                                  |                                  |                                  |
| Edema                    | 1                                 |                                  |                                  |                                  |
| Rigors (Chills)          | 1                                 |                                  |                                  |                                  |
| Asthenia                 |                                   |                                  | 1                                |                                  |
| leukocytosis             | 2                                 |                                  |                                  |                                  |
| Neutrophils Atypical     | 2                                 |                                  |                                  |                                  |
| Lymphopenia              | 1                                 |                                  |                                  |                                  |
| Rash                     | 1                                 |                                  |                                  |                                  |
| Urticaria                |                                   | 1                                |                                  |                                  |
| Headache                 |                                   | 1                                | 1                                | 1                                |
| Dizziness                |                                   |                                  | 1                                | 1                                |
| Paraesthesia             |                                   |                                  |                                  | 1                                |
| Aggressive Reaction      | 1                                 |                                  |                                  |                                  |
| Depression               |                                   |                                  | 1                                |                                  |
| Emotional lability       |                                   |                                  | 1                                |                                  |
| Insomnia                 |                                   |                                  | 1                                |                                  |
| hypokalemia              | 1                                 |                                  |                                  |                                  |
| Cushing Syndrome         | 1                                 |                                  | 1                                |                                  |
| Dyspnea                  | 1                                 |                                  |                                  |                                  |
| Palpitation              |                                   |                                  | 1                                |                                  |
| Pregnancy unintended     |                                   |                                  | 1                                | 1                                |

## 1.8 Changes in Laboratory Values

### 1.8.1 Laboratory values over time

Changes of laboratory values from baseline for standard laboratory variables in differences warranting further attention are presented in Table 48.

**Table 48: Comparisons between Treatments in Change from Baseline in Differences Warranting further Attention ( $p < 0.05$ )**

| Variable                   | Treatment                | n   | Change |       |     |     |
|----------------------------|--------------------------|-----|--------|-------|-----|-----|
|                            |                          |     | Mean   | SD    | Min | Max |
| Platelets ( $10^9/L$ )     | Placebo                  | 101 | 12.1   | 54.4  |     |     |
|                            | Entocort 9 mg            | 474 | -3.3   | 61.5  |     |     |
| ASAT ( $\mu\text{kat/L}$ ) | Placebo                  | 102 | 0.001  | 0.231 |     |     |
|                            | Entocort 15 mg           | 60  | -0.122 | 0.299 |     |     |
| ALP ( $\mu\text{kat/L}$ )  | Placebo                  | 102 | 0.07   | 0.49  |     |     |
|                            | Entocort 15 mg           | 60  | -0.15  | 0.34  |     |     |
|                            | Entocort 9 mg            | 471 | -0.13  | 0.50  |     |     |
| Potassium (mmol/L)         | Placebo                  | 102 | 0.04   | 0.46  |     |     |
|                            | Entocort 15mg            | 59  | -0.16  | 0.51  |     |     |
|                            | Entocort 9 mg            | 477 | -0.10  | 0.50  |     |     |
|                            | Prednisolone 40 mg taper | 125 | -0.12  | 0.50  |     |     |

(Source: Table 2.1. Part A1. Appendix 3)

The findings in Platelets, ASAT and ALP were of no clinical importance. No eosinophils count was across the reference limit during the treatment.

Regarding the findings in potassium the results paralleled those of the mean changes: Entocort 15 mg, 9 mg, and Prednisolone 40 mg taper -0.16, -0.10 and -0.12 mmol/L, respectively, vs. -0.01 for Entocort 3 mg, -0.01 for Mesalamine 4 g and +0.04 for Placebo.

### 1.8.2 Individual patient changes in laboratory values

Individual laboratory results at baseline were compared with values obtained at last observation on treatment. For variables related to hematology, the liver enzymes and bilirubin the results for Entocort 9 mg closely resembled those of placebo. For calcium, chloride, phosphate, potassium, and sodium, the percentage of patients with normal low (NL) or normal high (NH) shifts was below 3% for all treatments. For albumin, protein, urea and creatinine, the percentage of patients with NL or NH shifts was below 3% for all Entocort treatment groups. No eosinophils count was across the reference limit during the treatment.

Regarding Potassium, 6/477 patients (1%) shifted from normal-to-low (below 3.0 mmol/L) in the 9 mg Entocort group, compared to 0/102 in the placebo group and 1/125 (1%) in the Prednisolone 40mg taper group.

For the acute inflammatory phase proteins (CRP, Orosomucoid), a higher percentage of patients with normal-to-high shifts in the Entocort group than in the placebo group. These findings were not considered to be clinically important.

### 1.8.3 Plasma Cortisol, ACTH and Cortisyn Tests

In two clinical studies where prednisolone was used as a reference (Study 08-3002, 08-3013), the prednisolone dose was 40 mg qd in the first 2 weeks, with a gradual tapering to a final dose of 5 mg qd at 10-12 weeks. The suppressing effect of prednisolone on cortisol was considerably more pronounced than that of ENTOCORT 9-mg, and approximately twice as many patients treated with ENTOCORT had normal basal plasma cortisol levels ( $\geq 150$  nmol/L) after 8 weeks, as compared with prednisolone.

In Study 08-3013 where an ACTH test was performed before and after treatment with the investigational drugs, only 16% of the prednisolone treated patients had normal adrenal function after 8 weeks of treatment, as compared with 46% of the patients who had received ENTOCORT. Table 49 summarizes the number and proportion of patients with normal plasma cortisol levels ( $\geq 150$  nmol/L) after 8 weeks by studies.

**Table 49: Number and Proportion (%) of Patients with Normal Plasma Cortisol Levels ( $\geq 150$  nmol/L) after 8 weeks**

| Study   | mesalamine  | placebo     | Entocort 9mg/day | prednisolone | Safety Gain %* |
|---------|-------------|-------------|------------------|--------------|----------------|
| 08-3001 |             | 51/63 (81%) | 33/61 (54%)      |              |                |
| 08-3002 |             |             | 48/73 (66%)      | 20/71 (28%)  | 38%**          |
| 08-3013 |             |             | 65/109 (60%)     | 14/54 (26%)  | 34%**          |
| 08-3025 |             | 24/29 (83%) | 84/132 (64%)     |              |                |
| 08-3027 | 38/46 (83%) |             | 51/76 (67%)      |              |                |

\*safety gain % = % of patients with normal cortisol levels in the Entocort group - % of patients with normal cortisol levels in the prednisolone group

\*\*statistically significant difference,  $p < 0.0001$  (by FDA statistician)

Reviewer's table summarized from Vol. 36, page 236

In summary, Entocort had less suppressing effect on cortisol and adrenal function than prednisolone at clinical equivalent doses, but more effect than placebo.

### **1.9 Safety Summary in Controlled Studies in Patients with Active CD**

Treatment of patients with active CD with Entocort capsules 9 mg/day for up to 8-10 weeks was well tolerated. The overall AE incidence and AE profile were similar to those of placebo treatment except for those side effects that are the consequence of corticosteroid treatment. It is therefore concluded that ENTOCORT dose have glucocorticosteroid (GCS) effect. Almost half (48%) of the patients on Prednisolone reported at least one GCS side effect which was significantly higher than those in the Entocort 9 mg group (34%,  $p < 0.01$ ) or placebo group (27%) respectively. Two specific CCS side effects, acne and moon face, were reported in the prednisolone group 23% and 37% in comparison with 15% and 11% in the Entocort 9 mg group ( $p < 0.05$  and  $p < 0.001$ ). Acne and moon face were reported in 13% and 4% of the patients in the placebo group. In comparison with prednisolone, Entocort had statistically significant less AEs in endocrine, gastro-intestinal, skin & appendages ( $p < 0.05$ ) and psychiatric ( $p < 0.01$ ) systems disorders. After 8 weeks treatment, 60-66% of patients in the Entocort group and 26-28% of patients in the prednisolone group had normal cortisol levels ( $\geq 150$  nmol/L) and this indicated that Entocort had statistically significant less suppressing effect on plasma cortisol level and adrenal function at clinical equivalent doses ( $p < 0.0001$ ). There were no trends or patterns of AE that would not be expected with a corticosteroid in the treatment of patients with CD.

No patient died during the course of the five completed studies in active CD. Approximately 10% of the patients treated with Entocort experienced one or more SAEs. The great majority of the SAEs were symptoms of CD, underlying condition. Discontinuations due to AEs occurred in 4% of the Entocort patients. Approximately half of the AEs leading to withdrawal were gastrointestinal symptoms, most likely reflecting symptoms of CD.

An analysis of laboratory data did not show any variation that could not be attributed to the underlying disease. The only relevant findings were some reports of hypokalemia which probably reflected, in addition, increased sensitivity to this known effect of glucocorticosteroids.

## **2 Long-term Controlled Studies in Patients with Crohn's Disease**

Five one-year controlled maintenance studies (study 08-3003, 08-3004, 08-3014, 08-3046 and 08-3008) and one 16-22 week controlled study (study 08-3038, in steroid dependent CD switching from Prednisolone to Entocort capsules) have been conducted in patients with CD. Four of the five one-year studies (studies 08-3003, 08-3004, 08-3014 and 08-3046) were performed in patients who had achieved clinical improvement in a previous study in active CD. Another study (08-3008) in post-surgical prevention of CD recurrence in patients who had a surgical bowel resection was used to illustrate the overall tolerability profile of Entocort capsules in long term use. The similarity in the

patient population, the length of the studies and the similarity in the safety assessments performed made it appropriate to pool the post-surgical study with the other four studies.

A total of 505 patients were treated and evaluable for AEs in the five controlled one-year studies, 208 in the Entocort 6 mg group, 88 in the Entocort 3 mg group and 209 in the placebo group. It is important to note that Entocort 6 mg/day has not been evaluated for the efficacy and 3 mg/day had shown no effect in the treatment of active CD. There was no prednisolone long-term treatment data for comparison.

Across the five one-year studies the Entocort groups and the placebo group were similar with respect to demographic and baseline characteristics. Female patients constituted more than half of the patients (between 55% and 63%) in the groups. Ninety-nine percent (99%) or more of the patients were of Caucasian origin.

Across these five studies 78% of both the Entocort 6 mg group and the placebo group reported at least one AE. The corresponding figure in the Entocort 3 mg group was 67%.

Of the most commonly reported AEs Cushing Syndrome representing the preferred term for 7-11 glucocorticosteroid side effects obtained by a checklist in the studies, was reported in 38% of the patients in the Entocort 6 mg group and 24% in the placebo group. Acne was the most frequently reported glucocorticosteroid side effect, with 15% of patients in the Entocort 6 mg group and 9 % of the patients in the placebo. Bruising easily (11%), moon face (11%) and hirsutism (6%) were more common in the Entocort 6mg group than the placebo group (1%, 6% and 2% respectively). Reports of swollen ankles, buffalo hump and skin striae were more rare and occurred at similar rates in the Entocort 6 mg group and the placebo group. The additional four side effects (mood swings, depression, insomnia and hair loss) evaluated only in study 08-3046 occurred in 47% of the Entocort 6 mg patients and 42% of the placebo patients. Mood swings was reported in 33% of the Entocort 6 mg patients, as compared with 20% in the placebo group. Hair loss (9%) was also somewhat more common in the Entocort 6 mg group. The incidence of depression and insomnia was similar in the two groups.

No deaths were reported in the long-term controlled studies. SAEs occurred in 26 (13%) of the Entocort 6 mg patients, 9 (10%) of the Entocort 3 mg patients and 28 (13%) of the placebo patients. As in short-term studies, most SAEs were gastrointestinal symptoms, probable due to the underlying condition (CD). SAEs in other body systems occurred only as singular cases. Only two SAEs in the Entocort patients at the dose of 6mg/day: Melena in patient 901 and aseptic necrosis of the bone in patient 1126, both in study 08-3008, were considered causally related to the study drug.

Eight percent (8%) of the Entocort 6 mg patients, 5% of the Entocort 3 mg patients and 10% of the placebo patients were withdrawn due to AEs in the five one-year studies. Most AEs leading to withdrawal were gastrointestinal symptoms. Non-gastrointestinal symptoms leading to withdrawal in the Entocort 6 mg group included erythema nodosum, rash, infection viral, varicella, Cushing Syndrome, pharyngitis, pregnancy unintended and brain neoplasm malignant, but these occurred only as singular cases.

With regard to gender differences most gastrointestinal adverse events occurred at higher rates in female patients in the Entocort 6 mg group. The largest differences were seen in abdominal pain (17% compared to 10%), nausea (10% compared to 3%) and vomiting (10% compared to 2%), when comparing female to male patients. Glucocorticosteroid side effects, assembled as Cushing Syndrome occurred in 41% of the female and 35% of the male patients in the Entocort 6mg group. Sinusitis, emotional lability, sleep disorder, rash, skin dry, arthralgia, viral infection, urinary tract infection and purpura were more than 2% more common among female than the male patients in the Entocort 6 mg group. The AEs of sweating increased, abscess and hypertension were more than 2% more common in male patients.

With regard to age differences the group of patients over 64 years of age was too small to draw any conclusions regarding the AE profile in elderly patients.

With regard to laboratory AEs, the only relevant findings were some reports of hypokalemia, which probably reflect increased sensitivity to this known effect of glucocorticosteroids.

Two important safety assessments, immuno-suppression effects and effects on bone metabolism, should be done if the sponsor considers the indication of long-term maintenance therapy with Entocort.

### **3 Open Label Studies in Patients with CD**

Seven open label studies with Entocort 9 mg in active CD were performed. The length of the studies varied between 10 and 24 weeks. The studies comprised a total of 213 patients. The patients had a median age of 32 years, 98% were between 19 and 64 years old and 62% were female.

Median exposure time in the open label studies was 40 days, but treatment ranged between 3 and 203 days. Of the 213 patients in the open label studies 159 patients (75%) reported at least one AE. No deaths occurred in the studies. Seventeen percent (17%) of the patients experienced a SAE and 5% were withdrawn due to AE(s).

Symptoms included under gastrointestinal system disorders were reported in 44% of the patients, probably mainly reflecting symptoms of CD. AEs in general disorders, psychiatric disorders, central and peripheral nervous system disorders and endocrine disorders occurred in around 20% of the patients.

AEs reported in 10% or more of the patients were headache (17%), Cushing Syndrome comprising 7 symptoms included in a checklist for glucocorticosteroid side effects used in four of the studies (20%) and respiratory infection (10%).

In four of the open label studies a checklist was included to evaluate 7 different glucocorticosteroid side effects. Twenty-four percent (24%) of the patients in these studies reported at least one of the side effects. The most commonly reported side effect was bruising easily (13%), followed by swollen ankles and acne (7%). Hirsutism was

reported in 5% and moon face in 4%. Buffalo hump and hair loss occurred only in 1% of the patients.

Most of the AEs in all treatment groups were of mild or moderate severity.

Severe AEs were reported in 34 patients (16%) for a total of 42 AEs. Apart from gastrointestinal symptoms, probably reflecting symptoms of CD, the only AEs reported with severe intensity occurring in 1% or more were infection viral, back pain and migraine.

Sixty-one percent (61%) of the male patients and 82% of the female patients reported AEs in the open label studies. Crohn's Disease aggravated, abdominal pain, flatulence, gastroenteritis, intestinal obstruction, dyspepsia, nausea, vomiting, emotional lability, depression, nervousness, fatigue, pain, Cushing syndrome, respiratory infection and headache were reported in at least 2% more of the female than the male patients. The AEs insomnia, feeling of warmth and viral infection were reported in at least 2% more of the male patients.

No subanalyses were performed regarding age and race since the open label studies did not include any patient over 64 years of age or of Non-Caucasian origin.

#### **4 Phase I-IIA Pharmacokinetic/ Pharmacodynamic Studies in Subjects and Patients**

In the phase I-IIA studies 195 subjects (including 179 healthy subjects, 8 colectomized ulcerative colitis patients and 8 cirrhotic patients) and 43 patients with CD were treated and evaluable for safety.

Eight subjects/patients did not complete study treatment, 7 due to AEs and one due to other reason.

No deaths occurred in the phase I-IIA studies. Four SAEs were reported in 4 subjects/patients treated with Entocort capsules. Two of them, urticaria in a female subject and depression in a male subject were assessed as possibly related to the study drug. Seven subjects/patients (6 treated with Entocort and 1 treated with Prednisolone) discontinued due to AEs.

The most common AEs in the group treated with Entocort were respiratory infection (15%), headache (13%), abdominal pain (10%), fatigue (6%) flatulence, dizziness and insomnia (all 5%). Most of the remaining AEs occurred only in a few percent of the Entocort patients. Only 11 (5%) of the AEs reported in the Entocort group were categorized as severe.

Forty-eight percent (48%) of the male subjects/patients and 68% of the female subjects/patients reported AEs in the group treated with Entocort. Headache, respiratory infection, insomnia, euphoria and palpitation occurred in at least 2% more female than male subjects/patients, whereas pain and arthralgia occurred in at least 2% more of the male subjects/patients.

Regarding age, the study populations less than 18 years of age and above 64 years of age were too small to draw any conclusions about the AE profile in children and elderly.

## **5 Studies in Other Indications**

Only one study has been performed in any other indication than CD. Study 08-2026 was an open-label study performed in chronic HBsAg-negative (lupoid, autoimmune) hepatitis with Entocort 6mg/day for 6 weeks. Eleven patients took part in the study. One patient was withdrawn due to treatment failure. Six patients reported AEs. No SAE, deaths, or discontinuations due to AEs were reported.

## **6 Glucocorticosteroid Adverse Events**

This section analyses all the safety data available from 1160 patients treated with ENTOCORT in the Phase IIB-III clinical studies as it relates to various safety topics of special interest for glucocorticosteroids.

Systemic glucocorticosteroids such as prednisolone play an important role in the treatment of CD, particularly in its active phases, the indication targeted in the present application. Such treatment, however, is associated with clinically important AEs, such as hypothalamic-pituitary-adrenal axis suppression, and adrenal crisis and other Cushingoid symptoms. The latter that are characterized by cosmetically important side effects such as moon face, acne, hirsutism and buffalo hump which are often experienced as very negative by the patients.

AES with incidence rates  $\geq 2\%$  for ENTOCORT 9 mg in short-term treatment include:

- Hypercorticism
- Upper gastrointestinal symptoms (symptoms that may reflect injuries in the gastrointestinal mucosa and bleeding from the gastrointestinal tract)
- Infections, respiratory system and resistance mechanism disorders
- Psychiatric disorders
- Menstrual disorders
- Fluid and Electrolyte Disturbances

AEs with incidence rates  $< 2\%$  for ENTOCORT 9 mg in short-term treatment that are included in the analysis since they are expected, potentially serious side-effects for systemic glucocorticosteroids:

- Adrenal insufficiency
- Cataract
- Hyperglycemia

- Osteoporosis and fractures
- Osteonecrosis
- Thrombosis and arterial embolism

Treatment with systemic glucocorticosteroids may result in iatrogenic Cushing's Syndrome. The characteristic Cushingoid symptoms such as facial rounding, edema, acne, hirsutism may occur individually or in various combinations.

In the short-term controlled studies, the percentage of evaluable patients who reported glucocorticosteroid side effects was numerically higher in the ENTOCORT 9 mg group (34%) than in the placebo group (27%). On the other hand, this percentage (34%) for ENTOCORT was statistically significant lower in comparison with that for prednisolone, where 48% of the patients reported glucocorticosteroid side effects ( $p < 0.01$ ). There were also statistically significant differences between ENTOCORT 9 mg and prednisolone as to the specific glucocorticosteroid side effects acne and moon face. Table 50 presents incidence rates of various glucocorticosteroid side effects for ENTOCORT, prednisolone and placebo in controlled short-term and long-term studies.

**Table 50: Summary of Glucocorticosteroid Adverse Events**

|                | Short-term treatment                |                       |                  | Long-term treatment $\leq 1$ y         |                  |
|----------------|-------------------------------------|-----------------------|------------------|--|------------------|
|                | ENTOCORT<br>9mg, n=427 <sup>a</sup> | Prednisolone<br>N=145 | Placebo<br>N=107 | ENTOCORT<br>3-6mg <sup>b</sup> , n=296 | Placebo<br>N=209 |
| GCS AEs        | 145 (34%)                           | 69 (48%)**            | 29 (27%)         | 90 (30%)                               | 42 (20%)**       |
| Acne           | 63 (15%)                            | 33 (23%)*             | 14 (13%)         | 39 (13%)                               | 19 (9%)          |
| Moon face      | 46 (11%)                            | 53 (37%)***           | 4 (4%)           | 28 (9%)                                | 12 (6%)          |
| Bruise easily  | 63 (15%)                            | 13 (9%)               | 12 (11)          | 32 (11%)                               | 15 (7%)          |
| Swollen ankles | 32 (7%)                             | 13 (9%)               | 6 (6%)           | 11 (4%)                                | 7 (3%)           |
| Hirsutism      | 22 (5%)                             | 5 (3%)                | 2 (2%)           | 16 (5%)                                | 5 (2%)           |
| Skin striae    | 4 (1%)                              | 0                     | 2 (2%)           | 3 (1%)                                 | 2 (1%)           |
| Buffalo hump   | 6 (1%)                              | 5 (3%)                | 2 (2%)           | 5 (2%)                                 | 4 (2%)           |

\* = statistically significantly different from ENTOCORT 9 mg,  $p < 0.05$

\*\*= statistically significantly different from ENTOCORT 9 mg,  $p < 0.01$

\*\*\*=statistically significantly different from ENTOCORT 9 mg,  $p < 0.001$

a= Pooled from studies 08-3001, 08-3002, 08-3013 and 08-3025. Specific GCS evaluation was not done for Study 3027.

b= 3 and 6 mg in studies 08-3003,08-3004 and 08-3014; 6 mg in studies 08-3008 and 08-3046 sponsor's table, modified from Vol.36, page 225.

In the long-term controlled studies the percentage of evaluable patients who reported glucocorticosteroid side effects was statistically significantly higher (30% vs. 20%,  $p < 0.01$ ) in the ENTOCORT group than in the placebo group. Specific glucocorticosteroid side effects, such as acne, moon face, bruise easily and hirsutism, were reported more in the ENTOCORT treated patients than placebo treated patients but the difference were not statistically significant.

In conclusion, the present data show that the patients treated with Entocort had an increased frequency of systemic glucocorticosteroid side effects in comparison with patients treated with placebo and a decreased frequency in comparison with the patients treated with prednisolone. Moon face was the side effect that showed the greatest difference between ENTOCORT 9 mg and prednisolone which could mean that moon face is a side effect that is particularly sensitive to glucocorticosteroids. This is also in agreement with results obtained in other Body systems (see Upper gastrointestinal symptoms, Psychiatric disorders, Menstrual disorders) where graded side effect responses were seen. Placebo and prednisolone consistently exhibited the lowest and highest frequencies of side effects, respectively, while ENTOCORT was positioned between the two extremes.

## **7. Postmarketing Experience**

As of 1 June 2000, Entocort capsules have been approved for marketing for the induction of remission of CD localized to the ileum and ascending colon in 42 countries and the indication of maintenance of remission has been approved in 24 countries. The number of units of ENTOCORT that have been sold through 30 June, 2000 \_\_\_\_\_

As of 01 June 2000, 182 AE reports, comprised of 383 symptoms from the marketed use of ENTOCORT have been reported to the sponsor which included 23 SAEs and one death.

In the post-marketing reports the AEs showed a somewhat different pattern, mainly due to the fact that, compared to clinical trials and compassionate use, reports of deterioration of CD demanding withdrawal or hospitalization would normally not be reported. The most commonly reported AE in the post-marketing reports were within the skin and appendages disorders with 51 reports, followed by body as a whole with 45 reports, and gastro-intestinal disorders with 32 reports. Table 51 displays commonly reported AEs in post-marketing surveillance of Entocort capsules.

**Table 51: Common AEs (Reported in >2 Patients) in the Post-marketing Surveillance (All Symptoms <sup>a</sup>)**

| Preferred Term                               | No. of Reports | Preferred Term                 | No. of Reports |
|--|----------------|--------------------------------|----------------|
| Rash   | 13             | Arthralgia                     | 4              |
| Myalgia                                      | 11             | Asthenia                       | 4              |
| Cramps                                       | 10             | Crohn's Disease Aggravated     | 4              |
| Headache                                     | 10             | Dizziness                      | 4              |
| Events of Non-Medical Character <sup>b</sup> | 9              | Face Edema                     | 4              |
| Pruritus                                     | 9              | Flushing                       | 4              |
| Vision Abnormal                              | 9              | Paraesthesia                   | 4              |
| Glucocorticoids Increased                    | 8              | Skin Striae                    | 4              |
| Menstrual Disorder                           | 8              | Tachycardia                    | 4              |
| Pain   | 8              | Therapeutic Response decreased | 4              |
| Purpura                                      | 7              | Amenorrhea                     | 3              |
| Abdominal Pain                               | 6              | Back Pain                      | 3              |
| Acne   | 6              | Depression                     | 3              |
| Urticaria                                    | 6              | Dyspepsia                      | 3              |
| Alopecia                                     | 5              | Emotional Lability             | 3              |
| Anxiety                                      | 5              | Hypertension                   | 3              |
| Diarrhea                                     | 5              | Jaundice                       | 3              |
| Fatigue                                      | 5              | Malaise                        | 3              |
| Hypertrichosis                               | 5              | Nervousness                    | 3              |
| Hypokalemia                                  | 5              | Edema Dependent                | 3              |
| Nausea                                       | 5              | Palpitation                    | 3              |
| Rash Erythematous                            | 5              | Pancreatitis                   | 3              |
| Weight Increase                              | 5              | Vomiting                       | 3              |
| Adrenal insufficiency                        | 4              |                                |                |

<sup>a</sup> A report may have included more than one adverse event

<sup>b</sup> Reports of use during pregnancy.

### 7.1 Summary of Deaths

One death has been reported from the post-marketing use of ENTOCORT, a 25-year-old female patient (No. 8-218) who died from multiorgan failure following anemia aplastic. The patient had been treated with ENTOCORT (unknown dose) for 14 days when the diagnosis was confirmed. The event was not considered causally related to ENTOCORT.

## 7.2 Summary of Nonfatal Serious Adverse Events

Twenty-three (23) nonfatal SAEs have been reported from the post-marketing use of ENTOCORT. The majority of the events were considered by the reporter to be causally related to the drug. Table 52 summarizes nonfatal SAEs in the post-marketing use by preferred term.

**Table 52: Summary of Nonfatal SAEs Reported in Post-marketing Use of Entocort Capsules**

| Preferred Term             | No. of Event | Causality of Entocort by investigator |
|----------------------------|--------------|---------------------------------------|
| Pancreatitis               | 2            | 2 suspected                           |
| Crohn's Disease Aggravated | 2            | 1 suspected, 1 not suspected          |
| Hypokalemia                | 2            | 2 suspected                           |
| Convulsions                | 1            | suspected                             |
| Adrenal Insufficiency      | 1            | suspected                             |
| Tenesmus                   | 1            | suspected                             |
| Intestinal Perforation     | 1            | suspected                             |
| Tachycardia                | 1            | Not classified                        |
| Jaundice                   | 1            | suspected                             |
| Weight Increase            | 1            | suspected                             |
| Hypomagnesemia             | 1            | suspected                             |
| Diabetes Mellitus          | 1            | suspected                             |
| Suicide Attempt            | 1            | suspected                             |
| Manic Reaction             | 1            | Not classified                        |
| Abscess                    | 1            | Not suspected                         |
| Infection CMV              | 1            | suspected                             |
| Rash                       | 1            | suspected                             |
| Skin Striae                | 1            | suspected                             |
| Angioedema                 | 1            | suspected                             |
| Lymphopenia                | 1            | suspected                             |

Suspected = investigator considered that this AE may be caused by Entocort

On April 11, 2001 the sponsor submitted a 15-day safety report of Pierre Robin Syndrome. The patient was a 34 years old woman in Australia who had been receiving Entocort 3 mg daily since 1996 for CD. The woman gave birth in January 2001 to a boy with Pierre Robins Syndrome (an autosomal recessive disorder). The woman had a medical history of CD since she was 17 years old. Concomitant medication during the pregnancy was Mesasal 6 tablets daily. The reporter assessed a possible relationship to the congenital birth defect and both budesonide and mesasal treatments. Budesonide is labeling as pregnancy category C as with other corticosteroids and no adequate and well-controlled studies in pregnant women were done. This is first Pierre Robin Syndrome case report after more than 10 years on the market and is not necessary to be listed on the label.

On June 2001, one article in Journal of Child Neurology reported that 3 adolescents with CD and poor nutritional status developed benign intracranial hypertension while receiving oral budesonide. All 3 patients had previously received multiple courses of prednisone during the course of their disease, without developing intracranial hypertension. Benign intracranial hypertension resolved after medication withdrawal and did not recur with subsequent use of prednisone. The authors considered this side effect might be associated with poor nutritional status. Benign intracranial hypertension is severe side effect and should be listed in the labeling.

## **8 Relation to Drug-Drug and Drug-Food Interactions**

Entocort is unlikely to inhibit the metabolism of other drugs, including CYP3A4 substrates. CYP3A4 inhibitors will inhibit the metabolism of budesonide resulting in increases in the systemic availability of budesonide. If treatment with ketoconazole, or any other inhibitor of CYP3A4 activity, together with budesonide is indicated, reduction of the budesonide dose should be considered if side effects typical of systemic glucocorticoids occur.

Low-dose oral contraceptives do not alter the plasma levels of budesonide.

The pharmacokinetics of budesonide was not significantly influenced by concomitant intake of cimetidine or omeprazole.

### **D. Safety Update**

The cut-off date of the Integrated Summary of Safety for ENTOCORT as part of the NDA 21-324 was June 1, 2000. The sponsor submitted a safety update on May 25, 2001 which covered the period of June 1, 2000 through December 31, 2000. Because the number of patients covered in this Safety Update Report is small and safety profiles are very similar to that in the NDA, safety update review will be incorporated in this NDA integrated summary of safety and will not be reviewed separately.

There were 10 ongoing studies as of June 1, only 1 of the studies has had a completed study report-Study BU-008-0005. This study is a double blind, randomized, parallel group study evaluating the efficacy of a flexible (3, 6 or 9 mg qd) versus fixed dosing (6 mg qd) schedule of ENTOCORT for the maintenance of remission from ileal or ileocecal CD, over a period of 12 months by comparing the percentage of treatment failures. A total of 143 patients were randomized and 142 were included in the safety analysis in this study. The overall incidence of AEs was higher (97 and 100% of patients reporting) than in the pooled studies reported in the Long-term study section of the ISS (ENTOCORT 6 mg, 78%). Most of the AEs reported in the study were classified as of mild to moderate intensity and non-serious. The most common AEs reported on both treatment regimens were gastrointestinal disturbances which are probably signs of the underlying CD. No deaths occurred during the study. The incidence of AE discontinuations was similar to the pooled Long-term study (9%). However, GCS side effects were not actively evaluated in this study.

One 5-year open-label study is ongoing. A total of 30 patients were enrolled and 11 SAEs were reported, which included 3 cases of intestinal obstructions, 2 cases of gastroenteritis, 2 cases of abscess, one case each of GI fistula, ovarian cyst, allergic reaction and electrolyte imbalance.

A total of 7 SAE cases and 16 non-serious cases have been reported from the marketed use of ENTOCORT during the reporting period of this Safety Update. The review of these cases does not provide evidence that requires an update to the safety profile emerging from the ISS.

In conclusion, the present review does not provide new information that would significantly alter the adverse reaction section of the original NDA review.

#### **E. Summary of Critical Safety Findings and Limitations of Data**

The clinical Phase I-III program for ENTOCORT capsules included a total of 2076 patients and subjects who received at least one dose of study drug or comparators. Of these patients and subjects 1400 received at least one dose of Entocort capsules.

Across the 5 controlled trials in active CD, a total of 993 patients were treated. A total of 651 patients with active CD were treated in the Entocort groups which included 3 different daily doses (3, 9 or 15mg) and 2 different regimens (qd or bid). A total of 107, 146 and 89 patients with active CD were treated with either placebo, prednisolone or mesalamine separately in those 5 clinical studies. The sponsor's clinical development was sound because it allows comparison of the safety profile of ENTOCORT to a) placebo; b) a widely used glucocorticosteroid (prednisolone) and c) sulfasalazine-like compound (mesalazine).

In those 5 controlled studies in active CD between 58% and 88% of patients were exposed to study drug 8 weeks or more. In the Entocort 9 mg group 84% of the patients were exposed to 8-week treatment or more. The corresponding figures for the placebo and prednisolone groups were 57% and 88%. Across all treatment groups only 3% or less of the patients received less than one week of treatment.

The median time of exposure was similar in the ENTOCORT 9 mg, placebo and prednisolone groups (68-72 days). In the mesalamine 4 g group the median exposure time was higher (110 days). Thus, based on length of exposure only, more AEs might be expected in the mesalamine group in comparison to the others.

Safety assessments were adequate. There were done at baseline and every follow-up visit.

Short-term treatment of patients with active CD with ENTOCORT capsules 9 mg/day for up to 8-10 weeks was well tolerated. The overall AE incidence and AE profile were similar to those of placebo treatment except for those side effects that are the consequence of corticosteroid treatment. It is therefore concluded that ENTOCORT does not have a glucocorticosteroid (GCS) effect. Almost half (48%) of the patients on prednisolone reported at least one GCS side effect which was significantly higher than those in the ENTOCORT 9 mg group (34%,  $p < 0.01$ ) or placebo group (27%) respectively. Two

specific CCS side effects, acne and moon face, were reported in the prednisolone group 23% and 37% in comparison with 15% and 11% in the ENTOCORT 9 mg group ( $p < 0.05$  and  $p < 0.001$ ). Acne and moon face were reported in 13% and 4% of the patients in the placebo group. In comparison with prednisolone, ENTOCORT had statistically significant less AEs in endocrine ( $p < 0.05$ ), gastro-intestinal ( $p < 0.05$ ), skin & appendages ( $p < 0.05$ ) and psychiatric ( $p < 0.01$ ) systems. After 8 weeks treatment, 60-66% of patients in the ENTOCORT group and 26-28% of patients in the prednisolone group had normal cortisol levels ( $\geq 150$  nmol/L) and this indicated that ENTOCORT had statistically significant less suppressing effect on plasma cortisol level and adrenal function at clinical equivalent doses ( $p < 0.0001$ ). There were no trends or patterns of AE that would not be expected with a corticosteroid in the treatment of patients with CD.

No deaths occurred during the course of the trial among the patients in the controlled studies in active CD. The incidence rate of SAE was 10% in the Entocort 9 mg group, 13% in the prednisolone 40 mg taper group, 19% in the mesalamine 4 g group and 6% in the placebo group. The majority of the SAEs reported in ENTOCORT-treated patient (50 out of 66) were gastrointestinal symptoms associated with deterioration of the underlying CD demanding in-patient hospitalization.

A total of 505 patients were treated and evaluable for AEs in the five controlled long-term (one-year) studies, 208 in the Entocort 6 mg group, 88 in the Entocort 3 mg group and 209 in the placebo group. Across these five one-year studies 78% of both the ENTOCORT 6 mg group and the placebo group reported at least one AE. The corresponding figure in the ENTOCORT 3 mg group was 67%. Of the most commonly reported AE upon one year administration, Cushing Syndrome was reported in 38% of the patients in the ENTOCORT 6 mg group and 24% in the placebo group. Acne was the most frequently reported glucocorticosteroid side effect, with 15% of the ENTOCORT 6mg patients and 9% of placebo patients. Bruising easily (11%), moon face (11%) and hirsutism (6%) were more common in the ENTOCORT 6 mg group than the placebo group (1%, 6% and 2% respectively). No deaths were reported in the long-term controlled studies. Eight percent (8%) of the ENTOCORT 6 mg patients, 5% of the ENTOCORT 3 mg patients and 10% of the placebo patients were withdrawn due to AEs in the five one-year studies.

In both short-term and long-term studies, the only relevant findings from analysis of laboratory data were some reports of hypokalemia, which probably reflect increased sensitivity to this known effect of glucocorticosteroids.

Due to small numbers of geriatric, pediatric and racial origin other than Caucasian patients no conclusions can be drawn about the safety of ENTOCORT in these populations. The safety of ENTOCORT in pregnancy has not been adequately assessed.

Since orally administrated budesonide is normally cleared to 85 to 90% by hepatic biotransformation, a compromised liver function can be expected to increase the systemic bioavailability and systemic effects of the drug. Therefore, patients with moderate to severe liver disease should be monitored for increased sign and/or symptoms of hypercorticism and reducing the dose of ENTOCORT should be considered.

As of 01 June 2000, 182 AE reports, comprised of 383 symptoms from the marketed use of ENTOCORT have been reported to the sponsor which included 23 SAEs and one death. Post-marketing surveillance reports differed slightly in that the most commonly reported AEs were within the skin and appendages disorders with 51 reports, followed by body as a whole with 45 reports. This might be due to the fact that, compared to clinical trials and compassionate use, reports of deterioration of CD demanding withdrawal or hospitalization would normally not be reported.

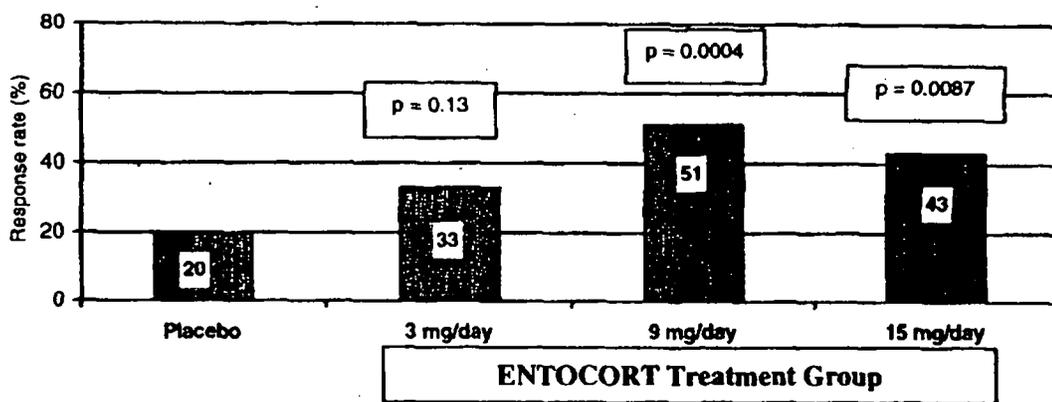
ENTOCORT is unlikely to inhibit the metabolism of other drugs, including CYP3A4 substrates. CYP3A4 inhibitors will inhibit the metabolism of budesonide resulting in increases in the systemic availability of budesonide. If treatment with ketoconazole, or any other inhibitor of CYP3A4 activity, together with budesonide is indicated, reduction of the budesonide dose should be considered if side effects typical of systemic glucocorticoids occur. Low-dose oral contraceptives do not alter the plasma levels of budesonide. The pharmacokinetics of budesonide was not significantly influenced by concomitant intake of cimetidine or omeprazole.

### VIII DOSING, REGIMEN, AND ADMINISTRATION ISSUES

The sponsor proposed that adult dosage for the treatment of mild to moderate active CD involving the ileum and/or the ascending colon is 9 mg taken once daily in the morning for up to 8 weeks.

Figure 3 shows the clinical improvement response rates observed after 8 weeks of treatment with twice-daily doses of 1.5, 4.5 and 7.5 mg ENTOCORT in Study 08-3001.

**FIGURE 3**  
**Dose Response Relationship for ENTOCORT: Proportion of Patients Exhibiting CDAI of  $\leq$  150 (Clinical Improvement) at Week 8 (Study 08-3001)**

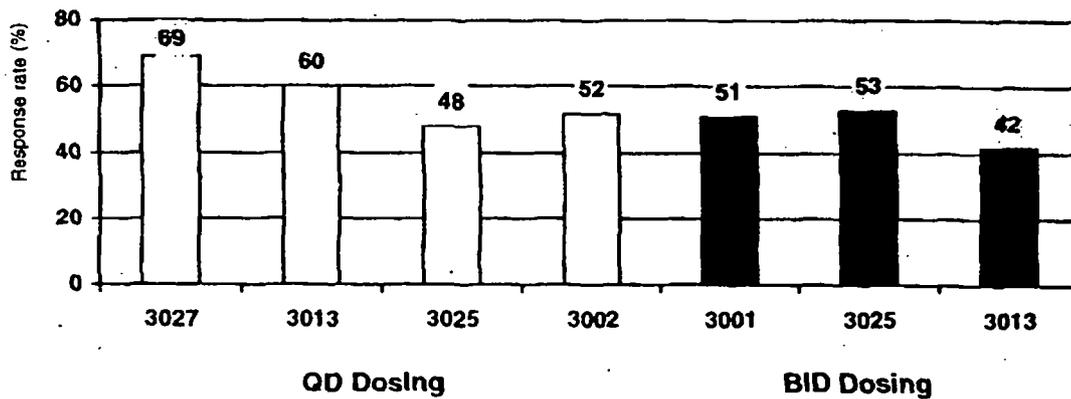


Note: p-values denote significance of pair wise comparison with placebo.

Based upon the results of this trial, all subsequent clinical evaluations of ENTOCORT in active CD used a dose of 9 mg/day, the lowest effective dose.

In the controlled trials with ENTOCORT in active CD, the 9 mg/day dose was administered as a 9-mg once-a-day regimen or as a 4.5-mg twice-a-day regimen. Four clinical trials included 9mg qd regimen and remission rate ranges between 48% and 69% (21% of difference between the trials). In 3 clinical trials with 4.5 mg bid regimen, remission rate varied from 42% to 53% (Figure 4).

**FIGURE 4**  
**Clinical Improvement Response Rates (% with CDAI of  $\leq$  150) at Week 8 of Treatment with 9 mg/day ENTOCORT**



In two of the trials, the qd and bid dosing regimens for ENTOCORT were studied and compared to a reference treatment (placebo in Study 08-3025 and prednisolone in Study 08-3013). There were 18% of difference in the study 3013 and 5% of difference in the study 3025 in the efficacy of ENTOCORT 9 mg/day as a function of dosing regimen (see Figure 4 and Table 41), although there was no statistically significant difference.

Once-daily and twice-daily dosing regimens for ENTOCORT in treating active CD were also compared for safety and pharmacodynamic results. In the two controlled clinical trials which directly compared the 9 mg qd and 4.5 mg bid dosing regimens (Study 08-3025 and Study 08-3013), there were no differences between the two dosing groups with respect to the rate or type of treatment-emergent glucocorticosteroid associated AEs, general AE profile or magnitude of cortisol suppression as reflected by basal morning p-cortisol levels or plasma cortisol levels in response to a short ACTH test. Table 53 summarizes the comparability of the qd and bid dosing regimens of ENTOCORT with respect to safety and cortisol suppression findings in Study 08-3025 and Study 08-3013.

**Table 53: Comparability of Safety Profile and Cortisol Suppression with QD and BID Dosing Regimens for ENTOCORT 9 mg/day in Study 08-3025 and Study 08-3013**

|   | Study 08-3025 [Ref(s). 35] |                        | Study 08-3013 [Ref(s). 34] |                        |
|---|----------------------------|------------------------|----------------------------|------------------------|
|   | ENTOCORT<br>9 mg qd        | ENTOCORT<br>4.5 mg bid | ENTOCORT<br>9 mg qd        | ENTOCORT<br>4.5 mg bid |
| % with GCS adverse events                   | 37%                        | 41%                    | 50%                        | 44%                    |
| Overall AE incidence rate                   | 91%                        | 94%                    | 78%                        | 90%                    |
| % with P-cortisol<br>≤ 150 nmol/L at Week 8 | 34%                        | 37%                    | 41%                        | 36%                    |
| % with normal adrenal<br>function at Week 8 | 57%                        | 48%                    | 62%                        | 60%                    |

In a phase I clinical pharmacology study among healthy patients (Study 08-3018), the administration of 9 mg/day ENTOCORT, given as a 9 mg qd regimen or 4.5 mg bid regimen, for 5 days resulted in virtually identical cortisol suppression. Plasma cortisol, evaluated using the area under the plasma concentration time curve over 24 hours, was suppressed by 45% with the qd regimen and by 51% with the bid regimen.

Thus, from a clinical perspective there is no apparent difference in the efficacy, pharmacodynamics or safety of ENTOCORT 9 mg/day when given as a once-a-day or two divided dosing regimen. Once-daily dosing is more convenient for the patient. Traditional glucocorticosteroids are typically given once daily in the morning.

## **IX USE IN SPECIAL POPULATIONS**

In each trial subgroup analyses were performed examining the CDAI clinical improvement response rate and, for some trials, the quantitative change from baseline in CDAI score as a function of various demographic and baseline disease characteristics.

### **A. Gender Effect**

The higher response rate to the placebo treatment by male than female patients (33% vs. 13% in study 08-3001 and 39% vs. 29% in study 08-3025) was observed. Table 54 summarizes the results of subgroup analysis of gender on response rate at week 8 by clinical trials.

**Table 54: Results of Subgroup Analysis of Gender on Response Rate at Week 8**

| Study   | Gender | Entocort |           | Control<br>n (%)         | sex  | p-value<br>treatment | Trt.+ sex |
|---------|--------|----------|-----------|--------------------------|------|----------------------|-----------|
|         |        | 9mg,qd   | 4.5mg,bid |                          |      |                      |           |
| 08-3001 | Male   |          | 23 (43%)  | 24 (33%)                 | 0.18 | 0.003                | 0.059     |
|         | Female |          | 38 (55%)  | 40 (13%)                 |      |                      |           |
| 08-3027 | Male   | 30 (61%) |           | Mesalamine<br>28 (44%)   | 0.41 | 0.001                | 0.44      |
|         | Female | 63 (73%) |           | 61 (45%)                 |      |                      |           |
| 08-3025 | Male   | 18 (50%) | 35 (51%)  | 18 (39%)                 | 0.14 | 0.77                 | 0.82      |
|         | Female | 59 (47%) | 43 (53%)  | 21 (29%)                 |      |                      |           |
| 08-3013 | Male   | 21 (48%) | 27 (48%)  | Prednisolone<br>23 (61%) | 0.8  | 0.066                | 0.23      |
|         | Female | 37 (68%) | 33 (36%)  | 35 (60%)                 |      |                      |           |

Reviewer's table summarized from Vol. 35 page 287, Vol.70, page 192

The majority of the patients included in the safety evaluation in the controlled studies in active CD were female. The percentage of female patients varied from 55% in the ENTOCORT 15 mg group to 70% in the ENTOCORT 3 mg group. In all treatment groups a higher percentage of female patients reported AEs, e.g. in the ENTOCORT 9mg group 87% of the female patients, compared to 77% of the male patients. This difference was even more pronounced in the comparator and placebo groups. The percentage of patients by gender group, who had a SAE or discontinued due to AE in the ENTOCORT groups were similar, as summarized in Table 55.

**Table 55: Incidence of AE by Gender in Active CD in combination of 5 clinical trials**

|  | Entocort<br>Total<br>N=651 | Entocort<br>15 mg<br>N=64 | Entocort<br>9 mg<br>N=520 | Entocort<br>3 mg<br>N=67 | Placebo<br>N=107 | Prednisolone<br>40 mg taper<br>N=145 | Mesalamine<br>4 g<br>N=88 |
|--|----------------------------|---------------------------|---------------------------|--------------------------|------------------|--------------------------------------|---------------------------|
| Gender, N (%)  |                            |                           |                           |                          |                  |                                      |                           |
| Male (%)   | 235 (36%)                  | 29 (45%)                  | 186 (36%)                 | 20 (30%)                 | 43 (40%)         | 60 (41%)                             | 28 (32%)                  |
| Female (%)   | 416 (64%)                  | 35 (55%)                  | 334 (64%)                 | 47 (70%)                 | 64 (60%)         | 85 (59%)                             | 60 (68%)                  |
| Experienced At Least<br>One Adverse Event<br>Male (%)            | 183 (78%)                  | 24 (83%)                  | 144 (77%)                 | 15 (75%)                 | 32 (74%)         | 46 (77%)                             | 18 (64%)                  |
| Female (%)   | 361 (87%)                  | 32 (91%)                  | 290 (87%)                 | 39 (83%)                 | 56 (88%)         | 81 (95%)                             | 46 (77%)                  |
| Experienced At Least<br>One Serious Adverse<br>Event<br>Male (%) | 24 (10%)                   | 3 (10%)                   | 19 (10%)                  | 2 (10%)                  | 2 (5%)           | 5 (8%)                               | 6 (21%)                   |
| Female (%)   | 37 (9%)                    | 3 (9%)                    | 32 (10%)                  | 2 (4%)                   | 5 (6%)           | 14 (16%)                             | 11 (18%)                  |
| Discontinued due to<br>Adverse Event(s)<br>Male (%)              | 13 (6%)                    | 3 (10%)                   | 9 (5%)                    | 1 (5%)                   | 1 (2%)           | 1 (2%)                               | 3 (11%)                   |
| Female (%)   | 16 (4%)                    | 2 (6%)                    | 13 (4%)                   | 1 (2%)                   | 5 (8%)           | 4 (5%)                               | 5 (8%)                    |

(Source: Entocort safety database)

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The higher incidence of AEs in female patients applied to almost all body systems. Gastrointestinal symptoms like nausea, abdominal pain, flatulence, vomiting, constipation and epigastric pain seemed to be more common in the female than the male patients in the ENTOCORT 9 mg group. For nausea, flatulence and vomiting similar differences between male and female patients were seen in the placebo group. Other AEs that seemed more common in female ENTOCORT patients were dizziness, headache, insomnia, rash, sweating increased, vision abnormal and flu-like disorder. For headache, insomnia, rash and sweating increased this difference was also true in the placebo group.

## **B. Age, Race and Ethnicity Effects**

Safety subgroup analysis was done for patients' age less than 65 years and 65 years or older. Among the different treatment groups only between 0 and 3.4% of the patients included in the safety analysis of the controlled studies in active CD were 65 years or older. There was no patient treated with ENTOCORT who was over 74 years old. Two female patients in the prednisolone group were over 74 years old.

Some AEs, abdominal pain, vomiting, pain, arthralgia, rash, melena, sweating increased, constipation, arthropathy, rhinitis, paraesthesia, hemorrhoids, hypertension, depression and dysuria were more common among the older patients than the younger in the Entocort 9 mg group. Other AEs (tracheitis, stiffness of legs) occurred only among the older Entocort 9 mg patients. It should be noted that the very small number of patients 65 years and older makes it difficult to draw any conclusions regarding any particular pattern of the AE profile in this category of patients.

In the controlled studies in active CD only 30 out of 991 patients were of a racial origin other than Caucasian. Six patients were black, 3 oriental and 21 patients were characterized as of 'other' racial origin. Since the groups of non-Caucasian patients were small, subgroup analysis of race on response rate did not seem meaningful.

None of the non-Caucasian patients were withdrawn from the study due to AE(s). In the ENTOCORT 9 mg group one patient of Oriental origin (patient 1104 in study 08-3001), one patient of Black origin (patient 1001 in study 08-3001) and in the mesalamine 4 g group 2 patients of 'Other' origin (patient 2310 and 2316 in 08-3027) experienced a SAEs (preferred term Intestinal Obstruction for all patients), and were withdrawn in connection with these events. Reasons for discontinuation given by the investigators for these patients were lack of efficacy.

## **C. Pediatric Development Plan**

### **1. Background**

The incidence of CD in children in high-prevalence areas can be estimated as 1.7-3.5/100,000. Most pediatric cases are diagnosed between the ages of 10-19 years. It has been reported that 2% of 168 children presented with CD between 0-9 years of age. Males and females are equally affected in adulthood but in childhood there is a 2:1 male:female ratio. This constellation of signs and symptoms with their frequencies includes

diarrhea (80%), abdominal pain (75%), bleeding (50%), growth failure (35%), perianal and rectal disease (15 and 25%, respectively) and extraintestinal signs (15%). Growth failure may occur in the presence or absence of steroid therapy. Although evidence exists that corticosteroids suppresses linear growth, their use in controlling CD permits growth to resume at normal rates. Characteristically, the presentation of CD in children is often predicated on the presence of growth failure as the hallmark of this disorder. Specifically, the prevalence of growth failure was 24%, 23%, and 39% by height velocity, Z score, and height- for-age criteria, respectively in children with CD. A delay in linear growth persisted throughout puberty and was not reversed after surgery. Patients who had CD were twice as likely to have growth abnormalities than patients who had ulcerative colitis.

Corticosteroids can effect short-term remissions of active small bowel disease in 70% of patients. Unfortunately 70% of responders will relapse within a year. Treatment modalities for children with CD include aminosalicylates, steroids including prednisone, methylprednisolone and steroid enemas, immunosuppressive therapy, antibiotics and enteral and parenteral nutrition.

## **2. Partial waiver pediatric studies for patients 5 years of age or less**

The sponsor requests a partial waiver due to the necessary pediatric studies are impossible or highly impractical due to the very small number of patients,  $\leq 5$  years of age, diagnosed with CD. Based on several studies, incidence of CD in children in high-prevalence areas can be estimated as 1.7-3.5/100,000; most pediatric cases are diagnosed between the ages of 10-19 years and CD in the younger age of  $<6$  years occurs less frequently. Approximately 25% of all new cases occur in individuals younger than 20 years of age. It has been reported that 2% of 168 children presented with CD between 0-9 years of age. The Office of Orphan Products Development denied the orphan designation request for ENTOCORT, because the prevalence for CD (about 370,300 patients in this country) exceeds the statutory limit of 200,000 patients in the US (see letter dated April 26, 2001 from Office of Orphan Products Development on ENTOCORT). Based on this estimate, there are less 3000 patients with CD between 0-9 years of age (based on 40% of all CD present in the period of childhood and adolescence and 2% of children with CD are between 0-9 years of age).

I recommend that partial waiver pediatric studies for patients  $\leq 5$  years of age be granted, because of so limited number of patients with CD  $\leq 5$  years of age.

## **3. Defer Submission of Pediatric Data**

The sponsor requests that submission of pediatric data be deferred until after approval of this NDA, as the pediatric development program is still ongoing. The reviewer agrees with the sponsor's request. In addition, I recommend that well control studies have to be done in patients with CD at the age of 6-17 years old to evaluate the safety and efficacy of ENTOCORT in this pediatric population. Until these data are submitted, reviewed and found to be adequate, no pediatric information should be included in the Package Inset.

#### **4. Sponsor's Proposed Label for Pediatric Population**

In the package insert, under the section of DOSAGE AND ADMINISTRATION, it was stated that for children weighing 30 kg or more, the recommended starting dose of ENTOCORT is 9 mg taken once daily.

I recommend that no pediatric information be included in the Package Insert at this time. No adequate efficacy and safety data have been submitted to support the dose regimen for children weighing 30 kg or more.

#### **5. Conclusion and Recommendations for Pediatric Study**

The exposure of ENTOCORT in pediatric patients is limited. One clinical study (SD-008-3037) in children with CD and another open-label PK study in children and adults with CD are ongoing. Based on available data on this submission, I recommend that no pediatric information be included in the Package Insert at this time. Because of so limited number of patients with CD  $\leq$  5 years of age, I recommend that partial waiver pediatric studies for patients  $\leq$  5 years of age be granted. Well control studies have to be done in patients with CD at the age of 6-17 years old to evaluate the safety and efficacy of ENTOCORT in this pediatric population. I also recommend that, because the pediatric program is ongoing, submission of pediatric data be deferred until after approval of NDA 21-324.

#### **D. Other Populations**

##### **1 Pregnancy**

The safety of ENTOCORT in pregnancies has not been adequately evaluated. In the clinical trials 7 pregnancies were reported. Five of the pregnancies resulted in healthy infants, one pregnancy was terminated, and in one pregnancy the outcome is not known. In the post-marketing and compassionate use 14 cases involving pregnancies have been reported. Eleven pregnancies did not involve any complications. Two pregnancies were coded within body system 'female reproductive disorders'; one unplanned pregnancy and one pregnancy with bleeding during first trimester. One pregnancy resulted in a fetus malformation. On April 11, 2001 the sponsor submitted a 15-days safety report of Pierre Robin Syndrome. A about 34 years old woman in Australia who had been receiving Entocort 3 mg daily PO since 1996 for CD. The woman gave birth in January 2001 to a boy with Pierre Robin Syndrome (an autosomal recessive disorder).

Animal studies indicate an increased risk for injury to the fetus (cleft palate, skeletal malformation) when the mother is treated with glucocorticoids, the relevance of this to man is unclear.

##### **2 Patients with Hepatic Insufficiency**

Plasma levels of drugs that are extensively metabolized in the liver are likely to be

influenced by changes in the liver function. Since oral budesonide is normally cleared to 85-90% by hepatic biotransformation, a compromised liver function can be expected to increase the systemic bioavailability and systemic effects of the drug.

Eight patients with biopsy-verified cirrhosis (3 primary biliary cirrhosis, 3 viral hepatitis, 2 alcohol-related), with reduced liver blood flow and impaired liver function were compared with a group of healthy subjects. They were given micronized budesonide orally and intravenous budesonide as a reference. The elimination rate was slower in the cirrhotic patients compared with the healthy subjects (plasma half-life  $4.6 \pm 1.0$  h. vs.  $3.6 \pm 0.5$  h). Although plasma clearance was only 16% lower in the cirrhotics than in the controls, the resulting decrease in first-pass metabolism increased systemic availability of budesonide 2.5 times in the cirrhotic patients ( $18.6 \pm 11.2\%$  vs.  $7.4 \pm 2.4\%$ ) compared with the control group. The mean peak plasma concentration of budesonide in the cirrhotic patients and the healthy subjects was  $5.1 \pm 3.4$  nmol/L and  $1.7 \pm 0.3$  nmol/L, respectively. Absorption parameters were not altered, and for the intravenous dose, no major differences in clearance or volume of distribution were observed. Plasma cortisol was suppressed approximately twice as much in the cirrhotic patients as in the healthy subjects after oral administration of 4mg of budesonide.

Therefore, patients with moderate to severe liver disease should be monitored for increased sign and/or symptoms of hypercorticism and reducing the dose of Entocort should be considered.

### 3. Subgroup analysis by Severity of disease at baseline

Results of subgroup analyses indicated that the clinical improvement response rates at Week 8 were significantly lower among patients with more severe disease at study entry (i.e, CDAI  $\geq 300$ ) in comparison with patients who had CDAI  $<300$ . Table 56 summarizes the subgroup analysis results by severity of disease at baseline.

**Table 56: Results of Subgroup Analysis of Severity of Disease at Baseline on Response Rate at Week 8 by Clinical Trials.**

| Study   | CDAI       | Entocort |           | control                  | p-value |           |           |
|---------|------------|----------|-----------|--------------------------|---------|-----------|-----------|
|         |            | 9mg,qd   | 4.5mg,bid |                          | CDAI    | treatment | Trt.+CDAI |
| 08-3001 | <300       |          | 36 (53%)  | Placebo<br>40 (28%)      | 0.0011  | 0.0014    | 0.45      |
|         | $\geq 300$ |          | 25 (48%)  | 24 (8%)                  |         |           |           |
| 08-3025 | <300       | 53 (55%) | 53 (58%)  | 27 (44%)                 | 0.0043  | 0.13      | 0.68      |
|         | $\geq 300$ | 24 (33%) | 24 (42%)  | 11 (9%)                  |         |           |           |
| 08-3027 | <300       | 66 (80%) |           | Mesalamine<br>57 (53%)   | 0.0001  | 0.001     | 0.46      |
|         | $\geq 300$ | 27 (44%) |           | 32 (29%)                 |         |           |           |
| 08-3013 | <300       | 44 (70%) | 40 (53%)  | Prednisolone<br>44 (64%) | 0.0007  | 0.077     | 0.31      |
|         | $\geq 300$ | 13 (31%) | 18 (17%)  | 13 (54%)                 |         |           |           |

Reviewer's table, summarized from Vol. 70, page 192, Vol. 35, page 287 and 299

Comparison of two placebo groups in studies 08-3001 and 08-3025, less patients with CDAI  $\geq$  300 (29%) were enrolled in study 08-3025 than in the study 08-3001 (38%). It may partly explain higher response rate in study 08-3025 placebo group.

## **X CONCLUSION AND RECOMMENDATIONS**

### **A. Conclusions**

The clinical program with ENTOCORT supported that administration of ENTOCORT at a dose of 9 mg once daily is effective in treating mild to moderate CD involving the ileum and/or ascending colon. One study demonstrated that ENTOCORT 9 mg once daily in the morning was statistically significantly better in inducing remission of CD in comparison with mesalamine ( $p=0.001$ ) with 24% therapeutic gain. Although mesalamine is not approved for CD in the US, it is widely used in this country to treat active CD in clinical practice. In comparison with placebo, one study shown that ENTOCORT 4.5 mg bid was statistically significantly better in inducing remission of CD ( $p=0.0004$ ) with 31% therapeutic gain. Although Entocort 4.5 mg bid in this study was different from the 9 mg qd proposed regimen, from a clinical perspective there is no apparent difference in the efficacy, pharmacodynamics or safety of ENTOCORT 9 mg/day when given as a once-a-day or two divided dosing regimen. An additional placebo-control study showed that ENTOCORT 9 mg once daily in the morning was numerically better in inducing remission of CD with 15% therapeutic gain. The lack of statistically significant difference in this study might be the consequence of less patients enrolled in the placebo group (2:1 enrollment,  $n=41$ ) and more patients with mild disease enrolled (median CDAI=253, 71% < 300) in comparison with in the first placebo study (median CDAI=287, 62% < 300). These imbalances might have resulted in a higher placebo response rate (33% vs. 20%) and lower dropout rate. In comparison with prednisolone, equal remission rates (60%) were found in the Entocort 9 mg once daily group and the prednisolone group in Study 08-3013, whereas there was a 13% less remission rate (52%) in the Entocort than in the prednisolone group (65%) in Study 08-3002. In the latter study, however, the difference between the two arms was not statistically significant with  $p=0.12$ . To date glucocorticosteroids have been the most effective drugs in actively suppressing inflammation and inducing clinical remission in patients with CD. It is therefore concluded that ENTOCORT at a dose of 9 mg once daily is effective in treating mild to moderate CD involving the ileum and/or ascending colon. Owing to inconsistent results, no firm conclusion can be drawn, although Entocort might be less effective than prednisolone.

The clinical studies established a favorable safety and tolerability profile for ENTOCORT in the intended population. At therapeutically comparable doses, ENTOCORT 9 mg/day was associated with a significantly lower incidence of glucocorticosteroid (GCS) AEs compared to prednisolone (total GCS side effect  $p<0.01$ , moon face  $p<0.001$  and acne  $p<0.05$ ) and ENTOCORT had statistically significant less suppressing effect on plasma cortisol level and adrenal function at clinical equivalent doses ( $p<0.0001$ ). However, ENTOCORT does have GCS activity because a numerically higher incidence of GCS adverse effects was reported in comparison with placebo.

It is therefore concluded that the therapy with ENTOCORT 9 mg qd has a favorable risk-benefit ratio when considering it as a treatment option for patients with mild to moderate active CD involving the ileum and/or ascending colon.

## **B. Recommendations**

1. ENTOCORT is approvable as a treatment option for patients with mild to moderate active CD involving the ileum and/or ascending colon from a clinical perspective. The recommended dose of ENTOCORT is 9 mg once daily in the morning for up to 8 weeks. To get ENTOCORT approved, the sponsor has to follow all of the recommendations listed below and do all of the necessary changes in the ENTOCORT labeling.
2. The regimen for “those patients who do not achieve clinical improvement in 8 weeks, an additional 8 weeks of treatment should be considered” should not be approved. There were no data to support this regimen. Four of 5 clinical trials used 8-10 weeks treatment only. Only one study lasted 16 weeks (study 08-3027) and in fact, study 08-3027 showed that treatment with ENTOCORT for an additional 8 weeks did not result in a further decrease in CDAI. Furthermore, ENTOCORT does have systematic GCS activity, although much less than prednisolone.
3. Pediatric information should not be included in the package insert, because at this time no adequate efficacy and safety data to support use of ENTOCORT in children have been provided.
4. Partial waiver request for pediatric studies in patients  $\leq 5$  years of age should be granted, because the number of patients with CD  $\leq 5$  years of age is very limited.
5. Submission of pediatric data should be deferred until after approval of NDA 21-324.
6. Well control studies should be done in CD patients 6 to 17 years of age to evaluate the safety and efficacy of ENTOCORT in these pediatric populations as a phase 4 study commitments.

Please see section of Appendix B – Medical officer’s labeling review and Consumer Safety Officer’s labeling review for more detail recommendations regard of the changes of ENTOCORT label.

The requests and recommendations above and in labeling review should be communicated to the sponsor.

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Ruyi He, MD

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**APPEARS THIS WAY  
ON ORIGINAL**

**XI. APPENDIX**

**A: LIST OF ABBREVIATIONS AND DEFINITIONS OF TERM**

|        |  |
|--------|--|
| ACTH   | Adrenocorticotrophic Hormone             |
| AE     | Adverse Event                            |
| ALP    | Alkaline Phosphatase                     |
| ALAT   | Alanine Aminotransferase                 |
| ANOVA  | Analysis of Variance                     |
| APT    | All Patients Treated                     |
| ASA    | Aminosalicylic Acid                      |
| ASAT   | Asparate Aminotransferase                |
| b.i.d. | bis in die (twice a day)                 |
| BUN    | Blood Urea Nitrogen                      |
| CD     | Crohn's Disease                          |
| CDAI   | Crohn's Disease Activity Index           |
| CIR    | Controlled Ileal Release                 |
| CRF    | Case Report Form                         |
| ESR    | Erythrocyte Sedimentation Rate           |
| GCS    | Glucocorticosteroid                      |
| IBD    | Inflammatory Bowel Disease               |
| IBDQ   | Inflammatory Bowel Disease Questionnaire |
| MCS    | Mental Component Summary                 |
| NSAID  | Non-Steroidal Anti-Inflammatory Drug     |
| q.d.   | quaque die (every day)                   |
| SAE    | Serious Adverse Event                    |

**APPENDIX B:**

**Medical Officer's Labeling Review for NDA 21-324, ENTOCORT**

The sponsor's proposed **CLINICAL STUDIES** section in the ENTOCORT labeling is unacceptable. The reviewer recommends **CLINICAL STUDIES** section as following:

**CLINICAL STUDIES**

The safety and efficacy of ENTOCORT were evaluated in 994 patients with active Crohn's disease of the ileum and/or ascending colon in 5 randomized and double-blind studies. The study patients ranged in age from 17 to 85 (mean 35), 40% were male and 97% were white. Of those patients, 651 were treated with ENTOCORT, 17 (2.6%) were  $\geq 65$  years of age and no patients were  $> 74$  years of age. The Crohn's Disease Activity Index (CDAI) was the main clinical assessment used for determining efficacy in these 5 studies. The CDAI is a validated index based on subjective aspects rated by the patient (frequency of liquid or very soft stools, abdominal pain rating and general well-being) and objective observations (number of extraintestinal symptoms, need for antidiarrheal drugs, presence of abdominal mass, body weight and hematocrit). Clinical improvement, defined as a CDAI score of  $\leq 150$ , was the primary efficacy variable in these 5 comparative efficacy studies of ENTOCORT capsules. Safety assessments in these studies included monitoring of adverse experiences, including a checklist of potential symptoms of hypercorticism.

One study (Study 1) compared the safety and efficacy of ENTOCORT 9 mg qd in the morning to a experimental comparator. At baseline, the median CDAI was 272, with no statistically significant differences between treatment arms. ENTOCORT 9 mg qd induced significantly greater clinical improvement rate at Week 8 than the comparator (Table 1).

**Table 1: Clinical Improvement Rates (CDAI  $\leq 150$ ) After 8 weeks of Treatment**

| Clinical Study | ENTOCORT    |             | Comparator <sup>a</sup> | Placebo     | Prednisolone | p-value |
|----------------|-------------|-------------|-------------------------|-------------|--------------|---------|
|                | 9 mg QD     | 4.5mg BID   |                         |             |              |         |
| 1              | 62/91(69%)  |             | 37/83 (45%)             |             |              | 0.001   |
| 2              |             | 31/61 (51%) |                         | 13/64 (20%) |              | 0.0004  |
| 3              | 38/79 (48%) | 41/78 (53%) |                         | 13/40 (33%) |              | N.S.    |
| 4              | 35/58 (60%) | 25/60 (42%) |                         |             | 35/58 (60%)  | N.S.    |
| 5              | 45/86 (52%) |             |                         |             | 56/85 (65%)  | N.S.    |

<sup>a</sup> Although this comparator is used in the U.S. to treat active Crohn's disease in clinical practice, this drug is not approved for the treatment of Crohn's disease in this country. N.S. = No statistically significant difference.

Two placebo-controlled clinical trials (Studies 2 and 3) were conducted. The first involved 258 patients and tested the effects of grading doses of ENTOCORT (1.5, 4.5 or

7.5 mg bid) versus placebo. At baseline, the median CDAI was 290, with no statistically significant differences between treatment arms. The 3 mg per day dose level (data not shown) could not be differentiated from placebo. The 9 mg per day arm was statistically different from placebo (Table 1), while no additional benefit was seen when the daily ENTOCORT dose was increased to 15 mg per day (data not shown). In the other placebo-controlled study the median CDAI at baseline was 263. Neither 9 mg qd nor 4.5 mg bid ENTOCORT dose levels was statistically different from placebo (Table 1).

Two clinical trials (Studies 4 and 5) compared ENTOCORT capsules with oral prednisolone (initial dose 40 mg per day). At baseline, the median CDAI was 277, with no statistically significant differences between treatment arms. Equal clinical improvement rates (60%) were seen in the ENTOCORT 9 mg qd and the prednisolone groups in Study 4, whereas there was a 13% less clinical improvement rate in the ENTOCORT group than in the prednisolone group in Study 5 (Table 1).

The mean decrease in plasma cortisol was significantly larger in the prednisolone group in both trials after 8 weeks of treatment. The proportion of patients with normal plasma cortisol values ( $\geq 150$  nmol/L) was significantly higher in the ENTOCORT groups in both trials (60 to 66%) than in the prednisolone groups (26 to 28%,  $p < 0.0001$ ) at week 8.

The recommendations for the labeling changes in the remainder sections of the labeling are listed in the table below.

| Sponsor's Proposed labeling | Reviewer's Proposed Modifications to the Labeling | Rationale |
|-----------------------------|---|-----------|
|-----------------------------|---|-----------|

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