CLINICAL REVIEW

EXECUTIVE SUMMARY

1. RECOMMENDATIONS

1.1 Recommendations of Approvability

Approvable, pending review of the one-year data. Based on review of interim 6-month data, this Reviewer recommended that the sponsor receive pediatric exclusivity, since the requested study was conducted in agreement with the Written Request. Changes to the product labeling should be made after receipt and review of data from the completed 12-month study.

1.2 Recommendations of Postmarketing Studies/or Risk Management

None

2. SUMMARY OF CLINICAL PROGRAM

2.1 Brief Overview of Clinical Program

As part of the Pediatric Exclusivity legislation, the Agency issued a 12 November 2002 Written Request to Johnson and Johnson, requesting that the company conduct a clinical study to examine the efficacy and safety of the oral contraceptive, ORTHO TRI-CYCLEN (0.180-0.250 mg norgestimate and 0.035 mg ethinyl estradiol), when used to treat low bone mineral density (BMD) in pediatric patients with anorexia nervosa. The requested study was a randomized, double-blind, placebo-controlled, 12-month study of female patients, aged 12 to < 18 years, with anorexia nervosa and below average BMD of the lumbar spine (LS). The Written Request required submission of 6-month data for granting of exclusivity.

The primary efficacy endpoint was a comparison between active and placebo treatment in the change from baseline to Month 6 in LS BMD. All subjects had a DSM-IV diagnosis of anorexia nervosa, had no contraindications to use of a hormonal oral contraceptive, and the majority had a baseline LS BMD Z-score

below average (i.e., Z < 0.0). The protocol allowed investigators to supplement patients with calcium and/or vitamin D.

2.2 Efficacy

A total of 123 patients were randomized to daily treatment with ORTHO TRI-CYCLEN or placebo: 61 to active treatment and 62 to placebo. The two groups were well matched for baseline characteristics. The average age of the patients was 15 years, 90% were Caucasian, the average duration of amenorrhea was 9.5 months, the average BMI was 17.5 kg/m^2, and the baseline LS BMD Z-score was approximately -0.80. Forty-nine ORTHO TRI-CYCLEN and 57 placebo patients completed 6 months of the study.

In the primary efficacy analysis, the mean change from baseline to Endpoint in LS BMD was 0.008 g/cm^2 in the placebo group and 0.018 g/cm^2 in the ORTHO TRI-CYCLEN group (p=0.041).

The mean percent change from baseline to Month 6 in LS BMD was 1.05% in the placebo group and 2.3% in the ORTHO TRI-CYCLEN group.

The mean percent change from baseline to Month 6 in total hip BMD was 0.4% in the placebo group and 1.3% in the ORTHO TRI-CYCLEN group.

The mean percent changes in LS bone mineral content from baseline to Endpoint in the ORTHO TRI-CYCLEN and placebo groups were 2.9% and 1.9%, respectively. The mean percent changes in hip bone mineral content from baseline to Endpoint in the ORTHO TRI-CYCLEN and placebo groups were 1.9% and 1.0%, respectively.

The mean change from baseline to Endpoint in body weight was 4.2 kg in the ORTHO TRI-CYCLEN group and 3.1 kg in the placebo group.

2.3 Safety

Eight subjects in the ORTHO TRI-CYCLEN group and 12 in the placebo group had at least one serious AE. The most commonly reported serious AE was anorexia nervosa: 3 in the active-drug group and 8 in the placebo group (this represents investigator's belief that the subject experienced a worsening of anorexia on-trial). In addition to anorexia, other serious AEs included depression, bradycardia, hypothermia, suicidal ideation, dehydration, pain, drug abuse, cachexia, urticaria, weight decrease. There were no meaningful differences between groups in the individual serious AEs reported.

There were no reports of venous thromboembolic events during the first 6 months of the study.

Three ORTHO TRI-CYCLEN and no placebo subjects withdrew prematurely from the trial due to an adverse event.

In general, the incidence of adverse events was low and similar in both treatment groups. Twenty-five percent of ORTHO TRI-CYCLEN and 36% of placebo patients complained of at least one psychiatric adverse event. Like serious AEs mentioned above, the largest between-group difference was observed for anorexia nervosa, with more placebo than ORTHO TRI-CYCLEN subjects reporting a worsening of the underlying condition. Dysmenorrhea was reported by 15% of the ORTHO TRI-CYCLEN subjects and none of the placebo subjects.

There were no clinically-meaningful differences between treatment groups in changes in routine laboratory parameters or vital signs.

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