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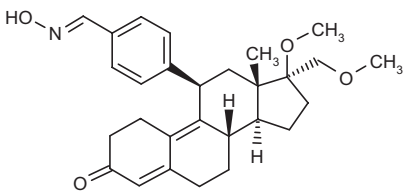
Asoprisnil

Prop INN; USAN

Endometriosis Therapy
Treatment of Uterine Fibroids
Selective Progesterone Receptor Modulator

J-867

11β-[4-[(*E*)-Hydroxyiminomethyl]phenyl]-17β-methoxy-17α-(methoxymethyl)estra-4,9-dien-3-one



$C_{28}H_{35}NO_4$
Mol wt: 449.5818

CAS: 199396-76-4

EN: 223488

Abstract

The development of selective progesterone receptor modulators (SPRMs) resulted from a program focused on the discovery of compounds which could interact with the progesterone receptor without inducing the side effects of progesterone agonists and antagonists. The goal was to identify agents with antiproliferative effects on the endometrium and breast, without interfering with ovarian estrogen secretion and its protective effects on bone and the cardiovascular system. In the course of the drug discovery program, the progesterone receptor binding affinity and agonist and antagonist activity of a number of compounds were tested and compared to those of progesterone antagonists. In these experiments, asoprisnil demonstrated the greatest progesterone-agonist effects and the lowest progesterone-antagonist effects; it is now the SPRM furthest along in clinical development. In phase II clinical trials in patients with uterine fibroids, once-daily oral asoprisnil was found to reduce the size of fibroids and decrease symptoms, while controlling excessive bleeding. Adverse events were mild and estradiol levels unaffected. The agent is currently undergoing phase III investigation in patients with uterine fibroids. In another phase II study, asoprisnil demonstrated efficacy in reducing nonmenstrual pelvic pain and dysmenorrhea in women with endometriosis and was well tolerated.

Synthesis

Asoprisnil can be prepared by several ways:

1) Protection of 4-bromobenzaldehyde (I) with triethyl orthoformate in MeOH affords the bromo ketal (II), which is converted to the corresponding Grignard reagent (III) with magnesium in THF. Conjugate addition of compound (III) to the steroid epoxide (IV) in the presence of CuCl in THF affords the 11β-aryl-steroid (V). Introduction of a 17-spiro oxirane moiety into the ketone (V) by reaction with the sulfur ylide generated from trimethylsulfonium iodide and potassium *tert*-butoxide in DMSO, yields the spiro steroid (VI). Subsequent epoxide opening in (VI) with NaOMe results in the methoxy alcohol (VII), which is further alkylated with iodomethane under Williamson's ether synthesis conditions to provide the dimethoxy derivative (VIII). Acid hydrolysis of both ketal groups of compound (VIII) with concomitant alcohol dehydration gives the dienone (IX). The aldehyde function of (IX) is finally converted to the target oxime by treatment with hydroxylamine hydrochloride in pyridine (1). Scheme 1.

2) Reaction of 3,3-dimethoxy-5α,10α-epoxyestra-9(11)-en-17-one (IV) with trimethylsulfonium iodide and *t*-BuOK in DMSO as before gives the spiranic epoxide (X), which is opened by means of NaOMe in MeOH to yield the 17β-hydroxy-17α-(methoxymethyl) derivative (XI). Methylation of the hydroxy group of (XI) by means of methyl iodide and *t*-BuOK in toluene affords the 17β-methoxy derivative (XII), which is submitted to a Grignard condensation with the protected 4-bromobenzaldehyde (XIII) and Mg in THF to provide the adduct (XIV). Hydrolysis of both ketal groups of compound (XIV) with concomitant alcohol dehydration with TsOH in *t*-BuOMe affords the dienone (IX), which is finally treated with hydroxylamine in pyridine as before (2, 3). Scheme 2.

Introduction

Understanding the role of progesterone in human reproduction and the discovery of the progesterone

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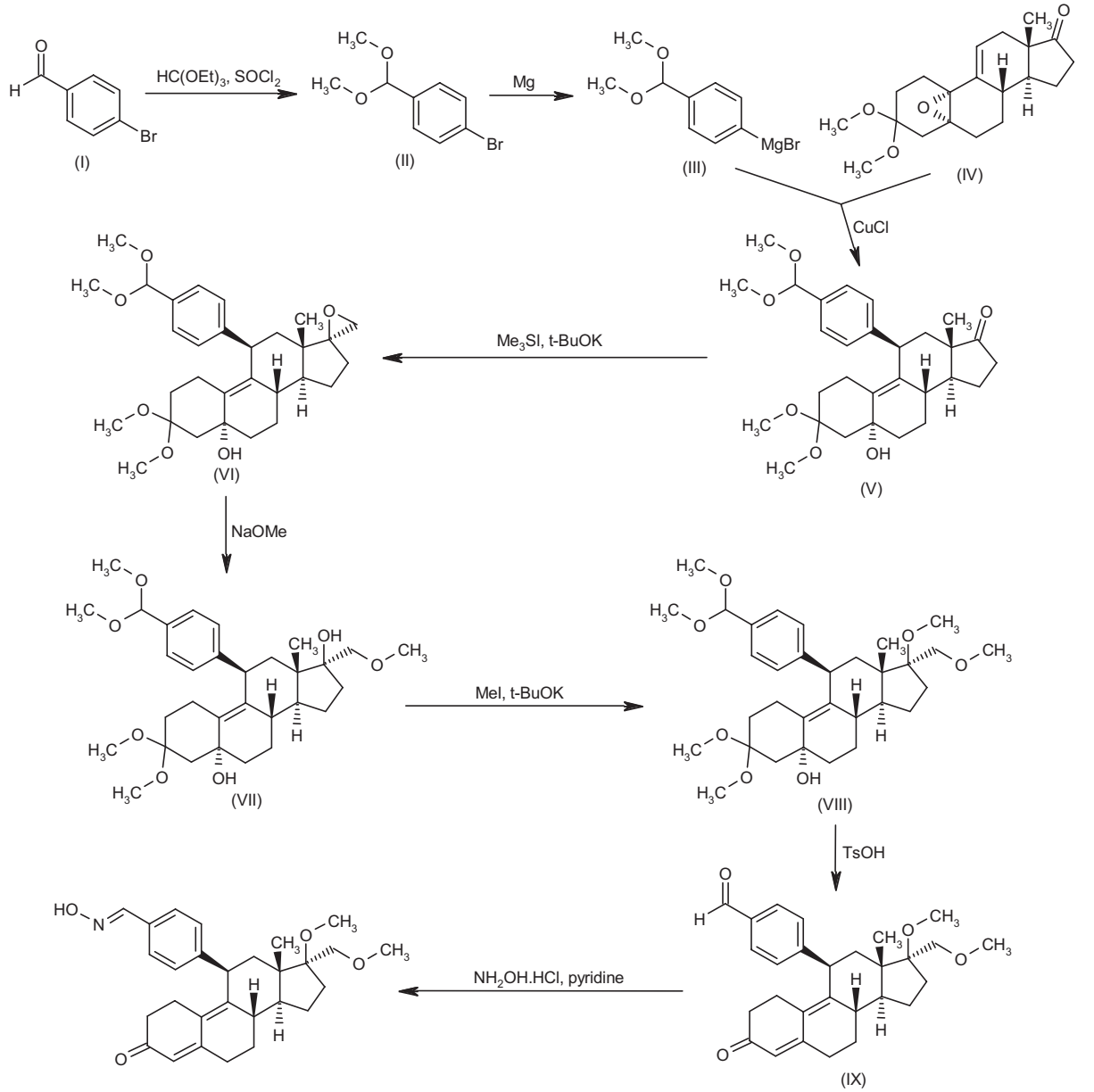
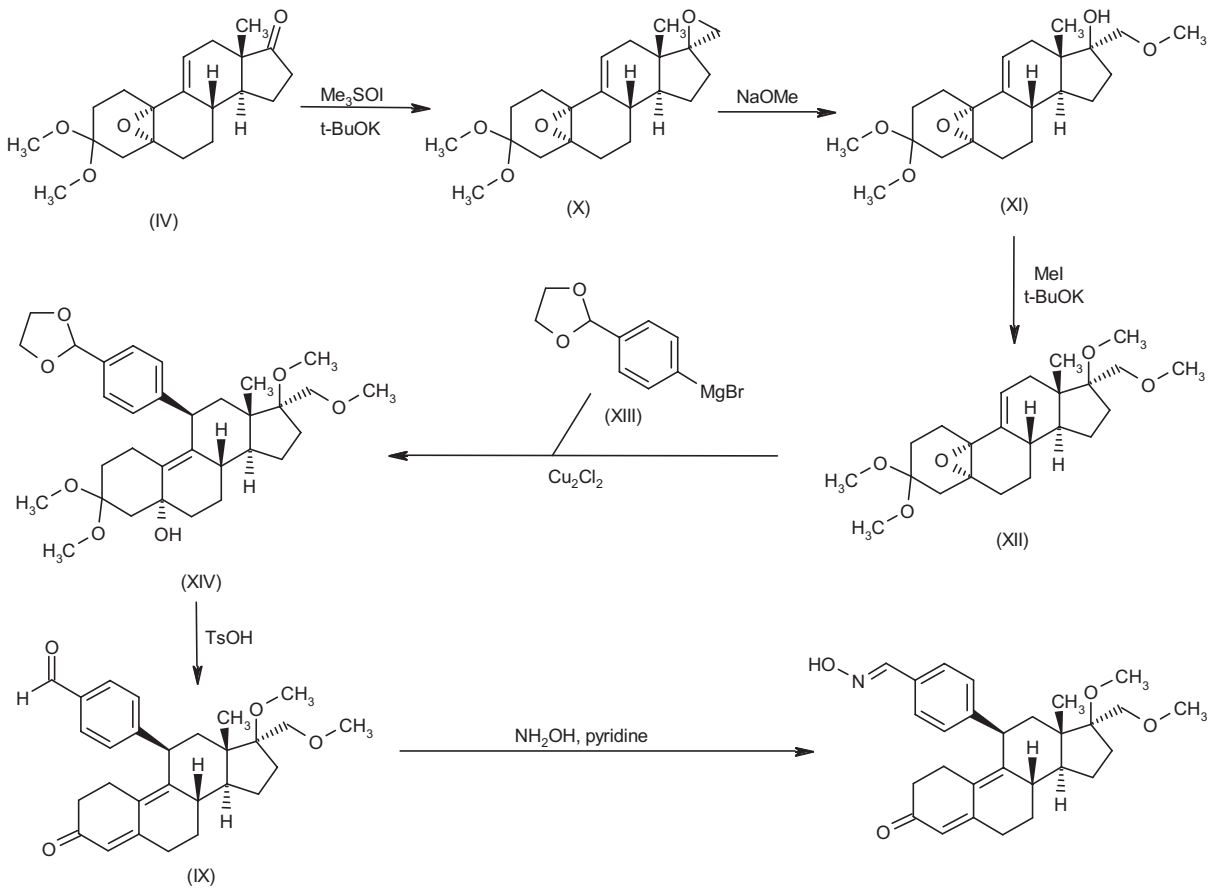
Scheme 1: Synthesis of Asoprisnil



receptor (PR) resulted in tremendous interest in the modulation of progesterone for therapeutic purposes. The effects of progesterone are varied and include differentiation of the endometrium, control of ovulation and implantation, and suppression of uterine contractility in the later stages of pregnancy (4-6). Interaction with the PR has been investigated with the development of PR agonists, or progestins, and PR antagonists. Progestins are widely used in oral contraceptives and have been used to treat endometriosis and abnormal uterine bleeding, as well as other gynecological disorders. Their long-term use, however, is complicated by side effects and an increased risk of breast cancer in postmenopausal women also receiving estrogen therapy (4, 7, 8). The introduction of mifepristone, a PR and glucocorticoid receptor (GR) antagonist used for postcoital contraception and pregnancy termination, spurred increased interest in PR antagonists, with efforts concentrated on increasing progesterone-antagonist activity and reducing antiglucocorticoid activity. Researchers also maintained the goal of harnessing the beneficial effects of progestins and PR antagonists, such as antiproliferative activity in the endometrium and breast, without altering the effect of estrogen on bone and the cardiovascular system (4, 5, 7).

Scheme 2: Synthesis of Asoprisnil



Uterine fibroids, or leiomyomata, are benign smooth muscle tumors originating from the uterine myometrium which are seen in 25-50% of women of reproductive age. They are a cause of abnormal uterine bleeding, for which patients often seek treatment, and pressure-related symptoms. Hysterectomy is the standard treatment for uterine fibroids, as there are no pharmacological treatments available for long-term use to reduce the size of fibroids. Evidence that progesterone and the PR are involved in uterine fibroid growth and development has been accumulating (9-11).

Endometriosis, or the development of endometrial tissue outside the uterus, results in pain (dysmenorrhea, noncyclic pelvic pain, dyspareunia) in 10-15% of women of reproductive age and is also associated with infertility. For treatment, gonadotropin-releasing hormone (GnRH) agonists or antagonists are prescribed to block ovarian estrogen secretion, or progestins or androgenic progestins are administered to inhibit estrogenic stimulation of the ectopic endometrium. Severe side effects have been seen with these treatments, however, including the hypoestrogenic state induced by GnRH antagonists, breakthrough bleeding and mood alterations with progestins, and acne, hirsutism and voice changes with androgens (4, 12).

The objective of obtaining compounds possessing only the beneficial effects of progestins and PR antagonists was pursued in a drug development program at EnTec and JenaPharm (Schering AG), resulting in the synthesis of 11β-benzaldoxime-substituted steroidal compounds with high PR affinity, lower GR affinity than mifepristone and mixed progesterone-agonist/antagonist activity *in vivo*. These agents are known as selective progesterone receptor modulators (SPRMs). 11β-Benzaldoxime-substituted SPRMs created during the drug development program were tested for their binding affinities for steroid receptors in cell-free systems and for their progesterone-agonist and -antagonist effects in animal models. Of all the SPRMs studied, asoprisnil (J-867) demonstrated high affinity for the PR and lower affinity for the GR, as well as the greatest progesterone-agonist effects and the lowest progesterone-antagonist effects (4, 13, 14). Asoprisnil is the first SPRM to reach an advanced stage of clinical development and is in phase III evalua-

tion for the treatment of symptomatic uterine fibroids and phase II investigation for endometriosis (15).

Pharmacological Actions

In receptor binding assays, the strongest binding to the progesterone receptor was observed with mifepristone, asoprisnil ecamate and asoprisnil (relative binding affinity [RBA; progesterone = 100%] = 506%, 345% and 299%, respectively), while the binding of the latter two compounds to the glucocorticoid receptor was much reduced compared to mifepristone (RBA [dexamethasone = 100%] = 685%, 154% and 77%, respectively, for mifepristone, asoprisnil ecamate and asoprisnil)). Neither asoprisnil nor J-912, its major metabolite, bind to estrogen or mineralocorticoid receptors and they exhibit low affinity for the androgen receptor (13, 16). Progesterone receptor binding affinities were not always predictive of pharmacodynamic effects in animal studies, however, although GR binding affinities were predictive of antiglucocorticoid effects *in vivo* (13).

In the McPhail assay for progesterone-agonist and -antagonist activities, rabbits were treated with estradiol benzoate and progesterone-like effects or antagonism of effects induced by exogenous progesterone were scored on a scale of 0-4. Asoprisnil 0.03-30 mg/day s.c. demonstrated partial agonist activity, as demonstrated by a dose-dependent increase in McPhail scores in the absence of progesterone, but not to the extent of progesterone itself. Scores were significantly increased at a dose of 0.1 mg/day s.c. and the maximum effect of asoprisnil was a score of 3.2 achieved with a dose of 10 mg/day s.c. The score was reduced to 1.9 with an asoprisnil dose of 100 mg/day. Asoprisnil likewise displayed partial antagonism, dose-dependently (0.03-30 mg/day s.c.) lowering scores in the presence of progesterone, but not to the extent of mifepristone (13, 16, 17).

The progesterone receptor-agonist and -antagonist effects of asoprisnil were also evaluated by examining luteolysis in cycling guinea pigs treated on days 10-17 of the estrous cycle. Onapristone, and to a lesser extent mifepristone, inhibited luteolysis, but asoprisnil did not inhibit luteolysis even at the highest dose tested (6 mg/day s.c.). Asoprisnil also inhibited ovulation and exhibited antiproliferative effects on the uterus and vagina, similar to progestins (13, 16, 18).

Asoprisnil and mifepristone dose-dependently inhibited implantation in rats treated on days 5-7 of pregnancy. Both agents afforded 100% inhibition at oral doses of 3 mg/day, although subcutaneous asoprisnil achieved 100% inhibition at a lower dose (1 mg/day) than subcutaneous mifepristone (3 mg/day) (16).

A small-animal model of human pregnancy and parturition, mid-term (43-44 days *post coitum*) and preterm (60 days *post coitum*) guinea pigs, was also used to assess the labor-inducing effects of asoprisnil relative to other agents. In mid-term animals, asoprisnil (3, 10, 30 and 100 mg/day s.c.) demonstrated marginal, non-dose-dependent labor-inducing properties, with less than half of the animals going into labor on the highest dose. Treatment of pregnant guinea pigs towards the end of their pregnancies with asoprisnil 1 and 10 mg had no labor-inducing effects (13, 16, 17).

Some, but not all, progesterone antagonists have been found to induce endometrial atrophy and amenorrhea in intact and ovariectomized estrogen-substituted monkeys. Asoprisnil induced amenorrhea, endometrial atrophy and stromal compaction in a 39-week study in sexually mature cynomolgus monkeys. Asoprisnil was administered by oral gavage at doses of 7.5, 15, 30 and 60 mg/kg/day during the early part of the study, followed by 20, 60, 160 and 480 mg/kg/day afterwards due to a change in vehicle. The effect of asoprisnil on the endometrium did not increase with dose. Serum estradiol concentrations declined to early proliferative levels, and serum progesterone concentrations in the luteal phase were significantly reduced compared to controls. All asoprisnil doses led to a halt in menstrual cyclicity after 2-3 weeks of treatment (16).

In ovariectomized Wistar rats treated with asoprisnil or J-912, no vaginal cornification, and thus no estrogenic activity, was seen. Rats treated with estradiol 0.1 μg/day had increased uterine weights, an effect partially blocked by doses of asoprisnil and J-912 of 10 mg s.c., indicating that the compounds have some antiestrogenic activity (16).

Asoprisnil and J-912 also demonstrated weak partial androgen-agonist/antagonist effects in castrated male rats treated subcutaneously for 7 days. High doses of the agents were found to induce a small increase in prostate weight, while high doses only slightly reduced the growth-inducing effects of testosterone (0.1 mg) (16). Asoprisnil (1, 3, 10 and 30 mg/day s.c. or p.o.) did not demonstrate significant glucocorticoid activity in immature rats, as determined by decreases in thymus weights. Some antiglucocorticoid activity was seen in rats and monkeys, although to a lesser extent than with mifepristone (16).

Experiments were conducted to compare the effects of asoprisnil, J-912 and mifepristone on progesterone receptor-mediated activation of progesterone-responsive target genes. In T47D breast cancer cells, asoprisnil demonstrated 1.9-fold stimulation of an MMTV reporter gene in the absence of progesterone, compared to 125-fold stimulation by progesterone. J-912 and mifepristone, however, repressed reporter gene activity to well below basal expression levels. The three compounds inhibited progesterone-induced gene activation, with asoprisnil having the weakest effect. Similar results were obtained when expression of the endogenous progesterone receptor target gene *sgk* (serum and glucocorticoid-responsive kinase) was assessed in T47D cells. The effects of the compounds on progesterone receptor recruitment of p160 coactivator complexes were also determined in T47D cells with endogenous *sgk* and a stable integrated MMTV promoter. Recruitment of p160 was strongest with progesterone, less pronounced with asoprisnil and not seen with mifepristone (19).

The potential for treating uterine myomas was supported by experiments where asoprisnil was found to

inhibit proliferative activity and stimulate apoptosis in cultured leiomyoma cells but not in cultured normal myometrial cells (20).

Pharmacokinetics and Metabolism

The absorption and excretion of oral and intravenous asoprisnil were assessed in Sprague-Dawley rats, CD-1 mice and cynomolgus monkeys which received radiolabeled drug at a dose of approximately 5 mg/kg. In rats and mice, most of the radioactivity was excreted within 24 h, and most of the radioactivity was excreted within 48 h in monkeys following both intravenous and oral dosing. Most of the radioactivity was recovered in feces in rats, mice and monkeys, regardless of gender and with both dosing routes. Urinary excretion was low in rats and higher in mice and monkeys. In bile duct-cannulated animals, biliary excretion was 84.6-86.6% of the intravenous dose and 77.9-81.2% of the oral dose in rats, 35.6-64.0% of the intravenous dose and 23.6-54.5% of the oral dose in mice and 80.1-84.8% of the intravenous dose and 15.7-41.6% of the oral dose in monkeys (21).

Asoprisnil was found to be extensively metabolized in mice, rats, dogs, guinea pigs, monkeys and human liver microsomes. J-912, the major cytochrome P-450-dependent metabolite, results from 17β-*O*-demethylation. In animals and humans, plasma concentrations of J-912 were higher than those of asoprisnil, the difference in humans being 5-fold. The parent drug and J-912 have similar elimination half-lives of approximately 4-5 h (22, 23).

Clinical Studies

Asoprisnil, at doses of 10 mg/day or more given for 1 month, reversibly and dose-dependently suppressed menstruation irrespective of effects on luteal phase serum progesterone concentrations indicative of luteinization in healthy volunteers with regular menstrual cycles included in a phase I study. The study included 60 healthy cycling women 18-45 years of age who received placebo or asoprisnil 5, 10 or 25 mg once daily or 5, 25 or 50 mg b.i.d. for 28 days starting at the beginning of the menstrual cycle. The suppression of progesterone to levels indicative of the absence of luteinization was seen in 7 of 8 women given the highest dose, but was inconsistent at lower doses. The treatment did not induce breakthrough bleeding, basal estrogen concentrations were unaltered and no antiglucocorticoid effects were seen. Endometrial biopsies revealed effects in line with mixed progesterone-agonist/antagonist activity and characterized by weakly secretory glands with little or no proliferation and effects on stroma varying from stromal compaction to focal predecidual reaction. These results indicated that the effects of asoprisnil on menstruation were largely due to its effect on the endometrium. The treatment was generally well tolerated, with a similar adverse event rate seen in placebo- and asoprisnil-treated patients. The most common events were mild headache, abdominal pain, nausea, dizziness and metrorrhagia (4, 24).

Asoprisnil was safe, well tolerated and did not prolong the Q-T interval in healthy female subjects given doses of 25 or 100 mg in a randomized, crossover study. Study subjects (n=70) received placebo, asoprisnil and moxifloxacin 400 mg with 4-day washout periods between doses. Mean maximum postdose corrected Q-T interval values were 418.8, 416.4, 418.5 and 434.3 ms, respectively, with placebo, asoprisnil 25 mg, asoprisnil 100 mg and moxifloxacin 400 mg. Q-T interval increases of 30 m or more from baseline occurred in 7%, 7%, 10% and 56% of subjects in these groups, respectively. Adverse events were noted in 21%, 14%, 16% and 24% of subjects, respectively, and mild nausea was the most common drug-related event (25).

The efficacy of asoprisnil in patients with uterine fibroids was evaluated in a randomized, double-blind phase II study. Study subjects were treated with placebo or asoprisnil 5, 10 or 25 mg p.o. once daily for 12 weeks beginning during the first 4 days of the menstrual cycle. The two higher doses were associated with reductions in uterine volumes and the volume of the largest leiomyoma, with a maximum decrease of 36% at the highest dose at week 12. These doses also reduced symptoms (bloating and pelvic pressure) and suppressed the duration and intensity of normal and abnormal uterine bleeding without inducing unscheduled bleeding. The highest dose induced amenorrhea in over 80% of subjects, and suppression of bleeding was seen in women with and without menorrhagia at baseline. Asoprisnil also increased hemoglobin concentrations compared with placebo. The drug did not reduce ovarian estrogen production and did not increase serum concentrations of cortisol or dehydroepiandrosterone sulfate, confirming the lack of antiglucocorticoid activity. The study drug was well tolerated and adverse events were mild, self-limiting and similar to those seen in the placebo group (4, 26-28).

The potential of asoprisnil to treat pain associated with endometriosis was examined in two randomized, dose-finding phase II studies. In one study, 130 patients with a laparoscopic diagnosis of endometriosis and moderate to severe pain received placebo or asoprisnil 5, 10 or 25 mg for 12 weeks. Daily pain was graded on a 4-point scale in patient diaries. Analysis of the data showed that all doses of asoprisnil significantly reduced mean daily combined nonmenstrual pelvic pain/dysmenorrhea scores at all treatment months compared with placebo. The mean reduction in pain scores during month 3 was approximately 0.5 with each asoprisnil dose compared to < 0.1 with placebo. Similar pain reductions were seen when nonmenstrual pelvic pain and dysmenorrhea were assessed separately. While the effects on pain were not dose-dependent, amenorreha was induced in 0%, 50%, 71% and 93% of patients on placebo, 5, 10 and 25 mg asoprisnil, respectively. Another phase II study compared placebo and lower asoprisnil doses (0.5, 1.5 and 5 mg) over 12 weeks. Here, the highest dose was found to be the minimum effective dose for pain relief. In both studies,

asoprisnil was well tolerated, with mostly mild and self-limiting adverse effects. No serious drug-related adverse effects were noted (4, 29).

Source

Schering AG (DE).

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