INVEGA® (paliperidone ER)
Adverse Event of INVEGA - Prolactin Effects

SUMMARY

- Similar to other drugs that antagonize dopamine D_2 receptors, paliperidone elevates prolactin levels and the elevation persists during chronic administration.[1]
- Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male subjects. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans, but the available evidence is too limited to be conclusive.[1]
- In 2 double-blind, randomized, 6-week, placebo-controlled studies of adult patients with schizoaffective disorder, prolactin concentrations increased in all paliperidone extended-release (ER) dose groups from baseline to endpoint.[2,3]
- In the pooled data from 3 pivotal, placebo-controlled, 6-week, fixed-dose studies,[4-6] potentially prolactin-related adverse events were reported by 1-2% of patients in the placebo and INVEGA 3, 6, 9, and 12 mg groups. The incidence was 4% in the INVEGA 15 mg group. Prolactin concentrations increased in all INVEGA dose groups from baseline to endpoint.[7]
- Results from a phase 1 study showed that both INVEGA or paliperidone immediate-release formulations and risperidone elevated prolactin levels to a similar extent following administration of single and multiple doses, with no meaningful differences between the groups.[8]
- According to a mechanistic pharmacokinetic/pharmacodynamic model, the recommended 6 mg/day dose of INVEGA will result in an approximate 2.5-fold increase in prolactin concentration from baseline.[9]

PRODUCT LABELING

Please refer to the following sections of the enclosed Full Prescribing Information[1] that are relevant to your inquiry: WARNING AND PRECAUTIONS, CONTRAINDICATIONS and ADVERSE REACTIONS.

BACKGROUND

Prolactin is a 199-amino acid polypeptide hormone that is secreted by the lactotroph cells in the anterior pituitary under the inhibitory control of D_2 receptors. Many antipsychotics, conventional and atypical, which block dopamine receptors in the tuberoinfundibular pathway of the hypothalamus, can increase prolactin secretion.[10,11]

Paliperidone has a prolactin-elevating effect similar to that seen with risperidone, a drug that is associated with higher levels of prolactin than other antipsychotic drugs.[8]

Long-standing hyperprolactinemia, when associated with hypogonadism, may lead to decreased bone density in both female and male subjects.[1,12] In the absence of hypogonadism, there is a lack of consistent evidence to establish whether antipsychotic-induced hyperprolactinemia is an independent risk factor for bone loss and osteoporosis.[12] While individuals with schizophrenia are known to have an increased risk for low bone mineral density and osteoporosis, prospective clinical trials to differentiate between etiological mechanisms and effects of disease and treatment have not been conducted.

Management of Hyperprolactinemia

Asymptomatic hyperprolactinemia

Most guidelines recommend against treating asymptomatic hyperprolactinemia induced by antipsychotics.[10]

Symptomatic hyperprolactinemia

The recommendations for the management of symptomatic hyperprolactinemia may include, reducing the dose of the prolactin-raising agent, switching to a low potency or prolactin-sparing agent, adding a full or partial dopamine agonist, or discontinuing the prolactin-elevating agent. Treatments noted with various degrees of support include aripiprazole, cabergoline, bromocriptine, amantadine, estrogen or testosterone, and metformin.[10,11,13]

Two separate algorithms, specific to male and female patients for the management of hyperprolactinemia, are also described in the publication.[10]

Concomitant use with aripiprazole

If aripiprazole monotherapy is not achievable, it may be considered as a substitute or in combination with the primary antipsychotic; however, caution should be exercised when combination therapy is utilized as the primary antipsychotic's efficacy might be reduced due to partial agonism by aripiprazole at D_2 receptors, leading to competitive receptor occupancy.[10]

PHARMACOKINETIC/PHARMACODYNAMIC MODEL

Friberg et al (2009)[9] presented a mechanistic, population pharmacokinetic/pharmacodynamic model describing the concentration-time profiles of prolactin after administration of different formulations of risperidone and paliperidone. Data from 1462 subjects (9022 prolactin concentrations) contributed to the model. The modeling process accounted for and evaluated the following: 1) the competition between risperidone or paliperidone and dopamine for the D_2 receptors that regulate prolactin release 2) the diurnal rhythm of the prolactin release rate 3) the drug concentration effect on stimulating the release of prolactin 4) tolerance development through a feedback loop with prolactin stimulating dopamine release. Other structural covariates evaluated included the higher prolactin levels found at baseline in female subjects.

The recommended dose of INVEGA (6 mg/day) will result in an approximately 2.5-fold increase in prolactin concentrations from baseline, regardless of gender. Use of this model concluded that there was no indication that paliperidone has a higher potency to stimulate prolactin release than risperidone. The model also predicted that a continuous administration of 6 mg paliperidone in the ER OROS formulation would result in prolactin elevations lower than those seen after continuous treatment with 2 mg risperidone in an immediate-release formulation.

CLINICAL STUDIES

Published Double-blind Trials

Lead Author/Trial Design & Treatment	Prolactin Results
Savitz et al (2015)[14] conducted a 26-week, randomized, double-blind study evaluating the safety and efficacy of paliperidone ER vs aripiprazole in adolescents (ages 12-17 years) with	• The mean duration of exposure was 153.9 days for paliperidone ER (n=112; mean dose: 6.75 mg) patients and 154.9 days for aripiprazole (n=114; mean dose 11.56 mg) patients.

schizophrenia for ≥1 year and a PANSS total score of 60-120 at baseline. Patients (N=228) were randomized to flexibly-dosed paliperidone ER or aripiprazole for an 8-week double-blind acute phase followed by an 18-week double-blind maintenance period.	• Overall, mean serum prolactin levels increased in the paliperidone ER group and decreased in the aripiprazole group. Larger mean prolactin changes in females vs males receiving paliperidone ER were observed from baseline to day 182. • Prolactin-related treatment-emergent adverse events (TEAEs) were reported in 4.4% of paliperidone ER patients vs 0.9% of aripiprazole patients.
Rui 2014[15] conducted a multicenter, randomized, double-blind, placebo-controlled study to evaluate the long-term efficacy of paliperidone ER in preventing relapse in Chinese patients who had schizophrenia for at least 1 year. The study included an 8-week run-in phase (n=201), a 6-week stabilization phase (n=161), and a variable duration double-blind phase (n=136). Patients received paliperidone ER 3, 6, 9, or 12 mg/day or placebo.	• From run-in baseline to the end of the stabilization phase, prolactin levels increased by 25.6 mcg/L in males and 78.8 mcg/L in females. • In the double-blind phase, prolactin decreased to normal levels in the placebo group, but stabilized or gradually decreased in the paliperidone ER group. • Prolactin-related adverse events (AEs) during the double-blind phase included galactorrhea (n=1), amenorrhea (n=2), and irregular menstruation (n=1) in the paliperidone ER group and irregular menstruation (n=1) in the placebo group.
Berwaerts 2012[16] conducted a double-blind, placebo-controlled, parallel study consisting of a 3-week acute treatment phase (AC), a 12-week continuation phase (CT), and a maintenance phase. The study compared the potential of paliperidone ER and olanzapine to prevent recurrences in clinically stable patients diagnosed with bipolar I disorder (safety analysis set: AC/CT, n=762; maintenance, n=379). Patients received paliperidone ER 3 to 12 mg/day, olanzapine 5 to 20 mg/day, or placebo.	• Median duration of exposure for paliperidone ER, olanzapine, and placebo was 234 (102 during AC/CT phases), 433, and 154 days, respectively. • Median average doses were 6 mg/day for paliperidone ER and 10 mg/day for olanzapine. ***Mean prolactin changes from AC baseline to AC/CT endpoint (ng/mL)***: *Paliperidone ER males*: +22.37; *females*: +72.23 *Olanzapine males*: +1.11; *females*: -3.81 ***Mean prolactin changes from maintenance baseline to endpoint (ng/mL)***: *Placebo males*: -25.85; *females*: -84.96 *Paliperidone ER males*: -7.19; *females*: -5.55 *Olanzapine males*: -3.57; *females*: +1.25 ***Potentially prolactin-related treatment-emergent AEs***: *Paliperidone ER (AC/CT)*: n=32 (5%); *(maintenance)*: n=8 (galactorrhea, n=3; decreased libido and amenorrhea, n=2, each; irregular menstruation and erectile dysfunction, n=1 each) • Two paliperidone ER patients discontinued treatment. One due to sexual dysfunction in the AC/CT phases and 1 due to galactorrhea in the maintenance phase. *Olanzapine (AC/CT)*: n=5 (3%) *Placebo (maintenance)*: n=1 (breast pain)
Singh 2011[17] conducted a 6-week, randomized, double-blind, placebo-controlled study in adolescents (aged 12-17 years) with schizophrenia (n=201, safety analysis set). Patients were randomized to receive 1 of 3 weight-based doses of paliperidone ER (low, medium, or high) or placebo: **Low** (n=54): 29 to <51 kg: 1.5 mg; ≥51 kg: 1.5 mg	• Potentially prolactin-related AEs were reported in 3 patients (all in the medium-dose group): galactorrhea (n=2) and amenorrhea (n=1) • The mean increase in prolactin levels in the low-dose group was similar to that seen in the placebo group; mean increases were similar between the medium-dose and high-dose groups and higher than the increases seen in the placebo or the low-dose groups

Medium (n=48): 29 to <51 kg: 3 mg; ≥51 kg: 6 mg **High** (n=47): 29 to <51 kg: 6 mg; ≥51 kg: 12 mg	
Berwaerts 2011[18] conducted a 6-week, double-blind, randomized, multicenter, flexible-dose, placebo-controlled trial in patients with bipolar I disorder who experienced acute manic or mixed episodes (n=299, safety analysis set). Patients were randomized to continue mood stabilizer monotherapy or to receive paliperidone ER (flexible dose; 3-12 mg/day) in combination with ongoing treatment with mood stabilizers.	• Mean changes in prolactin levels (ng/mL): *Mood stabilizer monotherapy males*: -3.1; *females*: +7.8 *Combination therapy males*: +25.8; *females*: +80.5 • Percentage of patients with treatment-emergent prolactin levels above reference range (normal values: males, 2-19 ng/mL; females, 1-24 ng/mL): *Mood stabilizer monotherapy males*: 9%; *females*: 1% *Combination therapy males*: 80%; *females*: 68% • Potentially prolactin-related treatment-emergent AE (sexual dysfunction) was reported in 1 patient receiving combination therapy.
Canuso 2010a[2] conducted a 6-week, double-blind, randomized, placebo-controlled, parallel-group study in adult patients with schizoaffective disorder who experienced acute exacerbations (n=309, safety analysis). Patients were randomized to receive paliperidone ER or placebo • Paliperidone ER was initiated at 6 mg/day followed by flexible dosing thereafter (3-12 mg/day); doses were fixed after day 15 • Mean modal dose of paliperidone ER: 8.6 mg/day	• Mean prolactin change (ng/mL) from baseline to week 6: • *Placebo males*: -2.1; *Placebo females*: -16.2 • *Paliperidone ER males*: +14.2; *Paliperidone ER females*: +62.9 • Potentially prolactin-related AEs were reported in 6 patients (2.8%) and included galactorrhea (n=3), loss of libido (n=1), breast discharge (n=1), and sexual dysfunction (n=1) • One patient reporting a potentially prolactin-related AE did not have hyperprolactinemia
Canuso 2010b[3] conducted a 6-week, randomized, placebo-controlled, parallel-group study in adults with schizoaffective disorder who experienced acute exacerbations (n=313, safety analysis). • Patients were randomized to receive lower-dose paliperidone ER, higher-dose paliperidone ER, or placebo • Paliperidone ER dose groups (doses were fixed after day 15): Lower dose: 6 mg/day with an option to reduce to 3 mg/day Higher dose: 12 mg/day with an option to reduce to 9 mg/day • Mean modal dose of paliperidone ER: Lower dose: 5.7 mg/day Higher dose: 11.6 mg/day	• Mean prolactin change (ng/mL) from baseline to week 6: *Placebo males*: -4.8 *Placebo females*: -11.8 *Lower-dose paliperidone ER males*: +8.0 *Lower-dose paliperidone ER females*: +37.8 *Higher-dose paliperidone ER males*: +14.5 *Higher-dose paliperidone ER females*: +48.8 Percentage of patients who shifted from normal prolactin levels at baseline to high prolactin levels at week 6: *Placebo*: 6.7% *Lower-dose paliperidone ER*: 41.1% *Higher-dose paliperidone ER*: 43.8% • Potentially prolactin-related events occurred in 4 patients: anorgasmia (higher-dose paliperidone ER, n=1) anorgasmia and loss of libido (placebo, n=1) erectile dysfunction (lower-dose paliperidone ER, n=1) breast pain, and galactorrhea (higher-dose paliperidone ER, n=1)
Canuso 2010c[19] reviewed pooled data from 2 randomized, 6-week, placebo-controlled studies in adult patients with schizoaffective disorder who experienced	• Mean change in prolactin levels (ng/mL): *Placebo males*: -3.6; *Placebo females*: -13.9 *Paliperidone ER males*: +12.6; *Paliperidone ER females*: +51.4

acute exacerbations (n=622, safety analysis set)[2,3] See Canuso et al 2010a,b[2,3]	• Potentially prolactin-related events were reported in 9 paliperidone ER-treated patients (2.1%) and 1 placebo-treated patient (0.5%)
Berwaerts 2010[8] conducted a phase 1, 6-day, double-blind, randomized, parallel-group study in patients with stable schizophrenia comparing serum prolactin concentrations following paliperidone ER and risperidone administration; patients were previously treated with oral risperidone for at least 1 month before screening. Patients were randomized to 1 of 3 treatment groups: (1) placebo on day 1 and 12 mg paliperidone ER days 2-6; [Group 1 excluded from analysis; delay in exposure to paliperidone by 1 day may differentially affect the serum prolactin concentration-time profiles 5 days after initiation of double-blind study drug] (2) 12 mg paliperidone ER days 1-6 (n=38); (3) risperidone 2 mg on day 1 and 4 mg on days 2–6 (n=38).	• There was a mean increase in prolactin levels with both paliperidone ER and risperidone. However, the peak-trough variation of prolactin levels was lower in the paliperidone ER groups versus risperidone. Day 6: • The $AUC_{0\text{-}24h}$ for paliperidone ER was 1389 ng·h/ml and 1306 ng·h/ml for risperidone. The C_{max} (ng/mL) for prolactin in serum samples was 68.5 for paliperidone ER and 71.4 for risperidone. The mean t_{max} (hrs) was 16.6 for paliperidone ER and 8.9 for risperidone. No potentially prolactin-related AEs were reported. • Administration of paliperidone ER 12 mg/day and risperidone 4 mg/day over 6 days results in similar increases in prolactin concentration based on the $AUC_{0\text{-}24h}$.
Vieta 2010[20] conducted a multicenter, double-blind, randomized, placebo and active-controlled trial in patients with acute manic or mixed episodes associated with bipolar I disorder (n=491 safety analysis set; n=486 ITT analysis set [mean age: 39 years; 58% male]). ***Washout phase (1 week)*** ***Acute phase (3 weeks)***: (1) paliperidone ER 3-12 mg/day (n=195) (2) quetiapine 400-800 mg/day (n=193) (3) placebo (n=105) ***Maintenance phase (9 weeks)***: Active drug treatment continued while placebo patients were switched in a blinded fashion to flexibly dosed paliperidone ER. (1) paliperidone ER 3-12 mg/day (n=219) (2) quetiapine 400-800 mg/day (n=152)	• Mean duration of exposure and median mode dose (safety analysis set): *paliperidone ER*: 53 days; 9 mg (acute phase and 12 weeks) *placebo/paliperidone ER*: 38 days; 6 mg (12 weeks) *quetiapine*: 56 days; 600 mg (acute phase and 12 weeks) • Mean changes in serum prolactin from baseline to 3-week endpoint (ng/mL): *paliperidone ER*: +24.61 (males)/ +89.77 (females) *quetiapine*: -1.32 (males) / +0.3 (females) *placebo*: -1.03 (males) / +7.15 (females) • Paliperidone ER patients experienced a higher proportion of treatment-emergent prolactin levels outside the reference range compared to patients receiving either placebo/paliperidone ER or quetiapine (acute + maintenance phases). *paliperidone ER*: 63% (males) / 61% (females) *quetiapine*: 17% (males) / 16% (females) *placebo/paliperidone*: 30% (males) / 30% (females)
Meltzer 2008[7] conducted a pooled analysis of 3 similarly designed 6-week, double-blind, randomized, multicenter, fixed-dose, placebo-controlled studies in patients with an acute episode of schizophrenia (n=1682 safety analysis set)[4-6]. The 3 studies represented in this pooled analysis include Marder 2007 (n=439), Davidson 2007 (n=614), and Kane 2007 (n=629). Patients were randomized to placebo, paliperidone ER (3, 6, 9, 12, or 15 mg/day), or olanzapine 10 mg/day.	• Mean and median prolactin concentrations increased in all paliperidone ER dose groups from baseline to endpoint. The median increases in prolactin concentrations were 81 ng/mL and 24 ng/mL in female and male patients treated with paliperidone ER, respectively. The incidence of prolactin-related AEs was higher (4%) in the paliperidone ER 15 mg group. • Mean prolactin levels (baseline/endpoint; ng/mL): Placebo (pooled data) males: 13.3/12.5; females: 34.3/20.8 *Paliperidone ER 3 mg males*: 14.1/29.5; *females*: 53.6/115.7

Marder 2007: paliperidone ER 6 or 12 mg/day Davidson 2007: paliperidone ER 3, 9, or 15 mg/day Kane 2007: paliperidone ER 6, 9, or 12 mg/day	*Paliperidone ER 6 mg males*: 15.1/39.5; *females*: 32.3/105.2 *Paliperidone ER 9 mg males*: 17.6/45.3; *females*: 37.3/125.0 *Paliperidone ER 12 mg males*: 17.1/44.4; *females*: 31.7/127.9 *Paliperidone ER 15 mg males*: 17.5/52.8; *females*: 23.2/130.1 • Median prolactin concentrations generally peaked on day 15 and decreased slightly thereafter, although prolactin levels remained above the upper limit of normal at the endpoint (24.20 ng/mL in females; 18.77 ng/mL in males). • Marder 2007: Four patients (0.9%) experienced potentially prolactin-related AEs. Events experienced by the paliperidone ER 12 mg group (n=1 male; n=1 female) were nonpeurperal lactation and decreased libido. None of these events resulted in study discontinuation. • Davidson 2007: Prolactin-related (lactation and nonpuerperal) and potentially prolactin-related (anorgasmia, impotence, and decreased libido) treatment-emergent AEs were reported (n=3 males; n=3 females), but none of these events were considered severe or led to study discontinuation. • Kane 2007: Potentially prolactin-related AEs were reported by 1% of patients. These events occurred in 3 males (1 in each of the paliperidone ER groups) and 4 females (1 in each of the paliperidone ER groups and 1 in the olanzapine group) and resulted in 2 study discontinuations.
Kramer 2007[21] conducted a long-term, double-blind, randomized, multicenter, placebo-controlled trial to assess symptom recurrence in patients with an acute episode of schizophrenia. The study was terminated early on the basis of significant efficacy results as determined by a prespecified interim analysis after 43 recurrence events (n=206 safety analysis set). Two open-label phases (run-in 8 weeks, stabilization 6 weeks) preceded the double-blind phase (variable duration). During the double-blind phase, patients were randomized to placebo or paliperidone ER (flexible dose: 3, 6, 9, 12, or 15 mg/day).	***Double-blind phase results*** • The incidence of potentially prolactin-related AEs was 4% and 0% in the paliperidone ER and placebo groups, respectively. • There was a mean increase in prolactin levels with paliperidone ER, and mean prolactin levels decreased in the placebo group.
Tzimos 2008[22] conducted a 6-week, double-blind, randomized, multicenter, flexible-dose, placebo-controlled trial in elderly patients (≥65 years) with an acute episode of schizophrenia (n=114 safety analysis set). There was an optional, 24-week open-label extension during which all patients received paliperidone ER (n=88).	***Double-blind phase (paliperidone ER group)*** • % of patients with elevated prolactin levels: males, 45%; females, 49% • Mean prolactin concentrations generally peaked after 2 weeks (mean change: females, 75.3 ng/mL; males, 27.2 ng/mL) and decreased thereafter. Median prolactin levels at the double-blind endpoint remained above the upper limit of normal:

Patients were randomized to placebo or paliperidone ER 6 mg. After 7 days on paliperidone ER 6 mg/day, patients received flexible dosing of paliperidone ER 3-12 mg/day.	• *Females*: 85.3 ng/mL (range 10.0-458.2); *Males*: 32.0 ng/mL (range 12.0-165.6) ***Open-label phase*** • Median prolactin levels remained relatively stable for patients randomized to paliperidone ER but increased for patients randomized to placebo in the double-blind phase • There were no reports of potentially prolactin-related AEs throughout the entire study

Published Open-Label Trials

Lead Author/Trial Design & Treatment	Prolactin Results
Park et al (2016)[23] enrolled 245 patients, 49.4% male, maintained on one of six atypical antipsychotics for at least a 2-week period to evaluate prolactin/macroprolactin levels and atypical antipsychotics. Patients were on monotherapy and at a consistent dose during the 2-week period. Samples were collected at a single time point. The occurrence of hyperprolactinemia and related adverse events were recorded as well as prolactin/macroprolactin levels. Atypical antipsychotics included: aripiprazole, blonanserin, olanzapine, paliperidone, quetiapine, and risperidone.	• Mean total prolactin levels (ng/ml) were: aripiprazole 11.91; blonanserin 20.73; olanzapine 16.41; paliperidone 50.83; quetiapine 12.84; and risperidone 59.1 and macroprolactin levels ranged from 0.5-14.2 ng/ml • Mean prolactin and macroprolactin levels were significantly higher among patients on risperidone and paliperidone ($P<0.01$). • 35.5% of patients experienced prolactin-associated symptoms while 31.9% were asymptomatic • Prolactin levels did not differ significantly between those with and without prolactin-associated symptoms (26.89 vs 28.82 ng/ml) • Both male (32.2%) and female (38.7%) patients reported sexual dysfunction however prolactin levels did not differ significantly between patients with or without sexual dysfunction. • 30 female patients reported abnormal menstruation; 20 of these patients had prolactin levels within the normal range • Three male patients on risperidone or paliperidone reported gynecomastia and all three had hyperprolactinemia.
Savitz et al (2015)[24] conducted a 2-year, single-arm, open-label, flexible-dose study to evaluate the long-term safety and tolerability of paliperidone ER in adolescents (12-17 years of age) with schizophrenia. Participants may have either completed or discontinued from a 6-week, randomized, double-blind, placebo-controlled study[17] that preceded the open-label study or, if they had previously been adequately treated with an antipsychotic, they could be directly enrolled into the open-label study after a screening and washout phase of up to 3 weeks. Patients (N=400; directly enrolled, n=243; continuing from double-blind; n=157) began treatment with 6 mg of paliperidone ER. Doses could be subsequently titrated up or down in increments of 3 mg, after a minimum of 5 days at a given dose, to a	• Prolactin levels that were above normal occurred in a majority (60%) of males and in approximately half (48%) of females. • There were 37 reports (9.3%) of potentially prolactin-related TEAEs, mostly of mild to moderate severity; the most common of these events were galactorrhea (4% overall) and amenorrhea (5% of girls). • Other prolactin-related adverse events included breast hypertrophy/gynecomastia, breast discharge and pain, hyperprolactinemia, decreased libido, erectile dysfunction, and irregular menstruation. • Increases in prolactin levels were seen early in treatment, with later stabilization.

maximum of 12 mg/day or a minimum of 1.5 mg/day.	
Amatniek 2014[25] conducted a multicenter, single-sequence crossover study evaluating the safety and efficacy in outpatients (≥18 years old) with schizophrenia or schizoaffective disorder and stable hepatic illness (e.g. viral hepatitis, alcohol cirrhosis) with Child-Pugh scores of well-compensated (class A) to functionally compromised (class B) hepatic illness (Child-Pugh score <10). Patients (n=84) were maintained on their usual antipsychotic treatment (UAT) for 4 weeks (phase 1) followed by a 1-week cross-titration phase and 4 weeks of paliperidone ER (phase 2). The initial dose during the titration phase was 6 mg/day. Paliperidone ER was flexibly dosed within a range of 3-12 mg/day.	• Mean prolactin change from paliperidone ER baseline to endpoint: 21.3 ng/mL • One (1.2%) TEAE (increase in serum prolactin level) was reported during the 4-week UAT while 3 (3.6%) AEs were reported during treatment with paliperidone alone and none during cross titration.
Hu 2013[26] conducted a 12-week, open-label, parallel-group study of patients aged 18-45 years diagnosed with schizophrenia (n=80). Patients were randomized into 2 groups (flexibly dosed paliperidone ER [n=40] or olanzapine [n=40]). Mean doses of paliperidone ER and olanzapine were 7.55 mg/day and 15.87 mg/day, respectively.	Mean prolactin levels (mcg/L): • Baseline: paliperidone ER (25.98), olanzapine (21.42); *P*=0.454 • 4 weeks: paliperidone ER (52.90), olanzapine (23.54); *P*=0.005 • 8 weeks: paliperidone ER (50.26), olanzapine (26.52); *P*=0.004 • 12 weeks: paliperidone ER (55.00), olanzapine (26.55); *P*=0.001
Kim 2013[27] conducted a 48-week, open-label, prospective study of patients aged 18-65 years diagnosed with schizophrenia who were previously on any oral antipsychotic for at least 2 weeks before trial initiation (n=184). Patients were stratified based on previous antipsychotics received (Risperidone or non-risperidone group). Patients received paliperidone ER 3 to 12 mg/day. Previous oral antipsychotic medications were immediately discontinued or tapered down over a 4-week period. Mean doses of paliperidone ER at endpoint: • Risperidone patients (n=91): 8.3 mg/day • Non-risperidone patients (n=93): 8.7 mg/day	Baseline prolactin levels (pmol/L): • Risperidone patients: 1360.9 (males), 3947.8 (females) • Non-risperidone patients: 987.0 (males), 2178.2 (females) Mean change in prolactin levels from baseline to endpoint (pmol/L): • Patients switching from risperidone: +30.4 (males), -117.4 (females) • Patients switching from other oral antipsychotics: +39.1 (males), +1578.3 (females)
Kim 2012[28] conducted a 24-week, open-label study evaluating the subjective well-being and attitudes toward antipsychotic medication in patients with schizophrenia switched to paliperidone ER (N=243; mean age: 36.4 years; 52.7% female). • All patients received flexibly dosed paliperidone ER (3-12 mg/day).	• Mean doses of paliperidone ER at endpoint and week 24 were 8.4 mg/day and 9.2 mg/day, respectively. • Previous antipsychotics included: risperidone (46.9%), olanzapine (12.3%), amisulpride (11.9%), aripiprazole (9.5%), haloperidol (6.2%), ziprasidone (4.9%), quetiapine (4.5%) and others (3.7%) • Of the patients whose serum prolactin levels were measured at least once following the switch to paliperidone ER, 73.6% (n=78) presented with

• During the first 4 weeks of the study, paliperidone ER doses were initiated at 6 mg/day and adjusted at the discretion of the investigator while previous antipsychotics were tapered off. • Concomitant medications included as-needed anticholinergics, propranolol, and/or hypnotics in addition to, antidepressants and mood stabilizers which had been used for >1 month before enrollment.	hyperprolactinemia (>25 ng/mL). However, prolactin levels did not change significantly compared to baseline.
Kramer 2010[29] conducted a 52-week, open-label extension (OLE) evaluating the long-term safety and tolerability of paliperidone ER in adults (N=235) with schizophrenia All enrolled patients participated in a prevention of symptom recurrence study.[21] Paliperidone ER was initiated at 9 mg/day with flexible dosing thereafter (3-15 mg/day). Continued use of certain antidepressants if the dose was stable	• Potentially prolactin-related treatment-emergent AEs were amenorrhea (n=12) and irregular menstruation (n=1) • One patient discontinued treatment due to amenorrhea • Median prolactin levels increased in the group of patients who received placebo during the double-blind phase of the study • Median prolactin levels remained stable or decreased in patients who entered the OLE from the run-in phase and in those who received paliperidone ER during the double-blind phase
Emsley 2008[30] pooled data from 3 52-week, multicenter, OLE studies of 3 6-week, double-blind studies[4-6] in patients with schizophrenia (N=1083). All patients received flexibly dosed paliperidone ER (3-15 mg/day) The starting dose of paliperidone ER was 9 mg/day.	• Mean change in prolactin levels (ng/mL) during the OLE (grouped according to previous treatment): ○ *paliperidone ER/paliperidone ER*: -23.97 (females); -5.16 (males) ○ *placebo/paliperidone ER*: +92.14 (females); +27.5 (males) ○ *olanzapine/paliperidone ER*: +78.8 (females); +20.1 in (males) • Potentially prolactin-related AEs: *irregular menstruation*: 5% of females (placebo/paliperidone ER group) *erectile dysfunction*: 3% of males (olanzapine/paliperidone ER group) *amenorrhea*: 4% of females in all groups • All other prolactin-related AEs: ≤1%

OTHER RELEVANT LITERATURE

Several additional publications[31-37] and case reports[38-46] are cited for your reference.

LITERATURE SEARCH

A literature search of MEDLINE®, EMBASE®, BIOSIS Previews®, and DERWENT Drug File (and/or other resources, including internal/external databases) pertaining to this topic was conducted on 22 April 2024.

REFERENCES

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