אפריל 2023

רופא/ה נכבד/ה

רוקח/ת נכבד/ה

Prozac 20 mg

פרוזק 20 מ"ג

חברת אלי לילי ישראל בע"מ מבקשת להודיעכם על אישור משרד הבריאות להתוויה חדשה ושינוי משטר מינון עבור המוצר שבנידון.

בהודעה זו מצוינים רק השינויים בהתוויה או במשטר המינון. כמו כן, מצוינים סעיפים בהם נעשו שינוים המהווים החמרה.
קיימים עדכונים נוספים.

טקסט שהתווסף מסומן בכחול ומידע שהוסר מסומן באדום.

העלונים המעודכנים לרופא ולצרכן מפורסמים במאגר התרופות שבאתר משרד הבריאות וניתן לקבלם מודפסים על ידי פנייה לבעל הרישום:

אלי לילי ישראל בע"מ, רח' השיזף 4, רעננה , טל': 09-9606234

בברכה,

הדס השכל
רוקחת ממונה

Prozac 20 mg capsules
פרוזק 20 מ"ג כמוסות

Each capsule contains 20 mg of fluoxetine (as fluoxetine hydrochloride).

התוויה המאושרת לתכשיר:

Adults:
Major depressive episodes.
Obsessive-compulsive disorder (OCD).
Bulimia nervosa: Fluoxetine is indicated as a complement of psychotherapy for the reduction of binge-eating and purging activity.

Children and adolescents aged 8 years and above:
Moderate to severe major depressive episode, if depression is unresponsive to psychological therapy after 4-6 sessions. Antidepressant medication should be offered to a child or young person with moderate to severe depression only in combination with a concurrent psychological therapy.

העדכונים העיקריים בעלון לרופא הינם:

4.1 Therapeutic indications

Adults:
~~Treatment of depression.~~ Major depressive episodes.
Obsessive-compulsive disorder~~s~~ (OCD).

Bulimia nervosa: Fluoxetine is indicated as a complement of psychotherapy for the reduction of binge-eating and purging activity. ~~Fluoxetine is also indicated for the treatment of binge-eating and vomiting behaviors in bulimia nervosa.~~

Children and adolescents aged 8 years and above:
Moderate to severe major depressive episode, if depression is unresponsive to psychological therapy after 4–6 sessions. Antidepressant medication should be offered to a child or young person with moderate to severe depression only in combination with a concurrent psychological therapy.

4.2 Posology and method of administration

Posology

Adults

Major Depressive Disorder
Adults and the elderly: The recommended dose is 20 mg daily. Dosage should be reviewed and adjusted if necessary within 3 to 4 weeks of initiation of therapy and thereafter as judged clinically appropriate. Although there may be an increased potential for undesirable effects at higher doses, in some patients, with insufficient response to 20 mg, the dose may be increased gradually up to a maximum of 60 mg (see section 5.1). Dosage adjustments should be made carefully on an individual patient basis, to maintain the patients at the lowest effective dose.

Patients with depression should be treated for a sufficient period of at least 6 months to ensure that they are free from symptoms.

~~*Initial Treatment*~~
~~*Adults* — In controlled trials used to support the efficacy of fluoxetine, patients were administered morning doses ranging from 20 to 80 mg/day. Studies comparing fluoxetine 20, 40, and 60 mg/day to placebo indicate that 20 mg/day is sufficient to obtain a satisfactory response in Major Depressive Disorder in most cases. Consequently, a dose of 20 mg/day, administered in the morning, is recommended as the initial dose.~~
~~A dose increase may be considered after several weeks if insufficient clinical improvement is observed. Doses above 20 mg/day may be administered on a once-a-day (morning) or BID schedule (i.e., morning and noon) and should not exceed a maximum dose of 80 mg/day.~~
~~*All patients* — As with other drugs effective in the treatment of Major Depressive Disorder, the full effect may be delayed until 4 weeks of treatment or longer.~~
~~Patients with depression should be treated for a sufficient period of at least 6 months to ensure that they are free from symptoms.~~
~~*Maintenance/Continuation/Extended Treatment* — It is generally agreed that acute episodes of Major Depressive Disorder require several months or longer of sustained pharmacologic therapy. Whether the dose needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown.~~
~~*Daily Dosing* — Systematic evaluation of PROZAC in adult patients has shown that its efficacy in Major Depressive Disorder is maintained for periods of up to 38 weeks following 12 weeks of open-label acute treatment (50 weeks total) at a dose of 20 mg/day.~~
~~*Switching Patients to a Tricyclic Antidepressant (TCA)* — Dosage of a TCA may need to be reduced, and plasma TCA concentrations may need to be monitored temporarily when fluoxetine is coadministered or has been recently discontinued.~~

Obsessive Compulsive Disorder

Adults and the elderly: The recommended dose is 20 mg daily. Although there may be an increased potential for undesirable effects at higher doses, in some patients, if after two weeks there is insufficient response to 20 mg, the dose may be increased gradually up to a maximum of 60 mg.

If no improvement is observed within 10 weeks, treatment with fluoxetine should be reconsidered. If a good therapeutic response has been obtained, treatment can be continued at a dosage adjusted on an individual basis. While there are no systematic studies to answer the question of how long to continue fluoxetine treatment, OCD is a chronic condition and it is reasonable to consider continuation beyond 10 weeks in responding patients. Dosage adjustments should be made carefully on an individual patient basis, to maintain the patient at the lowest effective dose. The need for treatment should be reassessed periodically. Some clinicians advocate concomitant behavioral psychotherapy for patients who have done well on pharmacotherapy. Long-term efficacy (more than 24 weeks) has not been demonstrated in OCD.

~~*Initial Treatment*~~

~~*Adults* — In the controlled clinical trials of fluoxetine supporting its effectiveness in the treatment of OCD, patients were administered fixed daily doses of 20, 40, or 60 mg of fluoxetine or placebo. In one of these studies, no dose-response relationship for effectiveness was demonstrated. Consequently, a dose of 20 mg/day, administered in the morning, is recommended as the initial dose. Since there was a suggestion of a possible dose-response relationship for effectiveness in the second study, a dose increase may be considered after several weeks if insufficient clinical improvement is observed. The full therapeutic effect may be delayed until 5 weeks of treatment or longer. If no improvement is observed within 10 weeks, treatment with fluoxetine should be reconsidered.~~

~~Doses above 20 mg/day may be administered on a once daily (i.e., morning) or BID schedule (i.e., morning and noon). A dose range of 20 to 60 mg/day is recommended; however, doses of up to 80 mg/day have been well tolerated in open studies of OCD. The maximum fluoxetine dose should not exceed 80 mg/day.~~

~~*Maintenance/Continuation Treatment* — While there are no systematic studies that answer the question of how long to continue PROZAC, OCD is a chronic condition and it is reasonable to consider continuation for a responding patient. Although the efficacy of PROZAC after 13 weeks has not been documented in controlled trials, adult patients have been continued in therapy under double-blind conditions for up to an additional 6 months without loss of benefit. However, dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for treatment.~~

Bulimia Nervosa

Adults and the elderly: A dose of 60 mg/day is recommended. Long-term efficacy (more than 3 months) has not been demonstrated in bulimia nervosa.

All indications

The recommended dose may be increased or decreased. Doses above 80 mg/day have not been systematically evaluated.

Pediatric population - Children and adolescents aged 8 years and above (Moderate to severe major depressive episode)

Treatment should be initiated and monitored under specialist supervision. The starting dose is 10 mg/day fluoxetine (as hydrochloride) given as oral solution (there is a drug from another company, which comes as a solution). Dose adjustments should be made carefully, on an individual basis, to maintain the patient at the lowest effective dose.

After one to two weeks, the dose may be increased to 20 mg/day. Clinical trial experience with daily doses greater than 20 mg is minimal. There is only limited data on treatment beyond 9 weeks.

Lower weight children:

Due to higher plasma levels in lower weight children, the therapeutic effect may be achieved with lower doses (see section 5.2).

For pediatric patients who respond to treatment, the need for continued treatment after 6 months should be reviewed. If no clinical benefit is achieved within 9 weeks, treatment should be reconsidered.

~~*Initial Treatment* — In the controlled clinical trials of fluoxetine supporting its effectiveness in the treatment of Bulimia Nervosa, patients were administered fixed daily fluoxetine doses of 20 or 60 mg, or placebo. Only the 60 mg dose was statistically significantly superior to placebo in reducing the frequency of binge eating and vomiting. Consequently, the recommended dose is 60 mg/day, administered in the morning. For some patients it may be advisable to titrate up to this target dose over several days. Fluoxetine doses above 60 mg/day have not been systematically studied in patients with bulimia.~~

~~*Maintenance/Continuation Treatment* — Systematic evaluation of continuing PROZAC 60 mg/day for periods of up to 52 weeks in patients with bulimia who have responded while taking PROZAC 60 mg/day during an 8-week acute treatment phase has demonstrated a benefit of such maintenance treatment. Nevertheless, patients should be periodically reassessed to determine the need for maintenance treatment.~~

Withdrawal symptoms seen on discontinuation of Prozac: Abrupt discontinuation should be avoided. When stopping treatment with Prozac the dose should be gradually reduced over a period of at least one to two weeks in order to reduce the risk of withdrawal reactions (see sections 4.4 and 4.8). If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate.

~~**Dosing in Specific Populations**~~

~~*Treatment of Pregnant Women* — When treating pregnant women with PROZAC, the physician should carefully consider the potential risks and potential benefits of treatment. Neonates exposed to SSRI or SNRIs late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding.~~

~~*Geriatric* — A lower or less frequent dosage should be considered for the elderly.~~

~~*Hepatic Impairment* — As with many other medications, use a lower or less frequent dosage should be used in patients with hepatic impairment.~~

~~*Concomitant Illness* — Patients with concurrent disease or on multiple concomitant medications may require dosage adjustments.~~

~~**Discontinuation of Treatment**~~

~~Symptoms associated with discontinuation of fluoxetine, SNRIs, and SSRIs, have been reported.~~

~~**Switching a Patient To or From a Monoamine Oxidase Inhibitor (MAOI) Intended to Treat Psychiatric Disorders**~~

~~At least 14 days should elapse between discontinuation of an MAOI intended to treat psychiatric disorders and initiation of therapy with PROZAC. Conversely, at least 5 weeks should be allowed after stopping PROZAC before starting an MAOI intended to treat psychiatric disorders.~~

~~**Use of PROZAC with Other MAOIs such as Linezolid or Methylene Blue**~~

~~Do not start PROZAC in a patient who is being treated with linezolid or intravenous methylene blue because there is an increased risk of serotonin syndrome. In a patient who requires more urgent treatment of a psychiatric condition, other interventions, including hospitalization, should be considered.~~

~~In some cases, a patient already receiving PROZAC therapy may require urgent treatment with linezolid or intravenous methylene blue. If acceptable alternatives to linezolid or intravenous methylene blue treatment are not available and the potential benefits of linezolid or intravenous methylene blue treatment are judged to outweigh the risks of serotonin syndrome in a particular patient, PROZAC should be stopped promptly, and linezolid or intravenous methylene blue can be administered. The patient should be monitored for symptoms of serotonin syndrome for five weeks or until 24 hours after the last dose of linezolid or intravenous methylene blue, whichever comes first. Therapy with PROZAC may be resumed 24 hours after the last dose of linezolid or intravenous methylene blue.~~

~~The risk of administering methylene blue by non-intravenous routes (such as oral tablets or by local injection) or in intravenous doses much lower than 1 mg/kg with PROZAC is unclear. The clinician should, nevertheless, be aware of the possibility of emergent symptoms of serotonin syndrome with such use.~~

4.4 Special warnings and precautions for use

Pediatric population - Children and adolescents under 18 years of age

Suicide-related behaviors (suicide attempt and suicidal thoughts), and hostility (predominantly aggression, oppositional behavior and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. Prozac should only be used in children and adolescents aged 8 to 18 years for the treatment of moderate to severe major depressive episodes and it should not be used in other indications. If, based on clinical need, a decision to treat is nevertheless taken, the patient should be carefully monitored for the appearance of suicidal symptoms. In addition, only limited evidence is available concerning long-term effect on safety in children and adolescents, including effects on growth, sexual maturation and cognitive, emotional and behavioral developments (see section 5.3).

In a 19-week clinical trial decreased height and weight gain was observed in children and adolescents treated with fluoxetine (see section 5.1). It has not been established whether there is an effect on achieving normal adult height. The possibility of a delay in puberty cannot be ruled out (see sections 5.3 and 4.8). Growth and pubertal development (height, weight and TANNER staging) should therefore be monitored during and after treatment with fluoxetine. If either is slowed, referral to a paediatrician should be considered.

In pediatric trials, mania and hypomania were commonly reported (see section 4.8). Therefore, regular monitoring for the occurrence of mania/hypomania is recommended. Fluoxetine should be discontinued in any patient entering a manic phase.

It is important that the prescriber discusses carefully the risks and benefits of treatment with the child/young person and/or their parents.

4.8 Undesirable effects

d. Pediatric population (see sections 4.4 and 5.1)

Adverse reactions that have been observed specifically or with a different frequency in this population are described below. Frequencies for these events are based on pediatric clinical trial exposures (n = 610).

In pediatric clinical trials, suicide-related behaviors (suicide attempt and suicidal thoughts), hostility (the events reported were: anger, irritability, aggression, agitation, activation syndrome), manic reactions, including mania and hypomania (no prior episodes reported in these patients) and epistaxis, were commonly reported and were more frequently observed among children and adolescents treated with antidepressants compared to those treated with placebo.

Isolated cases of growth retardation have been reported from clinical use (See also section 5.1).

In pediatric clinical trials, fluoxetine treatment was also associated with a decrease in alkaline phosphatase levels.

Isolated cases of adverse events potentially indicating delayed sexual maturation or sexual dysfunction have been reported from pediatric clinical use (see also section 5.3).

5.1 Pharmacodynamic properties

Pediatric population

Major depressive episodes: Clinical trials in children and adolescents aged 8 years and above have been conducted versus placebo. Prozac, at a dose of 20 mg, has been shown to be significantly more effective than placebo in two short-term pivotal studies, as measured by the reduction of Childhood Depression Rating Scale-Revised (CDRS-R) total scores and Clinical Global Impression of Improvement (CGI-I) scores. In both studies, patients met criteria for moderate to severe MDD (DSM-III or DSM-IV) at three different evaluations by practicing child psychiatrists. Efficacy in the fluoxetine trials may depend on the inclusion of a selective patient population (one that has not spontaneously recovered within a period of 3-5 weeks and whose depression persisted in the face of considerable attention). There is only limited data on safety and efficacy beyond 9 weeks. In general, efficacy of fluoxetine was modest. Response rates (the primary endpoint, defined as a 30% decrease in the CDRS-R score) demonstrated a statistically significant difference in one of the two pivotal studies (58% for fluoxetine versus 32% for placebo, P=0.013 and 65% for fluoxetine versus 54% for placebo, P=0.093). In these two studies the mean absolute changes in CDRS-R from baseline to endpoint were 20 for fluoxetine versus 11 for placebo, P=0.002 and 22 for fluoxetine versus 15 for placebo, P<0.001.

Effects on growth, see sections 4.4 and 4.8:
After 19 weeks of treatment, pediatric subjects treated with fluoxetine in a clinical trial gained an average of 1.1 cm less in height (p=0.004) and 1.1 kg less in weight (p=0.008) than subjects treated with placebo.

In a retrospective matched control observational study with a mean of 1.8 years of exposure to fluoxetine, pediatric subjects treated with fluoxetine had no difference in growth adjusted for expected growth in height from their matched, untreated controls (0.0 cm, p=0.9673).

5.2 Pharmacokinetic properties

Pediatric population: The mean fluoxetine concentration in children is approximately 2-fold higher than that observed in adolescents and the mean norfluoxetine concentration 1.5-fold higher. Steady state plasma concentrations are dependent on body weight and are higher in lower weight children (see section 4.2). As in adults, fluoxetine and norfluoxetine accumulated extensively following multiple oral dosing; steady-state concentrations were achieved within 3 to 4 weeks of daily dosing.

העדכונים העיקריים בעלון לצרכן הינם:

1. למה מיועדת התרופה?

פרוזק מיועדת לטיפול ב:
מבוגרים:
- אפיזודות דיכאון מג'וריות
- הפרעה כפייתית טורדנית (OCD)
- בולמוס אכילה (בולימיה נרבוזה): פלואוקסטין ניתנת כטיפול משלים לפסיכותרפיה לצורך הפחתה של התקפי זלילה בלתי נשלטים והפרעת הטהרות.

ילדים ומתבגרים מגיל 8 ומעלה:
- אפיזודה בינונית עד חמורה של דיכאון מג'ורי, אם הדיכאון לא הגיב לטיפול פסיכולוגי של 4-6 מפגשים. לילד או אדם צעיר עם דיכאון בינוני עד חמור יש להציע תרופות נוגדות דיכאון רק בשילוב עם טיפול פסיכולוגי הניתן במקביל.

2. לפני השימוש בתרופה

~~**תרופה זו אינה מיועדת לשימוש בילדים.**~~
ילדים ומתבגרים מגיל 8 עד 18

מטופלים מתחת לגיל 18 נמצאים בסיכון מוגבר לסבול מתופעות לוואי, כגון נסיון התאבדות, מחשבות אובדניות ועוינות (בעיקר תוקפנות, התנהגות מתנגדת וכעס) בעת נטילת תרופות מסוג זה. בילדים ומתבגרים מגיל 8 עד 18 יש להשתמש ב**פרוזק** רק לטיפול באפיזודות דיכאון מג'וריות בינוניות עד חמורות (בשילוב עם טיפול פסיכולוגי) ואין להשתמש בתרופה זו לטיפול במצבים אחרים.

בנוסף, קיים רק מידע מוגבל בנוגע לבטיחות ארוכת הטווח של **פרוזק** לגבי גדילה, התבגרות וההתפתחות הנפשית, הרגשית וההתנהגותית בקבוצת גיל זו. למרות זאת, במידה ואתה מתחת לגיל 18, יתכן כי הרופא שלך ירשום לך **פרוזק** לטיפול באפיזודות דיכאון מג'וריות בינוניות עד חמורות, בשילוב עם טיפול פסיכולוגי, מכיוון שהחליט שזה לטובתך. אם אתה מתחת לגיל 18 והרופא שלך רשם לך **פרוזק**, ואתה רוצה לדון בכך, אנא חזור לרופא שלך. במידה ואתה מתחת לגיל 18, עליך ליידע את הרופא שלך אם אחד מהתסמינים המפורטים לעיל מתפתח או מחמיר בעת נטילת **פרוזק**.

אין להשתמש ב**פרוזק** בילדים מתחת לגיל 8.

3. כיצד תשתמש בתרופה?

שימוש בילדים ומתבגרים מגיל 8 עד 18 הסובלים מדיכאון:
יש להתחיל בטיפול ולהיות תחת השגחה של רופא מומחה. המינון ההתחלתי הוא 10 מ"ג/יום פלואוקסטין (כהידרוכלוריד) הניתן כתמיסה פומית (יש תרופה של חברה אחרת, שמגיעה כתמיסה). לאחר 1-2 שבועות, יתכן

כי הרופא יעלה את המינון ל-20 מ"ג/יום. יש להעלות את המינון בזהירות כדי להבטיח שאתה מקבל את המינון האפקטיבי הנמוך ביותר. ילדים במשקל נמוך עשויים להזדקק למינונים נמוכים יותר. אם ישנה תגובה משביעת רצון לטיפול, הרופא יבדוק את הצורך בהמשך הטיפול מעבר ל-6 חודשים. אם אין שיפור בתוך 9 שבועות, הרופא יעריך מחדש את הטיפול שלך.

4. תופעות לוואי

בילדים ומתבגרים (8-18 שנים): בנוסף לתופעות הלוואי האפשריות המפורטות לעיל, **פרוזק** עלולה להאט את קצב הגדילה או אולי לעכב את ההתבגרות המינית. התנהגויות הקשורות להתאבדות (נסיון התאבדות ומחשבות אובדניות), עוינות, מאניה ודימומים מהאף דווחו גם הן בדרך כלל בילדים.