רופא/ה נכבד/ה,

רוקח/ת נכבד/ה,

חברת AbbVie Biopharmaceuticals Ltd. מודיעה כי העלון לרופא והעלונים לצרכן של התכשיר Humira 40mg עודכנו.
בהודעה זו מצוינים סעיפים בהם נעשה שינוי אשר מהווה החמרה או שינוי מהותי.
עדכונים נוספים אשר אינם מהווים החמרה או שאינם מהותיים, אינם נכללים בהודעה זו (שינוי שהינו הוספה מסומן בקו תחתון, מחיקה מסומנת בקו אמצעי).

Humira 40 mg

יומירה 40 מ"ג

Solution for Injection

Adalimumab 40mg/0.8ml

ההתוויות המאושרות לתכשיר:

❖ Rheumatoid arthritis

Humira in combination with methotrexate, is indicated for:

- The treatment of moderate to severe, active rheumatoid arthritis in adult patients when the response to disease-modifying anti-rheumatic drugs including methotrexate has been inadequate.
- The treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.

Humira can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

Humira has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function, when given in combination with methotrexate.

❖ Polyarticular juvenile idiopathic arthritis

Humira in combination with methotrexate is indicated for the treatment of active polyarticular juvenile idiopathic arthritis, in children and adolescents aged 4 to 17 years who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). Humira can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate. Humira has not been studied in children aged less than 4 years.

❖ Axial spondyloarthritis

- Ankylosing spondylitis(AS)

Humira is indicated for the treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy.

- Axial spondyloarthritis without radiographic evidence of AS

Humira is indicated for the treatment of adults with severe axial spondyloarthritis without radiographic evidence of AS, but with objective signs of inflammation by radiological and/or laboratory tests including MRI and serum CRP levels , who have had an inadequate response to, or are intolerant to, non - steroidal anti-inflammatory drugs.

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❖ Psoriatic arthritis

Humira is indicated for the treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate. Humira has been shown to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease and to improve physical function.

❖ Psoriasis

Humira is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or PUVA.

❖ Crohn's disease

Humira is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. Humira is indicated for reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab.

❖ Paediatric Crohn's Disease

Humira is indicated for the treatment of severe active Crohn's disease in paediatric patients (6-17 years of age) who have had an inadequate response to conventional therapy including primary nutrition therapy, a corticosteroid, and an immunomodulator, or who are intolerant to or have contraindications for such therapies.

❖ Ulcerative colitis

Humira is indicated for treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

העלונים לצרכן עודכנו בסעיפים:

1) למה מיועדת התרופה?

מהות השינוי:

יומירה מיועדת לטיפול ב:

מחלת קרוהן (Crohn's disease) בילדים מגיל 6 עד 17 שנים ובמבוגרים כאשר טיפול מקובל אחר לא הצליח.

2) לפני שימוש בתרופה

מהות השינוי:

נהיגה ושימוש במכונות

ליומירה עלולה להיות השפעה ~~משנית~~ זעירה על היכולת לנהוג, לרכב על אופניים או להפעיל מכונות. לאחר טיפול ביומירה תיתכן תחושת סחרחורת והפרעות בראייה.

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4) תופעות לוואי

מהות השינוי:

מופיעות לעיתים נדירות

- דלקת כבד

תופעות לוואי נוספות (שכיחות לא ידועה):

- לימפומה של תאי T שבכבד ובטחול (סרטן דם נדיר שלעיתים קרובות גורם למוות).
- קרצינומה של התאים על שם מרקל (סוג של סרטן עור)
- כשל כבדי
- החמרה בדרמטומיוזיטיס (נראית כפריחה בעור המלווה בחולשת שרירים)

לחלק מתופעות הלוואי, שנצפו ~~במחקרים קליניים~~ בשימוש ביומירה, אין תסמינים וניתן לגלותם בבדיקות דם בלבד. וביניהן:

תופעת לוואי נוספת:

- כשל כבדי

* לרשימת תופעות הלוואי המלאה של התרופה יש לעיין בעלון לצרכן.

5) איך לאחסן את התרופה?

מהות השינוי:

מזרק מוכן לשימוש

- אחסן בקרור (2°C- 8°C: טווח טמפרטורות זה שורר על פי רוב במקרר ביתי).
- יש לשמור את המזרקים בתוך אריזת הקרטון המקורית על מנת להגן מאור.
- אין להקפיא.

תנאי אחסון נוספים:

- בעת הצורך (למשל כאשר אתה בנסיעה), ניתן לאחסן מזרק **אחד** מוכן מראש מתחת ל- 25° C עד 14 ימים – יש להגן על המזרק מפני אור.
- יש לתעד את התאריך שבו הוצא המזרק מן המקרר לראשונה ואת התאריך שלאחריו יש להשליך את המזרק.
- לאחר הוצאת המזרק מהמקרר והעברתו לטמפרטורה מתחת ל- 25° C, יש להשתמש במזרק תוך 14 ימים או להשליכו, אפילו אם החזרת אותו למקרר.

עט מוכן להזרקה

- אחסן בקרור (2°C- 8°C: טווח טמפרטורות זה שורר על פי רוב במקרר ביתי).
- אין להקפיא.
- יש לשמור את העט באריזתו המקורית על מנת להגן מאור.

תנאי אחסון נוספים:

- בעת הצורך (למשל כאשר אתה בנסיעה), ניתן לאחסן עט **אחד** מוכן מראש מתחת ל- 25° C עד 14 ימים – יש להגן על העט מפני אור.

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- יש לתעד את התאריך שבו הוצא העט מן המקרר לראשונה ואת התאריך שלאחריו יש להשליך את ההעט.
- לאחר הוצאת העט מהמקרר והעברתו לטמפרטורה מתחת ל- 25° C, יש להשתמש בעט תוך 14 ימים או להשליכו, אפילו אם החזרת אותו למקרר.

תמיסה להזרקה בקבוקון לשימוש חד פעמי

- אחסן בקרור (2°C- 8°C: טווח טמפרטורות זה שורר על פי רוב במקרר ביתי).
- אין להקפיא
- יש לאחסן את הבקבוקון באריזת הקרטון המקורית על מנת להגן מאור.

העלון לרופא עודכן בסעיפים:

4. CLINICAL PARTICULARS

מהות השינוי:

4.1 Therapeutic indications

Paediatric Crohn's Disease
Humira is indicated for the treatment of severe active Crohn's disease in paediatric patients (6-17 years of age) who have had an inadequate response to conventional therapy including primary nutrition therapy, a corticosteroid, and an immunomodulator, or who are intolerant to or have contraindications for such therapies.

4.2 Posology and method of administration

Posology

Paediatric psoriasis

The safety and efficacy of Humira in children aged 4-17 years have not been established. No data are available. There is no relevant use of Humira in children aged <4 years in this indication.

Paediatric Crohn's disease

Paediatric Crohn's disease patients < 40 kg:
The recommended Humira induction dose regimen for paediatric subjects with severe Crohn's disease is 40 mg at Week 0 followed by 20 mg at Week 2. In case there is a need for a more rapid response to therapy, the regimen 80 mg at Week 0 (dose can be administered as two injections in one day), 40 mg at Week 2 can be used, with the awareness that the risk for adverse events may be higher with use of the higher induction dose.

After induction treatment, the recommended dose is 20 mg every other week via subcutaneous injection. Some subjects who experience insufficient response may benefit from an increase in dosing frequency to 20 mg Humira every week.

Paediatric Crohn's disease patients ≥ 40 kg:
The recommended Humira induction dose regimen for paediatric subjects with severe Crohn's disease is 80 mg at Week 0 followed by 40 mg at Week 2. In case there is a need for a more rapid response to therapy, the regimen 160 mg at Week 0 (dose can be administered as four injections in one day or as two injections per day for two consecutive days), 80 mg at Week 2 can be used, with the awareness that the risk for adverse events may be higher with use of the higher induction dose.

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After induction treatment, the recommended dose is 40 mg every other week via subcutaneous injection. Some subjects who experience insufficient response may benefit from an increase in dosing frequency to 40 mg Humira every week.

Continued therapy should be carefully considered in a subject not responding by Week 12.

There is no relevant use of Humira in children aged below 6 years in this indication.

Paediatric ulcerative colitis
The safety and efficacy of Humira in children aged 4-17 years have not yet been established. No data are available. There is no relevant use of Humira in children aged <4 years in this indication.

Psoriatic arthritis and axial spondyloarthritis including ankylosing spondylitis
There is no relevant use of Humira in the paediatric population in the indications, ankylosing spondylitis and psoriatic arthritis.

Method of administration

Humira is administered by subcutaneous injection. Full instructions for use are provided in the package leaflet.

A 40 mg paediatric vial is available for patients who need to administer less than the full 40 mg dose.

4.4 Special warnings and precautions for use

Allergic reactions
Serious allergic reactions associated with Humira were rare during clinical trials.
~~Serious allergic adverse reactions have not been reported with subcutaneous administration of Humira during clinical trials.~~

Malignancies and lymphoproliferative disorders
Melanoma and Merkel cell carcinoma have also been reported in patients treated with TNF-antagonists including adalimumab (see section 4.8).

4.8 Undesirable effects

Table 2 - Undesirable Effects

System Organ Class	Frequency	Adverse Reaction
Hepato-biliary disorders*	Rare	hepatitis
	Not known	Liver failure[1)]
Skin and subcutaneous tissue disorders	Not known	Worsening of symptoms of dermatomyositis[1)]

1) including spontaneous reporting data
*This table contains only new safety information. Please refer to the prescribing information for the full summary of adverse reactions.

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Description of selected adverse reactions

Infections
In the pivotal controlled trials in adults and children, the rate of infection was 1.52 ~~1.51~~ per patient year in the Humira treated patients and 1.454 per patient year in the placebo and active control-treated patients. The infections consisted primarily of nasopharyngitis, upper respiratory tract infection, sinusitis and urinary tract infection. Most patients continued on Humira after the infection resolved.

Hepato-biliary events

In controlled Phase 3 trials of Humira in patients with rheumatoid arthritis and psoriatic arthritis with a control period duration ranging from 4 to 104 weeks, ALT elevations ≥ 3 x ULN occurred in 3.7% of Humira-treated patients and 1.6% of control-treated patients.

~~Hepato-biliary events:~~
~~Rheumatoid arthritis clinical trials: in controlled rheumatoid arthritis clinical trials (RA studies I – IV), elevations of ALT were similar in patients receiving adalimumab or placebo. In patients with early rheumatoid arthritis (disease duration of less than 3 years) (RA study V), elevations of ALT were more common in the combination arm (Humira /methotrexate) compared to the methotrexate monotherapy arm or the Humira monotherapy arm. . In the JIA trial the few transaminase elevations were small and similar in the placebo and adalimumab exposed patients, and mostly occurred in combination with methotrexate.~~

~~Psoriatic arthritis clinical trials: elevations in ALT were more common in psoriatic arthritis patients ((PsA studies I - II) compared with patients in rheumatoid arthritis clinical studies.~~

~~In all rheumatoid arthritis, polyarticular juvenile idiopathic arthritis and psoriatic arthritis studies, patients with raised ALT were asymptomatic and in most cases elevations were transient and resolved on continued treatment.~~

~~Psoriasis clinical trials: in controlled psoriasis clinical trials, elevations of ALT were similar in patients receiving adalimumab or placebo.~~

Across all indications in clinical trials patients with raised ALT were asymptomatic and in most cases elevations were transient and resolved on continued treatment. However, there have also been post-marketing reports of liver failure as well as less severe liver disorders that may precede liver failure, such as hepatitis including autoimmune hepatitis in patients receiving adalimumab.

~~There have been post-marketing reports of severe hepatic reactions including autoimmune hepatitis in patients receiving adalimumab~~

Concurrent treatment with azathioprine/6-mercaptopurine
In adult Crohn's disease studies, higher incidences of malignant and serious infection-related adverse events were seen with the combination of Humira and azathioprine/6-mercaptopurine compared with Humira alone.

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5. PHARMACOLOGICAL PROPERTIES

מהות השינוי:

5.1 Pharmacodynamic properties

Clinical efficacy and safety - Crohn's disease:

117/854 patients had draining fistulas both at screening and at baseline. For the assessment of fistula healing, the data for both doses of adalimumab used in the study were pooled. The proportion of subjects (IIT population) with fistula healing at Week 26 was statistically significantly greater in patients treated with adalimumab [21/70 (30.0%)] compared to placebo [6/47 (12.8%)]. Complete fistula healing was maintained through Week 56 in 23/70 (32.9%) and 6/47 (12.8%) patients (ITT population) in the adalimumab and placebo groups, respectively.

6. PHARMACEUTICAL PARTICULARS

מהות השינוי:

6.4 Special precautions for storage

Pre-filled syringe:
Store in a refrigerator (2°C – 8°C). Keep the syringe in the outer carton in order to protect from light. Do not freeze.
A single Humira pre-filled syringe may be stored at temperatures below 25°C for a period of up to 14 days.
The syringe must be protected from light, and discarded if not used within the 14-day period.

Pre-filled pen:
Store in a refrigerator (2°C – 8°C). Do not freeze.
Keep the pre-filled pen in the outer carton in order to protect from light.
A single Humira pen may be stored at temperatures below 25°C for a period of up to 14 days.
The pen must be protected from light, and discarded if not used within the 14-day period.

Humira 40 mg solution for injection glass vial:
Store in a refrigerator (2°C – 8°C). Keep the vial in the outer carton in order to protect from light. Do not freeze.

העלון המעודכן לרופא והעלונים המעודכנים לצרכן נשלחו למאגר התרופות שבאתר משרד הבריאות, וניתן לקבלם מודפסים על ידי פניה לבעל הרישום, AbbVie Biopharmaceuticals Ltd, רחוב החרש 4, הוד השרון או בטלפון 7909600 – 09.

בברכה,

נעמי רביב

רוקחת ממונה

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