יוני 2022

רופא/ה רוקח/ת נכבד/ה,

חברת פאדאגיס ישראל סוכנויות בע"מ מבקשת להודיע על **אישור תוספת התוויות IBD לילדים** ועל העדכונים הבאים המפורטים בהמשך עבור התכשיר:

REMSIMA 100 MG I.V. / רמסימה 100 מ"ג תוך-ורידי

החומר הפעיל בתכשיר וחוזקו: Infliximab 100 mg/vial

<u>התוויות רשומות לתכשיר בישראל :</u>

* Rheumatoid arthritis:
Remsima, in combination with methotrexate, is indicated for the reduction of signs and symptoms as well as the improvement in physical function in:
• adult patients with active disease when the response to disease modifying antirheumatic drugs (DMARDs), including methotrexate, has been inadequate.
• adult patients with severe, active and progressive disease not previously treated with methotrexate or other DMARDs.
In these patient populations, a reduction in the rate of the progression of joint damage, as measured by X ray, has been demonstrated.

* Ankylosing spondylitis:
Remsima is indicated for treatment of severe, active ankylosing spondylitis, in adult patients who have responded inadequately to conventional therapy.

* Psoriatic arthritis:
Remsima is indicated for treatment of active and progressive psoriatic arthritis in adult patients when the response to previous DMARD therapy has been inadequate.
* Remsima should be administered:
• in combination with methotrexate
• or alone in patients who show intolerance to methotrexate or for whom methotrexate is contraindicated.
Infliximab has been shown to improve physical function in patients with psoriatic arthritis, and to reduce the rate of progression of peripheral joint damage as measured by X ray in patients with polyarticular symmetrical subtypes of the disease.

* Psoriasis:
Remsima is indicated for treatment of moderate to severe 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 psoralen ultra-violet A (PUVA)

* Adult Crohn’s disease
Remsima is indicated for treatment:
• of moderately to severely active Crohn’s disease, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies.
• treatment of fistulising, active Crohn’s disease, in adult patients who have not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage and immunosuppressive therapy).

* Ulcerative colitis
• Remsima 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.

להלן ההתוויות הרשומות לילדים שנוספו:

Paediatric Crohn's disease
Remsima is indicated for treatment of severe, active Crohn's disease in children and adolescents aged 6 to 17 years, who have not responded to conventional therapy including a corticosteroid, an immunomodulator and primary nutrition therapy; or who are intolerant to or have contraindications for such therapies. Infliximab has been studied only in combination with conventional immunosuppressive therapy.

Paediatric ulcerative colitis
Remsima is indicated for treatment of severely active ulcerative colitis in children and adolescents aged 6 to 17 years, who have had an inadequate response to conventional therapy including corticosteroids and 6 MP or AZA, or who are intolerant to or have medical contraindications for such therapies.

מהות העדכון:
בהודעה זו מצוינים ומסומנים ברקע צהוב השינויים המתייחסים לתוספת ההתוויה וכן עדכוני בטיחות. העלונים כוללים גם עדכונים נוספים אשר אינם קשורים לתוספת ההתוויה (בעיקר שינויי נוסח והתאמה לפורמט משרד הבריאות).

העלונים המעודכנים לרופא ולצרכן נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות:
http://www.health.gov.il

בברכה,
פאדאגיס ישראל סוכנויות בע"מ

עלון לרופא

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[…]

- Paediatric Crohn's disease:

Remsima 100 mg I.V.is indicated for treatment of severe, active Crohn's disease in children and adolescents aged 6 to 17 years, who have not responded to conventional therapy including a corticosteroid, an immunomodulator and primary nutrition therapy; or who are intolerant to or have contraindications for such therapies. Infliximab has been studied only in combination with conventional immunosuppressive therapy.

[…]

- Paediatric ulcerative colitis:

Remsima 100 mg I.V.is indicated for treatment of severely active ulcerative colitis in children and adolescents aged 6 to 17 years, who have had an inadequate response to conventional therapy including corticosteroids and 6-MP or AZA, or who are intolerant to or have medical contraindications for such therapies.

[…]

4.2 Posology and method of administration

[…]

It is important to check the product labels to ensure that the correct formulation (intravenous or subcutaneous) is being administered to the patient, as prescribed. Remsima subcutaneous formulation is not intended for intravenous administration and should be administered via a subcutaneous injection only.

[…]

Posology

[…]

Paediatric population

Crohn's disease (6 to 17 years)

5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter.

Available data do not support further infliximab treatment in children and adolescents not responding within the first 10 weeks of treatment (see section 5.1).

Some patients may require a shorter dosing interval to maintain clinical benefit, while for others a longer dosing interval may be sufficient. Patients who have had their dose interval shortened to less than 8 weeks may be at greater risk for adverse reactions. Continued therapy with a shortened interval should be carefully considered in those patients who show no evidence of additional therapeutic benefit after a change in dosing interval.

The safety and efficacy of infliximab have not been studied in children with Crohn's disease below the age of 6 years. Currently available pharmacokinetic data are described in section 5.2 but no recommendation on a posology can be made in children younger than 6 years.

Ulcerative colitis (6 to 17 years)
5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. Available data do not support further infliximab treatment in paediatric patients not responding within the first 8 weeks of treatment (see section 5.1).

The safety and efficacy of infliximab have not been studied in children with ulcerative colitis below the age of 6 years. Currently available pharmacokinetic data are described in section 5.2 but no recommendation on a posology can be made in children younger than 6 years.
[…]

4.4 Special warnings and precautions for use

[…]
Infant exposure via breast milk
Administration of a live vaccine to a breastfed infant while the mother is receiving infliximab is not recommended unless infant infliximab serum levels are undetectable (see section 4.6).
[…]

Paediatric population

Infections
In clinical studies, infections have been reported in a higher proportion of paediatric patients compared to adult patients (see section 4.8).

Vaccinations
It is recommended that paediatric patients, if possible, be brought up to date with all vaccinations in agreement with current vaccination guidelines prior to initiating Remsima 100 mg I.V. therapy. Paediatric patients on infliximab may receive concurrent vaccinations, except for live vaccines (see sections 4.5 and 4.6).

Malignancies and lymphoproliferative disorders
Malignancies, some fatal, have been reported among children, adolescents and young adults (up to 22 years of age) treated with TNF-blocking agents (initiation of therapy ≤ 18 years of age), including infliximab in the post-marketing setting. Approximately half the cases were lymphomas. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression. A risk for the development of malignancies in children and adolescents treated with TNF-blockers cannot be excluded.

Post-marketing cases of hepatosplenic T-cell lymphoma have been reported in patients treated with TNF-blocking agents including infliximab. This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. Almost all patients had received treatment with AZA or 6-MP concomitantly with or immediately prior to a TNF-blocker. The vast majority of infliximab cases have occurred in patients with Crohn's disease or ulcerative colitis and most were reported in adolescent or young adult males. The potential risk with the combination of AZA or 6-MP and Remsima 100 mg I.V. should be carefully considered.

A risk for the development for hepatosplenic T-cell lymphoma in patients treated with Remsima 100 mg I.V. cannot be excluded (see section 4.8).

[…]

4.5 Interaction with other medicinal products and other forms of interaction

[…]
Administration of a live vaccine to a breastfed infant while the mother is receiving infliximab is not recommended unless infant infliximab serum levels are undetectable (see sections 4.4 and 4.6).
[…]

4.6 Fertility, pregnancy and lactation
[…]
Breast-feeding
Limited data from published literature indicate ~~It is unknown whether~~ infliximab has been detected at low levels ~~is excreted~~ in human milk ~~or absorbed systemically after ingestion.~~ at concentrations up to 5% of the maternal serum level Infliximab has also been detected in infant serum after exposure to infliximab via breast milk. While systemic exposure in a breastfed infant is expected to be low because infliximab is largely degraded in the gastrointestinal tract, the administration of live vaccines to a breastfed infant when the mother is receiving infliximab is not recommended unless infant infliximab serum levels are undetectable. Infliximab could be considered for use during breast-feeding.
~~Because human immunoglobulins are excreted in milk, women must not breast feed for at least 6 months after infliximab treatment.~~
[…]

4.8 Undesirable effects
[…]

Table 1
Undesirable effects in clinical studies and from post-marketing experience
[…]

Neoplasms benign, malignant and unspecified (including cysts and polyps)		
	Rare:	Lymphoma, non-Hodgkin's lymphoma, Hodgkin's disease, leukaemia, melanoma, cervical cancer
	Not known:	Hepatosplenic T-cell lymphoma (primarily in adolescents and young adult males with Crohn's disease or ulcerative colitis), Merkel cell carcinoma, Kaposi's sarcoma.

[…]

Metabolism and nutrition disorders		
	Uncommon:	Dyslipidaemia

[…]

Table 2: Proportion of patients with increased ALT activity in clinical studies

Indication	Number of patients[3]		Median follow-up (wks)[4]		≥3 x ULN		≥5 x ULN	
	placebo	infliximab	placebo	infliximab	placebo	infliximab	placebo	infliximab
Rheumatoid arthritis[1]	375	1,087	58.1	58.3	3.2%	3.9%	0.8%	0.9%
Crohn's disease[2]	324	1,034	53.7	54.0	2.2%	4.9%	0.0%	1.5%
Paediatric Crohn's disease	N/A	139	N/A	53.0	N/A	4.4%	N/A	1.5%
Ulcerative colitis	242	482	30.1	30.8	1.2%	2.5%	0.4%	0.6%
Paediatric Ulcerative colitis	N/A	60	N/A	49.4	N/A	6.7%	N/A	1.7%
Ankylosing spondylitis	76	275	24.1	101.9	0.0%	9.5%	0.0%	3.6%
Psoriatic arthritis	98	191	18.1	39.1	0.0%	6.8%	0.0%	2.1%
Plaque psoriasis	281	1,175	16.1	50.1	0.4%	7.7%	0.0%	3.4%

[…]

Paediatric population

[…]

Paediatric Crohn's disease patients:

The following adverse reactions were reported more commonly in paediatric Crohn's disease patients in the REACH study (see section 5.1) than in adult Crohn's disease patients: anaemia (10.7%), blood in stool (9.7%), leucopenia (8.7%), flushing (8.7%), viral infection (7.8%), neutropenia (6.8%), bacterial infection (5.8%), and respiratory tract allergic reaction (5.8%). In addition, bone fracture (6.8%) was reported, however, a causal association has not been established. Other special considerations are discussed below.

Infusion-related reactions

In REACH, 17.5% of randomised patients experienced 1 or more infusion reactions. There were no serious infusion reactions, and 2 subjects in REACH had non-serious anaphylactic reactions.

Immunogenicity

Antibodies to infliximab were detected in 3 (2.9%) paediatric patients.

Infections

In the REACH study, infections were reported in 56.3% of randomised subjects treated with infliximab. Infections were reported more frequently for subjects who received q8 week as opposed to
q12 week infusions (73.6% and 38.0%, respectively), while serious infections were reported for 3 subjects in the q8 week and 4 subjects in the q12 week maintenance treatment group. The most commonly reported infections were upper respiratory tract infection and pharyngitis, and the most commonly reported serious infection was abscess. Three cases of pneumonia (1 serious) and 2 cases of herpes zoster (both non-serious) were reported.

Paediatric ulcerative colitis patients:

Overall, the adverse reactions reported in the paediatric ulcerative colitis trial (C0168T72) and adult ulcerative colitis (ACT 1 and ACT 2) studies were generally consistent. In

C0168T72, the most common adverse reactions were upper respiratory tract infection, pharyngitis, abdominal pain, fever, and headache. The most common adverse event was worsening of ulcerative colitis, the incidence of which was higher in patients on the q12 week vs. the q8 week dosing regimen.

Infusion-related reactions
Overall, 8 (13.3%) of 60 treated patients experienced one or more infusion reactions, with 4 of 22 (18.2%) in the q8 week and 3 of 23 (13.0%) in the q12 week treatment maintenance group. No serious infusion reactions were reported. All infusion reactions were mild or moderate in intensity.

Immunogenicity
Antibodies to infliximab were detected in 4 (7.7%) patients through week 54.

Infections
Infections were reported in 31 (51.7%) of 60 treated patients in C0168T72 and 22 (36.7%) required oral or parenteral antimicrobial treatment. The proportion of patients with infections in C0168T72 was similar to that in the paediatric Crohn's disease study (REACH) but higher than the proportion in the adults ulcerative colitis studies (ACT 1 and ACT 2). The overall incidence of infections in C0168T72 was 13/22 (59%) in the every 8 week maintenance treatment group and 14/23 (60.9%) in the every 12 week maintenance treatment group. Upper respiratory tract infection (7/60 [12%]) and pharyngitis (5/60 [8%]) were the most frequently reported respiratory system infections. Serious infections were reported in 12% (7/60) of all treated patients.

In this study, there were more patients in the 12 to 17 year age group than in the 6 to 11 year age group (45/60 [75.0%]) vs.15/60 [25.0%]). While the numbers of patients in each subgroup are too small to make any definitive conclusions about the effect of age on safety events, there were higher proportions of patients with serious adverse events and discontinuation due to adverse events in the younger age group than in the older age group. While the proportion of patients with infections was also higher in the younger age group, for serious infections, the proportions were similar in the two age groups.
Overall proportions of adverse events and infusion reactions were similar between the 6 to 11 and 12 to 17 year age groups.
[…]

5.1 Pharmacodynamic properties

[…]

Paediatric population

Paediatric Crohn's disease (6 to17 years)
In the REACH study, 112 patients (6 to 17 years, median age 13.0 years) with moderate to severe, active Crohn's disease (median paediatric CDAI of 40) and an inadequate response to conventional therapies were to receive 5 mg/kg infliximab at weeks 0, 2, and 6. All patients were required to be on a stable dose of 6-MP, AZA or MTX (35% were also receiving corticosteroids at baseline). Patients assessed by the investigator to be in clinical response at week 10 were randomised and received 5 mg/kg infliximab at either q8 weeks or q12 weeks as a maintenance treatment regimen. If response was lost during maintenance treatment, crossing over to a higher dose (10 mg/kg) and/or shorter dosing interval (q8 weeks) was allowed. Thirty two (32) evaluable paediatric patients crossed over (9 subjects in the q8 weeks and 23 subjects in the q12 weeks maintenance groups). Twenty four of these patients (75.0%) regained clinical response after crossing over.
The proportion of subjects in clinical response at week 10 was 88.4% (99/112). The proportion of subjects achieving clinical remission at week 10 was 58.9% (66/112).
At week 30, the proportion of subjects in clinical remission was higher in the q8 week

(59.6%, 31/52) than the q12 week maintenance treatment group (35.3%, 18/51; p=0.013). At week 54, the figures were 55.8% (29/52) and 23.5% (12/51) in the q8 weeks and q12 weeks maintenance groups, respectively (p < 0.001).
Data about fistulas were derived from PCDAI scores. Of the 22 subjects that had fistulas at baseline, 63.6% (14/22), 59.1% (13/22) and 68.2% (15/22) were in complete fistula response at week 10, 30 and 54, respectively, in the combined q8 weeks and q12 weeks maintenance groups.

In addition, statistically and clinically significant improvements in quality of life and height, as well as a significant reduction in corticosteroid use, were observed versus baseline.

Paediatric ulcerative colitis (6 to 17 years)

The safety and efficacy of infliximab were assessed in a multicenter, randomised, open-label, parallel- group clinical study (C0168T72) in 60 paediatric patients aged 6 through 17 years (median age 14.5 years) with moderately to severely active ulcerative colitis (Mayo score of 6 to 12; endoscopic subscore ≥ 2) with an inadequate response to conventional therapies. At baseline 53% of patients were receiving immunomodulator therapy (6-MP, AZA and/or MTX) and 62% of patients were receiving corticosteroids. Discontinuation of immunomodulators and corticosteroid taper were permitted after week 0.

All patients received an induction regimen of 5 mg/kg infliximab at weeks 0, 2, and 6. Patients who did not respond to infliximab at week 8 (n=15) received no further medicinal product and returned for safety follow-up. At week 8, 45 patients were randomised and received 5 mg/kg infliximab at either q8 weeks or q12 weeks as a maintenance treatment regimen. The proportion of patients in clinical response at week 8 was 73.3% (44/60). Clinical response at week 8 was similar between those with or without concomitant immunomodulator use at baseline. Clinical remission at week 8 was 33.3% (17/51) as measured by the Paediatric Ulcerative Colitis Activity Index (PUCAI) score.

At week 54, the proportion of patients in clinical remission as measured by the PUCAI score was 38% (8/21) in the q8 week maintenance group and 18% (4/22) in the q12 week maintenance treatment group. For patients receiving corticosteroids at baseline, the proportion of patients in remission and not receiving corticosteroids at week 54 was 38.5% (5/13) for the q8 week and 0% (0/13) for the q12 week maintenance treatment group.

In this study, there were more patients in the 12 to 17 year age group than in the 6 to 11 year age group (45/60 vs.15/60). While the numbers of patients in each subgroup are too small to draw definitive conclusions about the effect of age, there was a higher number of patients in the younger age group who stepped up in dose or discontinued treatment due to inadequate efficacy.

Other paediatric indications
[…]

עלון לצרכן

[...]

עבור ילדים:

~~**תכשיר זה לא מיועד לשימוש בילדים.**~~

לתשומת ליבך, חשוב שבכל פעם שאתה מקבל את התרופה בבית המרקחת, תוודא שאתה מקבל את אותה התרופה שרשם לך הרופא המומחה המטפל בך. אם התרופה שקיבלת נראית שונה מזו שאתה מקבל בדרך כלל או שהנחיות השימוש השתנו, אנא פנה מיד לרוקח לוודא שקיבלת את התרופה הנכונה. כל החלפה או שינוי מינון של תרופה המכילה אינפליקסימאב (החומר הפעיל בתרופה) חייבים להתבצע אך ורק על-ידי הרופא המומחה המטפל.

אנא בדוק כי שמו המסחרי של התכשיר שרשם לך הרופא המומחה במרשם, הינו זהה לשם התרופה שקיבלת מהרוקח.

1. למה מיועדת התרופה?

[...]

מחלת קרוהן בילדים:

לטיפול במחלת קרוהן פעילה בדרגה חמורה בילדים ומתבגרים מגיל 6-17 אשר לא הגיבו לטיפול קונבנציונאלי הכולל קורטיקוסטרואידים, אימונומודולטורים, וטיפול תזונתי ראשוני, או שיש להם אי סבילות או התוויית נגד לטיפולים אלו.

אינפליקסימאב נבחנת רק בשילוב עם טיפול אימונוסופרסיבי קונבנציונאלי.

[...]

דלקת כיבית של המעי הגס בילדים:

לטיפול במחלה פעילה בדרגה חמורה בקוליטיס כיבית בילדים ומתבגרים בגיל 6-17 שנים, אשר לא הגיבו באופן מספק, או שיש להם אי סבילות או התוויית נגד לטיפול קונבנציונאלי כולל קורטיקוסטרואידים, 6-MP, או AZA.

[...]

2. לפני השימוש בתרופה:

[...]

אזהרות מיוחדות הנוגעות לשימוש בתרופה:

[...]

זיהומים

- טרם התחלת הטיפול ברמסימה 100 מ"ג תוך-ורידי, ספר לרופא אם אתה סובל מזיהום כלשהו, גם אם זהו זיהום קל מאוד.

[...]

חיסונים

[...]

- אם את מניקה, חשוב שתספרי לרופאו של תינוקך ולאנשי צוות רפואי אחרים, שאת מטופלת ברמסימה 100 מ"ג תוך-ורידי לפני שתינוקך מקבל חיסון כלשהו. למידע נוסף ראי סעיף "הריון, הנקה ופוריות".

[...]

ילדים ומתבגרים

המידע הנזכר לעיל מתייחס גם לילדים ומתבגרים. בנוסף:

- היו מקרים של ילדים ומתבגרים שקיבלו תרופות מסוג חוסמי TNF כגון אינפליקסימאב פיתחו סוגי סרטן, כולל סוגים לא רגילים, שלעיתים הסתיימו במוות.
- בהשוואה למבוגרים, יותר ילדים המטופלים באינפליקסימאב פיתחו זיהומים.
- יש לתת לילדים חיסונים מומלצים טרם התחלת הטיפול ברמסימה 100 מ"ג תוך-ורידי.

ניתן לתת לילדים חיסונים מסוימים במהלך הטיפול ברמסימה 100 מ"ג תוך-ורידי, אך הם אינם יכולים לקבל חיסון חי במהלך הטיפול.

[...]

אינטראקציות/תגובות בין תרופתיות

אם אתה לוקח, או אם לקחת לאחרונה, תרופות אחרות כולל תרופות ללא מרשם ותוספי תזונה, ספר על כך לרופא או לרוקח. במיוחד יש ליידע את הרופא או הרוקח אם אתה לוקח:

תרופות אחרות שהינך משתמש בהן או שהשתמשת לאחרונה לטיפול במחלת קרוהן (Crohn's disease) ובדלקת כיבית של המעי הגס (Ulcerative colitis), בדלקת מפרקים שגרונית (Rheumatoid arthritis), בדלקת חוליות מקשחת (Ankylosing spondylitis), בדלקת מפרקים ספחתית (Psoriatic arthritis) או בספחת (Psoriasis), ובמיוחד אם אתה לוקח:

[...]

אין לקבל חיסונים חיים בזמן הטיפול ברמסימה 100 מ"ג תוך-ורידי. במידה והשתמשת ברמסימה 100 מ"ג תוך-ורידי במהלך ההריון או שאת מטופלת ברמסימה 100 מ"ג תוך-ורידי במהלך הנקה, ידעי את הרופא של התינוק או אנשי צוות רפואי אחרים המטפלים בתינוקך כי השתמשת ברמסימה 100 מ"ג תוך-ורידי לפני שהתינוק מקבל חיסון כלשהו.

[...]

הריון, הנקה ופוריות

- יש להיוועץ ברופא לפני השימוש ברמסימה 100 מ"ג תוך-ורידי אם את בהריון, מניקה, חושבת שאת בהריון, או מתכננת להיכנס להריון. ניתן להשתמש ברמסימה 100 מ"ג תוך-ורידי במהלך הריון או הנקה רק אם הרופא חושב כי זה הכרחי עבורך.

[...]

- אם הנך מניקה חשוב שתספרי לרופאו של תינוקך ולאנשי צוות רפואי אחרים, שאת מטופלת ברמסימה 100 מ"ג תוך-ורידי לפני שתינוקך מקבל חיסון כלשהו.

[...]

3. כיצד תשתמש בתרופה?

[...]

שימוש בילדים:

ניתן לתת רמסימה 100 מ"ג תוך-ורידי לילדים לטיפול במחלת קרוהן ובדלקת כיבית של המעי הגס בלבד. על הילדים להיות בגיל 6 שנים או יותר.

[...]

4. תופעות לוואי

[...]

תופעות לוואי שאינן שכיחות (uncommon) - תופעות שמופיעות ב-1-10 משתמשים מתוך 1,000:

[...]

שינויים ברמות כולסטרול ושומנים בדם

[...]

תופעות לוואי ששכיחותן אינה ידועה (תופעות ששכיחותן טרם נקבעה)

סרטן בילדים ובמבוגרים

[...]

תופעות לוואי נוספות בילדים ומתבגרים

בילדים אשר נטלו אינפליקסימאב לטיפול במחלת הקרוהן נראו הבדלים מסוימים בתופעות הלוואי לעומת מבוגרים שלקחו אינפליקסימאב לאותה המחלה. תופעות הלוואי שהתרחשו יותר בילדים הן: רמה נמוכה של תאי דם אדומים (אנמיה), דם בצואה, רמה נמוכה כוללת של תאי דם לבנים (לויקופניה), אדמומיות או הסמקה, זיהומים ויראליים, רמה נמוכה של תאי דם לבנים אשר נלחמים בזיהומים (נויטרופניה), שברים בעצמות, זיהומים חיידקיים, תגובות אלרגיות של מערכת הנשימה.

[...]