הודעה על החמרה (מידע בטיחות) בעלון לצרכן

תאריך: 17.05.2016

שם תכשיר באנגלית: TOPAMAX 25, 50,100,200

מספרי רישום:

טופמקס טבליות 25 מ"ג: 107 55 29031 00

טופמקס טבליות 50 מ"ג: 107 56 29032 00

טופמקס טבליות 100 מ"ג: 107 57 29033 00

טופמקס טבליות 200 מ"ג: 107 58 29034 00

שם בעל הרישום: J-C Health care

ההחמרות המבוקשות

פרק בעלון	טקסט נוכחי	טקסט חדש
אין להשתמש בתרופה מבלי להיוועץ ברופא לפני התחלת הטיפול אם	- אם הנך בהריון , עשויה להיכנס להריון, או חושבת שהנך בהריון (ראי סעיף "הריון והנקה" למידע נוסף). - אם הנך מניקה (ראי סעיף "הריון והנקה" למידע נוסף). - אם הנך סובל או סבלת בעבר מתפקוד לקוי של הכליה, במיוחד במקרה שאתה סובל מאבנים בכליות או שהנך חולה המטופל בדיאליזה - אם יש לך היסטוריה של בעיות הקשורה לנוזלי הדם	~~- אם הנך בהריון , עשויה להיכנס להריון, או חושבת שהנך בהריון (ראי סעיף "הריון והנקה" למידע נוסף).~~ ~~- אם הנך מניקה (ראי סעיף "הריון והנקה" למידע נוסף).~~ - ~~אם הנך סובל או סבלת בעבר~~ מתפקוד לקוי של הכליה, ~~במיוחד במקרה שאתה סובל~~ בעיות בכליות, בייחוד ~~מ~~אבנים בכליות או שהנך חולה המטופל בדיאליזה - ~~אם יש לך~~ היסטוריה של בעיות הקשורה לנוזלי הדם והגוף (חמצת מטבולית metabolic acidosis). - ~~אם הנך סובל או סבלת בעבר מתפקוד לקוי של הכבד~~ בעיות בכבד

הינך סובל מ	והגוף (חמצת מטבולית metabolic acidosis). - אם הנך סובל או סבלת בעבר מתפקוד לקוי של הכבד - אם הנך סובל או סבלת בעבר מתפקוד לקוי של העיניים (בייחוד אם הנך סובל/~~ת~~ מגלאוקומה) - אם יש לך בעיות גדילה - אם הנך מבצע דיאטה קטוגנית (דיאטה דלת פחמימות ורבת שומנים) -אם הנך סובל או סבלת בעבר מדיכאון, בעיות מצב רוח או מחשבות או התנהגות אובדניות. -אם הנך סובל מעצמות פריכות , חלשות, רכות , ירידה בצפיפות עצם (osteomalacia, osteoporosis, osteopenia) -אם הנך סובל מבעיות בריאות או בעיות נשימה -אם הנך משלשל -אם הנך עומד לעבור ניתוח - אם הנך רגיש למזון כלשהו או לתרופה כלשהי, עליך להודיע על כך לרופא לפני נטילת התרופה. -מומלץ שנשים בגיל הפוריות תשתמשנה באמצעי מניעה נאותים (בהתייעצות עם הרופא) במשך הטיפול בתכשיר -אין להפסיק שימוש בתרופה לפני התייעצות עם הרופא.	- ~~אם הנך סובל או סבלת בעבר~~ מתפקוד ~~לקוי של העיניים~~ בעיות בעיניים (בייחוד אם הנך סובל מגלאוקומה) ~~- אם יש לך~~ בעיות גדילה - אם הנך מבצע דיאטה קטוגנית (דיאטה דלת פחמימות ורבת שומנים) -הינך בהריון או עשויה להיכנס להריון (ראי סעיף הריון והנקה למידע נוסף) ~~- אם הנך מבצע דיאטה קטוגנית (דיאטה דלת פחמימות ורבת שומנים)~~ ~~-אם הנך סובל או סבלת בעבר מדיכאון, בעיות מצב רוח או מחשבות או התנהגות אובדניות.~~ ~~-אם הנך סובל מעצמות פריכות , חלשות, רכות , ירידה בצפיפות עצם (osteomalacia, osteoporosis, osteopenia)~~ ~~-אם הנך סובל מבעיות בריאות או בעיות נשימה~~ ~~-אם הנך משלשל~~ ~~-אם הנך עומד לעבור ניתוח~~ ~~- אם הנך רגיש למזון כלשהו או לתרופה כלשהי, עליך להודיע על כך לרופא לפני נטילת התרופה.~~ ~~-מומלץ שנשים בגיל הפוריות תשתמשנה באמצעי מניעה נאותים (בהתייעצות עם הרופא) במשך הטיפול בתכשיר~~ ~~-אין להפסיק שימוש בתרופה לפני התייעצות עם הרופא~~ אם אחד מהמצבים מעלה רלוונטים אליך, שוחח עם הרופא טרם השימוש בתרופה. חשוב כי לא תפסיק לקחת את התרופה ללא התייעצות תחילה עם הרופא. -אין לקחת כל תרופה אחרת המכילה טופירמט הניתנת לך כתחליף לתרופה זו ללא התייעצות תחילה עם הרופא. - יתכן ובזמן השימוש בטופמקס תאבד ממשקלך. יש להישקל באופן קבוע

		בזמן הטיפול עם טופמקס. אם הנך מאבד משקל רב או ילד המטופל בטופמקס אינו עולה מספיק במשקל, יש להיוועץ ברופא.
שימוש בתרופה וצריכת אלכוהול	אין לשתות יינות או משקאות חריפים בתקופת הטיפול עם התרופה	~~אין לשתות יינות או משקאות חריפים בתקופת הטיפול עם התרופה~~ יש להמנע משתיית אלכוהול בתקופת הטיפול עם התרופה.
הריון והנקה	אם הנך בהריון או מניקה, חושבת שהנך עשויה להיות בהריון או מתכננת להיכנס להריון, התייעצי עם הרופא לפני תחילת הטיפול. הרופא יחליט האם את יכולה לקחת טופמקס	אם הנך בהריון או מניקה, חושבת שהנך עשויה להיות בהריון או מתכננת להיכנס להריון, התייעצי עם הרופא לפני תחילת הטיפול. הרופא ישוחח עמך על שימוש באמצעי מניעה, כמו גם האם טופמקס מתאימה לך
נהיגה ושימוש במכונות	השימוש בתרופה יכול לגרום לסחרחורת, עייפות ובעיות ראייה וכן לפגום בערנות ועל כן מחייב זהירות בנהיגה ברכב, בהפעלת מכונות מסוכנות ובכל פעילות המחייבת ערנות. באשר לילדים יש להזהירם מרכיבה על אופניים או ממשחקים בקירבת הכביש וכדומה	השימוש בתרופה יכול לגרום לסחרחורת, עייפות ובעיות ראייה .~~כן לפגום בערנות ועל כן מחייב זהירות בנהיגה ברכב, בהפעלת מכונות מסוכנות ובכל פעילות המחייבת ערנות. באשר לילדים יש להזהירם מרכיבה על אופניים או ממשחקים בקירבת הכביש וכדומה.~~ אל תנהג או תשתמש במכונות מסוכנות לפני שתשוחח תחילה עם הרופא. באשר לילדים יש להזהירם מרכיבה על אופניים או ממשחקים בקרבת הכביש וכדומה.
כיצד תשתמש בתרופה?	אם נטלת מנת יתר יתכן ותחוש ישנוני,עייף או פחות עירני, חוסר קואורדינציה, תנועות גוף לא רגילות, קשיים בעמידה ובהליכה, קושי בדיבור או קושי בריכוז,ראייה כפולה או ראייה מטושטשת, תחושת דיכאון או עצבנות, כאב בטן, פירכוסים לא רגילים, סחרחורת עקב לחץ דם נמוך או פעימות לב לא רגילות. מינון יתר יכול להתרחש כאשר אתה נוטל תרופות אחרות יחד עם טופמקס.	אם נטלת מנת יתר יתכן ותחוש ישנוני,עייף או פחות עירני, חוסר קואורדינציה, ~~תנועות גוף לא רגילות, קשיים בעמידה ובהליכה,~~ קושי בדיבור או קושי בריכוז,ראייה כפולה או ראייה מטושטשת, תחושת דיכאון או עצבנות~~,~~ כאב בטן, פירכוסים ~~לא רגילים~~, סחרחורת עקב לחץ דם נמוך ~~או פעימות לב לא רגילות~~. מינון יתר יכול להתרחש כאשר אתה נוטל תרופות אחרות יחד עם טופמקס

<u>תופעות לוואי</u>	**פנה לרופא באופן מיידי אם הנך מבחין באחת התופעות הבאות:** **תופעות לוואי שכיחות מאד- תופעות שמופיעות ביותר ממשתמש אחד מעשרה**: דיכאון (חדש או החמרה) **תופעות לוואי שכיחות - תופעות שמופיעות ב- 1-10 משתמשים מתוך 100**: פירכוסים, חרדה, עצבנות, שינויים במצב הרוח, בילבול, אי-התמצאות, הפרעות בריכוז, האטה בחשיבה, איבוד זיכרון, בעיות בזיכרון (חדש, שינוי פתאומי או החמרה), אבנים בכליות, השתנה תכופה או כואבת. **תופעות לוואי שאינן שכיחות - תופעות שמופיעות ב- 1-10 משתמשים מתוך 1,000**: עלייה ברמת החומצה בדם (עלול לגרום לבעיות בנשימה כולל קוצר נשימה, איבוד תיאבון, בחילה,הקאות, עייפות מוגזמת ודפיקות לב מהירות ו או לא שוות), ירידה או אובדן ההזעה , מחשבות וניסיונות לפגיעה עצמית חמורה. **תופעות לוואי נוספות אשר במידה ומחמירות יידע את הרופא:** **תופעות לוואי שכיחות מאד- תופעות שמופיעות ביותר ממשתמש אחד מעשרה:** • גודש באף, נזלת ו או כאב גרון • דקירה, כאב ו/או חוסר תחושה בחלקים שונים בגוף • נמנום או ישנוניות • עייפות • סחרחורת • שלשול • בחילה • ירידה במשקל	**פנה לרופא באופן מיידי אם הנך מבחין באחת התופעות הבאות:** **תופעות לוואי שכיחות מאד- תופעות שמופיעות ביותר ממשתמש אחד מעשרה**: דיכאון (חדש או החמרה) **תופעות לוואי שכיחות - תופעות שמופיעות בעד 1 מתוך 10 משתמשים ~~ב- 1-10 משתמשים מתוך 100~~**: פירכוסים, חרדה, עצבנות, שינויים במצב הרוח, בילבול, אי-התמצאות, הפרעות בריכוז, האטה בחשיבה, איבוד זיכרון, בעיות בזיכרון (חדש, שינוי פתאומי או החמרה), אבנים בכליות, השתנה תכופה או כואבת. **תופעות לוואי שאינן שכיחות - תופעות שמופיעות בעד 1 מתוך 100 משתמשים ~~ב- 1-10 משתמשים מתוך 1,000~~**: עלייה ברמת החומצה בדם (עלול לגרום לבעיות בנשימה כולל קוצר נשימה, איבוד תיאבון, בחילה,הקאות, עייפות מוגזמת ודפיקות לב מהירות ו או לא שוות), ירידה או אובדן ההזעה (בייחוד בילדים צעירים החשופים לטמפרטורות גבוהות) , מחשבות וניסיונות לפגיעה עצמית חמורה, איבוד חלק משדה הראייה. **תופעות לוואי נוספות אשר במידה ומחמירות יידע את הרופא:** **תופעות לוואי שכיחות מאד- תופעות שמופיעות ביותר ממשתמש אחד מעשרה:** • גודש באף, נזלת ו או כאב גרון • דקירה, כאב ו/או חוסר תחושה בחלקים שונים בגוף • נמנום או ישנוניות • עייפות • סחרחורת • שלשול • בחילה • ירידה במשקל **תופעות לוואי שכיחות - תופעות שמופיעות בעד 1 מתוך 10 משתמשים ~~ב- 1-10 משתמשים מתוך 100~~**

	תופעות לוואי שכיחות - תופעות שמופיעות בעד 1 מתוך 10 משתמשים ב- 1-10 משתמשים מתוך 100 : אנמיה (ספירת דם נמוכה) • תגובה אלרגית (כגון פריחה בעור, אדמומיות, גרד, נפיחות בפנים, סרפדת) • ירידה בתיאבון או אובדן תיאבון • תוקפנות, חרדה, כעס • התכווצות או עווית בשרירים, פרכוס שרירים, כאבים או חולשת שרירים **תופעות לוואי נדירות - תופעות שמופיעות ב- 1-10 משתמשים מתוך 10,000:** • מצב רוח מרומם באופן לא רגיל • אובדן הכרה • עיוורון בעין אחת, עיוורון זמני, עיוורון לילה • עין עצלה • נפיחות ברקמה שמסביב לעין תופעות לוואי נוספות, ששכיחותן אינה ידועה: • "מקולופטיה" – מחלה של אזור ה"כתם (מקולה)" בעין. זוהי הנקודה הקטנה ברשתית שבה הראייה הינה החדה ביותר. במידה והנך מבחין בשינוי או בירידה בראייה – יש לפנות לרופא. • תסמונת אפידרמיס רעיל Toxic epidermal necrolysis – תופעה עורית חמורה יותר מסינדרום סטיבנס ג'ונסון ומסכנת חיים המאופיינת בשלפוחיות מפושטות והיפרדות העור . (ראה/י תופעות לוואי נדירות). • רמות אמוניה גבוהות בדם. רמות אמוניה גבוהות בדם עלולות להשפיעה על פעילות מנטלית, להאט ערנות,	אנמיה (ספירת דם נמוכה) • תגובה אלרגית (כגון פריחה בעור, אדמומיות, גרד, נפיחות בפנים, סרפדת) • ירידה בתיאבון או אובדן תיאבון • תוקפנות, חרדה, כעס, התנהגות לא רגילה • התכווצות או עווית בשרירים, ~~פרכוס שרירים~~, כאבים או חולשת שרירים **תופעות לוואי נדירות - תופעות שמופיעות בעד 1 מתוך 1000 משתמשים ב- ~~10,000~~ 1-10 משתמשים מתוך ~~10,000~~:** • מצב רוח מרומם באופן לא רגיל • אובדן הכרה • עיוורון בעין אחת, עיוורון זמני, עיוורון לילה • עין עצלה • ~~נפיחות ברקמה שמסביב לעין~~ נפיחות בעין ומסביב לעין תופעות לוואי נוספות, ששכיחותן אינה ידועה: • "מקולופטיה" – מחלה של אזור ה"כתם (מקולה)" בעין. זוהי הנקודה הקטנה ברשתית שבה הראייה הינה החדה ביותר. במידה והנך מבחין בשינוי או בירידה בראייה – יש לפנות לרופא. • תסמונת אפידרמיס רעיל Toxic epidermal necrolysis – תופעה עורית חמורה יותר מסינדרום סטיבנס ג'ונסון ומסכנת חיים המאופיינת בשלפוחיות מפושטות והיפרדות העור . (ראה/י תופעות לוואי נדירות). • ~~רמות אמוניה גבוהות בדם. רמות אמוניה גבוהות בדם עלולות להשפיעה על פעילות מנטלית, להאט ערנות, לגרום לעייפות ולהקאות. הדבר מתרחש כאשר טופמקס נילקח עם תרופה הנקראת חומצה ולפרואית.~~ <u>תופעות לוואי בילדים</u> ~~<u>ומתבגרים</u>~~ תופעות הלוואי בילדים דומות באופן כללי לאלו במבוגרים. אולם תופעות

	לגרום לעייפות ולהקאות. הדבר מתרחש כאשר טופמקס נילקח עם תרופה הנקראת חומצה ולפרואית. <u>תופעות לוואי בילדים ומתבגרים</u> תופעות הלוואי בילדים דומות באופן כללי לאלו במבוגרים אולם, תופעות לוואי מסוימות נראות בתדירות גבוהה יותר בילדים ו/או יכולות להיות חמורות יותר בילדים מאשר מבוגרים. תופעות לוואי אשר הינן חמורות יותר כוללות ירידה או איבוד הזעה ועליה ברמת החומצה בדם. תופעות לוואי שעלולות להתרחש בתדירות גבוהה יותר בילדים כוללות מחלות של דרכי הנשימה העליונות. - יש לשים לב במיוחד בילדים לירידה בכמות ההזעה ועליה בטמפרטורת הגוף.	הלוואי הבאות עלולות להיות שכיחות יותר בילדים מאשר מבוגרים: -בעיות בריכוז -עלייה ברמת החומצה בדם -מחשבות על פגיעה עצמית חמורה -עייפות -ירידה או עלייה בתאבון -תוקפנות, התנהגות לא רגילה -קושי להירדם או לישון -תחושת חוסר יציבות בהליכה -הרגשה לא טובה -ירידה ברמות אשלגן בדם -חוסר הצגה או חוסר תחושה של רגשות -עיניים דומעות -קצב לב איטי או לא רגיל תופעות לוואי אחרות העלולות להתרחש בילדים: **תופעות לוואי שכיחות - מופיעות בעד 1 מתוך 10 משתמשים** -תחושת סיחרור (ורטיגו) -הקאה -חום **תופעות לוואי לא שכיחות - מופיעות בעד 1 מתוך 100 משתמשים** -עליה ברמת האזונופילים (סוג של כדורית דם לבנה) בדם -היפראקטיביות -תחושת חום -קשיי למידה ~~אולם, תופעות לוואי מסוימות נראות בתדירות גבוהה יותר בילדים ו/או יכולות להיות חמורות יותר בילדים מאשר מבוגרים.~~ ~~תופעות לוואי אשר הינן חמורות יותר כוללות ירידה או איבוד הזעה ועליה ברמת החומצה בדם. תופעות לוואי שעלולות להתרחש בתדירות גבוהה יותר בילדים כוללות מחלות של דרכי הנשימה העליונות.~~

		~~יש לשים לב במיוחד בילדים ליבידה בכמות ההזעה ועליה בטמפרטורת הגוף.~~

הודעה על החמרה (מידע בטיחות) בעלון לרופא

פרטים על השינוי/ים המבוקש/ים		
פרק בעלון	**טקסט נוכחי**	**טקסט חדש**
QUALITATIVE AND QUANTITATIVE COMPOSITION		Excipients with known effect Also includes lactose monohydrate: 25 mg tablet contains 30.85 mg lactose monohydrate; 50 mg tablet contains 61.70 mg lactose monohydrate; 100 mg tablet contains 123.40 mg lactose monohydrate; 200 mg tablet contains 43.50 mg lactose monohydrate. For the full list of excipients, see section 6.1.

Migraine **Adults** The recommended total daily dose of topiramate for prophylaxis of migraine headache is 100 mg/day administered in two divided doses. Titration should begin at 25 mg nightly for 1 week. The dosage should then be increased in increments of 25 mg/day administered at 1-week intervals. If the patient is unable to tolerate the titration regimen, longer intervals between dose adjustments can be used. Some patients may experience a benefit at a total daily dose of 50 mg/day. Patients have received a total daily dose up to 200 mg/day. This dose may be benefit in some patients, nevertheless, caution is advised due to an increase incidence of side effects. Dose and titration rate should be guided by clinical outcome (See Pharmacodynamic Properties).	Migraine **Adults** The recommended total daily dose of topiramate for prophylaxis of migraine headache is 100 mg/day administered in two divided doses. Titration should begin at 25 mg nightly for 1 week. The dosage should then be increased in increments of 25 mg/day administered at 1-week intervals. If the patient is unable to tolerate the titration regimen, longer intervals between dose adjustments can be used. Some patients may experience a benefit at a total daily dose of 50 mg/day. Patients have received a total daily dose up to 200 mg/day. Dose and titration rate should be guided by clinical outcome (See Pharmacodynamic Properties).	**Posology And Method Of Administration**

Paediatric population Topamax (topiramate) is not recommended for treatment or prevention of migraine in children due to insufficient data on safety and efficacy. Special Populations **Elderly** No dose adjustment is required in the elderly population providing renal function is intact.		
Migraine prophylaxis in pregnancy and in women of childbearing potential if not using a highly effective methods of contraception.	Migraine prophylaxis in pregnancy and in women of childbearing potential if not using effective methods of contraception.	**Contraindications**
~~Renal Impairment~~ ~~The major route of elimination of unchanged topiramate and its metabolites is via the kidney. Renal elimination is dependent on renal function and is independent of age. Patients with moderate or severe renal impairment may take 10 to 15 days to reach steady-state plasma concentrations as~~	Renal Impairment The major route of elimination of unchanged topiramate and its metabolites is via the kidney. Renal elimination is dependent on renal function and is independent of age. Patients with moderate or severe renal impairment may take 10 to 15 days to reach	**Special warnings and precautions for use**

~~compared to 4 to 8 days in patients with normal renal function.~~

~~As with all patients, the titration schedule should be guided by clinical outcome (i.e., seizure control, avoidance of side effects) with the knowledge that subjects with known renal impairment may require a longer time to reach steady-state at each dose (See Posology and Method of Administration; Pharmacokinetic Properties).~~

Suicide/Suicidal Ideation

~~Antiepileptic drugs (AEDs), including, TOPAMAX®, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. A meta-analysis of randomized placebo-controlled trials of anti-epileptic drugs has shown an increased risk of suicidal ideation and behavior (0.43% on anti-epileptic drugs versus 0.24% on placebo). The mechanism of this risk is not known.~~

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo-controlled trials of AEDs has shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for topiramate.

steady-state plasma concentrations as compared to 4 to 8 days in patients with normal renal function.

As with all patients, the titration schedule should be guided by clinical outcome (i.e., seizure control, avoidance of side effects) with the knowledge that subjects with known renal impairment may require a longer time to reach steady-state at each dose (See Posology and Method of Administration; Pharmacokinetic Properties).

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In double-blind clinical trials, suicide related events (suicidal ideation, suicide attempts, and suicide) occurred at a frequency of 0.5% in topiramate treated patients (46 out of 8,652 patients treated) compared to 0.2% treated with placebo (8 out of 4,045 patients treated). One completed suicide was

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Metabolic Acidosis

Hyperchloremic, non-anion gap, metabolic acidosis (i.e., decreased serum bicarbonate below the normal reference range in the absence of ~~chronic~~ respiratory alkalosis) is associated with topiramate treatment. This decrease in serum bicarbonate is due to the inhibitory effect of topiramate on renal carbonic anhydrase. Generally, the decrease in bicarbonate occurs early in treatment although it can occur at any time during treatment. These decreases are usually mild to moderate (average decrease of 4 mmol/L at doses of 100 mg/day or above in adults and at approximately 6 mg/kg/day in pediatric patients)~~;~~. Rarely, patients can experience decreases to values below 10 mmol/L. Conditions or therapies that predispose to acidosis (such as renal disease, severe respiratory disorders, status epilepticus, diarrhea, surgery, ketogenic diet, or certain medicinal products ~~drugs~~)

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Chronic metabolic acidosis increases the risk of renal stone formation and may potentially lead to osteopenia.

~~Chronic, untreated metabolic acidosis may increase the risk for nephrolithiasis or nephrocalcinosis, and may also result in osteomalacia (referred to as rickets in pediatric patients) and/or osteoporosis with an increased risk for fractures.~~

Chronic metabolic acidosis in pediatric patients can reduce growth rates. The effect of topiramate on ~~growth and~~ bone-related sequelae has not been systematically investigated in pediatric or adult populations.

~~Hyperammonemia and Encephalopathy (Without and With Concomitant Valproic Acid [VPA] Use)~~

~~**Hyperammonemia/Encephalopathy Without Concomitant Valproic Acid (VPA)**~~

~~Topiramate treatment has produced hyperammonemia (in some instances dose-related) in clinical investigational programs of adolescents (12-16 years) who were treated with topiramate monotherapy for migraine prophylaxis (incidence~~

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Hyperammonemia and Encephalopathy (Without and With Concomitant Valproic Acid [VPA] Use)

Hyperammonemia/Encephalopathy Without Concomitant Valproic Acid (VPA)

Topiramate treatment has produced hyperammonemia (in some instances dose-related) in clinical investigational programs of adolescents (12-16 years) who were

~~above the upper limit of normal, 22% for placebo, 26% for 50 mg/day, 41% for 100 mg/day) and in very young pediatric patients (124 months) who were treated with adjunctive topiramate for partial onset epilepsy (8% for placebo, 10% for 5 mg/kg/day, 0% for 15 mg/kg/day, 9% for 25 mg/kg/day). TOPAMAX® is not approved as monotherapy for migraine prophylaxis in adolescent patients or as adjunctive treatment of partial onset seizures in pediatric patients less than 2 years old. In some patients, ammonia was markedly increased (>50% above upper limit of normal). In adolescent patients, the incidence of markedly increased hyperammonemia was 6% for placebo, 6% for 50 mg, and 12% for 100 mg topiramate daily.~~ ~~The hyperammonemia associated with topiramate treatment occurred with and without encephalopathy in placebo-controlled trials and in an open-label, extension trial. Dose-related hyperammonemia was also observed in the extension trial in pediatric patients up to 2 years old. Clinical symptoms of hyperammonemic encephalopathy often include acute alterations in level of consciousness and/or cognitive function with lethargy or vomiting.~~ ~~Hyperammonemia with and without encephalopathy~~	treated with topiramate monotherapy for migraine prophylaxis (incidence above the upper limit of normal, 22% for placebo, 26% for 50 mg/day, 41% for 100 mg/day) and in very young pediatric patients (124 months) who were treated with adjunctive topiramate for partial onset epilepsy (8% for placebo, 10% for 5 mg/kg/day, 0% for 15 mg/kg/day, 9% for 25 mg/kg/day). TOPAMAX® is not approved as monotherapy for migraine prophylaxis in adolescent patients or as adjunctive treatment of partial onset seizures in pediatric patients less than 2 years old. In some patients, ammonia was markedly increased (>50% above upper limit of normal). In adolescent patients, the incidence of markedly increased hyperammonemia was 6% for placebo, 6% for 50 mg, and 12% for 100 mg topiramate daily. The hyperammonemia associated with topiramate treatment occurred with and without encephalopathy in placebo-controlled trials and in an open-label, extension trial. Dose-related hyperammonemia was also observed in the extension trial in pediatric patients up to 2	

~~has also been observed in post-marketing reports in patients who were taking topiramate without concomitant valproic acid (VPA).~~

~~**Hyperammonemia/Encephalopathy With Concomitant Valproic Acid (VPA)**~~

~~Concomitant administration of topiramate and valproic acid (VPA) has been associated with hyperammonemia with or without encephalopathy in patients who have tolerated either drug alone based upon post-marketing reports. Although hyperammonemia may be asymptomatic, clinical symptoms of hyperammonemic encephalopathy often include acute alterations in level of consciousness and/or cognitive function with lethargy or vomiting. In most cases, symptoms and signs abated with discontinuation of either drug. This adverse reaction is not due to a pharmacokinetic interaction.~~

~~Although TOPAMAX® is not indicated for use in infants/toddlers (1-24 months), TOPAMAX® with concomitant VPA clearly produced a dose-related increase in the incidence of treatment-emergent hyperammonemia (above the upper limit of normal, 0% for placebo, 12% for 5 mg/kg/day, 7% for 15 mg/kg/day, 17% for 25 mg/kg/day) in an~~

years old. Clinical symptoms of hyperammonemic encephalopathy often include acute alterations in level of consciousness and/or cognitive function with lethargy or vomiting.

Hyperammonemia with and without encephalopathy has also been observed in post-marketing reports in patients who were taking topiramate without concomitant valproic acid (VPA).

Hyperammonemia/Encephalopathy With Concomitant Valproic Acid (VPA)

Concomitant administration of topiramate and valproic acid (VPA) has been associated with hyperammonemia with or without encephalopathy in patients who have tolerated either drug alone based upon post-marketing reports. Although hyperammonemia may be asymptomatic, clinical symptoms of hyperammonemic encephalopathy often include acute alterations in level of consciousness and/or cognitive function with lethargy or vomiting. In most cases, symptoms and signs abated with discontinuation of either drug. This

~~investigational program. Markedly increased, dose-related hyperammonemia (0% for placebo and 5 mg/kg/day, 7% for 15 mg/kg/day, 8% for 25 mg/kg/day) also occurred in these infants/toddlers. Dose-related hyperammonemia was similarly observed in a long-term extension trial in these very young, pediatric patients .~~ ~~Hyperammonemia with and without encephalopathy has also been observed in post-marketing reports in patients taking topiramate with VPA.~~ ~~The hyperammonemia associated with topiramate treatment appears to be more common when topiramate is used concomitantly with VPA.~~ **~~Monitoring for Hyperammonemia~~** ~~Patients with inborn errors of metabolism or reduced hepatic mitochondrial activity may be at an increased risk for hyperammonemia with or without encephalopathy. Although not studied, topiramate treatment or an interaction of concomitant topiramate and valproic acid treatment may exacerbate existing defects or unmask deficiencies in susceptible persons.~~ ~~In patients who develop unexplained lethargy, vomiting, or changes in mental status associated with any topiramate treatment, hyperammonemic~~	adverse reaction is not due to a pharmacokinetic interaction. Although TOPAMAX® is not indicated for use in infants/toddlers (1-24 months), TOPAMAX® with concomitant VPA clearly produced a dose-related increase in the incidence of treatment-emergent hyperammonemia (above the upper limit of normal, 0% for placebo, 12% for 5 mg/kg/day, 7% for 15 mg/kg/day, 17% for 25 mg/kg/day) in an investigational program. Markedly increased, dose-related hyperammonemia (0% for placebo and 5 mg/kg/day, 7% for 15 mg/kg/day, 8% for 25 mg/kg/day) also occurred in these infants/toddlers. Dose-related hyperammonemia was similarly observed in a long-term extension trial in these very young, pediatric patients . Hyperammonemia with and without encephalopathy has also been observed in post-marketing reports in patients taking topiramate with VPA. The hyperammonemia associated with topiramate treatment appears to be more common when topiramate is used	

~~encephalopathy should be considered and an ammonia level should be measured.~~ ~~Hypothermia with Concomitant Valproic Acid (VPA) Use~~ ~~Hypothermia, defined as an unintentional drop in body core temperature to <35°C, has been reported in association with topiramate use with concomitant valproic acid (VPA) both in conjunction with hyperammonemia and in the absence of hyperammonemia. This adverse reaction in patients using concomitant topiramate and valproate can occur after starting topiramate treatment or after increasing the daily dose of topiramate . Consideration should be given to stopping topiramate or valproate in patients who develop hypothermia, which may be manifested by a variety of clinical abnormalities including lethargy, confusion, coma, and significant alterations in other major organ systems such as the cardiovascular and respiratory systems. Clinical management and assessment should include examination of blood ammonia levels.~~ ~~Paresthesia~~ ~~Paresthesia (usually tingling of the extremities), an effect associated with the use of other carbonic anhydrase inhibitors, appears to be a common effect of TOPAMAX® . Paresthesia was more~~	concomitantly with VPA. **Monitoring for Hyperammonemia** Patients with inborn errors of metabolism or reduced hepatic mitochondrial activity may be at an increased risk for hyperammonemia with or without encephalopathy. Although not studied, topiramate treatment or an interaction of concomitant topiramate and valproic acid treatment may exacerbate existing defects or unmask deficiencies in susceptible persons. In patients who develop unexplained lethargy, vomiting, or changes in mental status associated with any topiramate treatment, hyperammonemic encephalopathy should be considered and an ammonia level should be measured. Hypothermia with Concomitant Valproic Acid (VPA) Use Hypothermia, defined as an unintentional drop in body core temperature to <35°C, has been reported in association with topiramate use with concomitant valproic acid (VPA) both in conjunction with	

~~frequently reported in the monotherapy epilepsy trials and migraine prophylaxis trials than in the adjunctive therapy epilepsy trials. In the majority of instances, paresthesia did not lead to treatment discontinuation.~~

Hyperammonemia and Encephalopathy (Without and With Concomitant Valproic Acid® [VPA] Use)

Hyperammonemia/Encephalopathy Without Concomitant Valproic Acid (VPA)

Topiramate treatment has produced hyperammonemia (in some instances dose-related) in a clinical investigational program in adolescent patients (12 to 17 years) given topiramate for migraine prophylaxis. The incidence of hyperammonemia (above the upper limit of normal reference) at any time in the trial was 9% for placebo, 14% for 50 mg, and 26% for 100 mg topiramate daily. In some patients, hyperammonemia was observed at the end of the trial at the final visit. The incidence of markedly increased hyperammonemia (at least 50% or higher above upper limit of normal) at any time in the trial in adolescent patients was also increased at 100 mg/day (9%) compared to 50 mg topiramate (0%) or placebo (3%). During this trial, markedly increased ammonia levels returned to normal in all but one patient (in whom the ammonia level fell to high instead of markedly abnormal).

Topiramate treatment has produced hyperammonemia in a clinical investigational program in very young pediatric

hyperammonemia and in the absence of hyperammonemia. This adverse reaction in patients using concomitant topiramate and valproate can occur after starting topiramate treatment or after increasing the daily dose of topiramate . Consideration should be given to stopping topiramate or valproate in patients who develop hypothermia, which may be manifested by a variety of clinical abnormalities including lethargy, confusion, coma, and significant alterations in other major organ systems such as the cardiovascular and respiratory systems. Clinical management and assessment should include examination of blood ammonia levels.

Paresthesia

Paresthesia (usually tingling of the extremities), an effect associated with the use of other carbonic anhydrase inhibitors, appears to be a common effect of TOPAMAX® . Paresthesia was more frequently reported in the monotherapy epilepsy trials and migraine prophylaxis trials than in the adjunctive therapy epilepsy trials. In the majority of instances, paresthesia did not lead to treatment

patients (1 to 24 months) who were treated with adjunctive topiramate for partial onset epilepsy (8% for placebo, 10% for 5 mg/kg/day, 0% for 15 mg/kg/day, 9% for 25 mg/kg/day). In some patients, ammonia was markedly increased (≥ 50% above upper limit of normal). The hyperammonemia associated with topiramate treatment occurred with and without encephalopathy in placebo-controlled trials and in an open-label, extension trial of infants with refractory epilepsy. Dose-related hyperammonemia was observed in the extension trial in pediatric patients up to 2 years old. Clinical symptoms of hyperammonemic encephalopathy often include acute alterations in level of consciousness and/or cognitive function with lethargy or vomiting. TOPAMAX is not approved as adjunctive treatment of partial onset seizures in pediatric patients less than 2 years old. Hyperammonemia with and without encephalopathy has also been observed in post-marketing reports in patients who were taking topiramate without concomitant valproic acid (VPA). Hyperammonemia/Encephalopathy With Concomitant Valproic Acid (VPA) Concomitant administration of topiramate and valproic acid (VPA) has been associated with hyperammonemia with or without encephalopathy in patients who have tolerated either drug alone based upon post-marketing reports. Although hyperammonemia may be asymptomatic, clinical symptoms of hyperammonemic encephalopathy often include acute alterations in level of	discontinuation.	

consciousness and/or cognitive function with lethargy or vomiting. In most cases, symptoms and signs abated with discontinuation of either drug. This adverse reaction is not due to a pharmacokinetic interaction.

Although TOPAMAX is not indicated for use in infants/toddlers (1–24 months), TOPAMAX with concomitant VPA clearly produced a dose-related increase in the incidence of treatment-emergent hyperammonemia (above the upper limit of normal, 0% for placebo, 12% for 5 mg/kg/day, 7% for 15mg/kg/day, 17% for 25 mg/kg/day) in an investigational program. Markedly increased, dose-related hyperammonemia (0% for placebo and 5 mg/kg/day, 7% for 15 mg/kg/day, 8% for 25 mg/kg/day) also occurred in these infants/toddlers. Dose-related hyperammonemia was similarly observed in a long-term extension trial in these very young, pediatric patients [see Use in Specific Populations (8.4)].

Hyperammonemia with and without encephalopathy has also been observed in post-marketing reports in patients taking topiramate with VPA.

The hyperammonemia associated with topiramate treatment appears to be more common when topiramate is used concomitantly with VPA.

Monitoring for Hyperammonemia

Patients with inborn errors of metabolism or reduced hepatic mitochondrial activity may be at an increased risk for hyperammonemia with or without encephalopathy. Although not studied, topiramate treatment or an

interaction of concomitant topiramate and valproic acid treatment may exacerbate existing defects or unmask deficiencies in susceptible persons. In patients who develop unexplained lethargy, vomiting, or changes in mental status associated with any topiramate treatment, hyperammonemic encephalopathy should be considered and an ammonia level should be measured		
Oral Contraceptives: In a pharmacokinetic interaction study in healthy volunteers with a concomitantly administered combination oral contraceptive product containing 1 mg norethindrone (NET) plus 35 mcg ethinyl estradiol (EE), TOPAMAX® given in the absence of other medications at doses of 50 to 200 mg/day was not associated with statistically significant changes in mean exposure (AUC) to either component of the oral contraceptive. In another study, exposure to EE was statistically significantly decreased at doses of 200, 400, and 800 mg/day (18%, 21%, and 30%, respectively) when given as adjunctive therapy in patients taking valproic acid. In both studies, TOPAMAX® ~~(50 mg/day to 800 mg/day)~~ (50-200mg/day in healthy volunteers and 200-800mg/day in epilepsy patients) did not significantly affect exposure to NET. Although there was a dose dependent decrease in EE exposure for doses between 200-800 mg/day (in epilepsy patients) ,	**Oral Contraceptives:** In a pharmacokinetic interaction study in healthy volunteers with a concomitantly administered combination oral contraceptive product containing 1 mg norethindrone (NET) plus 35 mcg ethinyl estradiol (EE), TOPAMAX® given in the absence of other medications at doses of 50 to 200 mg/day was not associated with statistically significant changes in mean exposure (AUC) to either component of the oral contraceptive. In another study, exposure to EE was statistically significantly decreased at doses of 200, 400, and 800 mg/day (18%, 21%, and 30%, respectively) when given as adjunctive therapy in patients taking valproic acid. In both studies, TOPAMAX® ~~(~~50 mg/day to 800 mg/day) did not significantly affect exposure to NET. Although there was a dose dependent decrease in EE exposure for doses between	**Interactions With Other Medicinal Products And Other Forms Of Interaction**

there was no significant dose dependent change in EE exposure for doses of 50-200 mg/day (in healthy volunteers). The clinical significance of the changes observed is not known.	200-800 mg/day, there was no significant dose dependent change in EE exposure for doses of 50-200 mg/day . The clinical significance of the changes observed is not known.	
~~USE DURING PREGNANCY~~ ~~Studies in animals have shown reproductive toxicity (see PRECLINICAL SAFETY DATA Section). In rats, topiramate crosses the placental barrier.~~ ~~There are no adequate and well-controlled studies using TOPAMAX® in pregnant women.~~ ~~TOPAMAX® can cause fetal harm when administered to a pregnant woman. Data from pregnancy registries indicate that infants exposed to topiramate *in utero* have an increased risk of congenital malformations (e.g., craniofacial defects, such as cleft lip/palate, hypospadias, and anomalies involving various body systems). This has been reported with topiramate monotherapy and topiramate as part of a polytherapy regimen.~~ ~~Compared with a reference group not taking antiepileptic drugs, registry data for TOPAMAX® monotherapy showed a higher prevalence of low~~	~~USE DURING PREGNANCY~~ ~~Studies in animals have shown reproductive toxicity (see PRECLINICAL SAFETY DATA Section). In rats, topiramate crosses the placental barrier.~~ ~~There are no adequate and well-controlled studies using TOPAMAX® in pregnant women.~~ ~~TOPAMAX® can cause fetal harm when administered to a pregnant woman. Data from pregnancy registries indicate that infants exposed to topiramate *in utero* have an increased risk of congenital malformations (e.g., craniofacial defects, such as cleft lip/palate, hypospadias, and anomalies involving various body systems). This has been reported with topiramate monotherapy and topiramate as part of a~~	**pregnancy**

~~birth weight (<2500 grams). A causal relationship has not been established.~~ ~~In addition, data from these registries and other studies indicate that, compared with monotherapy, there is an increased risk of teratogenic effects associated with the use of anti-epileptic drugs in combination therapy.~~ ~~TOPAMAX® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In treating and counseling women of childbearing potential, the prescribing physician should weigh the benefits of therapy against the risks and consider alternative therapeutic options. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.~~ ~~Topiramate is contraindicated in pregnancy and in women of childbearing potential if an effective method of contraception is not used .~~ **Pregnancy** *Risk related to epilepsy and AEDs in general* Specialist advice should be given to women who are of childbearing potential. The need for treatment	~~polytherapy regimen.~~ ~~Compared with a reference group not taking antiepileptic drugs, registry data for~~ TOPAMAX® monotherapy showed a higher prevalence of low birth weight (<2500 grams). A causal relationship has not been established. In addition, data from these registries and other studies indicate that, compared with monotherapy, there is an increased risk of teratogenic effects associated with the use of anti-epileptic drugs in combination therapy. TOPAMAX® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In treating and counseling women of childbearing potential, the prescribing physician should weigh the benefits of therapy against the risks and consider alternative therapeutic options. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Topiramate is contraindicated in pregnancy	

with AEDs should be reviewed when a woman is planning to become pregnant. In women being treated for epilepsy, sudden discontinuation of AED therapy should be avoided as this may lead to breakthrough seizures that could have serious consequences for the woman and the unborn child. Monotherapy should be preferred whenever possible because therapy with multiple AEDs could be associated with a higher risk of congenital malformations than monotherapy, depending on the associated antiepileptics. *Risk related to topiramate* Topiramate was teratogenic in mice, rats and rabbits (see section 5.3). In rats, topiramate crosses the placental barrier. Clinical data from pregnancy registries indicate that infants exposed to topiramate monotherapy have: • An increased risk of congenital malformations (particularly cleft lip/palate, hypospadias, and anomalies involving various body systems) following exposure during the first trimester. The	and in women of childbearing potential if an effective method of contraception is not used .	

	North American Antiepileptic Drug pregnancy registry data for topiramate monotherapy showed an approximate 3-fold higher incidence of major congenital malformations, compared with a reference group not taking AEDs. In addition, data from other studies indicate that, compared with monotherapy, there is an increased risk of teratogenic effects associated with the use of AEDs in combination therapy. • A higher prevalence of low birth weight (<2500 grams) compared with a reference group. • An increased prevalence of being small for gestational age (SGA; defined as birth weight below the 10th percentile corrected for their gestational age, stratified by sex). The long term consequences of the SGA findings could not be determined. It is recommended that women of child bearing potential use highly effective contraception (see section 4.5) and consider alternative therapeutic		

options. *Indication epilepsy* It is recommended to consider alternative therapeutic options in women of child bearing potential. If topirmate is used in women of child bearing potential, it is recommended that highly effective contraception be used (see section 4.5), and that the woman is fully informed of the known risks of uncontrolled epilepsy to the pregnancy and the potential risks of the medicinal product to the foetus. If a woman plans a pregnancy, a preconceptional visit is recommended in order to reassess the treatment, and to consider other therapeutic options. In case of administration during the first trimester, careful prenatal monitoring should be performed. *Indication migraine prophylaxis*		

Topiramate is contraindicated in pregnancy and in women of childbearing potential if a highly effective method of contraception is not used (see sections 4.3 and 4.5). ~~USE DURING LACTATION~~ Breast-feeding ~~Topiramate is excreted in the milk of lactating rats~~. Animal studies have shown excretion of topiramate in milk. The excretion of topiramate in human milk has not been evaluated in controlled studies. Limited observations in patients suggest an extensive excretion of topiramate into breast milk. Since many medicinal products ~~drugs~~ are excreted in human milk, a decision should be made whether to suspend ~~discontinue~~ breast feeding or to discontinue/ / abstain from topiramate therapy taking into account the importance of the medicinal product to the mother (see section 4.4). ~~the drug, taking into account the importance of the drug to the mother.~~		

Fertility Animal studies did not reveal impairment of fertility by topiramate (see section 5.3). The effect of topiramate on human fertility has not been established.		
Topamax has minor or moderate influence on the ability to drive and use machines.TOPAMAX® acts on the central nervous system and may produce drowsiness, dizziness or other related symptoms.It may also cause visual disturbances and/or blurred vision. These adverse events could potentially be dangerous in patients driving a vehicle or operating machinery, particularly until such time as the individual patient's experience with the medicinal product ~~drug~~ is established.	TOPAMAX® acts on the central nervous system and may produce drowsiness, dizziness or other related symptoms.It may also cause visual disturbances and/or blurred vision. These adverse events could potentially be dangerous in patients driving a vehicle or operating machinery, particularly until such time as the individual patient's experience with the drug is established.	**Effects On Ability To Drive And Use Machines**
~~The highest topiramate overdose reported was calculated to be between 96 and 110 g and resulted in coma lasting 20 to 24 hours followed by full recovery after 3 to 4 days.~~	The highest topiramate overdose reported was calculated to be between 96 and 110 g and resulted in coma lasting 20 to 24 hours followed by full recovery after 3 to 4 days.	**Overdose**

Adverse events:

Undesirable Effects

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of topiramate based on the comprehensive assessment of the available adverse event information. A causal relationship with topiramate cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Clinical Trial Data

The safety of TOPAMAX® was evaluated from a clinical trial database consisting of 4111 patients (3182 on TOPAMAX® and 929 on placebo) who participated in 20 double-blind trials and 2847 patients who participated in 34 open-label trials, respectively, for the treatment of primary generalized tonic-clonic seizures, partial onset seizures, seizures associated with Lennox-Gastaut syndrome, newly or recently diagnosed epilepsy or migraine. The information presented in this section was derived from pooled data.

The majority of all adverse reactions were mild to moderate in severity.

Double-Blind, Placebo-Controlled Data, Adjunctive Epilepsy Trials – Adult Patients

Adverse Drug Reactions (ADRs) reported in ≥1% of TOPAMAX®-treated adult patients in double-blind, placebo-controlled adjunctive epilepsy trials are shown in Table 1. ADRs that had an incidence >5% in the recommended dose range (200 to 400 mg/day) in adults in double-blind, placebo-controlled adjunctive epilepsy studies in descending order of frequency included somnolence, dizziness, fatigue, irritability, weight decreased, bradyphrenia, paresthesias, diplopia, coordination abnormal, nausea, nystgamus, lethargy, anorexia, dysarthria, vision blurred, decreased appetite, memory impairment and diarrhoea.

~~The recommended dose for adjunctive epilepsy therapy in adults is 200-400 mg/day~~

~~***Double-Blind, Placebo-Controlled Data, Adjunctive Epilepsy Trials – Pediatric Patients***~~

~~ADRs reported in >2% of TOPAMAX® treated pediatric patients (2 to 16 years of age) in double blind, placebo-controlled adjunctive epilepsy trials are shown in Table 2. ADRs that had an incidence >5% in the recommended dose range (5 to 9 mg/kg/day) in descending order of frequency included decreased appetite, fatigue, somnolence, lethargy, irritability, disturbance in attention, weight decreased, aggression, rash, abnormal behavior, anorexia, balance disorder, and constipation.~~

Table 2: Adverse Drug Reactions Reported by ≥2% of TOPAMAX®-Treated Pediatric patients in Double-Blind, Placebo-Controlled, Adjunctive Epilepsy Trials

System/Organ Class Adverse Reaction	TOPAMAX (N=104) %	PLACEBO (N=102) %
Metabolism and Nutrition Disorders		
Decreased appetite	19.2	12.7
Anorexia	5.8	1.0
Psychiatric Disorders		
Aggression	8.7	6.9
Abnormal behavior	5.8	3.9
Confusional state	2.9	2.0
Mood altered	2.9	2.0
Nervous System Disorders		
Somnolence	15.4	6.9
Lethargy	13.5	8.8
Disturbance in attention	10.6	2.0
Balance disorder	5.8	2.0
Dizziness	4.8	2.9
Memory impairment	3.8	1.0
Respiratory, Thoracic and Mediastinal Disorders		
Epistaxis	4.8	1.0
Gastrointestinal Disorders		
Constipation	5.8	4.9
Skin and Subcutaneous Tissue Disorders		
Rash	6.7	5.9
General Disorders and Administration Site Conditions		
Fatigue	16.3	4.9
Irritability	11.5	8.8
Gait disturbance	4.8	2.0
Investigations		
Weight decreased	9.6	1.0

The recommended dose for adjunctive epilepsy therapy in children (2-16 years of age) is 5 to 9 mg/kg/day.

~~***Double-Blind, Controlled Data, Monotherapy Epilepsy Trials – Adult Patients***~~

~~ADRs reported in ≥1% of TOPAMAX® -treated adult patients in double-blind, controlled monotherapy epilepsy trials are shown in Table 3. ADRs that had an incidence >5% at the recommended dose (400 mg/day) in descending order of frequency included paraesthesia, weight decreased, fatigue, anorexia, depression, memory impairment, anxiety, diarrhoea, asthenia, dysguesia, and hypoesthesia.~~

Table 3: Adverse Drug Reactions Reported by ≥1% of TOPAMAX® Treated Adult Patients in Double-Blind, Controlled Monotherapy Epilepsy Trials

System/Organ Class Adverse Reaction	TOPAMAX 50 mg/day (N=257) %	TOPAMAX 400 mg/day (N=153) %
Blood and Lymphatic System Disorders		
Anemia	0.8	2.0
Metabolism and Nutrition Disorders		
Anorexia	3.5	12.4
Decreased appetite	2.3	2.6
Psychiatric Disorders		
Depression	4.3	8.5
Anxiety	3.9	6.5
Bradyphrenia	2.3	4.6
Expressive language disorder	3.5	4.6
Depressed mood	0.8	2.6
Mood altered	0.4	2.0
Mood swings	1.6	2.0
Nervous System Disorders		
Paresthesia	18.7	40.5
Memory impairment	1.2	7.2
Dysgeusia	2.3	5.9
Hypoesthesia	4.3	5.2
Balance disorder	1.6	3.3
Dysarthria	1.6	2.6
Cognitive disorder	0.4	2.0
Lethargy	1.2	2.0
Mental impairment	0.8	2.0
Psychomotor skills impaired	0	2.0
Sedation	0	1.3
Visual field defect	0.4	1.3
Eye Disorders		
Dry eye	0	1.3
Ear and Labyrinth Disorders		
Ear pain	0	1.3
Tinnitus	1.6	1.3
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnea	1.2	2.0
Rhinorrhea	0	1.3
Gastrointestinal Disorders		
Diarrhea	5.4	6.5
Paresthesia oral	1.2	3.3
Dry mouth	0.4	2.6
Gastritis	0.8	2.6
Abdominal pain	1.2	2.0
Gastroesophageal reflux disease	0.4	2.0
Gingival bleeding	0	1.3
Skin and Subcutaneous Tissue Disorders		
Rash	0.4	3.9
Alopecia	1.6	3.3
Pruritus	0.4	3.3
Hypoesthesia facial	0.4	2.0
Pruritus generalized	0	1.3

Table 3: Adverse Drug Reactions Reported by ≥1% of TOPAMAX® Treated Adult Patients in Double-Blind, Controlled Monotherapy Epilepsy Trials

System/Organ Class Adverse Reaction	TOPAMAX 50 mg/day (N=257) %	TOPAMAX 400 mg/day (N=153) %
Musculoskeletal and Connective Tissue Disorders		
Muscle spasms	2.7	3.3
Arthralgia	1.9	2.0
Muscle twitching	0.4	1.3
Renal and Urinary Disorders		
Nephrolithiasis	0	2.6
Dysuria	0.8	2.0
Pollakiuria	0.8	2.0
Reproductive System and Breast Disorders		
Erectile dysfunction	0.8	1.3
General Disorders and Administration Site Conditions		
Fatigue	15.2	14.4
Asthenia	3.5	5.9
Irritability	3.1	3.3
Investigations		
Weight decreased	7.0	17.0

The recommended dose for monotherapy therapy in adults is 400 mg/day.

Double-Blind, Monotherapy Pediatric

ADRs reported in TOPAMAX® patients (10 to 16 years of age) in double-blind, monotherapy controlled epilepsy trials are shown in Table 4. ADRs that had an incidence >5% at the recommended dose (400 mg/day) in descending order of frequency included weight decreased, paraesthesia, diarrhoea, disturbance in attention, pyrexia, and alopecia.

Controlled Data, Epilepsy Trials – Patients

Table 4: Adverse Drug Reactions Reported by ≥2% of TOPAMAX®-Treated Pediatric Patients in Double-Blind, Controlled Monotherapy Epilepsy Trials

System/Organ Class Adverse Reaction	TOPAMAX 50 mg/day (N=77) %	TOPAMAX 400 mg/day (N=63) %
Metabolism and Nutrition Disorders		
Decreased appetite	1.3	4.8
Psychiatric Disorders		
Bradyphrenia	0	4.8
Mood altered	1.3	4.8
Depression	0	3.2
Nervous System Disorders		
Paresthesia	3.9	15.9
Disturbance in attention	3.9	7.9
Ear and Labyrinth Disorders		
Vertigo	0	3.2
Respiratory, Thoracic and Mediastinal Disorders		
Epistaxis	0	3.2
Gastrointestinal Disorders		
Diarrhea	3.9	9.5
Vomiting	3.9	4.8
Skin and Subcutaneous Tissue Disorders		
Alopecia	0	6.3
General Disorders and Administration Site Conditions		
Pyrexia	0	6.3
Asthenia	0	4.8
Investigations		
Weight decreased	7.8	20.6
Social Circumstances		
Learning disability	0	3.2

The recommended dose for monotherapy therapy in children 10 years and older is 400 mg/day.

~~***Double-Blind, Placebo-Controlled Data, Migraine Prophylaxis Trials – Adult Patients***~~

~~ADRs reported in ≥1% of TOPAMAX®-treated adult patients in double-blind, placebo-controlled migraine prophylaxis trials are shown in Table 5. ADRs that had an incidence >5% at the recommended dose (100 mg/day) in descending order of frequency included paresthesia, fatigue, nausea, diarrhea, weight decreased, dysguesia, anorexia, decreased appetite, insomnia, hypoesthesia, disturbance in attention, anxiety, somnolence, and expressive language disorder.~~

Table 5: Adverse Drug Reactions Reported by ≥1% of TOPAMAX® Treated Adult Patients in Double-Blind, Placebo-Controlled Migraine Prophylaxis Trials

System/Organ Class Adverse Reaction	TOPAMAX 50 mg/day (N=227) %	TOPAMAX 100 mg/day (N=374) %	TOPAMAX 200 mg/day (N=501) %	PLACEBO (N=436) %
Metabolism and Nutrition Disorders				
Anorexia	3.5	7.5	7.2	3.0
Decreased appetite	5.7	7.0	6.8	3.0
Psychiatric Disorders				
Insomnia	4.8	7.0	5.6	3.9
Anxiety	4.0	5.3	5.0	1.8
Expressive language disorder	6.6	5.1	5.2	1.4
Depression	3.5	4.8	7.4	4.1
Depressed mood	0.4	2.9	2.0	0.9
Confusional state	0.4	1.6	2.0	1.1
Mood swings	1.8	1.3	1.0	0.2
Affect lability	0.4	1.1	0.2	0.2
Bradyphrenia	1.8	1.1	3.4	1.4
Nervous System Disorders				
Paresthesia	35.7	50.0	48.5	5.0
Dysgeusia	15.4	8.0	12.6	0.9
Hypoesthesia	5.3	6.7	7.4	1.4
Disturbance in attention	2.6	6.4	9.2	2.3
Somnolence	6.2	5.1	6.8	3.0
Memory impairment	4.0	4.5	6.2	1.6
Amnesia	3.5	2.9	5.2	0.5
Tremor	1.3	1.9	2.4	1.4
Balance disorder	0.4	1.3	0.4	0
Mental impairment	0.4	1.1	1.8	0.9
Eye Disorders				
Vision blurred	4.0	2.4	4.4	2.5
Ear and Labyrinth Disorders				
Tinnitus	0.4	1.3	1.6	0.7
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnea	1.3	2.7	1.6	1.4
Epistaxis	0.4	1.1	0.6	0.5

Table 5: Adverse Drug Reactions Reported by ≥1% of TOPAMAX® Treated Adult Patients in Double-Blind, Placebo-Controlled Migraine Prophylaxis Trials

System/Organ Class Adverse Reaction	TOPAMAX 50 mg/day (N=227) %	TOPAMAX 100 mg/day (N=374) %	TOPAMAX 200 mg/day (N=501) %	PLACEBO (N=436) %
Gastrointestinal Disorders				
Nausea	9.3	13.6	14.6	8.3
Diarrhea	9.3	11.2	10.0	4.4
Dry mouth	1.8	3.2	5.0	2.5
Paresthesia oral	1.3	2.9	1.6	0.5
Constipation	1.8	2.1	1.8	1.4
Abdominal distension	0	1.3	0.2	0.2
Stomach discomfort	2.2	1.3	1.0	0.2
Gastroesophageal reflux disease	0.4	1.1	1.2	0.5
Musculoskeletal and Connective Tissue Disorders				
Muscle twitching	1.8	1.3	1.8	0.7
General Disorders and Administration Site Conditions				
Fatigue	15.0	15.2	19.2	11.2
Asthenia	0.9	2.1	2.6	0.5
Irritability	3.1	1.9	2.4	0.9
Thirst	1.3	1.6	1.0	0.5
Investigations				
Weight decreased	5.3	9.1	10.8	1.4

The recommended dose for migraine prophylaxis is 100 mg/day.

Other Clinical Trial Data

ADRs reported in double-blind controlled clinical trials in <1% of TOPAMAX®-treated adult patients or at any rate in open-label clinical trials of TOPAMAX®-treated adult patients are shown in Table 6.

Table 6. Adverse Drug Reactions Reported in Double-Blind Controlled Clinical Trials in <1% of TOPAMAX® Treated Adult Patients or at Any Rate in Open-Label Clinical Trials of TOPAMAX® Treated Adult Patients

Table 6. Adverse Drug Reactions Reported in Double-Blind Controlled Clinical Trials in <1% of TOPAMAX®-Treated Adult Patients or at Any Rate in Open-Label Clinical Trials of TOPAMAX®-Treated Adult Patients
Blood and Lymphatic System Disorders Leukopenia, lymphadenopathy, thrombocytopenia **Immune System Disorders** Hypersensitivity **Metabolism and Nutrition Disorders** Acidosis hyperchloremic, hypokalemia, increased appetite, metabolic acidosis, polydipsia **Psychiatric Disorders** Abnormal behavior, anorgasmia, apathy, crying, distractibility, disturbance in sexual arousal, dysphemia, early morning awakening, elevated mood, euphoric mood, flat affect, hallucination, hallucination auditory, hallucination visual, hypomania, initial insomnia, lack of spontaneous speech, libido decreased, listless, loss of libido, mania, middle insomnia, orgasmic sensation decreased, panic attack, panic disorder, panic reaction, paranoia, perseveration, reading disorder, restlessness, sleep disorder, suicidal ideation, suicide attempt, tearfulness, thinking abnormal **Nervous System Disorders** Ageusia, akinesia, anosmia, aphasia, apraxia, aura, burning sensation, cerebellar syndrome, circadian rhythm sleep disorder, clumsiness, complex partial seizure, convulsion, depressed level of consciousness, dizziness postural, drooling, dysesthesia, dysgraphia, dyskinesia, dysphasia, dystonia, essential tremor, formication, grand mal convulsion, hyperesthesia, hypersomnia, hypogeusia, hypokinesia, hyposmia, neuropathy peripheral, parosmia, poor quality sleep, presyncope, repetitive speech, sensory disturbance, sensory loss, stupor, syncope, unresponsive to stimuli **Eye Disorders** Accommodation disorder, altered visual depth perception, amblyopia, blepharospasm, blindness transient, blindness unilateral, glaucoma, lacrimation increased, mydriasis, night blindness, photopsia, presbyopia, scintillating scotoma, scotoma, visual acuity reduced **Ear and Labyrinth Disorders** Deafness, deafness neurosensory, deafness unilateral, ear discomfort, hearing impaired **Cardiac Disorders** Bradycardia, sinus bradycardia, palpitations **Vascular Disorders** Flushing, hot flush, orthostatic hypotension, Raynaud's phenomenon **Respiratory, Thoracic, and Mediastinal Disorders** Dysphonia, dyspnoea exertional, nasal congestion, paranasal sinus hypersecretion **Gastrointestinal Disorders** Abdominal discomfort, abdominal pain lower, abdominal tenderness, breath odour, epigastric discomfort, flatulence, glossodynia, hypoaesthesia oral, oral pain, pancreatitis, salivary

Table 6. Adverse Drug Reactions Reported in Double-Blind Controlled Clinical Trials in <1% of TOPAMAX®-Treated Adult Patients or at Any Rate in Open-Label Clinical Trials of TOPAMAX®-Treated Adult Patients
hypersecretion **Skin and Subcutaneous Tissue Disorders** Anhidrosis, dermatitis allergic, erythema, rash macular, skin discolouration, skin odour abnormal, swelling face, urticaria, urticaria localized **Musculoskeletal and Connective Tissue Disorders** Flank pain, muscle fatigue, muscular weakness, musculoskeletal stiffness **Renal and Urinary Disorders** Calculus ureteric, calculus urinary, hematuria, incontinence, micturition urgency, renal colic, renal pain, urinary incontinence **Reproductive System and Breast Disorders** Sexual dysfunction **General Disorders** Calcinosis, face edema, feeling abnormal, feeling drunk, feeling jittery, malaise, peripheral coldness, sluggishness **Investigations** Blood bicarbonate decreased, crystal urine present, tandem gait test abnormal, white blood cell count decreased

ADRs reported in double-blind controlled clinical trials in <2% of TOPAMAX®-treated pediatric patients or at any rate in open-label clinical trials of TOPAMAX®-treated pediatric patients are shown in Table 7.

Table 7. Adverse Drug Reactions Reported in Double-Blind Controlled Clinical Trials in <2% of TOPAMAX®-Treated Pediatric Patients or at Any Rate in Open-Label Clinical Trials of TOPAMAX®-Treated Pediatric Patients
Blood and Lymphatic System Disorders Eosinophilia, leukopenia, lymphadenopathy, thrombocytopenia **Immune System Disorders**

Table 7. Adverse Drug Reactions Reported in Double-Blind Controlled Clinical Trials in <2% of TOPAMAX®-Treated Pediatric Patients or at Any Rate in Open-Label Clinical Trials of TOPAMAX®-Treated Pediatric Patients
Hypersensitivity **Metabolism and Nutrition Disorders** Acidosis hyperchloremic, hypokalemia, increased appetite **Psychiatric Disorders** Anger, apathy, crying, distractibility, expressive language disorder, initial insomnia, insomnia, middle insomnia, mood swings, perseveration, sleep disorder, suicidal ideation, suicide attempt **Nervous System Disorders** Circadian rhythm sleep disorder, convulsion, dysarthria, dysgeusia, grand mal convulsion, hypoesthesia, mental impairment, nystagmus, parosmia, poor quality sleep, psychomotor hyperactivity, psychomotor skills impaired, syncope, tremor **Eye Disorders** Diplopia, lacrimation increased, vision blurred **Ear and Labyrinth Disorders** Ear pain **Cardiac Disorders** Palpitations, sinus bradycardia **Vascular Disorders** Orthostatic hypotension **Respiratory, Thoracic, and Mediastinal Disorders** Nasal congestion, paranasal sinus hypersecretion, rhinorrhea **Gastrointestinal Disorders** Abdominal discomfort, abdominal pain, dry mouth, flatulence, gastritis, gastroesophageal reflux disease, gingival bleeding, glossodynia, pancreatitis, paresthesia oral, stomach discomfort **Musculoskeletal and Connective Tissue Disorders** Arthralgia, musculoskeletal stiffness, myalgia **Renal and Urinary Disorders** Incontinence, micturition urgency, pollakiuria **General Disorders** Feeling abnormal, hyperthermia, malaise, sluggishness

Postmarketing Data

Adverse events first identified as ADRs during postmarketing experience with TOPAMAX® are included in Table 8. The frequencies are provided according to the following convention:

~~Very common ≥1/10~~
~~Common ≥1/100 to <1/10~~
~~Uncommon ≥1/1,000 to <1/100~~
~~Rare ≥1/10,000 to <1/1,000~~
~~Very rare <1/10,000, including isolated reports~~

~~In Table 8, ADRs are presented by frequency category based on spontaneous reporting rates.~~

Table 8: Adverse Drug Reactions Identified During Postmarketing Experience with TOPAMAX® by Frequency Category Estimated from Spontaneous Reporting Rates

Infections and Infestations
Very rare Nasopharyngitis
Blood and Lymphatic System Disorders
Very rare Neutropenia
Immune System Disorders
Very rare Allergic edema
Very rare Conjuctival edema
Psychiatric Disorders
Very rare Feeling of despair
Eye Disorders
Very rare Abnormal sensation in eye
Very rare Angle closure glaucoma
Very rare Eye movement disorder
Very rare Eyelid edema
Very rare Maculopathy
Very rare Myopia
Respiratory, Thoracic and Mediastinal Disorders
Very rare Cough
Skin and Subcutaneous Tissue Disorders
Very rare Erythema multiforme
Very rare Periorbital edema
Very rare Stevens-Johnson syndrome
Very rare Toxic epidermal necrolysis
Musculoskeletal and Connective Tissue Disorders
Very rare Joint swelling
Very rare Limb discomfort
Renal and Urinary Disorders
Very rare Renal tubular acidosis
General Disorders and Administration Site Reactions
Very rare Generalized edema
Very rare Influenza like illness
Investigations
Very rare Weight increased

~~Additional adverse events:~~
~~Psychotic disorder, photophobia, hepatitis, hepatic failure, increased liver enzyms~~

The safety of topiramate was evaluated from a clinical trial database consisting of 4,111 patients (3,182 on topiramate and 929 on placebo) who participated in 20 double-blind trials and 2,847 patients who participated in 34 open-label trials, respectively, for topiramate as adjunctive treatment of primary generalized tonic-clonic seizures, partial onset seizures, seizures associated with Lennox-Gastaut syndrome, monotherapy for newly or recently diagnosed epilepsy or migraine prophylaxis. The majority of adverse reactions were mild to moderate in severity. Adverse reactions identified in clinical trials, and during post-marketing experience (as indicated by "*") are listed by their incidence in clinical trials in Table 1. Assigned frequencies are as follows:

Very common ≥1/10

Common ≥1/100 to <1/10

Uncommon ≥1/1,000 to <1/100

Rare ≥1/10,000 to <1/1,000

Not known cannot be estimated from the available data

The most common adverse reactions (those with an incidence of >5% and greater than that observed in placebo in at least 1 indication in double-blind controlled studies with topiramate) include: anorexia, decreased appetite, bradyphrenia, depression, expressive language disorder, insomnia, coordination abnormal, disturbance in attention, dizziness, dysarthria, dysgeusia, hypoesthesia, lethargy, memory impairment, nystagmus, paresthesia, somnolence, tremor, diplopia, vision blurred,diarrhoea, nausea, fatigue, irritability, and weight decreased.

Table 1: Topiramate Adverse Reactions					
System Organ	**Very common**	**Common**	**Uncommon**	**Rare**	**Not known**
Infections and infestations	Nasopharyngitis*				
Blood and lymphatic system disorders		Anaemia	Leucopenia, Thrombocytopenia lymphadenopathy, eosinophilia	Neutropenia*	
Immune system disorders		Hypersensitivity			Allergic oedema*
Metabolism and nutrition disorders		Anorexia, decreased appetite	Metabolic acidosis, hypokalaemia, increased appetite, polydipsia	Acidosis hyperchloraemic	
Psychiatric disorders	Depression	Bradyphrenia, insomnia, expressive language disorder, anxiety, confusional state, disorientation, aggression, mood altered, agitation, mood swings, depressed mood, anger, abnormal behaviour	Suicidal ideation, suicide attempt, hallucination, psychotic disorder, hallucination auditory, hallucination visual, apathy, lack of spontaneous speech, sleep disorder, affect lability, libido decreased, restlessness, crying, dysphemia, euphoric mood, paranoia, perseveration, panic attack, tearfulness, reading disorder, initial insomnia,	Mania, panic disorder, feeling of despair*, hypomania	

			flat affect, thinking abnormal, loss of libido, listless, middle insomnia, distractibility, early morning awakening, panic reaction, elevated mood		
Nervous system disorders	Paraesthesia, somnolence Dizziness	Disturbance in attention, memory impairment, amnesia, cognitive disorder, mental impairment, psychomotor skills impaired, convulsion, coordination abnormal, tremor, lethargy, hypoaesthesia, nystagmus, dysgeusia, balance disorder, dysarthria, intention tremor, sedation	Depressed level of consciousness, grand mal convulsion, visual field defect, complex partial seizures, speech disorder, psychomotor hyperactivity, syncope, sensory disturbance, drooling, hypersomnia, aphasia, repetitive speech, hypokinesia, dyskinesia, dizziness postural, poor quality sleep, burning sensation, sensory loss, parosmia, cerebellar syndrome, dysaesthesia, hypogeusia, stupor, clumsiness, aura, ageusia,	Apraxia, circadian rhythm sleep disorder, hyperaesthesia, hyposmia, anosmia, essential tremor, akinesia, unresponsive to stimuli	

			dysgraphia, dysphasia, neuropathy peripheral, presyncope, dystonia, formication		
Eye disorders		Vision blurred, diplopia, visual disturbance	Visual acuity reduced, scotoma, myopia*, abnormal sensation in eye*, dry eye, photophobia, blepharospasm, lacrimation increased, photopsia, mydriasis, presbyopia	Blindness unilateral, blindness transient, glaucoma, accommodation disorder, altered visual depth perception, scintillating scotoma, eyelid oedema*, night blindness, amblyopia	Angle closure glaucoma*, Maculopathy*, eye movement disorder*, conjunctival oedema*
Ear and labyrinth disorders		Vertigo, tinnitus, ear pain	Deafness, deafness unilateral, deafness neurosensory, ear discomfort, hearing impaired		
Cardiac disorders			Bradycardia, sinus bradycardia, palpitations		
Vascular			Hypotension, orthostatic hypotension,	Raynaud's phenomenon	

disorders			flushing, hot flush		
Respiratory, thoracic and mediastinal disorders		Dyspnoea, epistaxis, nasal congestion, rhinorrhoea, cough*	Dyspnoea exertional, Paranasal sinus hypersecretion, dysphonia		
Gastrointestinal disorders	Nausea, diarrhoea	Vomiting, constipation, abdominal pain upper, dyspepsia, abdominal pain, dry mouth, stomach discomfort, paraesthesia oral, gastritis, abdominal discomfort	Pancreatitis, flatulence, gastrooesophageal reflux disease, abdominal pain lower, hypoaesthesia oral, gingival bleeding, abdominal distension, epigastric discomfort, abdominal tenderness, salivary hypersecretion, oral pain, breath odour, glossodynia		
Hepatobiliary disorders				Hepatitis, Hepatic failure	
Skin and subcutaneous tissue		Alopecia, rash,	Anhidrosis, hypoaesthesia facial,	Stevens-Johnson syndrome*	Toxic epidermal

disorders		pruritus	urticaria, erythema, pruritus generalised, rash macular, skin discolouration, dermatitis allergic, swelling face	erythema multiforme*, skin odour abnormal, periorbital oedema*, urticaria localised	necrolysis*
Musculoskeletal and connective tissue disorders		Arthralgia, muscle spasms, myalgia, muscle twitching, muscular weakness, musculoskeletal chest pain	Joint swelling*, musculoskeletal stiffness, flank pain, muscle fatigue	Limb discomfort*	
Renal and urinary disorders		Nephrolithiasis, pollakiuria, dysuria	Calculus urinary, urinary incontinence, haematuria, incontinence, micturition urgency, renal colic, renal pain	Calculus ureteric, renal tubular acidosis*	
Reproductive system and breast disorders			Erectile dysfunction, sexual dysfunction		
General disorders and administration site conditions	Fatigue	Pyrexia, asthenia, irritability, gait disturbance, feeling abnormal, malaise	Hyperthermia, thirst, influenza like illness*, sluggishness, peripheral coldness, feeling drunk, feeling jittery	Face oedema, calcinosis	

Investigations	Weight decreased	Weight increased*	Crystal urine present, tandem gait test abnormal, white blood cell count decreased, Increase in liver enzymes	Blood bicarbonate decreased	
Social circumstances			Learning disability		

* identified as an adverse reaction from postmarketing spontaneous reports. Its frequency was calculated based on clinical trial data.

Paediatric population

Adverse reactions reported more frequently (≥2-fold) in children than in adults in double-blind controlled studies include:

- Decreased appetite
- Increased appetite
- Hyperchloraemic acidosis
- Hypokalaemia
- Abnormal behaviour
- Aggression
- Apathy
- Initial insomnia
- Suicidal ideation
- Disturbance in attention
- Lethargy
- Circadian rhythm sleep disorder

- Poor quality sleep
- Lacrimation increased
- Sinus bradycardia
- Feeling abnormal
- **Gait disturbance.**

Adverse reactions that were reported in children but not in adults in double-blind controlled studies include:

- Eosinophilia
- Psychomotor hyperactivity
- Vertigo
- Vomiting
- Hyperthermia
- Pyrexia
- Learning disability.