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מרץ 2013

רופא/ה נכבד/ה
רוקח/ת נכבד/ת

ברצוננו להביא לידיעתכם את העדכונים בעלונים לרופא ולצרכן של התכשיר:
Concerta

השינויים מסומנים בעלונים המצורפים כאשר הטקסט המודגש באדום הוסף לעלון ואילו הטקסט המחוק בכחול נגרע ממנו.

העלונים מפורסמים במאגר התרופות שבאתר משרד הבריאות. כמו כן ניתן לקבלו מודפס על ידי פניה אלינו לטלפון 09-9591111 .

להלן העדכונים.

בברכה,

ליליאנה בלטר
רוקחת ממונה

עלון לצרכן לפי תקנות הרוקחים (תכשירים) התשמ"ו -1986

התרופה משווקת על פי מרשם רופא בלבד

שם התכשיר צורתו והחוזק

קונסרטה, טבליות בשחרור מושהה

כל טבליה של קונסרטה 18מכילה Methylphenidate Hydrochloride 18mg מתילפנידט הידרוכלוריד
כל טבליה של קונסרטה 27מכילה Methylphenidate Hydrochloride 27mg מתילפנידט הידרוכלוריד
כל טבליה של קונסרטה 36מכילה Methylphenidate Hydrochloride 36mg מתילפנידט הידרוכלוריד
כל טבליה של קונסרטה 54מכילה Methylphenidate Hydrochloride 54mg מתילפנידט הידרוכלוריד

חומרים בלתי פעילים ואלרגניים בתכשיר - ראה סעיף 6 "מידע נוסף"

קרא בעיון את העלון עד סופו בטרם תשתמש בתרופה. עלון זה מכיל מידע תמציתי על התרופה. אם יש לך שאלות נוספות, פני אל הרופא או אל הרוקח.

תרופה זו נרשמה לטיפול עבורך. אל תעביר אותה לאחרים. היא עלולה להזיק להם אפילו אם נראה לך כי מצבם הרפואי דומה.

1. למה מיועדת התרופה?

קונסרטה מיועדת לטיפול בהפרעת קשב וריכוז (ADHD) בילדים, מתבגרים ומבוגרים עד גיל 65, כחלק מתכנית טיפולית הכוללת בדרך כלל טיפול פסיכולוגי, חינוכי וסוציאלי.

קונסרטה יכולה לשפר את הקשב, את הריכוז, ולהקטין אימפולסיביות והיפראקטיביות באנשים עם ADHD.

~~התרופה אינה מיועדת לילדים מתחת לגיל 6~~

קבוצה תרפויטית: מעורר מערכת העצבים המרכזית

2. לפני השימוש בתרופה:

אין להשתמש בתרופה אם:

- התרופה אינה מיועדת לילדים מתחת לגיל 6
- אתה רגיש (אלרגי) לחומר הפעיל (Methylphenidate Hydrochloride) או לכל אחד מהמרכיבים הנוספים אשר מכילה התרופה (ראה סעיף 6 –"מידע נוסף").
- אתה סובל מבעיות בבלוטת התריס .
- יש לך גידול של בלוטת האדרנל (יותרת הכלייה) בשם Phaeochromocytoma .
- יש לך בעיות אכילה , כאשר אתה לא מרגיש רעב או לא רוצה לאכול, כגון "אנורקסיה נרבוזה".
- יש לך לחץ דם מאוד גבוה או היצרות של כלי דם, אשר עשוייה לגרום לכאבים בזרועות וברגליים.
- אתה סובל או סבלת בעבר מבעיות לב כגון התקף לב, קצב לב לא סדיר, כאבים ואי נוחות בחזה (אנגינה), אי ספיקת לב, מחלת לב או בעיה מולדת בלב.
- אתה סובל או סבלת בעבר מבעיות בכלי הדם במוח, כגון שבץ, התנפחות או החלשות של כלי דם (מפרצת-אנוריזם מוחי), היצרות או חסימה של כלי דם, או דלקת של כלי הדם (וסקוליטיס).
- אם הינך סובל מחרדות או ממתח נפשי חמורים מכיון שהטיפול בתרופה זו עלול להחמירם.

- אם הינך סובל בבעיות נפשיות כגון סכיזופרניה, פסיכוזות, הפרעות חמורות במצב הרוח כגון דיכאון, מאניה, מחשבות התאבדות.
- אם הינך סובל או שידועה היסטוריה משפחתית של סינדרום טורט (Tourette's Syndrome) המתבטא בעויתות חוזרות בלתי נשלטות בחלקי גוף שונים, ו/או בחוסר שליטה על חזרות מילוליות כלשהן.
- אם הינך סובל מלחץ תוך עיני מוגבר (גלאוקומה)
- אם הינך נוטל כעת או נטלת במהלך 14 יום לפני התחלת הטיפול בקונסרטה תכשירים לטיפול בדכאון ממשפחת מעכבי האנזים מונואמין אוקסידז MAO (monoamine oxidase inhibitor) .
- בכל מקרה שאין באפשרותך לבלוע טבליות בשלמותן.

אל תיטול או אל תתן לילדך קונסרטה אם אחת התופעות המתוארות מעלה נוגעות לך או לילדך. אם אינך בטוח פנה לרופא או לרוקח לפני נטילת התרופה, זאת משום שנטילת קונסרטה עלולה להחמיר תופעות אלו.

אזהרות מיוחדות הנוגעות לשימוש בתרופה:

- שימוש ממושך בלתי מבוקר עלול לגרום לתלות ולתופעות פסיכוטיות, לכן אין להשתמש בתרופה זו לעיתים קרובות או תקופה ממושכת בלי להיוועץ ברופא.
- השימוש בתרופה זו עלול לגרום לטשטוש הראיה
- מוות פתאומי דווח בהקשר לשימוש בתכשירים לטיפול בהפרעת קשב וריכוז (ADHD) בילדים הסובלים ממום בלב. בדרך כלל, אין להשתמש בקונסרטה בילדים, מתבגרים או מבוגרים הסובלים ממום בלב.
- יש לידע את הרופא במידה וקיימת היסטוריה משפחתית של מוות פתאומי או מוות שקשור לבעיות לב. במהלך הטיפול יש לעקוב אחר לחץ הדם וקצב הלב בתדירות שתקבע ע"י הרופא
- יש לבצע בדיקות דם תקופתיות במקרה של שימוש ממושך בתרופה.
- שימוש לטווח ארוך בתכשיר זה בילדים עלול לגרום להאטה בגדילה (במשקל או בגובה). הרופא רשאי להפסיק את הטיפול בתרופה במקרה כזה.
- אם אתה עומד לעבור ניתוח, יש ליידע את הרופא כי אתה נוטל קונסרטה. אין לקחת קונסרטה ביום הניתוח במידה ומשתמשים בסוג מסויים של מאלחש מאחר וקיים סיכוי לעלייה פתאומית בלחץ הדם במהלך הניתוח.
- קונסרטה יכולה לתת תוצאה חיובית שגויה בבדיקות מעבדה לגילוי אמפטמינים. הדבר כולל בדיקות הנערכות בענפי ספורט.
- ~~קונסרטה מכילה לקטוז. אם יש לך אי סבילות לסוכרים מסוימים יש להתייעץ עם הרופא לפני תחילת השימוש~~
- אם אתה רגיש למזון כלשהו או לתרופה כלשהי, עליך להודיע על כך לרופא לפני נטילת התרופה.

לפני התחלת הטיפול בקונסרטה ספר לרופא אם הינך סובל מאחד מהמצבים הבאים:

-אם את בהריון, מניקה או מתכוננת להרות, יש לדווח לרופא אשר יחליט האם הנך יכולה ליטול קונסרטה.

אם אתה סובל מבעיות בכבד או בכליות

אם יש לך בעיות בבליעה או בבליעת טבליות בשלמותן

- אם אתה סובל מהיצרות או חסימה במערכת העיכול (בושט, בקיבה או במעי) ~~קשיים בבליעה~~
- אם אתה סובל מפרכוסים, אפילפסיה, EEG לא תקין.
- אם אתה מכור או שהיית בעבר מכור לאלכוהול או לתרופות כלשהן או לסמי רחוב .
- אם אתה או מישהו ממשפחתך סובלים מסינדרום טורט, עויתות חוזרות בלתי נשלטות בחלקי גוף שונים, או חוסר שליטה על חזרות מילוליות כלשהן.
- אם אתה סובל או שסבלת בעבר מבעיות בתפקוד הלב (כולל היסטוריה משפחתית של מחלות לב), ממחלת כלי דם מתקדמת, מלחץ דם גבוה, שבץ או מהתקף לב

- בכל מצב רפואי שמושפע מיתר לחץ דם או עליה בדופק (כמו יתר פעילות של בלוטת התריס, אנגינה פקטוריס חמורה, או בעיות בקצב הלב).
- אם אתה סובל ממחלות הקשורות לפגם במבנה הלב או אם קיימת היסטוריה משפחתית של מוות פתאומי או מוות ממחלות לב. מוות פתאומי דווח בהקשר לשימוש בתכשירים לטיפול בהפרעת קשב וריכוז (ADHD) בילדים הסובלים ממום בלב. בדרך כלל, אין להשתמש בקונסרטה בילדים, מתבגרים או מבוגרים הסובלים ממום בלב.
- אם אתה מטופל ~~בתרופות~~ כנגד דיכאון או שהינך בעל סימפטומים של דיכאון כגון תחושת עצבות, תחושת חוסר הערכה עצמית ופסימיות או אם יש היסטוריה משפחתית של דיכאון או התאבדות
- אם אתה סובל ממחלה דו קוטבית (בי פולירית): תנודות קיצוניות במצבי הרוח. מצב הרוח נע בין מאניה - מצב רוח מרומם באופן קיצוני - לבין דיכאון.
- אם אתה סובל מהזיות (ממחשבות ~~או~~, חזיונות ~~לא שגרתיים~~ או ~~מ~~שמיעת קולות לא שגרתיים) או שאובחנה אצלך פסיכוזה, סוג של מחלת נפש.
- אם אתה סובל מדלוזיות (מחשבות ואמונות שאינן תואמות למציאות), מרגיש חשדן באופן מוגזם (פרנויה), מרגיש במתח, חרדה או אי שקט.
- אם התנהגותך הופכת לתוקפנית או שהתנהגות תוקפנית קיימת מחריפה
- אם העלייה במשקל ו/או הצמיחה לגובה בילדים ובני נוער מואטת. ייתכן והרופא ירצה לעקוב בקפדנות אחר המשקל והגובה.
- אם אתה סובל מבעיות בעיניים כגון ראייה מעורפלת, גלאוקומה, טשטוש ראייה, הפרעות ראייה ~~אם התפתח אחד מהמצבים או התסמינים המפורטים מעלה במהלך הטיפול בקונסרטה, יש לדווח לרופא מיידית.~~

אמור לרופא אם אתה סובל מאחד המצבים הרשומים מעלה לפני תחילת הטיפול עם קונסרטה. זאת ומאחר ומתיל פנידט (Methylphenidate) יכול להחמיר מצבים אלה. הרופא יחליט האם אתה יכול להשתמש בקונסרטה.

אם אתה לוקח, או אם לקחת לאחרונה, תרופות אחרות כולל תרופות ללא מרשם ותוספי מזון, ספר על כך לרופא או לרוקח.

אין ליטול קונסרטה אם אתה נוטל כעת או נטלת במהלך 14 יום לפני התחלת הטיפול בקונסרטה ~~את~~ תכשירים לטיפול בדכאון ממשפחת מעכבי האנזים מונואמין אוקסידז (MAOI), ~~אין ליטול קונסרטה~~ נטילה של מעכבי האנזים מונואמין אוקסידז יחד עם קונסרטה עלול לגרום לעלייה פתאומית בלחץ הדם.

במיוחד יש ליידע את הרופא או הרוקח אם אתה לוקח את אחד הבאים,

~~קונסרטה עלולה לשנות את האופן בו גופך מגיב לתרופות מסוימות, (ייתכן והרופא יצטרך לשנות את המנה של התרופות הללו אם הן ניטלות ביחד עם קונסרטה) בכלל זה:~~

- תרופות לטיפול בדיכאון כגון נוגדי דיכאון טריציקליים ומעכבי ספיגת סרוטונין (כגון פלואוקסטין, אימיפרמין, אמיטריפטילין, פרוקסטין, פלווקסמין, ציטלופרם ואחרים).
- תרופות לטיפול באפילפסיה (כגון: פנוברביטל, פניטואין, פרימדון)
- תרופות להורדת או העלאת לחץ הדם.
- אגוניסטים לרצפטור מסוג אלפה 2 כגון קלונידין
- תרופות המשפיעות על המערכת הדופאמינרגית (לטיפול במחלת הפרקינסון או בפסיכוזה)
- תכשירים מסויימים לטיפול בשיעול או צינון אשר מכילים חומרים העלולים להשפיע על לחץ הדם.

- תרופות נגד קרישת דם. **(כגון וורפרין ואחרים)**

שימוש בתרופה ומזון

יש לבלוע את הטבליה בשלמותה עם מים או נוזל אחר.

הטבליה יכולה להילקח עם או ללא מזון

שימוש בתרופה וצריכת אלכוהול

אל תשתה אלכוהול במהלך השימוש בתרופה. אלכוהול יכול להחמיר את תופעות הלוואי של התרופה. זכור כי ישנם מאכלים ותרופות המכילות אלכוהול.

הריון והנקה

אם את בהריון, מניקה או מתכוננת להרות, יש לדווח לרופא אשר יחליט האם הנך יכולה ליטול קונסרטה.

נהיגה ושימוש במכונות

חומרים ממריצים עלולים לפגום ביכולתך להפעיל מכונות מסוכנות או לנהוג ברכב.

יש לפעול בזהירות, ולבצע פעולות אלו רק כאשר אתה בטוח שהתרופה אינה משפיעה על יכולתך לנהוג או להפעיל מכונות מסוכנות. ~~בעת שימוש בתרופה, יש לפעול בזהירות בביצוע הפעולות הללו עד שהינך בטוח שהתרופה אינה משפיע על יכולתך לפעול בזהירות המתאימה~~.

מידע חשוב על חלק מהמרכיבים של התרופה

-קונסרטה מכילה לקטוז. אם יש לך אי סבילות לסוכרים מסויימים יש להתייעץ עם הרופא לפני תחילת השימוש

3. כיצד תשתמש בתרופה:

תמיד יש להשתמש לפי הוראות הרופא.

עליך לבדוק עם הרופא או הרוקח אם אינך בטוח לגבי אופן השימוש.

המינון ואופן הטיפול יקבעו על ידי הרופא בלבד.

יש ליטול את הטבליה פעם ביום, בבוקר.

המתן פרק זמן של יממה בטרם תיטול מנה נוספת

~~תרופה זו אינה מיועדת בדרך כלל לילדים ותינוקות מתחת לגיל 6.~~

יש לבלוע את הטבליה בשלמותה עם מים או נוזל אחר.

קונסרטה הינה טבליה בשיחרור ממושך. היא משחררת את התרופה לגוף לאורך היום. על כן אין ללעוס, אין לחצות או לשבור את הטבליה.

טבלית קונסרטה לא מתמוססת בשלמות בגוף לאחר שכל התרופה השתחררה, ייתכן כי תבחין לעיתים בטבליה ריקה בצואה, דבר זה נורמלי.

הטבליה יכולה להילקח עם או ללא מזון.

אין לעבור על המנה המומלצת

אם שכחת ליטול את התרופה בזמן הדרוש, אין לטול מנה כפולה. קח את המנה הבאה בזמן הרגיל והוועץ ברופא.

אם נטלת בטעות מינון יתר או אם בטעות בלע ילד מן התרופה, פנה מיד לרופא או לחדר מיון של בית חולים והבא אריזת התרופה איתך

יש להתמיד בטיפול כפי שהומלץ על ידי הרופא

ייתכן כי הרופא יפסיק מדי פעם את הטיפול בקונסרטה לתקופה מסויימת על מנת לבדוק סימני ADHD .

ייתכן והרופא ישלח אותך לבדיקות דם תקופתיות, יינטר באופן קבוע את קצב הלב ולחץ הדם במהלך הטיפול עם קונסרטה.

חש לנטר באופן קבוע את הגובה והמשקל של ילדים הנוטלים קונסרטה. ייתכן והטיפול בקונסרטה יופסק במידה ותמצא בעיה במהלך ניטור זה.

אם אתה מפסיק את נטילת התרופה, הסימפטומים של הפרעת הקשב והריכוז עלולים לחזור, או תופעות לוואי לא רצויות כגון דיכאון עלולות להופיע. ייתכן והרופא ירצה להוריד את מינון התרופה באופן הדרגתי, לפני הפסקה מוחלטת של התרפה. התייעץ עם הרופא טרם הפסקת השימוש בתרופה.

אין ליטול תרופות בחושך! בדוק התווית והמנה בכל פעם שהינך נוטל תרופה. הרכב משקפיים אם הינך זקוק להם.

אם יש לך שאלות נוספות בנוגע לשימוש בתרופה, היוועץ ברופא או ברוקח.

4. תופעות לוואי

כמו בכל תרופה, השימוש בקונסרטה טבליות עלול לגרום לתופעות לוואי בחלק מהמשתמשים. אל תיבהל למקרא רשימת תופעות הלוואי. יתכן ולא תסבול מאף אחת מהן.

יש לפנות מיד לרופא אם אתה מרגיש את אחד מהבאים :

- סימנים של אלרגיה כגון פריחה, גרד או חרלת על העור, נפיחות של הפנים, שפתיים, לשון או חלקים אחרים בגוף, קוצר נשימה, ציפצופים או קושי בנשימה.
- שיתוק או בעיות בתנועה ובראייה, קשיים בדיבור (אלו יכולים להיות סימנים של בעיות של כלי הדם במוח), דלקת או חסימה של עורקים במוח.
- כאבים בחזה או עליה בקצב לב או דפיקות לב, קוצר נשימה,עלפון , התקף לב, מוות פיתאומי.
- תנועות בלתי נשלטות, עויתות, פרכוסים
- חום גוף גבוה, נוקשות שרירים, ירידה בעירנות, אובדן הכרה (נדיר): הפסק טיפול ופנה לרופא
- מחשבות או חלומות חריגים, בלבול, חוסר עניין, שינוי בדפוסי שינה, דבור לא ברור, מחשבה או רצון להתאבד, נסיונות התאבדות, תחושת ריגוש לא רגילה, פעלתנות יתר וחוסר מעצורים (מאניה),
- חסימה בוושט, בקיבה, במעי הדק או הגס, במטופלים אשר סובלים כבר מהיצרות באיברים אלו.
- עליה בלחץ דם, חרדה, עצבנות, דיכאון, שינויים קיצוניים במצב הרוח, עוינות, פריחה, חום, פציעות מקריות חוזרות, הזיות, תנועתיות יתר של שרירים, דימום מהאף, נשירת שיער, גרד, תכיפות יתר בהשתנה, דם בשתן, האטה בקצב הגדילה, הפרעות מנטליות, הפרעות בעור, ראייה כפולה, טשטוש ראייה, קשיים במיקוד ראייה
- בשימוש ממושך בילדים, קונסרטה עלולה לגרום להאטה בקצב הגדילה (גובה ומשקל). הרופא יבצע מעקב אחר המשקל והגובה של הילד. אם ישנה האטה, יתכן כי הטיפול עם קונסרטה יופסק לזמן מה.

תופעות לוואי נוספות :

<u>תופעות לוואי שכיחות (העלולות להופיע ביותר מ 10 חולים מכל 100)</u>

כאב ראש, ירידה בתיאבון, יובש בפה, בחילה, נדודי שינה.

<u>תופעות לוואי נפוצות (העלולות להופיע בפחות מ 10 חולים מכל 100)</u>

הצטננות, דלקת גרון, דלקת בסינוסים, ~~ירידה בתיאבון~~, אובדן תאבון, חרדה, קושי להירדם, נדודי שינה ,מצב רוח ירוד, אי שקט, חוסר מנוחה, עצבנות, דיבור בלתי נשלט ותנועות גוף לא נשלטות (טורט), עוויתות שרירים , שחיקת שיניים, דיכאון, אי יציבות רגשית, ירידה בדחף מיני, התקפי חרדה, מתח, תוקפנות, שינויי מצב רוח, תחושת בילבול, סחרחורת, רעד, תחושת עקצוץ, כאב ראש, תחושת רוגע, קושי במיקוד הראייה, טשטוש ראייה, תחושה של ראש מסתובב, קצב לב מהיר, ~~עליה בקצב הלב~~, דפיקות לב, עלייה בלחץ הדם, תחושת

חום, שיעול, כאב גרון, קוצר נשימה, כאב בטן, הקאות, שלשול, קשיי עיכול, עצירות, הזעה מוגברת, פריחה בעור, גרד בעור, התכוצויות שרירים,קושי להגיע או לשמר זקפה, רגזנות, תשישות, חום, צמא, חולשה, הרגשת מתח ועצבנות, אובדן משקל, עליה ברמת האנזים אלנין אמינוטרנספרז בדם.

תופעות לוואי מופיעות לעיתים קרובות שכיחות של עד 1:100: ~~לא נפוצות (כאלו שעלולות להתרחש בפחות מ 1 מתוך 100 מהחולים):~~

ספירת כדוריות לבנות נמוכה, תחושת כעס, עירנות יתר, שינויים במצב הרוח, תנודות תכופות במצב הרוח, בעיות שינה, נטיה לבכי, נמנום, ישנוניות, פעילות מוחית מוגברת, יובש בעיניים, לחץ דם גבוה, פריחה בעור, קוצר נשימה, רשרוש בלב, מחשבה או רצון להתאבד, דם בשתן, מודעות ייתר לסביבה

תופעות לוואי מופיעות לעיתים רחוקות בין 1:100 ל- 1:1000 ~~נדירות (העלולות להופיע בפחות מ 1 מתוך 1000 מהחולים):~~

תגובה אלרגית כגון נפיחות, תגובה אלרגית חמורה, התנפחות של האוזן, שלפוחיות על פני העור, קילופי עור, חרלת (מחלת עור), גירוד, גירוי בעור, גבשושיות ו/או זיהום העור, ירידה בתגובה לתרופה, התנפחות השדיים בגברים.

תופעות לוואי מופיעות לעיתים נדירות ששכיחותן בין 1:1000 ל- 1:10000: ~~נדירות (העלולות להופיע בפחות מ 1 מתוך 10000 מהחולים):~~

ירידה בספירת כדוריות דם אדומות, ירידה בספירת כדוריות לבנות, ירידה בספירת טסיות בדם (טרמבוציטים), ספירת טסיות נמוכה מאד, דימום המאפיין ספירת טסיות נמוכה מאד, הרגשת חוסר התמצאות (דיסאורנטציה), הזיות שוא (חזותיות או קוליות), התרגשות יתר, דיבור מוגזם, התקף אפילפסיה, תנועה בלתי רצונית של השפתיים, הלשון או של איברים אחרים, ראייה כפולה, אישונים מורחבים, ראייה לא תקינה, דופק איטי, דופק לא סדיר, "דילוג" על פעימות לב, תחושת קור באצבעות, הידים והרגלים, נשירת שיער במקומות שונים בגוף, אדמומיות בעור, כאבי מפרקים, כאבי שרירים, עוויתות שרירים, כאבים בחזה, אי נוחות בחזה, ירידה בהשפעת התרופה, חום גבוה, עליה ברמת האנזים alkaline phosphates בדם, עליה ברמת בילירובין בדם, עליה ברמת אנזימי הכבד בדם, ספירת כדוריות וטסיות לבנות לא תקינה, ניסיון התאבדות.

~~תתכן הפרשת חלקים מהטבליה או הטבליה בשלמותה בצואה. אין מקום לדאגה מתופעה זו.~~

תופעות לוואי כתוצאה ממינון יתר:

בחילה, חרדה, רעד, עליה בתנועות בלתי נשלטות, עיוות שרירים, פירכוסים (ואחריהם קומה) , תחושת שמחה גדולה, תחושת בילבול, הזיות (ראיה, תחושה ושמיעה של דברים לא מציאותיים), הזעה, הסמקה, כאב ראש, חום גבוה, שינויים בקצב הלב , לחץ דם גבוה, הרחבת אישוני, יובש באף ובפה.

אם אתה סובל מאחת מהתופעות לוואי המוזכרות כאן, אם אחת מתופעות הלוואי מחמירה או כאשר אתה סובל מתופעות לוואי שלא הוזכרה בעלון, עליך להתייעץ עם הרופא

5. איך לאחסן את התרופה?

- מנע הרעלה! תרופה זו וכל תרופה אחרת יש לשמור במקום סגור מחוץ להישג ידם של ילדים ו/או תינוקות ועל ידי כך תמנע הרעלה. אל תגרום להקאה ללא הוראה מפורשת מהרופא.
- אין להשתמש בתרופה אחרי תאריך התפוגה (exp. Date) המופיע על גבי האריזה. תאריך התפוגה מתייחס ליום האחרון של אותו חודש.
- יש לאחסן בטמפרטורה נמוכה מ ~~שאינה עולה על~~ - 25°C .

- יש לשמור את הבקבוק סגור היטב
- יש להרחיק מהישג ידם ומשדה ראייתם של ילדים.

6. מידע נוסף

נוסף על החומרים הפעילים התרופה מכילה גם:

Butylated hydroxytoluene, carnauba wax, cellulose acetate, hypromellose, phosphoric acid, poloxamer, polyethylene oxides, povidone, sodium chloride, stearic acid, succinic acid, ferric oxides,.Cellulose acetate, opadry yellow, opadry clear, opadry gray, opadty white, opadry red, opacode black

כל טבליה של 18mg מכילה: Sodium Chloride 18mg סודיום כלוריד
כל טבליה של 27mg מכילה: Sodium Chloride 18mg סודיום כלוריד
כל טבליה של 36mg מכילה: Sodium Chloride 36mg סודיום כלוריד
כל טבליה של 54mg מכילה: Sodium Chloride 36mg סודיום כלוריד

כיצד נראית התרופה ומה תוכן האריזה:
18 מ"ג: טבליה בצורת קפסולה בצבע צהוב עליה הטבעה בדיו שחור של הסימון "alza 18"
27 מ"ג: טבליה בצורת קפסולה בצבע אפור עליה הטבעה בדיו שחור של הסימון "alza 27"
36 מ"ג: טבליה בצורת קפסולה בצבע לבן עליה הטבעה בדיו שחור של הסימון "alza 36"
54 מ"ג: טבליה בצורת קפסולה בצבע חום-אדום עליה הטבעה בדיו שחור של הסימון "alza54"
כל אריזה מכילה 30 טבליות

בעל הרישום וכתובתו : ג'יי סי הלת'קר בע"מ, קיבוץ שפיים, 60990.
שם היצרן: אורטו מקניל פרמהצוטיקל אינק. (GPSG), ארה"ב

עלון זה נבדק ואושר ע"י משרד הבריאות בתאריך:
מספר רישום התרופה בפנקס התרופות הממלכתי במשרד הבריאות :

קונסרטה 18 מ"ג – 126-85-30589
קונסרטה 27 מ"ג – 134-47-31123
קונסרטה 36 מ"ג – 126-86-30590
קונסרטה 54 מ"ג – 126-87-30591

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CONCERTA® safely and effectively. See full prescribing information for CONCERTA®.

CONCERTA® (methylphenidate HCl) Extended-Release Tablets CII

WARNING: DRUG DEPENDENCE

See full prescribing information for complete boxed warning.

CONCERTA® should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence, with varying degrees of abnormal behavior.

INDICATIONS AND USAGE

CONCERTA® is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) (1)

DOSAGE AND ADMINISTRATION

- CONCERTA® should be taken once daily in the morning and swallowed whole with the aid of liquids. CONCERTA® should not be chewed or crushed. CONCERTA® may be taken with or without food. (2.1)
- For children and adolescents new to methylphenidate, the recommended starting dosage is 18 mg once daily. Dosage may be increased by 18 mg/day at weekly intervals dose above 54 mg/day in children and 72 mg/day in adolescents are not recomended. (2.2)
- For adult patients new to methylphenidate, the recommended starting dose is 18 or 36 mg/day. Dosage may be increased by 18 mg/day at weekly intervals dose above 72 mg/day for adults are not recomended. (2.2)
- For patients currently using methylphenidate, dosing is based on current dose regimen and clinical judgment. (2.3)

DOSAGE FORMS AND STRENGTHS

Tablets: 18, 27, 36, and 54 mg (3)

CONTRAINDICATIONS

- Known hypersensitivity to the product (4.1)
- Marked anxiety, tension, or agitation (4.2)
- Glaucoma (4.3)
- Ties or a family history or diagnosis of Tourette's syndrome (4.4)
- Do not use CONCERTA® in patients currently using or within 2 weeks of using an MAO inhibitor (4.5)

WARNINGS AND PRECAUTIONS

- Serious Cardiovascular Events: Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Sudden death, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses for ADHD. Stimulant products generally should not be used in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious heart problems. (5.1)
- Increase in Blood Pressure: Monitor patients for changes in heart rate and blood pressure and use with caution in patients for whom an increase in blood pressure or heart rate would be problematic. (5.1)
- Psychiatric Adverse Events: Use of stimulants may cause treatment-emergent psychotic or manic symptoms in patients with no prior history, or exacerbation of symptoms in patients with preexisting psychiatric illness. Clinical evaluation for Bipolar Disorder is recommended prior to stimulant use. Monitor for aggressive behavior. (5.2)
- Seizures: Stimulants may lower the convulsive threshold. Discontinue in the presence of seizures. (5.3)
- Visual Disturbance: difficulties with accommodation and blurring of vision have been reported with stimulant treatment. (5.5)
- Long-Term Suppression of Growth: monitor height and weight at appropriate intervals in pediatric patients. (5.4)
- Gastrointestinal obstruction with preexisting GI narrowing. (5.6)
- Hematologic monitoring: Periodic CBC, differential, and platelet counts are advised during prolonged therapy. (5.7)

ADVERSE REACTIONS

The most common adverse reaction in double-blind clinical trials (>5%) in children and adolescents was abdominal pain upper. The most common adverse reactions in double-blind clinical trials (>5%) in adult patients were decreased appetite, headache, dry mouth, nausea, insomnia, anxiety, dizziness, weight decreased, irritability, and hyperhidrosis. (6.1 and 6.2)

The most common adverse reactions associated with discontinuation (≥1%) from either pediatric or adult clinical trials were anxiety, irritability, insomnia, and blood pressure increased. (6.3)

DRUG INTERACTIONS

- Do not use CONCERTA® in patients currently using or within 2 weeks of using an MAO inhibitor (7.1)
- CONCERTA® may increase blood pressure; use cautiously with vasopressors (7.2)
- Inhibition of metabolism of coumarin anticoagulants, anticonvulsants, and some antidepressants (7.3)

USE IN SPECIFIC POPULATIONS

- Caution should be exercised if administered to nursing mothers (8.3)
- Safety and efficacy has not been established in children less than six years old or elderly patients greater than 65 years of age (8.4 and 8.5)

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

CONCERTA® (methylphenidate HCl) Extended-Release Tablets
18,27,36,54 mg

FULL PRESCRIBING INFORMATION

DRUG DEPENDENCE
CONCERTA® should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during withdrawal from abusive use since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

1 INDICATIONS AND USAGE

CONCERTA® is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

A diagnosis of Attention Deficit Hyperactivity Disorder (ADHD; DSM-IV) implies the presence of hyperactive-impulsive or inattentive symptoms that caused impairment and were present before age 7 years. The symptoms must cause clinically significant impairment, e.g., in social, academic, or occupational functioning, and be present in two or more settings, e.g., school (or work) and at home. The symptoms must not be better accounted for by another mental disorder. For the Inattentive Type, at least six of the following symptoms must have persisted for at least 6 months: lack of attention to details/careless mistakes; lack of sustained attention; poor listener; failure to follow through on tasks; poor organization; avoids tasks requiring sustained mental effort; loses things; easily distracted; forgetful. For the Hyperactive-Impulsive Type, at least six of the following symptoms must have persisted for at least 6 months: fidgeting/squirming; leaving seat; inappropriate running/climbing; difficulty with quiet activities; “on the go;” excessive talking; blurting answers; can’t wait turn; intrusive. The Combined Type requires both inattentive and hyperactive-impulsive criteria to be met.

1.1 Special Diagnostic Considerations

Specific etiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use of medical and special psychological, educational, and social resources. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the patient and not solely on the presence of the required number of DSM-IV characteristics.

1.2 Need for Comprehensive Treatment Program

CONCERTA® is indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological, educational, social). Drug treatment may not be indicated for all patients with ADHD. Stimulants are not intended for use in patients who exhibit symptoms secondary to environmental factors and/or other primary psychiatric disorders, including psychosis. Appropriate educational placement is essential and psychosocial intervention is often helpful. When remedial measures alone are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the patient's symptoms.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

CONCERTA® should be administered orally once daily in the morning with or without food.

CONCERTA® must be swallowed whole with the aid of liquids, and must not be chewed, divided, or crushed *[see Patient Counseling Information (17)]*.

2.2 Patients New to Methylphenidate

The recommended starting dose of CONCERTA® for patients who are not currently taking methylphenidate or stimulants other than methylphenidate is 18 mg once daily for children and adolescents and 18 or 36 mg once daily for adults (see Table 1).

TABLE 1. CONCERTA® Recommended Starting Doses and Dose Ranges

Patient Age	Recommended Starting Dose	Recommended Dose Range
Children 6-12 years of age	18 mg/day	18 mg - 54 mg/day
Adolescents 13-17 years of age	18 mg/day	18 mg - 72 mg/day not to exceed 2 mg/kg/day
Adults 18-65 years of age	18 or 36 mg/day	18 mg - 72 mg/day

2.3 Patients Currently Using Methylphenidate

The recommended dose of CONCERTA® for patients who are currently taking methylphenidate twice daily or three times daily at doses of 10 to 60 mg/day is provided in Table 2. Dosing recommendations are based on current dose regimen and clinical judgment. Conversion dosage above 72 mg daily is not recomended.

TABLE 2. Recommended Dose Conversion from Methylphenidate Regimens to CONCERTA®

Previous Methylphenidate Daily Dose	Recommended CONCERTA® Starting Dose
5 mg Methylphenidate twice daily or three times daily	18 mg every morning
10 mg Methylphenidate twice daily or three times daily	36 mg every morning
15 mg Methylphenidate twice daily or three times daily	54 mg every morning
20 mg Methylphenidate twice daily or three times daily	72 mg every morning

Other methylphenidate regimens: Clinical judgment should be used when selecting the starting dose.

2.4 Dose Titration

Doses may be increased in 18 mg increments at weekly intervals for patients who have not achieved an optimal response at a lower dose. Daily dosages above 54 mg in children and 72 mg in adolescents have not been studied and are not recommended. Daily dosages above 72 mg in adults are not recommended.

A 27 mg dosage strength is available for physicians who wish to prescribe between the 18 mg and 36 mg dosages.

2.5 Maintenance/Extended Treatment

There is no body of evidence available from controlled trials to indicate how long the patient with ADHD should be treated with CONCERTA®. It is generally agreed, however, that pharmacological treatment of ADHD may be needed for extended periods.

The effectiveness of CONCERTA® for long-term use, i.e., for more than 7 weeks, has not been systematically evaluated in controlled trials. The physician who elects to use CONCERTA® for extended periods in patients with ADHD should periodically re-evaluate the long-term usefulness of the drug for the individual patient with trials off medication to assess the patient's functioning without pharmacotherapy. Improvement may be sustained when the drug is either temporarily or permanently discontinued.

2.6 Dose Reduction and Discontinuation

If paradoxical aggravation of symptoms or other adverse events occur, the dosage should be reduced, or, if necessary, the drug should be discontinued.

If improvement is not observed after appropriate dosage adjustment over a one-month period, the drug should be discontinued.

3 DOSAGE FORMS AND STRENGTHS

CONCERTA® (methylphenidate HCl) Extended-Release Tablets are available in the following dosage strengths: 18 mg tablets are yellow and imprinted with “alza 18,” 27 mg tablets are gray and imprinted with “alza 27,” 36 mg tablets are white and imprinted with “alza 36,” and 54 mg tablets are brownish-red and imprinted with “alza 54.”

4 CONTRAINDICATIONS

4.1 Hypersensitivity to Methylphenidate

Hypersensitivity reactions, such as angioedema and anaphylactic reactions, have been observed in patients treated with CONCERTA®. Therefore, CONCERTA® is contraindicated in patients known to be hypersensitive to methylphenidate or other components of the product *[see Adverse Reactions (6.6)]*.

4.2 Agitation

CONCERTA® is contraindicated in patients with marked anxiety, tension, and agitation, since the drug may aggravate these symptoms.

4.3 Glaucoma

CONCERTA® is contraindicated in patients with glaucoma.

4.4 Tics

CONCERTA® is contraindicated in patients with motor tics or with a family history or diagnosis of Tourette's syndrome *[see Adverse Reactions (6.4)]*.

4.5 Monoamine Oxidase Inhibitors

CONCERTA® is contraindicated during treatment with monoamine oxidase (MAO) inhibitors, and also within a minimum of 14 days following discontinuation of a MAO inhibitor (hypertensive crises may result) *[see Drug Interactions (7.1)]*.

4.6 Phaeochromocytoma

4.7 Hyperthyroidism or Thyrotoxicosis

4.8 Diagnosis or history of severe depression, anorexia nervosa/anorexic disorders, suicidal tendencies, psychotic symptoms, severe mood disorders, mania, schizophrenia, psychopathic/borderline personality disorder

4.9 Diagnosis or history of severe and episodic (Type I) Bipolar (affective) Disorder (that is not well-controlled)

4.10 Pre-existing cardiovascular disorders including severe hypertension, heart failure, arterial occlusive disease, angina, haemodynamically significant congenital heart disease, cardiomyopathies, myocardial infarction, potentially life-threatening arrhythmias and channelopathies (disorders caused by the dysfunction of ion channels)

4.11 Pre-existing cerebrovascular disorders cerebral aneurysm, vascular abnormalities including vasculitis or stroke

5 WARNINGS AND PRECAUTIONS

Long-term use (more than 12 months) in children and adolescents

The safety and efficacy of long-term use of methylphenidate has not been systematically evaluated in controlled trials. Methylphenidate treatment should not and need not, be indefinite. Methylphenidate treatment is usually discontinued during or after puberty.

Patients on long-term therapy must have careful ongoing monitoring according for cardiovascular status, growth,appetite, development of de novo or worsening of pre-existing psychiatric disorders. Psychiatric disorders to monitor for are described below, and include (but are not limited to) motor or vocal tics, aggressive or hostile behaviour, agitation, anxiety, depression, psychosis, mania, delusions, irritability, lack of spontaneity, withdrawal and excessive perseveration.

The physician who elects to use methylphenidate for extended periods (over 12 months) in children and adolescents with ADHD should periodically re-evaluate the long-term usefulness of the drug for the individual patient with trial periods off medication to assess the patient's functioning without pharmacotherapy. It is recommended that methylphenidate is de-challenged at least once yearly to assess the child's condition (preferably during times of school holidays). Improvement may be sustained when the drug is either temporarily or permanently discontinued.

Serious Cardiovascular Events

Sudden Death and Preexisting Structural Cardiac Abnormalities or Other Serious Heart Problems

Children and Adolescents

Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Although some serious heart problems alone carry an increased risk of sudden death, stimulant products generally should not be used in children or adolescents with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant drug.

Adults

Sudden deaths, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses for ADHD. Although the role of stimulants in these adult cases is also unknown, adults have a greater likelihood than children of having serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems. Adults with such abnormalities should also generally not be treated with stimulant drugs.

Hypertension and Other Cardiovascular Conditions

Stimulant medications cause a modest increase in average blood pressure (about 2 to 4 mm Hg) and average heart rate (about 3 to 6 bpm) *[see Adverse Reactions (6.5)]*, and individuals may have larger increases. While the mean changes alone would not be expected to have short-term consequences, all patients should be monitored for larger changes in heart rate and blood pressure. Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, e.g., those with preexisting hypertension, heart failure, recent myocardial infarction, or ventricular arrhythmia.

Assessing Cardiovascular Status in Patients Being Treated with Stimulant Medications

Children, adolescents, or adults who are being considered for treatment with stimulant medications should have a careful history (including assessment for a family history of sudden death or ventricular arrhythmia) and physical exam to assess for the presence of cardiac disease, and should receive further cardiac evaluation if findings suggest such disease (e.g., electrocardiogram and echocardiogram). Patients who develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease during stimulant treatment should undergo a prompt cardiac evaluation.

Cerebrovascular disorders

Patients with additional risk factors (such as a history of cardiovascular

disease, concomitant medications that elevate blood pressure) should be assessed at every

visit for neurological signs and symptoms after initiating treatment with methylphenidate. Cerebral vasculitis appears to be a very rare idiosyncratic reaction to methylphenidate exposure. There is little evidence to suggest that patients at higher risk can be identified and the initial onset of symptoms may be the first indication of an underlying clinical problem. Early diagnosis, based on a high index of suspicion, may allow the prompt withdrawal of methylphenidate and early treatment. The diagnosis should therefore be considered in any patient who develops new neurological symptoms that are consistent with cerebral ischemia during methylphenidate therapy. These symptoms could include severe headache, numbness, weakness, paralysis, and impairment of coordination, vision, speech, language or memory. Treatment with methylphenidate is not contraindicated in patients with hemiplegic cerebral palsy.

~~5.1 Psychiatric Adverse Events~~

~~Preexisting Psychosis~~

~~Administration of stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a preexisting psychotic disorder.~~

~~Bipolar Illness~~

~~Particular care should be taken in using stimulants to treat ADHD in patients with comorbid bipolar disorder because of concern for possible induction of a mixed/manic episode in such patients. Prior to initiating treatment with a stimulant, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression.~~

~~Emergence of New Psychotic or Manic Symptoms~~

~~Treatment-emergent psychotic or manic symptoms, e.g., hallucinations, delusional thinking, or mania in patients without a prior history of psychotic illness or mania can be caused by stimulants at usual doses. If such symptoms occur, consideration should be given to a possible causal role of the stimulant, and discontinuation of treatment may be appropriate. In a pooled analysis of multiple short-term, placebo-controlled studies, such symptoms occurred in about 0.1% (4 patients with events out of 3482 exposed to methylphenidate or amphetamine for several weeks at usual doses) of stimulant-treated patients compared to 0 in placebo-treated patients.~~

~~Aggression~~

~~Aggressive behavior or hostility is often observed in patients with ADHD, and has been reported in clinical trials and the postmarketing experience of some medications indicated for the treatment of ADHD. Although there is no systematic evidence that stimulants cause aggressive behavior or hostility, patients beginning treatment for ADHD should be monitored for the appearance of or worsening of aggressive behavior or hostility.~~

Psychiatric disorders

Co-morbidity of psychiatric disorders in ADHD is common and should be taken into account when prescribing stimulant products. In the case of emergent psychiatric symptoms or exacerbation of pre-existing psychiatric disorders, methylphenidate should not be given unless the benefits outweigh the risks to the patient.

Development or worsening of psychiatric disorders should be monitored at every adjustment of dose, then at least every 6 months, and at every visit; discontinuation of treatment may be appropriate.

Exacerbation of pre-existing psychotic or manic symptoms

In psychotic patients, administration of methylphenidate may exacerbate symptoms of behavioural disturbance and thought disorder.

Emergence of new psychotic or manic symptoms

Treatment-emergent psychotic symptoms (visual/tactile/auditory hallucinations and delusions) or mania in children and adolescents without prior history of psychotic illness or mania can be caused by methylphenidate at usual doses. If manic or psychotic symptoms occur, consideration should be given to a possible causal role for methylphenidate, and discontinuation of treatment may be appropriate.

Aggressive or hostile behavior

The emergence or worsening of aggression or hostility can be caused by treatment with stimulants. Patients treated with methylphenidate should be closely monitored for the emergence or worsening of aggressive behaviour or hostility at treatment initiation, at every dose adjustment and then at least every 6 months and every visit. Physicians should evaluate the need for adjustment of the treatment regimen in patients experiencing behaviour changes bearing in mind that upwards or downwards titration may be appropriate. Treatment interruption can be considered.

Suicidal tendency

Patients with emergent suicidal ideation or behaviour during treatment for ADHD should be evaluated immediately by their physician. Consideration should be given to the exacerbation of an underlying psychiatric condition and to a possible causal role of

methylphenidate treatment. Treatment of an underlying psychiatric condition may be necessary and consideration should be given to a possible discontinuation of methylphenidate.

Tics

Methylphenidate is associated with the onset or exacerbation of motor and verbal tics. Worsening of Tourette's syndrome has also been reported. Family history should be assessed and clinical evaluation for tics or Tourette's syndrome in children should precede use of methylphenidate. Patients should be regularly monitored for the emergence or worsening of tics during treatment with methylphenidate. **Monitoring should be at every adjustment of dose and then at least every 6 months or every visit.**

Anxiety, agitation or tension

Methylphenidate is associated with the worsening of pre-existing anxiety, agitation or tension. Clinical evaluation for anxiety, agitation or tension should precede use of methylphenidate and patients should be **regularly monitored for the emergence or worsening of these symptoms during treatment, at every adjustment of dose and then at least every 6 month or every visit.**

Forms of bipolar disorder

Particular care should be taken in using methylphenidate to treat ADHD in patients with comorbid bipolar disorder (including untreated Type I Bipolar Disorder or other forms of bipolar disorder) because of concern for possible precipitation of a mixed/manic episode in such patients. Prior to initiating treatment with methylphenidate, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. **Close ongoing monitoring is essential in these patients. Patients should be monitored for symptoms at every adjustment of dose, then at least every 6 months and at every visit.**

Seizures

There is some clinical evidence that stimulants may lower the convulsive threshold in patients with prior history of seizures, in patients with prior EEG abnormalities in absence of seizures, and, very rarely, in patients without a history of seizures and no prior EEG evidence of seizures. In the presence of seizures, the drug should be discontinued.

Long-Term Suppression of Growth

Careful follow-up of weight and height in children ages 7 to 10 years who were randomized to either methylphenidate or non-medication treatment groups over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and non-medication-treated children over 36 months (to the ages of 10 to 13 years), suggests that consistently medicated children

(i.e., treatment for 7 days per week throughout the year) have a temporary slowing in growth rate (on average, a total of about 2 cm less growth in height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this period of development. Published data are inadequate to determine whether chronic use of amphetamines may cause similar suppression of growth; however, it is anticipated that they likely have this effect as well. Therefore, growth should be monitored (height, weight and appetite should be recorded at least 6 monthly with maintenance of a growth chart) during treatment with stimulants, and patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

Abuse, misuse and diversion

Patients should be carefully monitored for the risk of diversion, misuse and abuse of methylphenidate.

Methylphenidate should be used with caution in patients with known drug or alcohol dependency because of a potential for abuse, misuse or diversion.

Chronic abuse of methylphenidate can lead to marked tolerance and psychological dependence with varying degrees of abnormal behaviour. Frank psychotic episodes can occur, especially in response to parenteral abuse.

Patient age, the presence of risk factors for substance use disorder (such as co-morbid oppositional-defiant or conduct disorder and bipolar disorder), previous or current substance abuse should all be taken into account when deciding on a course of treatment for ADHD. Caution is called for in emotionally unstable patients, such as those with a history of drug or alcohol dependence, because such patients may increase the dosage on their own initiative.

For some high-risk substance abuse patients, methylphenidate or other stimulants may not be suitable and non-stimulant treatment should be considered.

Withdrawal

Careful supervision is required during drug withdrawal, since this may unmask depression as well as chronic over-activity. Some patients may require long-term follow up.

Fatigue

Methylphenidate should not be used for the prevention or treatment of normal fatigue states.

Excipients: galactose intolerance

This medicinal product contains lactose: patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Choice of methylphenidate formulation

The choice of formulation of methylphenidate-containing product will have to be decided by the treating specialist on an individual basis and depends on the intended duration of effect.

Drug screening

This product contains methylphenidate which may induce a false positive laboratory test for amphetamines, particularly with immunoassay screen test.

Renal or hepatic insufficiency
There is no experience with the use of methylphenidate in patients with renal or hepatic insufficiency.

Haematological effects
The long-term safety of treatment with methylphenidate is not fully known. In the event of leukopenia, thrombocytopenia, anaemia or other alterations, including those indicative of serious renal or hepatic disorders, discontinuation of treatment should be considered.

Hematologic Monitoring
Periodic CBC, differential, and platelet counts are advised during prolonged therapy.

Visual Disturbance
Difficulties with accommodation and blurring of vision have been reported with stimulant treatment.

Potential for Gastrointestinal Obstruction
Because the CONCERTA® tablet is nondeformable and does not appreciably change in shape in the GI tract, CONCERTA® should not ordinarily be administered to patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic, for example: esophageal motility disorders, small bowel inflammatory disease, "short gut" syndrome due to adhesions or decreased transit time, past history of peritonitis, cystic fibrosis, chronic intestinal pseudoobstruction, or Meckel's diverticulum). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of drugs in nondeformable controlled-release formulations.

Due to the prolonged-release design of the tablet, CONCERTA should only be used in patients who are able to swallow the tablet whole. Patients should be informed that CONCERTA must be swallowed whole with the aid of liquids. Tablets should not be chewed, divided, or crushed. The medication is contained within a nonabsorbable shell designed to release the drug at a controlled rate. The tablet shell is eliminated from the body; patients should not be concerned if they occasionally notice in their stool something that looks like a tablet.

~~Due to the controlled-release design of the tablet, CONCERTA® should be used only in patients who are able to swallow the tablet whole *[see Patient Counseling Information (17)]*.~~

6 ADVERSE REACTIONS

The following are discussed in more detail in other sections of the labeling:

- Drug Dependence *[see Box Warning]*
- Hypersensitivity to Methylphenidate *[see Contraindications (4.1)]*
- Agitation *[see Contraindications (4.2)]*
- Glaucoma *[see Contraindications (4.3)]*
- Tics *[see Contraindications (4.4)]*
- Monoamine Oxidase Inhibitors *[see Contraindications (4.5) and Drug Interactions (7.1)]*
- Serious Cardiovascular Events *[see Warnings and Precautions (5.1)]*
- Psychiatric Adverse Events *[see Warnings and Precautions (5.2)]*
- Seizures *[see Warnings and Precautions (5.3)]*
- Long-Term Suppression of Growth *[see Warnings and Precautions (5.4)]*
- Visual Disturbance *[see Warnings and Precautions (5.5)]*
- Potential for Gastrointestinal Obstruction *[see Warnings and Precautions (5.6)]*
- Hematologic Monitoring *[see Warnings and Precautions (5.7)]*

The most common adverse reaction in double-blind clinical trials (>5%) in pediatric patients (children and adolescents) was abdominal pain upper. The most common adverse reactions in double-blind clinical trials (>5%) in adult patients were decreased appetite, headache, dry mouth, nausea, insomnia, anxiety, dizziness, weight decreased, irritability, and hyperhidrosis *[see Adverse Reactions (6.1)]*.

The most common adverse reactions associated with discontinuation (≥1%) from either pediatric or adult clinical trials were anxiety, irritability, insomnia, and blood pressure increased *[see Adverse Reactions (6.3)]*.

The development program for CONCERTA® included exposures in a total of 3906 participants in clinical trials. Children, adolescents, and adults with ADHD were evaluated in 6 controlled clinical studies and 11 open-label clinical studies (see Table 3). Safety was assessed by collecting adverse events, vital signs, weights, and ECGs, and by performing physical examinations and laboratory analyses.

Table 3. CONCERTA® Exposure in Double-Blind and Open-Label Clinical Studies

Patient Population	N	Dose Range
Children	2216	18 to 54 mg once daily
Adolescents	502	18 to 72 mg once daily
Adults	1188	18 to 108 mg once daily

Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using their own terminology. Consequently, to provide a meaningful estimate of the proportion of individuals experiencing adverse events, events were grouped in standardized categories using MedDRA terminology.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

Throughout this section, adverse reactions are reported. Adverse reactions are adverse events that were considered to be reasonably associated with the use of CONCERTA® based on the comprehensive assessment of the available adverse event information. A causal association for CONCERTA® often 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 clinical trials of another drug and may not reflect the rates observed in clinical practice.

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

6.1 Commonly Observed Adverse Reactions in Double-Blind, Placebo-Controlled Clinical Trials

Adverse reactions in either the pediatric or adult double-blind adverse reactions tables may be relevant for both patient populations.

Children and Adolescents

Table 4 lists the adverse reactions reported in 1% or more of CONCERTA®-treated children and adolescent subjects in 4 placebo-controlled, double-blind clinical trials.

Table 4. Adverse Reactions Reported by ≥1% of CONCERTA®-Treated Children and Adolescent Subjects in 4 Placebo-Controlled, Double-Blind Clinical Trials of CONCERTA®

System/Organ Class Adverse Reaction	CONCERTA® (n=321) %	Placebo (n=318) %
Gastrointestinal Disorders		
Abdominal pain upper	6.2	3.8
Vomiting	2.8	1.6
General Disorders and Administration Site Conditions		
Pyrexia	2.2	0.9
Infections and Infestations		
Nasopharyngitis	2.8	2.2
Nervous System Disorders		
Dizziness	1.9	0
Psychiatric Disorders		
Insomnia*	2.8	0.3
Respiratory, Thoracic and Mediastinal Disorders		
Cough	1.9	0.9
Oropharyngeal pain	1.2	0.9

*Terms of Initial insomnia (CONCERTA®=0.6%) and Insomnia (CONCERTA®=2.2%) are combined into Insomnia.

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

Adults

Table 5 lists the adverse reactions reported in 1% or more of CONCERTA®-treated adults in 2 placebo-controlled, double-blind clinical trials.

Table 5. Adverse Reactions Reported by ≥1% of CONCERTA®-Treated Adult Subjects in 2 Placebo-Controlled, Double-Blind Clinical Trials*

System/Organ Class Adverse Reaction	CONCERTA® (n=415) %	Placebo (n=212) %
Cardiac Disorders		
Tachycardia	4.8	0
Palpitations	3.1	0.9
Ear and Labyrinth Disorders		
Vertigo	1.7	0
Eye Disorders		
Vision blurred	1.7	0.5
Gastrointestinal Disorders		
Dry mouth	14.0	3.8
Nausea	12.8	3.3
Dyspepsia	2.2	0.9
Vomiting	1.7	0.5
Constipation	1.4	0.9
General Disorders and Administration Site Conditions		
Irritability	5.8	1.4
Infections and Infestations		
Upper respiratory tract infection	2.2	0.9
Investigations		
Weight decreased	6.5	3.3

System/Organ Class Adverse Reaction	CONCERTA® (n=415) %	Placebo (n=212) %
Metabolism and Nutrition Disorders		
Decreased appetite	25.3	6.6
Anorexia	1.7	0
Musculoskeletal and Connective Tissue Disorders		
Muscle tightness	1.9	0
Nervous System Disorders		
Headache	22.2	15.6
Dizziness	6.7	5.2
Tremor	2.7	0.5
Paresthesia	1.2	0
Sedation	1.2	0
Tension headache	1.2	0.5
Psychiatric Disorders		
Insomnia	12.3	6.1
Anxiety	8.2	2.4
Initial insomnia	4.3	2.8
Depressed mood	3.9	1.4
Nervousness	3.1	0.5
Restlessness	3.1	0
Agitation	2.2	0.5
Aggression	1.7	0.5
Bruxism	1.7	0.5
Depression	1.7	0.9
Libido decreased	1.7	0.5
Affect lability	1.4	0.9
Confusional state	1.2	0.5
Tension	1.2	0.5
Respiratory, Thoracic and Mediastinal Disorders		
Oropharyngeal pain	1.7	1.4
Skin and Subcutaneous Tissue Disorders		
Hyperhidrosis	5.1	0.9

* Included doses up to 108 mg.

The majority of ADRs were mild to moderate in severity.

6.2 Other Adverse Reactions Observed in CONCERTA® Clinical Trials

This section includes adverse reactions reported by CONCERTA®-treated subjects in double-blind trials that do not meet the criteria specified for Table 4 or Table 5 and all adverse reactions reported by CONCERTA®-treated subjects who participated in open-label and postmarketing clinical trials.

Blood and Lymphatic System Disorders: Leukopenia

Eye Disorders: Accommodation disorder, Dry eye

Vascular Disorders: Hot flush

Gastrointestinal Disorders: Abdominal discomfort, Abdominal pain, Diarrhea

General Disorders and Administrative Site Conditions: Asthenia, Fatigue, Feeling jittery, Thirst

Infections and Infestations: Sinusitis

Investigations: Alanine aminotransferase increased, Blood pressure increased, Cardiac murmur, Heart rate increased

Musculoskeletal and Connective Tissue Disorders: Muscle spasms

Nervous System Disorders: Lethargy, Psychomotor hyperactivity, Somnolence

Psychiatric Disorders: Anger, Hypervigilance, Mood altered, Mood swings, Panic attack, Sleep disorder, Tearfulness, Tic, Logorrhoea.

Reproductive System and Breast Disorders: Erectile dysfunction

Respiratory, Thoracic and Mediastinal Disorders: Dyspnea

Skin and Subcutaneous Tissue Disorders: Rash, Rash macular

Vascular Disorders: Hypertension

6.3 Discontinuation Due to Adverse Reactions

Adverse reactions In the 4 placebo-controlled studies of children and adolescents leading to discontinuation occurred in 2 CONCERTA® patients (0.6%) including depressed mood (1, 0.3%) and headache and insomnia (1, 0.3%), and 6 placebo patients (1.9%) including headache and insomnia (1, 0.3%), irritability (2, 0.6%), headache (1, 0.3%), psychomotor hyperactivity (1, 0.3%), and tic (1, 0.3%).

In the 2 placebo-controlled studies of adults, 25 CONCERTA® patients (6.0%) and 6 placebo patients (2.8%) discontinued due to an adverse reaction. Those events with an incidence of >0.5% in the CONCERTA® patients included anxiety (1.7%), irritability (1.4%), blood pressure increased (1.0%), and nervousness (0.7%). In placebo patients, blood pressure increased and depressed mood had an incidence of >0.5% (0.9%).

In the 11 open-label studies of children, adolescents, and adults, 266 CONCERTA® patients (7.0%) discontinued due to an adverse reaction. Those events with an incidence of >0.5% included insomnia (1.2%), irritability (0.8%), anxiety (0.7%), decreased appetite (0.7%), and tic (0.6%).

6.4 Tics

In a long-term uncontrolled study (n=432 children), the cumulative incidence of new onset of tics was 9% after 27 months of treatment with CONCERTA®.

In a second uncontrolled study (n=682 children) the cumulative incidence of new-onset tics was 1% (9/682 children). The treatment period was up to 9 months with mean treatment duration of 7.2 months.

6.5 Blood Pressure and Heart Rate Increases

In the laboratory classroom clinical trials in children (Studies 1 and 2), both CONCERTA® once daily and methylphenidate three times daily increased resting pulse by an average of 2 to 6 bpm and produced average increases of systolic and diastolic blood pressure of roughly 1 to 4 mm Hg during the day, relative to placebo. In the placebo-controlled adolescent trial (Study 4), mean increases from baseline in resting pulse rate were observed with CONCERTA® and placebo at the end of the double-blind phase (5 and 3 beats/minute, respectively). Mean increases from baseline in blood pressure at the end of the double-blind phase for CONCERTA® and placebo-treated patients were 0.7 and 0.7 mm Hg (systolic) and 2.6 and 1.4 mm Hg (diastolic), respectively. In one placebo-controlled study in adults (Study 6), dose-dependent mean increases of 3.9 to 9.8 bpm from baseline in standing pulse rate were observed with CONCERTA® at the end of the double-blind treatment vs. an increase of 2.7 beats/minute with placebo. Mean changes from baseline in standing blood pressure at the end of double-blind treatment ranged from 0.1 to 2.2 mm Hg (systolic) and -0.7 to 2.2 mm Hg (diastolic) for CONCERTA® and was 1.1 mm Hg (systolic) and -1.8 mm Hg (diastolic) for placebo. In a second placebo-controlled study in adults (Study 5), mean changes from baseline in resting pulse rate were observed for CONCERTA® and placebo at the end of the double-blind treatment (3.6 and –1.6 beats/minute, respectively). Mean changes from baseline in blood pressure at the end of the double–blind treatment for CONCERTA® and placebo-treated patients were –1.2 and –0.5 mm Hg (systolic) and 1.1 and 0.4 mm Hg (diastolic), respectively *[see Warnings and Precautions (5.1)]*.

6.6 Postmarketing Experience

The following additional adverse reactions have been identified during postapproval use of CONCERTA®. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency:

Blood and Lymphatic System Disorders: Pancytopenia, Thrombocytopenia, Thrombocytopenic purpura

Cardiac Disorders: Angina pectoris, Bradycardia, Extrasystoles, Supraventricular tachycardia, Ventricular extrasystoles

Eye Disorders: Diplopia, Mydriasis, Visual impairment

General Disorders: Chest pain, Chest discomfort, Drug effect decreased, Hyperpyrexia, Therapeutic response decreased

Immune System Disorders: Hypersensitivity reactions such as Angioedema, Anaphylactic reactions, Auricular swelling, Bullous conditions, Exfoliative conditions, Urticarias, Pruritus NEC, Rashes, Eruptions, and Exanthemas NEC

Investigations: Blood alkaline phosphatase increased, Blood bilirubin increased, Hepatic enzyme increased, Platelet count decreased, White blood cell count abnormal

Musculoskeletal, Connective Tissue and Bone Disorders: Arthralgia, Myalgia, Muscle twitching

Nervous System Disorders: Convulsion, Grand mal convulsion, Dyskinesia

Psychiatric Disorders: Disorientation, Hallucination, Hallucination auditory, Hallucination visual, Mania, Logorrhoea.

Skin and Subcutaneous Tissue Disorders: Alopecia, Erythema

Vascular Disorders: Raynaud's phenomenon

7 DRUG INTERACTIONS

7.1 MAO Inhibitors

CONCERTA® should not be used in patients being treated (currently or within the preceding 2 weeks) with MAO inhibitors *[see Contraindications (4.5)]*.

7.2 Vasopressor Agents

Because of possible increases in blood pressure, CONCERTA® should be used cautiously with vasopressor agents *[see Warnings and Precautions (5.1)]*.

7.3 Coumarin Anticoagulants, Antidepressants, and Selective Serotonin Reuptake Inhibitors

Human pharmacologic studies have shown that methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (eg, phenobarbital, phenytoin, primidone), and some antidepressants (tricyclics and selective serotonin reuptake inhibitors). Downward dose adjustment of these drugs may be required when given concomitantly with methylphenidate. It may be necessary to adjust the dosage and monitor

plasma drug concentrations (or, in the case of coumarin, coagulation times), when initiating or discontinuing concomitant methylphenidate.

7.4 Use with alcohol

Alcohol may exacerbate the adverse CNS effect of psychoactive drugs, including methylphenidate. It is therefore advisable for patients to abstain from alcohol during treatment.

7.5 Use with halogenated anaesthetics

There is a risk of sudden blood pressure increase during surgery. If surgery is planned, methylphenidate treatment should not be used on the day of surgery.

7.6 Use with centrally acting alpha-2 agonists (e.g. clonidine)

Serious adverse events, including sudden death, have been reported in concomitant use with clonidine. The safety of using methylphenidate in combination with clonidine or other centrally acting alpha-2 agonists has not been systematically evaluated.

7.7 Use with domapinergic drugs

Caution is recommended when administering methylphenidate with dopaminergic drugs, including antipsychotics. Because a predominant action of methylphenidate is to increase extracelluar dopamine levels, methylphenidate may be associated with pharmacodynamic interactions when co-administered with direct and indirect dopamine agonists (including DOPA and tricyclic antidepressants) or with dopamine antagonists including antipsychotics.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Methylphenidate has been shown to have teratogenic effects in rabbits when given in doses of 200 mg/kg/day, which is approximately 100 times and 40 times the maximum recommended human dose on a mg/kg and mg/m^2 basis, respectively.

A reproduction study in rats revealed no evidence of harm to the fetus at oral doses up to 30 mg/kg/day, approximately 15-fold and 3-fold the maximum recommended human dose of CONCERTA® on a mg/kg and mg/m^2 basis, respectively. The approximate plasma exposure to methylphenidate plus its main metabolite PPAA in pregnant rats was 1-2 times that seen in trials in volunteers and patients with the maximum recommended dose of CONCERTA® based on the AUC.

The safety of methylphenidate for use during human pregnancy has not been established. There are no adequate and well-controlled studies in pregnant women. CONCERTA® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.2 Labor and Delivery

The effect of CONCERTA® on labor and delivery in humans is unknown.

8.3 Nursing Mothers

It is not known whether methylphenidate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if CONCERTA® is administered to a nursing woman.

In lactating female rats treated with a single oral dose of 5 mg/kg radiolabeled methylphenidate, radioactivity (representing methylphenidate and/or its metabolites) was observed in milk and levels were generally similar to those in plasma.

8.4 Pediatric Use

CONCERTA® should not be used in children under six years, since safety and efficacy in this age group have not been established. Long-term effects of methylphenidate in children have not been well established.

8.5 Geriatric Use

CONCERTA® has not been studied in patients greater than 65 years of age.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Methylphenidate is a controlled substance.

9.2 Abuse

As noted in the Box Warning, CONCERTA® should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse.

In two placebo-controlled human abuse potential studies, single oral doses of CONCERTA® were compared to single oral doses of immediate-release methylphenidate (IR MPH) and placebo in subjects with a history of recreational stimulant use to assess relative abuse potential. For the purpose of this assessment, the response for each of the subjective measures was defined as the maximum effect within the first 8 hours after dose administration.

In one study (n=40), both CONCERTA® (108 mg) and 60 mg IR MPH compared to placebo produced statistically significantly greater responses on the five subjective measures suggestive of abuse potential. In comparisons between the two active treatments, however, CONCERTA® (108 mg) produced variable responses on positive subjective measures that were either statistically indistinguishable from (Abuse Potential, Drug Liking, Amphetamine, and Morphine Benzedrine Group [Euphoria]) or statistically less than (Stimulation – Euphoria) responses produced by 60 mg IR MPH.

In another study (n=49), both doses of CONCERTA® (54 mg and 108 mg) and both doses of IR MPH (50 mg and 90 mg) produced statistically significantly greater responses compared to placebo on the two primary scales used in the study (Drug Liking, Euphoria). When doses of CONCERTA® (54 mg and 108 mg) were compared to IR MPH (50 mg and 90 mg), respectively, CONCERTA® produced statistically significantly lower subjective responses on these two scales than IR MPH. CONCERTA® (108 mg) produced responses that were statistically indistinguishable from the responses on these two scales produced by IR MPH (50 mg). Differences in subjective responses to the respective doses should be considered in the context that only 22% of the total amount of methylphenidate in CONCERTA® tablets is available for immediate release from the drug overcoat [*see System Components and Performance (11.1)*].

Although these findings reveal a relatively lower response to CONCERTA® on subjective measures suggestive of abuse potential compared to IR MPH at roughly equivalent total

MPH doses, the relevance of these findings to the abuse potential of CONCERTA® in the community is unknown.

9.3 Dependence

As noted in the Box Warning, careful supervision is required during withdrawal from abusive use since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

10 OVERDOSAGE

10.1 Signs and Symptoms

Signs and symptoms of CONCERTA® overdosage, resulting principally from overstimulation of the CNS and from excessive sympathomimetic effects, may include the following: vomiting, agitation, muscle twitching, convulsion, grand mal convulsion, confusional state, hallucinations (auditory and/or visual), hyperhidrosis, headache, pyrexia, tachycardia, palpitations, heart rate increased, sinus arrhythmia, hypertension, mydriasis, and dry mouth.

10.2 Recommended Treatment

Treatment consists of appropriate supportive measures. The patient must be protected against self-injury and against external stimuli that would aggravate overstimulation already present. Gastric contents may be evacuated by gastric lavage as indicated. Before performing gastric lavage, control agitation and seizures if present and protect the airway. Other measures to detoxify the gut include administration of activated charcoal and a cathartic. Intensive care must be provided to maintain adequate circulation and respiratory exchange; external cooling procedures may be required for pyrexia.

Efficacy of peritoneal dialysis or extracorporeal hemodialysis for CONCERTA® overdosage has not been established.

The prolonged release of methylphenidate from CONCERTA® should be considered when treating patients with overdose.

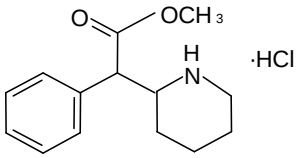
10.3 Poison Control Center

As with the management of all overdosage, the possibility of multiple-drug ingestion should be considered. The physician may wish to consider contacting a poison control center for up-to-date information on the management of overdosage with methylphenidate.

11 DESCRIPTION

CONCERTA® is a central nervous system (CNS) stimulant. CONCERTA® is available in four tablet strengths. Each extended-release tablet for once-a-day oral administration

contains 18, 27, 36, or 54 mg of methylphenidate HCl USP and is designed to have a 12-hour duration of effect. Chemically, methylphenidate HCl is d,l (racemic) methyl α-phenyl-2-piperidineacetate hydrochloride. Its empirical formula is $C_{14}H_{19}NO_2 \bullet HCl$. Its structural formula is:



Methylphenidate HCl USP is a white, odorless crystalline powder. Its solutions are acid to litmus. It is freely soluble in water and in methanol, soluble in alcohol, and slightly soluble in chloroform and in acetone. Its molecular weight is 269.77.

CONCERTA® also contains the following inert ingredients: butylated hydroxytoluene, carnauba wax, cellulose acetate, hypromellose, phosphoric acid, poloxamer, polyethylene oxides, povidone, sodium chloride, stearic acid, succinic acid ferric oxides,Cellulose acetate, opadry yellow, opadry clear, opadry gray, opadty white, opadry red, opacode black

11.1 System Components and Performance

CONCERTA® uses osmotic pressure to deliver methylphenidate HCl at a controlled rate. The system, which resembles a conventional tablet in appearance, comprises an osmotically active trilayer core surrounded by a semipermeable membrane with an immediate-release drug overcoat. The trilayer core is composed of two drug layers containing the drug and excipients, and a push layer containing osmotically active components. There is a precision-laser drilled orifice on the drug-layer end of the tablet. In an aqueous environment, such as the gastrointestinal tract, the drug overcoat dissolves within one hour, providing an initial dose of methylphenidate. Water permeates through the membrane into the tablet core. As the osmotically active polymer excipients expand, methylphenidate is released through the orifice. The membrane controls the rate at which water enters the tablet core, which in turn controls drug delivery. Furthermore, the drug release rate from the system increases with time over a period of 6 to 7 hours due to the drug-concentration gradient incorporated into the two drug layers of CONCERTA®. The biologically inert components of the tablet remain intact during gastrointestinal transit and are eliminated in the stool as a tablet shell along with insoluble core components. It is possible that CONCERTA® extended-release tablets may be visible on abdominal x-rays under certain circumstances, especially when digital enhancing techniques are utilized.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Methylphenidate HCl is a central nervous system (CNS) stimulant. The mode of therapeutic action in Attention Deficit Hyperactivity Disorder (ADHD) is not known. Methylphenidate is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space.

12.2 Pharmacodynamics

Methylphenidate is a racemic mixture comprised of the d- and l-isomers. The d-isomer is more pharmacologically active than the l-isomer.

12.3 Pharmacokinetics

Absorption

Methylphenidate is readily absorbed. Following oral administration of CONCERTA®, plasma methylphenidate concentrations increase rapidly, reaching an initial maximum at about 1 hour, followed by gradual ascending concentrations over the next 5 to 9 hours, after which a gradual decrease begins. Mean times to reach peak plasma concentrations across all doses of CONCERTA® occurred between 6 and 10 hours.

CONCERTA® once daily minimizes the fluctuations between peak and trough concentrations associated with immediate-release methylphenidate three times daily (see Figure 1). The relative bioavailability of CONCERTA® once daily and methylphenidate three times daily in adults is comparable.

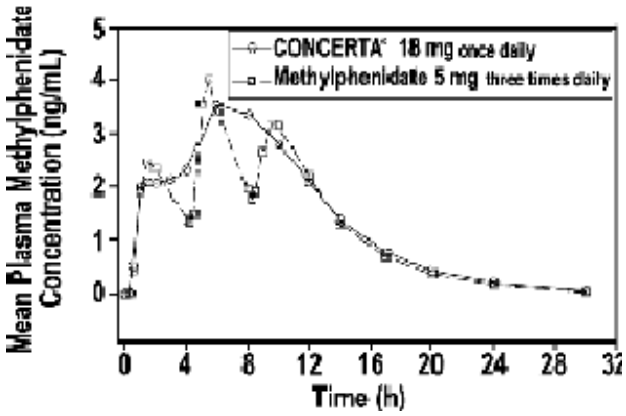


Figure 1. Mean methylphenidate plasma concentrations in 36 adults, following a single dose of CONCERTA® 18 mg once daily and immediate-release methylphenidate 5 mg three times daily administered every 4 hours.

The mean single-dose pharmacokinetic parameters in 36 healthy adults following the administration of CONCERTA® 18 mg once daily and methylphenidate 5 mg three times daily are summarized in Table 6.

TABLE 6. Pharmacokinetic Parameters (Mean ± SD) After Single Dose in Healthy Adults

Parameters	CONCERTA® (18 mg once daily) (n=36)	Methylphenidate (5 mg three times daily) (n=35)
C_{max} (ng/mL)	3.7 ± 1.0	4.2 ± 1.0
T_{max} (h)	6.8 ± 1.8	6.5 ± 1.8
AUC_{inf} (ng•h/mL)	41.8 ± 13.9	38.0 ± 11.0
$t_{½}$ (h)	3.5 ± 0.4	3.0 ± 0.5

The pharmacokinetics of CONCERTA® were evaluated in healthy adults following single- and multiple-dose administration (steady state) of doses up to 144 mg/day. The mean half-life was about 3.6 hours. No differences in the pharmacokinetics of CONCERTA® were noted following single and repeated once-daily dosing, indicating no significant drug accumulation. The AUC and $t_{1/2}$ following repeated once-daily dosing are similar to those following the first dose of CONCERTA® in a dose range of 18 to 144 mg.

Dose Proportionality

Following administration of CONCERTA® in single doses of 18, 36, and 54 mg/day to healthy adults, C_{max} and $AUC_{(0\text{-}inf)}$ of d-methylphenidate were proportional to dose, whereas l-methylphenidate C_{max} and $AUC_{(0\text{-}inf)}$ increased disproportionately with respect to dose. Following administration of CONCERTA®, plasma concentrations of the l-isomer were approximately 1/40 the plasma concentrations of the d-isomer.

In healthy adults, single and multiple dosing of once-daily CONCERTA® doses from 54 to 144 mg/day resulted in linear and dose-proportional increases in C_{max} and AUC_{inf} for total methylphenidate (MPH) and its major metabolite, α-phenyl-piperidine acetic acid (PPAA). There was no time dependency in the pharmacokinetics of methylphenidate. The ratio of metabolite (PPAA) to parent drug (MPH) was constant across doses from 54 to 144 mg/day, both after single dose and upon multiple dosing.

In a multiple-dose study in adolescent ADHD patients aged 13 to 16 administered their prescribed dose (18 to 72 mg/day) of CONCERTA®, mean C_{max} and AUC_{TAU} of d- and total methylphenidate increased proportionally with respect to dose.

Distribution

Plasma methylphenidate concentrations in adults and adolescents decline biexponentially following oral administration. The half-life of methylphenidate in adults and adolescents

following oral administration of CONCERTA® was approximately 3.5 hours.

Metabolism and Excretion

In humans, methylphenidate is metabolized primarily by de-esterification to PPAA, which has little or no pharmacologic activity. In adults the metabolism of CONCERTA® once daily as evaluated by metabolism to PPAA is similar to that of methylphenidate three times daily. The metabolism of single and repeated once-daily doses of CONCERTA® is similar.

After oral dosing of radiolabeled methylphenidate in humans, about 90% of the radioactivity was recovered in urine. The main urinary metabolite was PPAA, accounting for approximately 80% of the dose.

Food Effects

In patients, there were no differences in either the pharmacokinetics or the pharmacodynamic performance of CONCERTA® when administered after a high-fat breakfast. There is no evidence of dose dumping in the presence or absence of food.

Special Populations

Gender

In healthy adults, the mean dose-adjusted AUC $_{(0\text{-inf})}$ values for CONCERTA® were 36.7 ng•h/mL in men and 37.1 ng•h/mL in women, with no differences noted between the two groups.

Race

In adults receiving CONCERTA®, dose-adjusted AUC $_{(0\text{-inf})}$ was consistent across ethnic groups; however, the sample size may have been insufficient to detect ethnic variations in pharmacokinetics.

Age

Increase in age resulted in increased apparent oral clearance (CL/F) (58% increase in adolescents compared to children). Some of these differences could be explained by body-weight differences among these populations. This suggests that subjects with higher body weight may have lower exposures of total methylphenidate at similar doses.

The pharmacokinetics of CONCERTA® have not been studied in children less than 6 years of age.

Renal Insufficiency

There is no experience with the use of CONCERTA® in patients with renal insufficiency. After oral administration of radiolabeled methylphenidate in humans, methylphenidate

was extensively metabolized and approximately 80% of the radioactivity was excreted in the urine in the form of PPAA. Since renal clearance is not an important route of methylphenidate clearance, renal insufficiency is expected to have little effect on the pharmacokinetics of CONCERTA®.

Hepatic Insufficiency

There is no experience with the use of CONCERTA® in patients with hepatic insufficiency.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis

In a lifetime carcinogenicity study carried out in B6C3F1 mice, methylphenidate caused an increase in hepatocellular adenomas and, in males only, an increase in hepatoblastomas at a daily dose of approximately 60 mg/kg/day. This dose is approximately 30 times and 4 times the maximum recommended human dose of CONCERTA® on a mg/kg and mg/m^2 basis, respectively. Hepatoblastoma is a relatively rare rodent malignant tumor type. There was no increase in total malignant hepatic tumors. The mouse strain used is sensitive to the development of hepatic tumors, and the significance of these results to humans is unknown.

Methylphenidate did not cause any increases in tumors in a lifetime carcinogenicity study carried out in F344 rats; the highest dose used was approximately 45 mg/kg/day, which is approximately 22 times and 5 times the maximum recommended human dose of CONCERTA® on a mg/kg and mg/m^2 basis, respectively.

In a 24-week carcinogenicity study in the transgenic mouse strain p53+/-, which is sensitive to genotoxic carcinogens, there was no evidence of carcinogenicity. Male and female mice were fed diets containing the same concentration of methylphenidate as in the lifetime carcinogenicity study; the high-dose groups were exposed to 60 to 74 mg/kg/day of methylphenidate.

Mutagenesis

Methylphenidate was not mutagenic in the *in vitro* Ames reverse mutation assay or the *in vitro* mouse lymphoma cell forward mutation assay. Sister chromatid exchanges and chromosome aberrations were increased, indicative of a weak clastogenic response, in an *in vitro* assay in cultured Chinese Hamster Ovary cells. Methylphenidate was negative *in vivo* in males and females in the mouse bone marrow micronucleus assay.

Impairment of Fertility

Methylphenidate did not impair fertility in male or female mice that were fed diets containing the drug in an 18-week Continuous Breeding study. The study was conducted at doses up to 160 mg/kg/day, approximately 80-fold and 8-fold the highest recommended human dose of CONCERTA® on a mg/kg and mg/m^2 basis, respectively.

14 CLINICAL STUDIES

CONCERTA® was demonstrated to be effective in the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in 4 randomized, double-blind, placebo-controlled studies in children and adolescents and 2 double-blind placebo-controlled studies in adults who met the Diagnostic and Statistical Manual 4th edition (DSM-IV) criteria for ADHD.

14.1 Children

Three double-blind, active- and placebo-controlled studies were conducted in 416 children aged 6 to 12 years. The controlled studies compared CONCERTA® given once daily (18, 36, or 54 mg), methylphenidate given three times daily over 12 hours (15, 30, or 45 mg total daily dose), and placebo in two single-center, 3-week crossover studies (Studies 1 and 2) and in a multicenter, 4-week, parallel-group comparison (Study 3). The primary comparison of interest in all three trials was CONCERTA® versus placebo.

Symptoms of ADHD were evaluated by community schoolteachers using the Inattention / Overactivity with Aggression (IOWA) Conners scale. Statistically significant reduction in the Inattention / Overactivity subscale versus placebo was shown consistently across all three controlled studies for CONCERTA®. The scores for CONCERTA® and placebo for the three studies are presented in Figure 2.

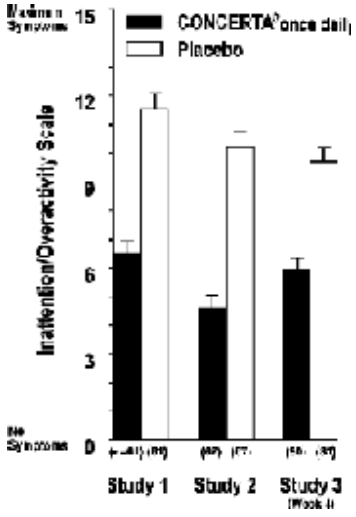


Figure 2: Mean Community School Teacher IOWA Conners Inattention/Overactivity Scores with CONCERTA® once daily (18, 36, or 54 mg) and placebo. Studies 1 and 2 involved a 3-way crossover of 1 week per treatment arm. Study 3 involved 4 weeks of parallel-group treatments with a Last Observation Carried Forward analysis at week 4. Error bars represent the mean plus standard error of the mean.

In Studies 1 and 2, symptoms of ADHD were evaluated by laboratory schoolteachers using the SKAMP* laboratory school rating scale. The combined results from these two studies demonstrated statistically significant improvements in attention and behavior in patients treated with CONCERTA® versus placebo that were maintained through 12 hours after dosing. Figure 3 presents the laboratory schoolteacher SKAMP ratings for CONCERTA® and placebo.

*Swanson, Kotkin, Agler, M-Fynn, and Pelham

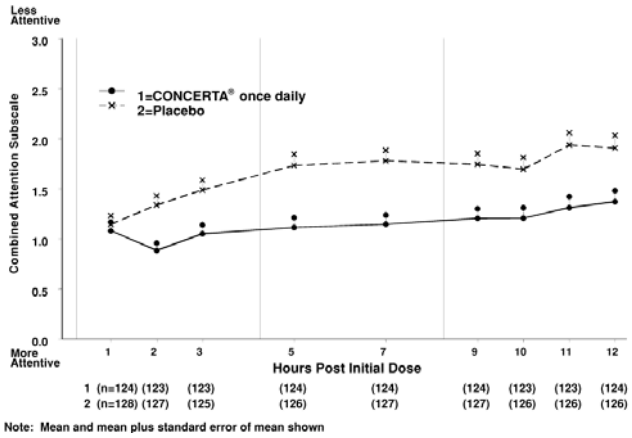


Figure 3: Laboratory School Teacher SKAMP Ratings: Mean (SEM) of Combined Attention (Studies 1 and 2)

14.2 Adolescents

In a randomized, double-blind, multicenter, placebo-controlled trial (Study 4) involving 177 patients, CONCERTA® was demonstrated to be effective in the treatment of ADHD in adolescents aged 13 to 18 years at doses up to 72 mg/day (1.4 mg/kg/day). Of 220 patients who entered an open 4-week titration phase, 177 were titrated to an individualized dose (maximum of 72 mg/day) based on meeting specific improvement criteria on the ADHD Rating Scale and the Global Assessment of Effectiveness with acceptable tolerability. Patients who met these criteria were then randomized to receive either their individualized dose of CONCERTA® (18 – 72 mg/day, n=87) or placebo (n=90) during a two-week double-blind phase. At the end of this phase, mean scores for the investigator rating on the

ADHD Rating Scale demonstrated that CONCERTA® was statistically significantly superior to placebo.

14.3 Adults

Two double-blind, placebo-controlled studies were conducted in 627 adults aged 18 to 65 years. The controlled studies compared CONCERTA® administered once daily and placebo in a multicenter, parallel-group, 7-week dose-titration study (Study 5) (36 to 108 mg/day) and in a multicenter, parallel-group, 5-week, fixed-dose study (Study 6) (18, 36, and 72 mg/day).

Study 5 demonstrated the effectiveness of CONCERTA® in the treatment of ADHD in adults aged 18 to 65 years at doses from 36 mg/day to 108 mg/day based on the change from baseline to final study visit on the Adult ADHD Investigator Rating Scale (AISRS). Of 226 patients who entered the 7-week trial, 110 were randomized to CONCERTA® and 116 were randomized to placebo. Treatment was initiated at 36 mg/day and patients continued with incremental increases of 18 mg/day (36 to 108 mg/day) based on meeting specific improvement criteria with acceptable tolerability. At the final study visit, mean change scores (LS Mean, SEM) for the investigator rating on the AISRS demonstrated that CONCERTA® was statistically significantly superior to placebo.

Study 6 was a multicenter, double-blind, randomized, placebo-controlled, parallel-group, dose-response study (5-week duration) with 3 fixed-dose groups (18, 36, and 72 mg). Patients were randomized to receive CONCERTA® administered at doses of 18 mg (n=101), 36 mg (n=102), 72 mg/day (n=102), or placebo (n=96). All three doses of CONCERTA® were statistically significantly more effective than placebo in improving CAARS (Conners' Adult ADHD Rating Scale) total scores at double-blind end point in adult subjects with ADHD.

15 REFERENCES

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington, DC: American Psychiatric Association, 1994.

16 HOW SUPPLIED/STORAGE AND HANDLING

CONCERTA® (methylphenidate HCl) Extended-release Tablets are available in 18 mg, 27 mg, 36 mg, and 54 mg dosage strengths. The 18 mg tablets are yellow and imprinted with "alza 18." The 27 mg tablets are gray and imprinted with "alza 27." The 36 mg tablets are white and imprinted with "alza 36." The 54 mg tablets are brownish-red and imprinted with "alza 54." All four dosage strengths are supplied in bottles containing 100 tablets.

18 mg 30 count bottle

27 mg	30 count bottle
36 mg	30 count bottle
54 mg	30 count bottle

Storage and Handling

~~Do not~~ Store below ~~above~~ ~~at~~ 25°C;

Keep out of the sight and reach of children.

17 PATIENT COUNSELING INFORMATION

17.1 Information for Patients

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with methylphenidate and should counsel them in its appropriate use. A patient Medication Guide is available for CONCERTA®. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Patients should be informed that CONCERTA® should be swallowed whole with the aid of liquids. Tablets should not be chewed, divided, or crushed. The medication is contained within a nonabsorbable shell designed to release the drug at a controlled rate. The tablet shell, along with insoluble core components, is eliminated from the body; patients should not be concerned if they occasionally notice in their stool something that looks like a tablet.

Stimulants may impair the ability of the patient to operate potentially hazardous machinery or vehicles. Patients should be cautioned accordingly until they are reasonably certain that CONCERTA® does not adversely affect their ability to engage in such activities.

Manufacturer: Ortho-McNeil Pharmaceuticals, Inc.New Jersey, USA
Registration holder: J-C Heath Care Ltd., Kibbutz Shefayim, 60990, Israel