كارباتول® أقراص

كاربامازيبين ٢٠٠ مجم

- **اقرأ جميع هذه النشرة بعناية قبل البدء في تناول هذا الدواء**
- حافظ على هذه النشرة. قد تحتاج لقراءتها مرة أخرى.
- إذا كان لديك أي أسئلة أخرى، اطلب الطبيب أو الصيدلي.
- هذا الدواء تم وصفه لك فلا تصفه للآخرين، حتى لو أشتكوا من أعراض مشابهة لما لك.
- إذا كان لديك أي من الآثار الجانبية الخطيرة، أو إذا لاحظت أي آثار جانبية غير مدرجة في هذه النشرة، يرجى إخبار الطبيب أو الصيدلي.

تحتوى هذه النشرة على:

١. ما هو كارباتول® و ما هي استخداماته
٢. ما يجب مراعاته قبل أن تتناول كارباتول®
٣. كيفية تناول كارباتول® أقراص
٤. الآثار الجانبية المحتملة
٥. كيفية تخزين كارباتول® أقراص
٦. مزيد من المعلومات

١. ما هو كارباتول® و ما هي استخداماته

المواد الفعالة: كاربامازيبين ٢٠٠ مجم

المواد الغير فعالة: استيارات الماغنيسيوم – بوفيدون – كروسبوفيدون – افيسل PH 102 - لاكتوز- تلك - كروس كرميلوز صوديوم.

كاربامازيبين هو العنصر النشط في كارباتول أقراص، يمكن أن يؤثر على الجسم بطرق مختلفة اذ انه دواء مضاد للتشنج كما يساعد على السيطرة على بعض انواع الألم واضطرابات المزاج.

يستخدم كارباتول®

- لعلاج بعض أنواع الصرع.
- لعلاج بعض الامراض التي تسبب الما بالوجه مثل التهاب العصب الثالث.
- للمساعدة في السيطرة على اضطرابات المزاج الخطيرة عندما تفشل الأدوية الأخرى.

٣. ما يجب مراعاته قبل أن تتناول كارباتول®

بعض الناس لا يجب أن تأخذ **كارباتول**® أقراص. تحدث إلى طبيبك إذا:

- كنت تعتقد أن لديك حساسية لمادة كاربامازيبين أو مواد أخرى مشابهة لها مثل اوكس كاربازيبين أو مجموعة دوائية مشابهة مثل تراى سيكليك انتي دبريسانات (أميتريبتيلين أو إيميبرامين).

إذا كان لديك حساسية من كاربامازيبين فهناك احتمال بنسبة (٢٥٪) ان يحدث لك حساسية أيضا من اوكس كاربازيبين

- اذا كان لديك حساسية من أي من المكونات الأخرى لكارباتول أقراص (مدرجة في نهاية النشرة). وتشمل دلائل وجود فرط الحساسية على: تورم الوجه أو الفم (وذمة وعائية)، مشاكل في التنفس، سيلان الأنف، طفح الجلدي، ظهور تقرحات أو تقشير.
- لديك قصور في القلب،
- حدوث اى امراض سابقة بالنخاع العظمى.
- حدوث اضطراب في الدم يسمى البورفيريا
- اذا تناولت ادوية مثبطات أوكسيديز أحادي الأمين، التي تستخدم لعلاج الاكتئاب، في غضون ال ١٤ يوما الماضية.

هناك عدد من الأشخاص الذين يعالجون بمضادات الصرع: مثل كاربامازيبين قد يحدث لهم أفكار إيذاء أو قتل أنفسهم. إذا شعرت بهذه الأفكار في أي وقت، فعلى الفور اتصل بطبيبك.

تم الإبلاغ عن حدوث طفح جلدي خطير (متلازمة ستيفنز جونسون، انحلال البشرة السمي) مع استخدام كاربامازبين. يظهر الطفح الجلدى في كثير من الأحيان في صورة قرح في الفم والحلق والأنف والأعضاء التناسلية والتهاب الملتحمة (أحمرار وتورم بالعين). قد يسبق هذا الطفح الجلدي أعراض تشبه الانفلونزا (حمى، صداع، آلام بالجسم). قد يتطور الطفح إلى ظهور تقرحات وتقشير بالجلد على نطاق واسع. وتزداد احتمالية حدوث هذه التفاعلات الجلدية الخطيرة خلال الأشهر الأولى من العلاج. كذلك تكون أكثر شيوعا في بعض البلدان الآسيوية مثل الصينيين أو ذو الأصول التايلاندية.

قد يقرر طبيبك إذا كان فحص الدم ضروري لك قبل أخذ الكاربامازبين ام لا.

إذا اصبت بهذا الطفح الجلدي أو اى من أعراضه، فيجب التوقف عن تناول الكاربامازبين والاتصال بالطبيب فورا. كما يجب عليك أن تسأل نفسك هذه الاسئلة قبل تناول أقراص كارباتول. إذا كانت الإجابة على أي من هذه الأسئلة هو نعم، فيجب مناقشة طبيبك أو الصيدلي اذ ان كارباتول أقراص قد لا يكون هو الدواء المناسب لك.

- هل أنت حامل أو تخططين لان تصبحى حاملا؟
- هل ترضعين رضاعة طبيعية؟
- هل تعاني من حدوث نوبات الصرع المختلطة ؟
- هل لديك أي مرض عقلي؟
- هل لديك حساسية من دواء للصرع يسمى الفينيتوين؟
- هل لديك قصور في الكبد؟
- هل لديك قصور في الكلى يرتبط بانخفاض مستوى الصوديوم في الدم أو هل تأخذ أدوية تؤدى الى انخفاض مستويات الصوديوم في الدم (مدرات البول: مثل هيدروكلوروثيازيد، فوروسيميد)
- هل أنت من كبار السن؟
- هل لديك أي أمراض في العين: مثل الجلوكوما (زيادة الضغط في العين) أو صعوبة في التحكم في البول؟
- المرضى المصابون بأمراض وراثية نادرة مثل عدم تحمل الجالاكتوز، نقص انزيم اللاكتوز، سوء امتصاص جلوكوز – جالاكتوز، يجب عليهم عدم تناول هذا الدواء.

هل تأخذ أي أدوية أخرى؟

يمكن أن يؤثر أويتأثر **كارباتول**® بالكثير من الأشياء الأخرى، مثل تناول الطعام أو أخذ أدوية أخرى. من المهم جدا التأكد من ان طبيبك يعرف كل شيء عن ما تأخذه، بما في ذلك ما تشتريه من الصيدلية أو متجر الأطعمة اذ قد يؤدى الى تغيير في جرعة بعض الأدوية أو التوقف عن تناول الاخرى تماما.

أخبر الطبيب إذا كنت تأخذ:

- وسائل منع الحمل الهرمونية، مثل حبوب منع الحمل، واللصقات، والحقن. قد يؤثر كارباتول على كفاءة عمل وسيلة منع الحمل في جسمك، وقد يسبب نزيف او يجعل وسيلة منع الحمل أقل فعالية، ويكون هناك احتمال حدوث الحمل.

استشر طبيبك حول هذا الموضوع، ويجب أن نفكر في استخدام وسائل أخرى لمنع الحمل.

- العلاج بالهرمونات البديلة. استخدام **كارباتول**® يمكن أن يجعلها أقل فعالية.
- أي أدوية لعلاج الاكتئاب أو القلق.
- الكورتيزون الذى يستخدم لعلاج الالتهابات: مثل الربو، ومرض التهاب الأمعاء والعضلات وآلام المفاصل.
- مضادات التخثر لوقف تخثر الدم.
- المضادات الحيوية لعلاج العدوى والالتهابات الجلدية و السل.
- مضادات الفطريات لعلاج الالتهابات الفطرية.
- مسكنات الالم التي تحتوي على الباراسيتامول، بروبوكسيفين، ترامادول، الميثادون أو البوبرينورفين.
- الأدوية الأخرى المستخدمة لعلاج الصرع.
- أدوية علاج ارتفاع ضغط الدم أو القصور في القلب.
- مضادات الهيستامين (أدوية لعلاج الحساسية: مثل حمى القش، الحكة، الخ).
- مدرات البول.
- سيميتيدين أو أوميبرازول (أدوية لعلاج قرحة المعدة).
- ايزوتريتنون (لعلاج حب الشباب).
- ميتوكلوبراميد و ابريبيتات (الأدوية المضادة للقيء).
- أسيتازولاميد (لعلاج الجلوكوما - زيادة الضغط في العين).
- دانازول أو جيسترينون (لعلاج التهاب بطانة الرحم).
- ثيوفيلين أو أمينوفيلين (المستخدمة في علاج الربو).
- سيكلوسبورين، تاكروليموس أو سيروليموس (تستخدم بعد عمليات زرع الاعضاء، و لعلاج التهاب المفاصل أو مرض الصدفية).
- الأدوية المستخدمة لعلاج الفصام (مثل باليبيريدون، اريبيبرازول).
- عقاقير مضادة للسرطان (مثل تمسيروليموس، لاباتينيب).
- الأدوية المضادة للملاريا، مثل ميفلوكين.
- أدوية علاج فيروس نقص المناعة البشرية.
- ليفوثيروكسين (التي تستخدم لعلاج قصور الغدة الدرقية).
- تادالافيل (التي تستخدم لعلاج الضعف الجنسي).
- البندازول (يستخدم لعلاج الديدان).
- بيوبروبيون (تستخدم للمساعدة في وقف التدخين).
- نوع من الدوية العشبية يسمى نبتة سانت جونز.
- الادوية التى تحتوي على فيتامين ب ٣ (نيكوتيناميد).

الحمل والرضاعة الطبيعية

يجب عليك مناقشة علاج الصرع مع طبيبك جيدا قبل أن تصبحين حاملا. إذا أصبحت حاملا أثناء العلاج **بكارباتول**® يجب إخبار الطبيب على الفور. كما هو الحال مع باقي أدوية علاج الصرع، هناك خطر من وقوع ضرر على الجنين. تأكدى من معرفتك التامة لمخاطر وفوائد تناول أقراص **كارباتول**®.

تستطيع الأمهات اللواتى تأخذن أقراص **كارباتول**® إرضاع أطفالهن، ولكن يجب إخبار الطبيب فورا إذا لاحظت أن الطفل يعاني من بعض الآثار الجانبية: مثل النعاس المفرط، والحساسية الجلدية أو اصفرار الجلد والعينين أوالبول الداكن أو البراز الشاحب.

القيادة او إستخدام الآلات؟

لا توجد مشكلة مع القيادة واستخدام الالات

يمكن أن يجعلك **كارباتول**® تشعر بالدوار أو النعاس، أو يسبب عدم وضوح الرؤية، الرؤية المزدوجة، أو يقلل من التوافق العضلي، وبخاصة في بداية العلاج أو عندما يتم تغيير الجرعة. إذا شعرت بأى من هذه الاعراض فيجب التوقف عن قيادة السيارة أو تشغيل الآلات.

تحذيرات خاصة أخرى

- شرب المشروبات الكحولية قد تؤثر عليك أكثر من المعتاد.
- تناول أو شرب عصير الجريب فروت، قد يزيد من إحتمال ظهور الآثار الجانبية.
- قد يرغب طبيبك في عمل اختبارات الدم قبل البدء بتناول كارباتول وكذلك من وقت لآخر أثناء العلاج. هذا أمر شائع جدا ولا يدعو للقلق

يحتوى **كارباتول**® على اللاكتوز، لا يستخدم في المرضى الذين ليس لديهم القدرة على تحمل بعض السكريات.

٣. كيفية تناول كارباتول أقراص

سوف يخبرك طبيبك عن جرعة الأقراص المطلوب تناولها وموعد اخذها، ويجب اتباع تعليماته بدقة. من المهم تناول الأقراص في الأوقات الصحيحة مع الاستمرار في تناولها حسب إرشادات الطبيب ما لم يحدث لك اى مشاكل، في هذه الحالة استشر طبيبك.

عادة يبدأ الطبيب بوصف **كارباتول**® بجرعة منخفضة نسبيا ومن ثم يمكن زيادتها حسب احتياجك. الجرعة المطلوبة تختلف بين المرضى. يمكنك أن تأخذ أقراص **كارباتول**® أثناء أو وسط أو بعد وجبات الطعام. يجب ابتلاع الاقراص مع الشراب. وعادة تؤخذ الجرعة مرتين أو ثلاث مرات في اليوم. إذا لزم الأمر يمكن كسر القرص عند الحز الوسطى.

لعلاج الصرع الجرعات المعتادة هي:

الكبار:

٨٠٠ –١٢٠٠ مجم يوميا، و ممكن زيادتها حسب الاحتياج. إذا كنت من كبار السن فقد يوصف لك جرعة أقل.

الأطفال:

الذين تتراوح أعمارهم بين ٥–١٠ سنوات: ٤٠٠–٦٠٠ مجم يوميا

الذين تتراوح أعمارهم بين ١٠–١٥ سنة: ٦٠٠–١٠٠٠ مجم يوميا.

لا ينصح باستخدامه للأطفال دون سن الخامسة.

لعلاج التهاب العصب الثالث : الجرعة المعتادة هي: ٦٠٠–٨٠٠ مجم يوميا. الجرعة القصوى هي ١٢٠٠ مجم يوميا. إذا كنت من كبار السن قد يوصف لك جرعة أقل.

لعلاج اضطراب المزاج : الجرعة المعتادة هي ٤٠٠–٦٠٠ مجم يوميا

ماذا لو نسيت أن تأخذ جرعة؟

إذا نسيت أن تأخذ جرعة، فيجب أن تأخذ واحدة في أقرب وقت ممكن. لكن اذا اقترب وقت تناول الجرعة التالية، فيجب فقط أن تأخذ الجرعة الجديدة و لا تعوض الجرعة المنسية.

ماذا لو تجاوزت الجرعة؟

إذا كنت من دون قصد قد تناولت الكثير من أقراص **كارباتول**®، فأستشر طبيبك أو اذهب الى أقرب مستشفى اليك و توجه الى قسم الطوارئ مع احضار علبة الدواء معك ليتأكد الطبيب من نوعها.

٤. الآثار الجانبية المحتملة

مثل جميع الأدوية ، يمكن أن يسبب تناول **كارباتول**® بعض الآثار الجانبية، على الرغم من عدم حدوثها مع جميع الحالات يجب التوقف عن تناول أقراص **كارباتول**® وإخبار الطبيب على الفور إذا لاحظت:

- تفاعلات جلدية خطيرة: مثل الطفح الجلدي، احمرار الجلد، ظهور تقرحات في الشفتين والعينين أو الفم أو الجلد يصاحبها ارتفاع في درجة الحرارة. ردود الفعل هذه قد تكون أكثر شيوعا في المرضى الصينيين و التايلانديين.
- تقرحات بالفم، كدمات أو نزيف غير متوقع.
- التهاب الحلق أو ارتفاع في درجة الحرارة، أو كلاهما.
- اصفرار بالجلد، شحوب بالعينين.
- تورم الكاحلين والقدمين أو أسفل الساقين.
- أي أعراض لمرض عصبي أو تشوش.
- ألم في المفاصل والعضلات، وظهور طفح جلدى ما بين الأنف والخدين و قصور في التنفس (قد تكون دلائل على وجود مرض الذئبة الحمراء).
- حمى وطفح جلدي وآلام بالمفاصل، وتغير في اختبارات الدم ووظائف الكبد (قد تكون علامة لمرض حساسية الأعضاء المتعددة).
- ضيق شعبى مع صفير وسعال وصعوبة في التنفس، والشعور بالإعياء، وطفح جلدي، تورم أو حكة بالوجه (قد تكون دلائل على وجود حساسية شديدة).
- ألم في منطقة اسفل المعدة.

تم الإبلاغ أيضا عن حدوث بعض الآثار الجانبية المذكورة أدناه.

أكثر من ١ :١٠:

نقص كرات الدم البيضاء (انخفاض عدد خلايا الدم المسئولة عن مكافحة العدوى مما يسهل التقاط العدوى). دوخة واجهاد. صعوبة في التحكم في الحركة. الشعور بالاعياء. حدوث بعض التغيرات في مستوي انزيمات الكبد (عادة دون أي الأعراض). طفح جلدى أحيانا يكون شديدا.

يصل إلى ١ : ١٠:

تغييرات في الدم بما قد تؤدى الى احتمال ظهور كدمات أو نزيف. احتباس السوائل و تورم. زيادة الوزن. انخفاض الصوديوم في الدم مما قد يؤدي إلى التشوش. صداع. عدم وضوح الرؤية أو الرؤية المزدوجة ؛ جفاف الفم.

يصل إلى ١ : ١٠٠:

حركات لا ارادية غير طبيعية مثل ارتعاشات أو تشنجات لاإرادية. ارتعاشات لا ارادية بالعين. حدوث إسهال.او إمساك.

يصل إلى ١ : ١٠٠٠:

مرض في الغدد الليمفاوية، نقص حمض الفوليك، حساسية مثل ظهور طفح جلدي، آلام بالمفاصل، حمى، قصور في الكلى وأعضاء أخرى؛ هلاوس. اكتئاب، فقدان الشهية؛ أرق؛ ارتباك، زيادة الحركة و العدوانية ، اضطرابات بالنطق، تخدير أو وخز في اليدين والقدمين، ضعف بالعضلات. ارتفاع ضغط الدم (والتي قد تجعلك تشعر بالدوار، مع سخونة بالوجه والصداع، والتعب والعصبية). انخفاض ضغط الدم (أعراضه الشعور بالإعياء، و الدوار، والتشوش، و عدم وضوح الرؤية)، اضطراب في ضربات القلب؛ آلام في المعدة، قصور في الكبد ،اليرقان، أعراض الذئبة الحمراء.

يصل إلى ١ : ١٠٠٠٠:

تغييرات فى تكوين الدم بما في ذلك فقر الدم، بورفيريا، التهاب سحائى. تورم الثديين ارتشاح اللبن التي قد تحدث في كل من الذكور والإناث، خلل في وظائف الغدة الدرقية، لين العظام (ألم عند المشي وتقوس فى عظام الساقين)، هشاشة العظام، زيادة مستويات الدهون في الدم. اختلال التذوق، التهاب الملتحمة، المياه الزرقاء، إعتام عدسة العين، اضطرابات السمع، قصور في القلب و الدورة الدموية، جلطات دموية (DVT)، ألم، تورم، وسخونة و تلون بالجلد، بروز الأوردة السطحية بارزة، قصور في التنفس، تفاعلات جلدية شديدة مثل متلازمة ستيفنز جونسون (تكون أكثر شيوعا في المرضى من أصل صيني أو تايلاندي)، التهاب الفم أو اللسان، قصور بالكبد. زيادة حساسية الجلد لأشعة الشمس، تغييرات في تصبغ الجلد، حب الشباب، التعرق المفرط.، تساقط الشعر؛ زيادة نمو الشعر على الجسم والوجه. آلام أو تشنج في العضلات. مشاكل تناسلية مثل انخفاض خصوبة الرجال وفقدان الرغبة الجنسية و العجز الجنسي. الفشل الكلوي، نزول دم في البول، زيادة أو انخفاض الرغبة في التبول أو صعوبة في التبول.

تم الإبلاغ أيضا عن الاعراض الجانبية التالية، ولكن لانستطيع تقدير معدلات حدوثها:

تفاعلات جلدية شديدة، توعك ، تغير في صورة الدم، إسهال، ألم في البطن، حمى (علامات التهاب القولون)، تنشيط فيروس الهربس (يمكن أن تكون خطيرة إذا كان جهاز المناعة به قصور)، تأكل الاظافر، وكسور بالعظام، انخفاض في كثافة العظام، نعاس، فقدان الذاكرة، احمرار و حكة بالجلد.

لا تندهش من هذه القائمة. معظم الناس تأخذ كارباتول® أقراص دون أي مشاكل.

إذا ظهر لك أي من الآثار الجانبية، أو إذا لاحظت أي آثار جانبية غير المذكورة في هذه النشرة، أخبر طبيبك ليصف لك دواء أخر.

هناك تقارير عن حدوث مشاكل بالعظام مثل هشاشة ولين العظام والكسور. راجع مع الطبيب المعالج أو الصيدلي إذا كنت مستمر في تناول ادوية الصرع على مدى طويل و لديك تاريخ مرضى لهشاشة العظام، أو تناول الادوية الاسترويدية.

٥-كيفية تخزين أقراص كارباتول®

تخزن في درجة حرارة لا تزيد عن ٣٠ درجة مئوية وفي مكان جاف.

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لا تأخذ أقراص **كارباتول**® بعد تاريخ انتهاء الصلاحية المدون على العلبة.

تحفظ جميع الأدوية بعيداً عن متناول الأطفال

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Carbatol® Tablets

carbamazepine 200mg

1. Name of the medicinal product: Carbatol® 200mg Tablets

2. Qualitative and quantitative composition

Active ingredient

Carbamazepine 200 mg

Inactive ingredients P.V.P. XL, Povidone K30, Avicel PH 102, Lactose Monohydrate, Croscarmellose Sodium, Talc Purified, Magnesium Stearate.

3. Pharmaceutical form: Tablets

4. Clinical particulars

4.1 Therapeutic indications - Epilepsy - generalised tonic-clonic and partial seizures. **Note:** Carbatol is not usually effective in absences (petit mal) and myoclonic seizures. Moreover, anecdotal evidence suggests that seizure exacerbation may occur in patients with atypical absences. -The paroxysmal pain of trigeminal neuralgia. - For the prophylaxis of manic-depressive psychosis in patients unresponsive to lithium therapy.

4.2 Posology and method of administration Carbatol is given orally, usually in two or three divided doses. Carbatol may be taken during, after or between meals, with a little liquid e.g. a glass of water. **Epilepsy:** The dose of carbamazepine should be adjusted to the needs of the individual patient to achieve adequate control of seizures. Determination of plasma levels may help in establishing the optimum dosage. In the treatment of epilepsy, the dose of carbamazepine usually requires total plasma-carbamazepine concentrations of about 4 to 12 micrograms/mL (17 to 50 micromoles/litre) (see warnings and precautions). **Adults:** It is advised that with all formulations of Carbatol, a gradually increasing dosage scheme is used and this should be adjusted to suit the needs of the individual patient. Carbatol should be taken in a number of divided doses although initially 100-200mg once or twice daily is recommended. This may be followed by a slow increase until the best response is obtained, often 800-1200mg daily. In some instances, 1600mg or even 2000mg daily may be necessary. **Elderly:** Due to the potential for drug interactions, the dosage of Carbatol should be selected with caution in elderly patients. **Children and adolescents**: It is advised that with all formulations of Carbatol, a gradually increasing dosage scheme is used and this should be adjusted to suit the needs of the individual patient. Usual dosage 10-20mg/kg bodyweight daily taken in several divided doses. Carbatol tablets are not recommended for very young children. 5-10 years: 400 to 600mg daily (2-3 x 200mg tablets per day, to be taken in divided doses). 10-15 years: 600 to 1000mg daily (3-5 x 200mg tablets per day, to be taken in several divided doses). >15 years of age: 800 to 1200mg daily (same as adult dose). ***Maximum recommended dose*** Up to 6 years of age: 35mg/kg/day 6-15 years of age: 1000mg/day >15 years of age: 1200mg/day. Wherever possible, anti-epileptic agents should be prescribed as the sole anti-epileptic agent but if used in polytherapy the same incremental dosage pattern is advised. When Carbatol is added to existing antiepileptic therapy, this should be done gradually while maintaining or, if necessary, adapting the dosage of the other antiepileptic(s) (see 4.5 Interaction with other Medicaments and other forms of Interaction). **Trigeminal neuralgia:**

Slowly raise the initial dosage of 200-400mg daily until freedom from pain is achieved (normally at 200mg 3-4 times daily). In the majority of patients a dosage of 200mg 3 or 4 times a day is sufficient to maintain a pain free state. In some instances, doses of 1600mg Carbatol daily may be needed. However, once the pain is in remission, the dosage should be gradually reduced to the lowest possible maintenance level. Maximum recommended dose is 1200mg/day. When pain relief has been obtained, attempts should be made to gradually discontinue therapy, until another attack occurs.

Elderly: Dosage in Trigeminal neuralgia Due to drug interactions and different antiepileptic drug pharmacokinetics, the dosage of Carbatol should be selected with caution in elderly patients. In elderly patients, an initial dose of 100mg twice daily is recommended. The initial dosage of 100mg twice daily should be slowly raised daily until freedom from pain is achieved (normally at 200mg 3 to 4 times daily). The dosage should then be gradually reduced to the lowest possible maintenance level. Maximum recommended dose is 1200mg/day. When pain relief has been obtained, attempts should be made to gradually discontinue therapy, until another attack occurs. **For the prophylaxis of manic depressive psychosis** in patients unresponsive to lithium therapy: Initial starting dose of 400mg daily, in divided doses, increasing gradually until symptoms are controlled or a total of 1600mg given in divided doses is reached. The usual dosage range is 400-600mg daily, given in divided doses. **Special populations Renal impairment / Hepatic impairment** No data are available on the pharmacokinetics of carbamazepine in patients with impaired hepatic or renal function.

4.3 Contraindications Known hypersensitivity to carbamazepine or structurally related drugs (e.g. tricyclic antidepressants) or any other component of the formulation. Patients with atrioventricular block, a history of bone marrow depression or a history of hepatic porphyrias (e.g. acute intermittent porphyria, variegate porphyria, porphyria cutanea tarda). The use of Carbatol is contraindicated in combination with monoamine oxidase inhibitors (MAOIs) (see section 4.5 Interaction with other medicinal products and other forms of interaction).

4.4 Special warnings and precautions for use. Warnings *The product contains Lactose, not to be used in patients with glucose-galactose intolerance. Agranulocytosis and aplastic anaemia have been associated with Carbamazepine; however, due to the very low incidence of these conditions, meaningful risk estimates for Carbatol are difficult to obtain. The overall risk in the general untreated population has been estimated at 4.7 persons per million per year for agranulocytosis and 2.0 persons per million per year for aplastic anaemia. Decreased platelet or white blood cell counts occur occasionally to frequently in association with the use of Carbamazepine. Nonetheless, complete pre-treatment blood counts, including platelets and possibly reticulocytes and serum iron, should be obtained as a baseline, and periodically thereafter. Patients and their relatives should be made aware of early toxic signs and symptoms indicative of a potential haematological problem, as well as symptoms of dermatological or hepatic reactions. If reactions such as fever, sore throat, rash, ulcers in the mouth, easy bruising, petechial or purpuric haemorrhage appear, the patient should be advised to consult his physician immediately. If the white blood cell or platelet count is definitely low or decreased during treatment, the patient and the complete blood count should be closely monitored. However, treatment with Carbatol should be discontinued if the patient develops leucopenia which is severe, progressive or accompanied by clinical manifestations, e.g. fever or sore throat. Carbatol should also be discontinued if any evidence of significant bone marrow depression appears. Liver function tests should also be performed before commencing treatment and periodically thereafter, particularly in patients with a history of liver disease and in elderly patients. The drug should be withdrawn immediately in cases of aggravated liver dysfunction or acute liver disease.

Some liver function tests in patients receiving carbamazepine may be found to be abnormal, particularly gamma glutamyl transferase. This is probably due to hepatic enzyme induction. Enzyme induction may also produce modest elevations in alkaline phosphatase. These enhancements of hepatic metabolising capacity are not an indication for the withdrawal of carbamazepine. Severe hepatic reactions to carbamazepine occur very rarely. The development of signs and symptoms of liver dysfunction or active liver disease should be urgently evaluated and treatment with Carbatol suspended pending the outcome of the evaluation. 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 anti-epileptic drugs has also shown 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 carbamazepine. Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge. Serious dermatological reactions, including toxic epidermal necrolysis (TEN: also known as Lyell's syndrome) and Stevens Johnson syndrome (SJS) have been reported very rarely with Carbamazepine. Patients with serious dermatological reactions may require hospitalization, as these conditions may be life-threatening and may be fatal. Most of the SJS/TEN cases appear in the first few months of treatment with Carbamazepine. These reactions are estimated to occur in 1 to 6 per 10,000 new users in countries with mainly Caucasian populations. If signs and symptoms suggestive of severe skin reactions (e.g. SJS, Lyell's syndrome/TEN) appear, Carbatol should be withdrawn at once and alternative therapy should be considered.

Cutaneous reactions Serious and sometimes fatal cutaneous reactions including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) have been reported during treatment with carbamazepine. These reactions are estimated to occur in 1-6 per 10 000 new users in countries with mainly Caucasian populations, but the risk in some Asian countries is estimated to be about 10 times higher. There is growing evidence of the role of different HLA alleles in predisposing patients to immune-mediated adverse reactions.

HLA-B*1502 allele - in Han Chinese, Thai and other Asian populations HLA-B*1502 in individuals of Han Chinese and Thai origin has been shown to be strongly associated with the risk of developing Stevens-Johnson syndrome (SJS) when treated with carbamazepine. The prevalence of HLA-B*1502 carrier is about 10% in Han Chinese and Thai populations. Whenever possible, these individuals should be screened for this allele before starting treatment with carbamazepine. If these individuals test positive, carbamazepine should not be started unless there is no other therapeutic option. Tested patients who are found to be negative for HLA-B*1502 have a low risk of SJS, although the reactions may still very rarely occur. There are some data that suggest an increased risk of serious carbamazepine-associated TEN/SJS in other Asian populations. Because of the prevalence of this allele in other Asian populations (e.g. above 15% in the Philippines and Malaysia), testing genetically at risk populations for the presence of HLA-B*1502 may be considered. The prevalence of the HLA-B*1502 allele is negligible in e.g. European descent, African, Hispanic populations sampled, and in Japanese and Koreans (< 1%). **HLA-A*3101 allele - European descent and Japanese populations** There are some data that suggest HLA-A*3101 is associated with an increased risk of carbamazepine induced cutaneous adverse drug reactions including SJS, TEN, Drug rash with eosinophilia (DRESS), or less severe acute generalized exanthematous pustulosis (AGEP) and maculopapular rash in people of European descent and the Japanese. The frequency of the HLA-A*3101 allele varies widely between ethnic populations. HLA-A*3101 allele has a prevalence of 2 to 5% in European populations and about 10% in Japanese population. The presence of HLA-A*3101 allele may increase the risk for carbamazepine induced cutaneous reactions (mostly less severe) from 5.0% in general population to 26.0% among subjects of Northern European ancestry, whereas its absence may reduce the risk from 5.0% to 3.8%. There are insufficient data supporting a recommendation for HLA-A*3101 screening before starting carbamazepine treatment. If patients of European descent or Japanese origin are known to be positive for HLA-A*3101 allele, the use of carbamazepine may be considered if the benefits are thought to exceed risks. **Other dermatologic reactions**

Mild skin reactions e.g. isolated macular or maculopapular exanthema, can also occur and are mostly transient and not hazardous. They usually disappear within a few days or weeks, either during the continued course of treatment or following a decrease in dosage. However, since it may be difficult to differentiate the early signs of more serious skin reactions from mild transient reactions, the patient should be kept under close surveillance with consideration given to immediately withdrawing the drug should the reaction worsen with continued use. The HLA-B*1502 allele has not been found to predict risk of less severe adverse cutaneous reactions from carbamazepine, such as anticonvulsant hypersensitivity syndrome or non-serious rash (maculopapular eruption). **Hypersensitivity** Carbamazepine may trigger hypersensitivity reactions, including Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), reactivation of HHV6 associated with DRESS, a delayed multi-organ hypersensitivity disorder with fever, rash, vasculitis, lymphadenopathy, pseudo lymphoma, arthralgia, leukopenia, eosinophilia, hepato-splenomegaly, abnormal liver function tests and vanishing bile duct syndrome (destruction and disappearance of the intrahepatic bile ducts), that may occur in various combinations. Other organs may also be affected (e.g. lungs, kidneys, pancreas, myocardium, colon). In general, if signs and symptoms suggestive of hypersensitivity reactions occur, Carbatol should be withdrawn immediately. Patients who have exhibited hypersensitivity reactions to carbamazepine should be informed that 25-30 % of these patients may experience hypersensitivity reactions with oxacarbazepine (Trileptal). Cross-hypersensitivity can occur between carbamazepine and phenytoin. Carbatol should be used with caution in patients with mixed seizures which include absences, either typical or atypical. In all these conditions, Carbamazepine may exacerbate seizures. In case of exacerbation of seizures, Carbatol should be discontinued. An increase in seizure frequency may occur during switchover from an oral formulation to suppositories. **Dose reduction and withdrawal effects** Abrupt withdrawal of Carbatol may precipitate seizures therefore carbamazepine withdrawal should be gradual. If treatment with Carbatol has to be withdrawn abruptly in a patient with epilepsy, the changeover to another anti-epileptic drug should if necessary be effected under the cover of a suitable drug. **Endocrinological effects** Breakthrough bleeding has been reported in women taking Carbatol while using hormonal contraceptives. The reliability of hormonal contraceptives may be adversely affected by Carbatol and women of childbearing potential should be advised to consider using alternative forms of birth control while taking Carbatol. Patients taking Carbatol and requiring hormonal contraception should receive a preparation containing not less than 50μg oestrogen or use of some alternative non-hormonal method of contraception should be considered. **Monitoring of plasma levels** Although correlations between dosages and plasma levels of carbamazepine, and between plasma levels and clinical efficacy or tolerability are rather tenuous, monitoring of the plasma levels may be useful in the following conditions: dramatic increase in seizure frequency/verification of patient compliance; during pregnancy; when treating children or adolescents; in suspected absorption disorders; in suspected toxicity when more than one drug is being used (see 4.5 Interaction with other Medicaments and other forms of Interaction). **Precautions** Carbatol should be prescribed only after a critical benefit-risk appraisal and under close monitoring in patients with a history of cardiac, hepatic or renal damage, adverse haematological reactions to other drugs, or interrupted courses of therapy with Carbatol. Baseline and periodic complete urinalysis and BUN determinations are recommended. **Hyponatremia** Hyponatremia is known to occur with carbamazepine. In patients with pre-existing renal conditions associated with low sodium or in patients treated concomitantly with sodium-lowering medicinal products (e.g. diuretics, medicinal products associated with inappropriate ADH secretion), serum sodium levels should be measured prior to initiating carbamazepine therapy. Thereafter, serum sodium levels should be measured after approximately two weeks and then at monthly intervals for the first three months during therapy, or according to clinical need. These risk factors may apply especially to elderly patients. If hyponatraemia is observed, water restriction is an important counter-measurement if clinically indicated. **Hypothyroidism** Carbamazepine may reduce serum concentrations of thyroid hormones through enzyme induction requiring an increase in dose of thyroid replacement therapy in patients with hypothyroidism. Hence thyroid function monitoring is suggested to adjust the dosage of thyroid replacement therapy. **Anticholinergic effects** Carbamazepine has shown mild anticholinergic activity; patients with increased intraocular pressure and urinary retention should therefore be closely observed during therapy. **Psychiatric effects** The possibility of activation of a latent psychosis and, in elderly patients, of confusion or agitation should be borne in mind. **Interactions** Co-administration of inhibitors of CYP3A4 or inhibitors of epoxide hydrolase with carbamazepine can induce adverse reactions (increase of carbamazepine or carbamazepine-10,11 epoxide plasma concentrations respectively). The dosage of Carbatol should be adjusted accordingly and/or the plasma levels monitored. Co-administration of CYP3A4 inducers with carbamazepine may decrease carbamazepine plasma concentrations and its therapeutic effect, while discontinuation of a CYP3A4 inducer may increase carbamazepine plasma concentrations. The dosage of Carbatol may have to be adjusted. Carbamazepine is a potent inducer of CYP3A4 and other phase I and phase II enzyme systems in the liver, and may therefore reduce plasma concentrations of co-medications mainly metabolized by CYP3A4 by induction of their metabolism. See section 4.5 Interactions. Female patients of childbearing potential should be warned that the concurrent use of Carbatol with hormonal contraceptives may render this type of contraceptive ineffective (see sections 4.5 Interactions and 4.6 Pregnancy and lactation). Alternative non-hormonal forms of contraception are recommended when using Carbatol.

* Patients with rare hereditary problems of galactose intolerance, the Lapp lactose deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction Cytochrome P450 3A4 (CYP 3A4) is the main enzyme catalysing formation of the active metabolite carbamazepine 10, 11-epoxide. Co-administration of inhibitors of CYP 3A4 may result in increased carbamazepine plasma concentrations which could induce adverse reactions. Co-administration of CYP 3A4 inducers might increase the rate of carbamazepine metabolism, thus leading to potential decreases in the carbamazepine serum level and therapeutic effect. Similarly, discontinuation of a CYP3A4 inducer may decrease the rate of metabolism of carbamazepine, leading to an increase in carbamazepine plasma levels. Carbamazepine is a potent inducer of CYP3A4 and other phase I and phase II enzyme systems in the liver, and may therefore reduce plasma concentrations of comedications mainly metabolized by CYP3A4 by induction of their metabolism. Human microsomal epoxide hydrolase has been identified as the enzyme responsible for the formation of the 10,11-transdiol derivative from carbamazepine-10,11 epoxide. Co-administration of inhibitors of human microsomal epoxide hydrolase may result in increased carbamazepine-10,11 epoxide plasma concentrations. **Interactions resulting in a contraindication** The use of Carbatol is contraindicated in combination with monoamine-oxidase inhibitors (MAOIs); before administering Carbatol MAOIs should be discontinued for a minimum of 2 weeks, or longer if the clinical situation permits. **Agents that may raise carbamazepine plasma levels:** Since raised plasma carbamazepine levels may result in adverse reactions (e.g. dizziness, drowsiness, ataxia, diplopia), the dosage of Carbatol should be adjusted accordingly and/or the plasma levels monitored when used concomitantly with the substances described below:

Analgesics, anti-inflammatory drugs: dextropropoxyphene. **Androgens:** danazol. **Antibiotics:** macrolide antibiotics (e.g. erythromycin, clarithromycin), ciprofloxacine. **Antidepressants:** fluoxetine, fluvoxamine, paroxetine, trazodone. **Antiepileptics:** vigabatrin. **Antifungals:** azoles (e.g. itraconazole, ketoconazole, fluconazole, voriconazole). Alternative anti-convulsants may be recommended in patients treated with voriconazole or itraconazole. **Antihistamines:** loratadine. **Antipsychotics:** olanzapine. **Antituberculosis:** isoniazid. **Antivirals:** protease inhibitors for HIV treatment (e.g. ritonavir). **Carbonic anhydrase inhibitors:** acetazolamide. **Cardiovascular drugs:** diltiazem, verapamil. **Gastrointestinal drugs:** possibly cimetidine, omeprazole. **Other interactions:** grapefruit juice, nicotinamide (only in high dosage). **Agents that may raise the active metabolite carbamazepine-10,11-epoxide plasma levels:** Since raised plasma carbamazepine-10,11-epoxide levels may result in adverse reactions (e.g. dizziness, drowsiness, ataxia, diplopia), the dosage of Carbatol should be adjusted accordingly and/or the plasma levels monitored when used concomitantly with the substances described below: Quetiapine, primidone, progabide, valproic acid, valnoctamide and valpromide. **Agents that may decrease carbamazepine plasma levels**: The dose of Carbatol may have to be adjusted when used concomitantly with the substances described below: **Antiepileptics:** oxcarbazepine, phenobarbital, phenytoin (to avoid phenytoin intoxication and subtherapeutic concentrations of carbamazepine it is recommended to adjust the plasma concentration of phenytoin to 13 micrograms /mL before adding carbamazepine to the treatment) and fosphenytoin, primidone, and, although the data are partly contradictory, possibly also clonazepam. **Antineoplastics:** cisplatin or doxorubicin. **Antituberculosis**: rifampicin. **Bronchodilatators or anti-asthma drugs:** theophylline, aminophylline. **Dermatological drugs:** isotretinoin. **Other interactions:** herbal preparations containing St John's wort (Hypericum perforatum).

Effect of Carbatol on plasma levels of concomitant agents: Carbamazepine may lower the plasma level, diminish or even abolish the activity of certain drugs. The dosage of the following drugs may have to be adjusted to clinical requirement: **Analgesics, anti-inflammatory agents:** buprenorphine, methadone, paracetamol (long term administration of carbamazepine and paracetamol (acetaminophen) may be associated with hepatotoxicity), tramadol. **Antibiotics:** doxycycline, rifabutin. **Anticoagulants:** oral anticoagulants (e.g. warfarin and acenocoumarol). **Antidepressants:** bupropion, citalopram, mianserin, sertraline, trazodone, tricyclic antidepressants (e.g. imipramine, amitriptyline, nortriptyline, clomipramine). **Antiemetics:** aprepitant **Antiepileptics:** clobazam, clonazepam, ethosuximide, lamotrigine, oxcarbazepine, primidone, tiagabine, topiramate, valproic acid, zonisamide. To avoid phenytoin intoxication and subtherapeutic concentrations of carbamazepine it is recommended to adjust the plasma concentration of phenytoin to 13 micrograms /mL before adding carbamazepine to the treatment. There have been rare reports of an increase in plasma mephenytoin levels. **Antifungals:** itraconazole, voriconazole. Alternative anti-convulsants may be recommended in patients treated with voriconazole or itraconazole. **Antihelmintics:** albendazole. **Antineoplastics:** imatinib, cyclophosphamide, lapatinib, temsirolimus. **Antipsychotics:** clozapine, haloperidol and bromperidol, olanzapine, quetiapine, risperidone, aripiprazole, paliperidone. **Antivirals:** protease inhibitors for HIV treatment (e.g. indinavir, ritonavir, saquinavir). **Anxiolytics:** alprazolam. **Bronchodilatators or anti-asthma drugs:** theophylline. **Contraceptives:** hormonal contraceptives (alternative contraceptive methods should be considered). Cardiovascular drugs: calcium channel blockers (dihydropyridine group) e.g. felodipine, digoxin, simvastatin, atorvastatin, lovastatin, cerivastatin, ivabradine. **Corticosteroids:** corticosteroids (e.g. prednisolone, dexamethasone).

Drugs used in erectile dysfunction: tadalafil. **Immunosuppressants:** ciclosporin, everolimus, tacrolimus, sirolimus. **Thyroid agents:** levothyroxine. **Other drug interactions:** products containing oestrogens and/or progesterones. **Combinations that require specific consideration:** Concomitant use of carbamazepine and levetiracetam has been reported to increase carbamazepine-induced toxicity. Concomitant use of carbamazepine and isoniazid has been reported to increase isoniazid-induced hepatotoxicity. The combination of lithium and carbamazepine may cause enhanced neurotoxicity inspite of lithium plasma concentrations being within the therapeutic range. Combined use of carbamazepine with metoclopramide or major tranquillisers, e.g. haloperidol, thioridazine, may also result in an increase in neurological side-effects. Concomitant medication with Carbatol and some diuretics (hydrochlorothiazide, furosemide) may lead to symptomatic hyponatraemia. Carbamazepine may antagonise the effects of non-depolarising muscle relaxants (e.g. pancuronium). Their dosage should be raised and patients monitored closely for a more rapid recovery from neuromuscular blockade than expected. Carbamazepine, like other psychoactive drugs, may reduce alcohol tolerance. It is therefore advisable for the patient to abstain from alcohol. **Interference with serological testing** Carbamazepine may result in false positive perphenazine concentrations in HPLC analysis due to interference. Carbamazepine and the 10,11-epoxide metabolite may result in false positive tricyclic antidepressant concentration in fluorescence polarized immunoassay method.

4.6 Pregnancy and lactation

Pregnancy: Offspring of epileptic mothers with untreated epilepsy are known to be more prone to developmental disorders, including malformations. Developmental disorders and malformations, including spina bifida, and also other congenital anomalies e.g. craniofacial defects such as clept lip/palate, cardiovascular malformations, hypospadias and anomalies involving various body systems, have been reported in association with the use of Carbatol. Patients should be counselled regarding the possibility of an increased risk of malformations and given the opportunity of antenatal screening. Based on data in a North American pregnancy registry, the rate of major congenital malformations, defined as a structural abnormality with surgical, medical, or cosmetic importance, diagnosed within 12 weeks of birth was 3.0% (95% CI 2.1 to 4.2%) among mothers exposed to carbamazepine monotherapy in the first trimester and 1.1% (95% CI 0.35 to 2.5%) among pregnant women not taking any antiepileptic drug (relative risk 2.7, 95% CI 1.1 to 7.0). Taking these data into consideration: - Pregnant women with epilepsy should be treated with special care. - If women receiving Carbatol become pregnant or plan to become pregnant, or if the problem of initiating treatment with Carbatol arises during pregnancy, the drug's expected benefits must be carefully weighed against its possible hazards, particularly in the first 3 months of pregnancy. - In women of childbearing potential Carbatol should, wherever possible, be prescribed as monotherapy, because the incidence of congenital abnormalities in the offspring of women treated with a combination of antiepileptic drugs is greater than in those of mothers receiving the individual drugs as monotherapy. The risk of malformations following exposure to carbamazepine as polytherapy may vary depending on the specific drugs used and may be higher in polytherapy combinations that include valproate. - Minimum effective doses should be given and monitoring of plasma levels is recommended. The plasma concentration could be maintained in the lower side of the therapeutic range 4 to 12 micrograms/mL provided seizure control is maintained. There is evidence to suggest that the risk of malformation with carbamazepine may be dose-dependent i.e. at a dose < 400mg per day, the rates of malformation were lower than with higher doses of carbamazepine. - Patients should be counseled regarding the possibility of an increased risk of malformations and given the opportunity of antenatal screening. - During pregnancy, an effective antiepileptic treatment should not be interrupted, since the aggravation of the illness is detrimental to both the mother and the fetus. **Monitoring and prevention** Folic acid deficiency is known to occur in pregnancy. Antiepileptic drugs have been reported to aggravate deficiency. This deficiency may contribute to the increased incidence of birth defects in the offspring of treated epileptic women. Folic acid supplementation has therefore been recommended before and during pregnancy. **In the neonate** In order to prevent bleeding disorders in the offspring, it has also been recommended that vitamin K1 be given to the mother during the last weeks of pregnancy as well as to the neonate. There have been a few cases of neonatal seizures and/or respiratory depression associated with malernal Carbatol and other concomitant antiepileptic drug use. A few cases of neonatal vomiting, diarrhoea and/or decreased feeding have also been reported in association with maternal Carbatol use. These reactions may represent a neonatal withdrawal syndrome. **Women of child-bearing potential and contraceptive measures** Due to enzyme induction, Carbatol may result in a failure of the therapeutic effect of oral contraceptive drugs containing oestrogen and/or progesterone. Women of child bearing potential should be advised to use alternative contraceptive methods while on treatment with Carbatol. **Breast-feeding:** Carbamazepine passes into the breast milk (about 25-60% of the plasma concentrations). The benefits of breast-feeding should be weighed against the remote possibility of adverse effects occurring in the infant. Mothers taking Carbatol may breast-feed their infants, provided the infant is observed for possible adverse reactions (e.g. excessive somnolence, allergic skin reaction). There have been some reports of cholestatic hepatitis in neonates exposed to carbamazepine during antenatal and or during breast feeding. Therefore breast-fed infants of mothers treated with carbamazepine should be carefully observed for adverse hepatobiliary effects. **Fertility:** There have been very rare reports of impaired male fertility and/or abnormal spermatogenesis.

4.7 Effects on ability to drive and use machines The patient's ability to react may be impaired by the medical condition resulting in seizures and adverse reactions including dizziness, drowsiness, ataxia, diplopia, impaired accommodation and blurred vision reported with Carbatol, especially at the start of treatment or in connection with dose adjustments. Patients should therefore exercise due caution when driving a vehicle or operating machinery.

4.8 Undesirable effects Summary of the safety profile Particularly at the start of treatment with Carbatol, or if the initial dosage is too high, or when treating elderly patients, certain types of adverse reaction occur very commonly or commonly, e.g. CNS adverse reactions (dizziness, headache, ataxia, drowsiness, fatigue, diplopia); gastrointestinal disturbances (nausea, vomiting), as well as allergic skin reactions. The dose-related adverse reactions usually abate within a few days, either spontaneously or after a transient dosage reduction. The occurrence of CNS adverse reactions may be a manifestation of relative overdosage or significant fluctuation in plasma levels. In such cases it is advisable to monitor the plasma levels and divide the daily dosage into smaller (i.e. 3-4) fractional doses. **Tabulated summary of adverse drug reactions compiled from clinical trials and from spontaneous reports** Adverse drug reactions from clinical trials are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): 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).

Blood and lymphatic system disorders	
Very common:	leucopenia.
Common:	thrombocytopenia, eosinophilia.
Rare:	leucocytosis, lymphadenopathy.
Very rare:	agranulocytosis, aplastic anaemia, pancytopenia, aplasia pure red cell, anaemia, anaemia megaloblastic, reticulocytosis, haemolytic anaemia.
Not known:	bone marrow depression.
Immune system disorders	
Rare:	a delayed multi-organ hypersensitivity disorder with fever, rashes, vasculitis, lymphadenopathy, pseudo lymphoma, arthralgia, leucopenia, eosinophilia, hepato-splenomegaly, abnormal liver function tests and vanishing bile duct syndrome (destruction and disappearance of the intrahepatic bile ducts) occurring in various combinations. Other organs may also be affected (e.g. liver, lungs, kidneys, pancreas, myocardium, colon).
Very rare:	anaphylactic reaction, oedema angioedema, hypogammaglobulinaemia.
Not known**:	Drug Rash with Eosinophilia and Systemic Symptoms (DRESS).
Infections and infestations	
Not known**:	reactivation of Human herpesvirus 6 infection.
Endocrine disorders	
Common:	Oedema, fluid retention, weight increase, hyponatraemia and blood osmolarity decreased due to an antidiuretic hormone (ADH)-like effect, leading in rare cases to water intoxication accompanied by lethargy, vomiting, headache, confusional state, neurological disorders.
Very rare:	galactorrhoea, gynaecomastia,
Metabolism and nutrition disorders	
Rare:	folate deficiency, decreased appetite.
Very rare:	porphyria acute (acute intermittent porphyria and variegate porphyria), porphyria non-acute (porphyria cutanea tarda).
Psychiatric disorders	
Rare:	hallucinations (visual or auditory), depression, aggression, agitation, restlessness, confusional state.
Very rare:	activation of psychosis.
Nervous system disorders	
Very common:	ataxia, dizziness, somnolence.
Common:	diplopia, headache.
Uncommon:	abnormal involuntary movements (e.g. tremor, asterixis, dystonia, tics), nystagmus.
Rare:	dyskinesia, eye movement disorder, speech disorders (e.g. dysarthria or slurred speech), choreoathetosis, neuropathy peripheral, paraesthesia, and paresis.
Very rare:	neuroleptic malignant syndrome, aseptic meningitis with myoclonus and peripheral eosinophilia, dysgeusia.
Not known**:	sedation, memory impairment
Eye disorders	
Common:	accommodation disorders (e.g. blurred vision)
Very rare:	lenticular opacities, conjunctivitis.
Ear and labyrinth disorders	
Very rare:	hearing disorders, e.g. tinnitus, hyperacusis, hypoacusis, change in pitch perception.
Cardiac disorders	
Rare:	cardiac conduction disorders.
Very rare:	arrhythmia, atrioventricular block with syncope, bradycardia, cardiac failure congestive, coronary artery disease aggravated.
Vascular disorders	
Rare:	hypertension or hypotension.
Very Rare:	circulatory collapse, embolism (e.g. pulmonary embolism), thrombophlebitis.
Respiratory, thoracic and mediastinal disorders	
Very rare:	pulmonary hypersensitivity characterised e.g. by fever, dyspnoea, pneumonitis or pneumonia.
Gastro-intestinal disorders	
Very common:	vomiting, nausea.
Common:	dry mouth, with suppositories rectal irritation may occur.
Uncommon:	diarrhoea, constipation.
Rare:	abdominal pain.
Very rare:	Pancreatitis, glossitis, stomatitis,.
Not known**:	colitis.
Hepatobiliary disorders	
Rare:	hepatitis of cholestatic, parenchymal (hepatocellular) or mixed type, vanishing bile duct syndrome, jaundice.
Very rare:	hepatic failure, granulomatous liver disease.
Skin and subcutaneous tissue disorders:	
Very common:	urticaria, which may be severe dermatitus allergic,
Uncommon:	dermatitis exfoliative.
Rare:	systemic lupus erythematosus, pruritus.
Very rare:	Stevens-Johnson syndrome*, toxic epidermal necrolysis, photosensitivity reaction, erythema multiforme, erythema nodosum, pigmentation disorder, purpura, acne, hyperhydrosis, alopecia, hirsutism.
Not known**:	Acute Generalized Exanthematous Pustulosis (AGEP)**, lichenoid keratosis, onychomadesis.
Musculoskeletal, connective tissue and bone disorders	
Rare:	muscular weakness.
Very rare:	bone metabolism disorders (decrease in plasma calcium and blood 25-hydroxy-cholecalciferol) leading to osteomalacia/osteoporosis, arthralgia, myalgia, muscle spasms.
Not known**:	fracture.
Renal and urinary disorders	
Very rare:	tubulointerstitial nephritis, renal failure, renal impairment (e.g. albuminuria, haematuria, oliguria and blood urea/ azotaemia), urinary retention, urinary frequency.
Reproductive System	
Very rare:	sexual disturbances/erecticle dysfunction spermatogenesis abnormal (with decreased sperm count and/or motility).
General disorders and administration site conditions	
Very common:	fatigue.
Investigations	
Very common:	gamma-glutamyltransferase increased (due to hepatic enzyme induction), usually not clinically relevant.
Common:	blood alkaline phosphatase increased.
Uncommon:	transaminases increased.
Very rare:	intraocular pressure increased, blood cholesterol increased, high density lipoprotein increased, blood triglycerides increased. Thyroid function test abnormal: decreased L-Thyroxin (free thyroxine, thyroxine, tri-iodothyronine) and increased blood thyroid stimulating hormone, usually without clinical manifestations, blood prolactin increased,
Not known**:	bone density decreased.

* **In some** Asian countries also reported as rare. See also section 4.4 Special warnings and precautions for use.

**Additional adverse drug reactions from spontaneous reports (frequency not known)

The following adverse drug reactions have been derived from post-marketing experience with Carbatol via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

There have been reports of decreased bone mineral density, osteopenia, osteoporosis and fractures in patients on long-term therapy with carbamazepine. The mechanism by which carbamazepine affects bone metabolism has not been identified.

There is increasing evidence regarding the association of genetic markers and the occurrence of cutaneous ADRs such as SJS, TEN, DRESS, AGEP and maculopapular rash. In Japanese and European patients, these reactions have been reported to be associated with the use of carbamazepine and the presence of the HLA-A*3101 allele. Another marker, HLA-B*1502 has been shown to be strongly associated with SJS and TEN among individuals of Han Chinese, Thai and some other Asian ancestry.

4.9 Overdose

Signs and symptoms

The presenting signs and symptoms of overdosage involve the central nervous, cardiovascular, respiratory systems and the adverse drug reactions mentioned under section 4.8.

Central nervous system: CNS depression; disorientation, depressed level of consciousness, somnolence, agitation, hallucination, coma; blurred vision, slurred speech, dysarthria, nystagmus, ataxia, dyskinesia, initially hyperreflexia, later hyporeflexia; convulsions, psychomotor disturbances, myoclonus, hypothermia, mydriasis. Respiratory system: Respiratory depression, pulmonary oedema.

Cardiovascular system: Tachycardia, hypotension and at times hypertension, conduction disturbance with widening of QRS complex; syncope in association with cardiac arrest. Gastro-intestinal system: Vomiting, delayed gastric emptying, reduced bowel motility. Musculoskeletal system: There have been some cases which reported rhabdomyolysis in association with carbamazepine toxicity.

Renal function: Retention of urine, oliguria or anuria; fluid retention, water intoxication due to ADH-like effect of carbamazepine. Laboratory findings: Hyponatraemia, possibly metabolic acidosis, possibly hyperglycaemia, increased muscle creatine phosphokinase.

Treatment There is no specific antidote. Management should initially be guided by the patient's clinical condition; admission to hospital. Measurement of the plasma level to confirm carbamazepine poisoning and to ascertain the size of the overdose. Evacuation of the stomach, gastric lavage, and administration of activated charcoal. Delay in evacuating the stomach may result in delayed absorption, leading to relapse during recovery from intoxication. Supportive medical care in an intensive care unit with cardiac monitoring and careful correction of electrolyte imbalance.

Special recommendations: Charcoal haemoperfusion has been recommended. Hemodialysis is the effective treatment modality in the management of the carbamazepine overdose.

Relapse and aggravation of symptomatology on the 2nd and 3rd day after overdose, due to delayed absorption, should be anticipated.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Therapeutic class: Anti-epileptic, neurotropic and psychotropic agent; (ATC Code: N03 AF01). Dibenzazepine derivative.

As an antiepileptic agent its spectrum of activity embraces: partial seizures (simple and complex) with and without secondary generalisation; generalised tonic-clonic seizures, as well as combinations of these types of seizures. The mechanism of action of carbamazepine, the active substance of Carbatol, has only been partially elucidated. Carbamazepine stabilises hyperexcited nerve membranes, inhibits repetitive neuronal discharges, and reduces synaptic propagation of excitatory impulses. It is conceivable that prevention of repetitive firing of sodium-dependent action potentials in depolarised neurons via use- and voltage-dependent blockade of sodium channels may be its main mechanism of action.

Whereas reduction of glutamate release and stabilisation of neuronal membranes may account for the antiepileptic effects, the depressant effect on dopamine and noradrenaline turnover could be responsible for the antimanic properties of carbamazepine.

5.2 Pharmacokinetic properties: Absorption

Carbamazepine is absorbed almost completely but relatively slowly from the tablets. The conventional tablets yield mean peak plasma concentrations of the unchanged substance within 12 hours (chewable tablets 6 hours; syrup 2 hours) following single oral doses. With respect to the amount of active substance absorbed, there is no clinically relevant difference between the oral dosage forms. After a single oral dose of 400mg carbamazepine (tablets) the mean peak concentration of unchanged carbamazepine in the plasma is approx. 4.5μg/ml.

The bioavailability of Carbatol in various oral formulations has been shown to lie between 85-100%.

Ingestion of food has no significant influence on the rate and extent of absorption, regardless of the dosage form of Carbatol. Steady-state plasma concentrations of carbamazepine are attained within about 1-2 weeks, depending individually upon auto-induction by carbamazepine and hetero-induction by other enzyme-inducing drugs, as well as on pre-treatment status, dosage, and duration of treatment.

Different preparations of carbamazepine may vary in bioavailability; to avoid reduced effect or risk of breakthrough seizures or excessive side effects, it may be prudent to avoid changing the formulation.

Distribution Carbamazepine is bound to serum proteins to the extent of 70-80%. The concentration of unchanged substance in cerebrospinal fluid and saliva reflects the non-protein bound portion in plasma (20-30%). Concentrations in breast milk were found to be equivalent to 25-60% of the corresponding plasma levels.

Carbamazepine crosses the placental barrier. Assuming complete absorption of carbamazepine, the apparent volume of distribution ranges from 0.8 to 1.9 L/kg.

Biotransformation

Carbamazepine is metabolised in the liver, where the epoxide pathway of biotransformation is the most important one, yielding the 10, 11-transdiol derivative and its glucuronide as the main metabolites.

Cytochrome P450 3A4 has been identified as the major isoform responsible for the formation of carbamazepine 10, 11-epoxide from carbamazepine. Human microsomal epoxide hydrolase has been identified as the enzyme responsible for the formation of the 10,11-transdiol derivative from carbamazepine-10,11 epoxide. 9-Hydroxy-methyl-10-carbamoyl acridan is a minor metabolite related to this pathway. After a single oral dose of carbamazepine about 30% appears in the urine as end-products of the epoxide pathway.

Other important biotransformation pathways for carbamazepine lead to various monohydroxylated compounds, as well as to the N-glucuronide of carbamazepine produced by UGT2B7.

Elimination

The elimination half-life of unchanged carbamazepine averages approx. 36 hours following a single oral dose, whereas after repeated administration it averages only 16-24 hours (auto-induction of the hepatic mono-oxygenase system), depending on the duration of the medication. In patients receiving concomitant treatment with other enzyme-inducing drugs (e.g. phenytoin, phenobarbitone), half-life values averaging 9-10 hours have been found. The mean elimination half-life of the 10, 11-epoxide metabolite in the plasma is about 6 hours following single oral doses of the epoxide itself. After administration of a single oral dose of 400mg carbamazepine, 72% is excreted in the urine and 28% in the faeces. In the urine, about 2% of the dose is recovered as unchanged drug and about 1% as the pharmacologically active 10, 11-epoxide metabolite.

Characteristics in patients

The steady-state plasma concentrations of carbamazepine considered as “therapeutic range” vary considerably inter-individually; for the majority of patients a range between 4-12μg/ml corresponding to 17-50μmol/l has been reported. Concentrations of carbamazepine 10, 11-epoxide (pharmacologically active metabolite): about 30% of carbamazepine levels. Owing to enhanced carbamazepine elimination, children may require higher doses of carbamazepine (in mg/kg) than adults to maintain therapeutic concentrations.

There is no indication of altered pharmacokinetics of carbamazepine in elderly patients as compared with young adults. No data are available on the pharmacokinetics of carbamazepine in patients with impaired hepatic or renal function.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of single and repeated dose toxicity, local tolerance, genotoxicity and carcinogenic potential. Reproductive toxicity studies in animals were insufficient to rule out a teratogenic effect of carbamazepine in humans.

Carcinogenicity

In rats treated with carbamazepine for two years, there was an increased incidence of hepatocellular tumours in females and benign testicular tumours in males. However, there is no evidence to date that these observations are of any relevance to the therapeutic use of carbamazepine in humans.

Reproductive toxicity

In animals studies in mice, rats and rabbits oral administration of carbamazepine during organogenesis led to increased embryo-fetal mortality and fetal growth retardation at daily doses which were associated with maternal toxicity (above 200mg/kg/day). Carbamazepine was teratogenic in a number of studies, particularly in mice, however showed no or only minor teratogenic potential at doses relevant to humans. In a reproduction study in rats, nursing offspring demonstrated a reduced weight gain at a maternal dosage level of 192 mg/kg/day.

Fertility

In chronic toxicity studies dose related testicular atrophy and aspermatogenesis occurred in rats receiving carbamazepine. The safety margin for this effect is not known.

6. Pharmaceutical particulars

6.1 Incompatibilities

None known

6.2 Shelf life

3 years

6.3 Special precautions for storage

Store at temperature not exceeding 30°C, in a dry place

6.4 How supplied

Carton Box Containing 1,2,3 (AL/Colorless transparent PVC/PVDC) Strips, each of 10 tablets + insert leaflet.

Keep all medicaments out of reach of children

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Product of:
AMOUN PHARMACEUTICAL CO.
S.A.E.
El-Obour City, Al Qalyubia, Egypt.