فنوسا®

رگورافنیب

قرص روکش‌دار

پیش از شروع مصرف فنوسا® محتوای دفترچه راهنما را به دقت مطالعه کنید. این دفترچه راهنما در برگیرنده پاسخ شایع‌ترین سوالات در مورد داروی فنوسا® است. درصورتی که پاسخ تمامی سوالات شما در این دفترچه راهنما نیامده است، می‌توانید با پزشک یا داروساز خود تماس بگیرید. این دارو برای بیماری فعلی شما تجویز شده است؛ لذا از مصرف آن در موارد مشابه یا توصیه آن به دیگران خودداری نمایید. اطلاعات این دفترچه راهنما در تاریخی که در آخرین صفحه آمده است، به روز رسانی شده و ممکن است در برگیرنده آخرین اطلاعات علمی در مورد داروی شما نباشد. برای اطلاع از آخرین داده‌های علمی در مورد داروی خود با پزشک یا داروساز مشورت کنید. همچنین برای دسترسی به آخرین ویرایش این دفترچه راهنما می‌توانید به وب‌سایت شرکت داروسازی نانوالوند به آدرس www.nanoalvand.com مراجعه فرمایید.

در این دفترچه به سوالات زیر پاسخ داده می‌شود:

- فنوسا® چیست و در چه مواردی تجویز می‌شود؟
- چه افرادی نباید فنوسا® را دریافت کنند؟
- پیش از دریافت فنوسا® یا در طول درمان با آن چه مواردی را حتماً باید به پزشک خود اطلاع دهید؟
- آیا فنوسا® در کودکان و نوجوانان قابل تجویز است؟
- آیا فنوسا® با سایر داروها تداخل دارد؟
- آیا فنوسا® با غذا و نوشیدنی‌ها تداخل دارد؟

- ایمنی مصرف فنوسا® در دوران بارداری و شیردهی چگونه است؟
- آیا در طول مدت مصرف فنوسا® رانندگی و کار با ماشین آلات مجاز است؟
- آیا فنوسا® حاوی سدیم است؟
- آیا فنوسا® حاوی لسیتین است؟
- دوز، فواصل تجویز و طول دوره درمان با فنوسا® چقدر است؟
- در صورت مصرف بیش از حد فنوسا® چه باید کرد؟
- در صورت فراموشی مصرف فنوسا® چه باید کرد؟
- فنوسا® ممکن است چه اثرات نامطلوبی داشته باشد؟

- فنوسا® را در چه شرایطی باید نگهداری کرد؟
- فنوسا ® از چه اجزایی تشکیل شده است و بسته‌بندی آن چگونه است؟

فنوسا® چیست و در چه مواردی تجویز می‌شود؟

نام اختصاصی داروی شما فنوسا® و نام ژنریک آن رگورافنیب است. فنوسا® یک داروی ضد سرطان است که با قطع خون‌رسانی به سلول‌های سرطانی باعث کاهش سرعت رشد و تکثیر آن‌ها می‌شود. فنوسا® در درمان سرطان‌های زیر کاربرد دارد:

سرطان متاستاتیک روده بزرگ و مقعد؛ در بیمارانی که به داروهای درمانی‌های

قبلی پاسخ نداده‌اند یا قادر به مصرف سایر داروها (شیمی درمانی بر پایه فلوئوروپیریمیدین‌ها، درمان با مهارکننده‌های فاکتور رشد اندوتلیال عروقی، درمان با مهارکننده‌های گیرنده فاکتور رشد اپیدرمال) نیستند.

تومورهای استرومای گوارشی(GIST)؛ نوعی سرطان معده و روده، که به سایر قسمت‌های بدن گسترش یافته و یا قابل جراحی نیست. این دارو در بیمارانی کاربرد دارد که قبلاً تحت درمان با داروهای ضد سرطان دیگری (ایماتینیب و سونیتینیب) بوده‌اند.

سرطان کبد؛ در بیمارانی که قبلاً تحت درمان با داروی ضد سرطان دیگری (سورافنیب) بوده‌اند.

فنوسا® ممکن است در مواردی غیر از آن‌چه که در این دفترچه راهنما به آن‌ها اشاره شده است نیز، تجویز شود. در صورتی که در مورد علت تجویز این دارو و نحوه عملکرد آن سؤالی دارید، از پزشک خود بپرسید.

چه افرادی نباید فنوسا® را دریافت کنند؟

اگر در گذشته سابقه واکنش حساسیتی به رگورافنیب و یا مواد جانبی موجود در فنوسا® را داشته‌اید، نباید این دارو را دریافت کنید. (لیست این مواد در قسمت آخر دفترچه راهنما آمده است.)

پیش از دریافت فنوسا® یا در طول درمان با آن، چه مواردی را حتماً باید به پزشک خود اطلاع دهید؟

- **اگر مبتلا به مشکلات کبدی هستید؛** از جمله سندرم گیلبرت با علائمی مانند زردی پوست و چشم، تیره شدن رنگ ادرار و گیجی. مصرف فنوسا® می‌تواند منجر به افزایش احتمال بروز مشکلات کبدی شود. پزشک شما پیش از شروع و در طول درمان با فنوسا® برای بررسی عملکرد کبدتان، آزمایش خون تجویز می‌کند. در صورتی که عملکرد کبد دچار اختلال شدید باشد، فنوسا® برای شما تجویز نمی‌شود، در حال حاضر اطلاعات کافی در خصوص مصرف این دارو در بیماران مبتلا به اختلال عملکرد

کبدی وجـود ندارد.

- **اگـر دچارعفونـت شُـدید؛** علائـم آن می‌تواند شـامل: تـب بالا، سـرفه‌های شـدید با یـا بـدون افزایـش مخـاط (خلط)، گلـودرد شـدید، تنگـی نفـس، درد یا سـوزش هنگام دفـع ادرار، ترشـحات و تحریـک غیرطبیعـی واژن، قرمـزی، تورم و/یـا درد در هر نقطه از بـدن باشـد. در ایـن شـرایط ممکن اسـت پزشـک شـما مصـرف دارو را موقتاً قطـع نماید.
- **اگـر دچـار مشـکلات خونریزی‌دهنـده بوده‌ایـد یـا هسـتید؛** و اگـر در حـال مصـرف وارفاریـن، فنپروکومـون یـا سـایر داروهـای ضـد انعقـاد خـون هسـتید. مصرف فنوسـا® می‌توانـد منجـر بـه افزایـش احتمـال خونریـزی شـود. ممکـن اسـت پیـش از

شـروع مصـرف ایـن دارو، پزشـک برای شـما آزمایش خـون تجویز کند. فنوسـا® ممکن اسـت باعـث خونریـزی شـدید در دسـتگاه گـوارش (دهـان، معـده، گلـو، مقعـد و روده) ریه‌هـا، کلیه‌هـا، واژن و/یـا مغز شـود. در صـورت مشـاهده علائمی مانند وجـود خون در مدفـوع یـا ادرار، دفـع مدفوع سـیاه‌رنگ، درد معده و سـرفه یا اسـتفراغ خونـی، بلافاصله به پزشـک یـا اورژانـس مراجعـه کنید.

- **اگـر دچار مشـکلات شـدید معده و روده شُـدید** (سـوراخ شـدن دسـتگاه گوارش یـا فیسـتول)، پزشـک شـما باید در مـورد ادامه یـا قطع مصـرف دارو تصمیـم بگیرد. در صـورت مشـاهده علائمـی ماننـد درد شـدید یـا مداوم معـده، اسـتفراغ خونـی و مدفوع سـیاه یـا قرمـز، بلافاصلـه به پزشـک یا اورژانـس مراجعـه کنید.

- **اگـر دچار درد قفسـه سـینه شُـدید یا هرگونـه مشـکل قلبی داریـد،** پیش از شـروع و در طـول درمـان بـا فنوسـا®، پزشـک شـما عملکرد قلب‌تـان را کنتـرل خواهد کـرد. در صـورت بـروز علائمـی که می‌تواننـد نشـان‌دهنده حمله قلبی یـا کاهش جریان خـون بـه قلـب باشـند، بلافاصلـه بـه پزشـک یـا اورژانـس مراجعـه کنیـد. ایـن علائم عبارتند از احسـاس درد یا ناراحتی متناوب در قفسـه سـینه (که ممکن اسـت از قفسـه سـینه بـه شـانه‌ها، بازوها، پشـت، گـردن، دندان‌هـا، فک یا معده گسـترش یابـد)، تنگی نفـس، تعریـق ناگهانـی همـراه با پوسـت سـرد و مرطوب، سـبکی سـر یا از هـوش رفتن.
- **اگر دچار سردرد شدید و مداوم، اختلالات بینایی، تشنج یا تغییر در وضعیت ذهنی**

(مانند گیجی، فراموشی یا از دست دادن آگاهی نسبت به زمان و مکان) شُدید، فوراً به پزشک خود اطلاع دهید.
- **اگـر فشـار خـون بـالا داریـد؛** فنوسـا® می‌توانـد باعـث افزایـش فشـار خون شـود. پزشـک شـما پیـش از شـروع و در طـول درمـان بـا فنوسـا® فشـار خون‌تـان را کنتـرل خواهـد کـرد و در صـورت نیـاز، بـرای درمـان فشـار خـون بـالا، دارو تجویـز خواهـد کرد.
- **اگـر سـابقه آنوریسـم (بـزرگ و ضعیـف شـدن دیـواره رگ‌هـای خونـی) یا پارگـی دیـواره رگ‌هـای خونـی دارید.**
- **اگـر اخیـراً عمـل جراحـی داشـته‌اید یـا قصـد انجـام آن را داریـد،** فنوسـا®

می‌تواند بهبود زخم‌ها را تحت تاثیر قرار دهد، در نتیجه ممکن است نیاز باشد، تا زمان بهبود زخم‌ها، مصرف فنوسا® را قطع کنید.

- **اگر دچار مشکلات پوستی شُدید؛** فنوسا® می‌تواند باعث قرمزی، درد، التهاب یا تاول روی کف دست‌ها و پاها شود. در صورت مشاهده هر نوع تغییر پوستی به پزشک خود اطلاع دهید. در صورت بروز این عارضه، پزشک ممکن است دوز دارو را تغییر دهد یا مصرف آن را تا زمان بهبود علائم قطع کند. ضمناً برای کنترل این علائم، پزشک ممکن است مصرف کرم‌ها یا استفاده از دستکش و کفی کفش را توصیه کند.

پیش از مصرف فنوسا® در صورتی که هر یک از شرایط ذکر شده را داشتید به پزشک خود اطلاع دهید؛ زیرا ممکن است نیاز به درمان یا انجام آزمایش‌های بیشتری وجود داشته باشد.

آیا فنوسا® در کودکان و نوجوانان قابل تجویز است؟

فنوسا® برای درمان سرطان متاستاتیک روده بزرگ و مقعد، و همچنین سرطان کبد در کودکان و نوجوانان کاربرد ندارد. اثربخشی و ایمنی این دارو برای درمان تومورهای متاستاتیک استرومای گوارشی در کودکان و نوجوانان نیز تاکنون تایید نشده است.

آیا فنوسا® با سایر داروها تداخل دارد؟

بسیاری از داروها ممکن است با فنوسا® تداخل داشته باشند؛ لذا در صورتی که در حال مصرف هر نوع دارویی اعم از داروهای نسخه‌ای، بدون نسخه، فرآورده‌های طبیعی، گیاهی و ویتامین‌ها هستید، اخیراً دارویی مصرف کرده و یا حتی قصد مصرف دارویی را دارید، با پزشک یا داروساز خود مشورت کنید. برخی از این داروها عبارتند از:

- داروهایی که برای درمان عفونت‌های قارچی استفاده می‌شوند؛ مانند کتوکونازول، ایتراکونازول، پوساکونازول و وریکونازول

- برخی داروهای مسکن؛ مانند مفنامیک اسید، دیفلونیسال و نیفلومیک اسید
- برخی داروهایی که برای درمان عفونت‌های باکتریایی استفاده می‌شوند؛ مانند ریفامپیسین، کلاریترومایسین و تلیترومایسین
- داروهایی که برای درمان صرع و تشنج استفاده می‌شوند؛ مانند فنی‌توئین، کاربامازپین و فنوباربیتال
- متوترکسات
- رزوواستاتین، فلوواستاتین، آتورواستاتین؛ داروهایی که برای درمان کلسترول خون بالا استفاده می‌شوند.

- وارفارین یا فنپروکومون، داروهای ضد انعقاد
- علف چای (*Hypericum perforatum*)؛ داروی گیاهی که ممکن است بدون نسخه نیز به فروش برسد و در درمان افسردگی کاربرد دارد.

تداخلات مطرح شده شامل تمامی تداخلات دارویی فنوسا® نیست، لذا در خصوص تمام داروهای مصرفی خود با پزشک معالج یا داروساز مشورت کنید.

آیا فنوسا® با غذا و نوشیدنی‌ها تداخل دارد؟

در طول درمان با فنوسا® از نوشیدن آب گریپ‌فروت خودداری کنید؛ زیرا می‌تواند

بر عملکرد فنوسا® تأثیر بگذارد.

ایمنی مصرف فنوسا® در دوران بارداری و شیردهی چگونه است؟

اگر باردار هستید یا قصد بارداری دارید، قبل از مصرف فنوسا® حتماً به پزشک خود اطلاع دهید. فنوسا® نباید در دوران بارداری مصرف شود مگر اینکه پزشک شما با ارزیابی خطرات احتمالی ناشی از مصرف این دارو در دوران بارداری، همچنان تجویز آن را ضروری بداند.

فنوسا® باعث آسیب به جنین می‌شود، بنابراین در صورتی که شما یا شریک جنسیتان

در سـن بـاروری قـرار داریـد، طـی مصـرف ایـن دارو و تـا حداقـل ۸ هفتـه پـس از پایـان دوره مصـرف آن از روش‌هـای مطمئـن بـرای جلوگیـری از بارداری اسـتفاده کنیـد. چنانچه علی‌رغـم آنچـه گفتـه شـد بـارداری اتفـاق افتاد، به پزشـک خـود اطـلاع دهید.

در طـول درمـان بـا فنوسـا® از شـیردهی خـودداری نماییـد؛ زیـرا ایـن دارو می‌تواند روند رشـد و تکامـل نـوزاد را مختـل کنـد. اگـر درحال شـیردهی هسـتید یـا قصد انجـام آن را داریـد، به پزشـک خـود اطـلاع دهید.

در خصـوص مـدت زمـان دقیـق مـورد نیاز برای پیشـگیری از بـارداری و شـیردهی پس از مصـرف آخریـن دوز دارو، بـا پزشـک خود مشـورت کنید.

فنوسـا® قـدرت بـاروری خانم‌هـا و آقایـان را کاهـش می‌دهد. پیش از شـروع مصـرف دارو با پزشـک خـود در ایـن خصوص مشـورت کنید.

آیـا در طـول مـدت مصـرف فنوسـا® رانندگـی و کار بـا ماشـین آلات مجاز اسـت؟

تأثیر فنوسـا® بر هوشـیاری و توانایی کار با ماشـین آلات مشـخص نیسـت. در صورتی که بعـد از مصـرف فنوسـا® دچـار عارضه‌ای شـدید کـه توانایی تمرکـز و عملکردتـان را تحت تأثیـر قـرار داد، تـا زمان رفـع علائـم از رانندگی و کار با ماشـین آلات خـودداری نمایید.

آیا فنوسا® حاوی سدیم است؟

فنوسا® حاوی ۵۵/۸ میلی‌گرم سدیم (جزء اصلی نمک خوراکی) در هر دوز مصرفی روزانه (۴ عدد قرص) است. این مقدار معادل ٪۳ حداکثر میزان سدیم پیشنهادی در رژیم روزانه بزرگسالان است.

آیا فنوسا® حاوی لسیتین است؟

فنوسا® حاوی ۱/۶۸ میلی‌گرم لسیتین (استخراج شده از سویا) در هر دوز مصرفی روزانه (۴ عدد قرص) است.

دوز، فواصل تجویز و طول دوره درمان با فنوسا® چقدر است؟

فنوسا® را دقیقاً مطابق دستور پزشک مصرف کنید. در صورتی که سؤالی در مورد نحوه مصرف این دارو دارید، حتماً از پزشک یا داروساز خود بپرسید.

دوز پیشنهادی روزانه در بزرگسالان، ۴ عدد قرص ۴۰ میلی‌گرمی فنوسا® (معادل ۱۶۰ میلی‌گرم رگورافنیب) است. اما پزشک ممکن است دوز دارو را برای شما تغییر دهد. هر دوره درمان با این دارو معمولا شامل ۳ هفته مصرف دارو و یک هفته عدم مصرف دارو است.

فنوسا® را هر روز در زمان ثابتی بعد از یک وعده غذایی سبک (حاوی کمتر از

٪۳۰ چربی) با یک لیوان کامل آب مصرف نمایید. به عنوان نمونه یک وعده غذایی سبک (کم چرب) شامل ۱ قسمت غلات (حدود ۳۰ گرم)، ۱ لیوان شیر بدون چربی، ۱ برش نان تست با مربا، ۱ لیوان آب سیب و ۱ فنجان قهوه یا چای (۵۲۰ کالری، ۲ گرم چربی) است.

از مصرف همزمان فنوسا® و آب گریپ فروت خودداری نمایید.

چنانچه بعد از مصرف فنوسا® استفراغ کردید، از مصرف مجدد آن دوز خودداری نمایید و به پزشک خود اطلاع دهید.

ممکن است پزشک شما دوز دارو را کاهش دهد یا موقتاً مصرف دارو را قطع کند.

معمولاً درمان با فنوسا® تا زمانی که برای شما مفید باشد و عارضه غیر قابل تحملی ایجاد نکند، ادامه می‌یابد.

چنانچه مبتلا به اختلال خفیف عملکرد کبدی هستید، نیازی به تنظیم دوز فنوسا® وجود ندارد. اما اگر در طول مدت مصرف فنوسا® دچار اختلال متوسط در عملکرد کبد شُدید، پزشک شرایط شما را به دقت کنترل خواهد کرد. از آنجا که اطلاعات کافی در خصوص مصرف فنوسا® در افرادی که اختلال شدید عملکرد کبدی دارند، وجود ندارد، اگر دچار این مشکل هستید، نباید فنوسا® را دریافت کنید.

در افرادی که دچار اختلال خفیف، متوسط یا شدید عملکرد کلیوی هستند، نیازی

بـه تنظیم دوز فنوسـا® وجـود ندارد.

در صورت مصرف بیش از حد فنوسا® چه باید کرد؟

در صـورت مصـرف فنوسـا® بیـش از میـزان تجویـز شـده، فـوراً بـه پزشـک خـود اطـلاع دهیـد، زیـرا ممکـن اسـت نیاز بـه اقدامـات درمانی فوری داشـته باشـید و پزشـک مصرف دارو را قطـع کنـد.

مصـرف بیـش از حـد فنوسـا® می‌توانـد شـدت یـا احتمال بـروز برخی عـوارض را بیشـتر کنـد؛ مانند:

- واکنش‌های پوستی (راش، تاول، قرمزی، درد، تورم، خارش یا پوسته پوسته شدن)
- تغییر یا گرفتگی صدا
- اسهال
- زخم‌های دهانی (التهاب مخاط)
- خشکی دهان
- کاهش اشتها
- افزایش فشار خون
- خستگی مفرط

در صورت فراموشی مصرف فنوسا® چه باید کرد؟

در صورتی که مصرف یک دوز فنوسا® را فراموش کردید، به محض یادآوری، دارو را در همان روز استفاده کنید. چنانچه مصرف فنوسا® را در یک روز فراموش کردید، از دو برابر کردن دوز آن در روز بعد خودداری کنید و به پزشک خود اطلاع دهید.

فنوسا® ممکن است چه اثرات نامطلوبی داشته باشد؟

فنوسا® نیز مانند سایر داروها می‌تواند موجب بروز عوارض ناخواسته شود. هرچند این عوارض در همه افراد مصرف‌کننده بروز نخواهد کرد.

جدی‌ترین عوارض جانبی که در مواردی منجر به مرگ شده است، عبارتند از:
- مشکلات شدید کبدی، خونریزی، سوراخ شدن دستگاه گوارش و عفونت

در صورت مشاهده علائم زیر فوراً به پزشک خود اطلاع دهید:

مشکلات کبدی:
- زردی پوست و چشم
- تیره شدن رنگ ادرار
- گیجی و/یا عدم آگاهی نسبت به زمان و مکان

این علائم می‌توانند نشان‌دهنده آسیب شدید کبدی باشند.

خونریزی:

- وجود خون در مدفوع یا مدفوع سیاه‌رنگ
- وجود خون در ادرار
- درد معده
- سرفه و استفراغ خونی

این علائم می‌توانند نشان‌دهنده خونریزی باشند.

مشکلات شدید معده و روده (سوراخ شدن دستگاه گوارش یا فیستول):

- درد شدید یا مداوم معده یا شکم

- استفراغ خونی
- مدفوع قرمز یا سیاه‌رنگ

این علائم می‌توانند نشان‌دهنده مشکلات شدید گوارشی باشند.

عفونت:

مصرف فنوسا® می‌تواند احتمال ابتلا به عفونت، به ویژه عفونت مجاری ادراری، بینی، گلو و ریه را افزایش دهد. مصرف این دارو همچنین می‌تواند منجر به افزایش احتمال ابتلا به عفونت‌های قارچی غشاهای مخاطی، پوست یا بدن شود. علائم زیر می‌توانند نشان‌دهنده وجود عفونت در بدن باشند:

- تب بالا
- سرفه شدید با یا بدون افزایش ترشح مخاط (خلط)
- گلودرد شدید
- تنگی نفس
- درد یا سوزش هنگام دفع ادرار
- ترشحات و تحریک غیر طبیعی واژن
- قرمزی، تورم و/یا درد در هر نقطه از بدن

سایر عوارض جانبی فنوسا® بر اساس میزان شیوع، به شرح زیر است:

عوارض خیلی شایع (با شیوع بیش از ٪۱۰) فنوسا® عبارتند از:

- کاهش تعداد پلاکت‌های خون، به آسانی کبود شدن یا خونریزی از علائم آن هستند.
- کاهش تعداد گلبول‌های قرمز
- کاهش اشتها
- افزایش فشارخون
- تغییر یا گرفتگی صدا

- اسهال
- خشکی یا درد در ناحیه دهان و زبان، زخم‌های دهانی
- حالت تهوع
- استفراغ
- افزایش سطح بیلی‌روبین خون
- افزایش آنزیم‌های کبدی (ترانس‌آمینازها)
- قرمزی، درد، تاول و تورم کف دست‌ها و پاها
- راش پوستی

- ضعف، کاهش انرژی، خستگی مفرط، خواب آلودگی غیرطبیعی
- درد
- تب
- کاهش وزن

عوارض شایع (با شیوع بین ٪۱ تا ٪۱۰) فنوسا® عبارتند از:

- کاهش تعداد گلبول‌های سفید خون
- کاهش فعالیت غده تیروئید
- کاهش سطح پتاسیم، فسفات، کلسیم، سدیم یا منیزیم خون

- افزایش سطح اسید اوریک خون
- از دست دادن مایعات بدن
- سردرد
- لرز
- تغییر در حواس مانند بی‌حسی، مور مور شدن، ضعف یا درد (نوروپاتی محیطی)
- اختلالات چشایی
- خشکی دهان
- سوزش سر دل (رفلاکس)

- عفونت یا تحریک معده و روده
- ریزش مو
- خشکی پوست
- راش‌های پوستی همراه با پوسته پوسته شدن یا جدا شدن پوست
- گرفتگی ناگهانی و غیر ارادی ماهیچه‌ها (اسپاسم عضلانی)
- دفع پروتئین در ادرار
- افزایش آنزیم‌های گوارشی (شامل آمیلاز و لیپاز)
- اختلالات انعقاد خون

عوارض غیرشایع (با شیوع ٪۰/۱ تا ٪۱) فنوسا® عبارتند از:

- علائم واکنش‌های حساسیتی شامل راش‌های پوستی شدید و گسترده، احساس ناخوشی، تب، تنگی نفس، زردی و تغییر در مواد شیمیایی که کبد تولید می‌کند.
- حمله قلبی، درد قفسه سینه
- بحران فشار خون بالا که می‌تواند همراه با سردرد، گیجی، تاری دید، تهوع، استفراغ و تشنج باشد.
- التهاب پانکراس که می‌تواند همراه با درد ناحیه شکم، تهوع، استفراغ و تب باشد. (پانکراتیت)

- برآمدگی یا ترک خوردن ناخن‌ها
- جوش‌های متعدد پوستی (اریتم مولتی فرم)

عوارض نادر (با شیوع کمتر از ٪۰/۱) فنوسا® عبارتند از:

- برخی سرطان‌های پوست
- سردرد، گیجی، تشنج و از دست دادن بینایی که ممکن است با همراه با فشار خون بالا باشد. (سندرم انسفالوپاتی برگشت‌پذیر خلفی)
- واکنش‌های شدید پوستی و/یا غشاهای مخاطی که ممکن است همراه با تاول‌های دردناک، تب و جدا شدن گسترده پوست باشد. (سندرم استیون-جانسون و نکرولیز توکسیک اپیدرمال)

عوارض فنوسا® با شیوع نامشخص عبارتند از:

- بزرگ شدن و ضعف یا پارگی دیواره رگ‌های خونی

عوارضی که در اینجا نام برده شده است، شامل همه عوارض فنوسا® نمی‌شوند. جهت کسب اطلاعات بیشتر در این زمینه از پزشک یا داروساز خود کمک بگیرید. ضمناً عوارض جانبی دارو به طور کامل در بروشور انگلیسی آورده شده است.

فنوسا® را در چه شرایطی باید نگهداری کرد؟

- فنوسا® را دور از دید و دسترس کودکان نگهداری نمایید.

- فنوسا® نباید بعد از تاریخ انقضایی که بر روی آن درج شده است، مصرف شود.
- جهت محافظت از رطوبت، فنوسا® را تا زمان مصرف در بسته‌بندی اصلی نگهداری نمایید.
- بعد از هر بار استفاده، درب قوطی را محکم ببندید.
- پس از باز شدن درب قوطی، فنوسا® تا ۷ هفته قابل استفاده است.
- فنوسا® را در دمای کمتر از ۳۰ درجه سانتی‌گراد نگهداری نمایید.
- هیچ دارویی را از طریق فاضلاب یا زباله‌های خانگی دفع نکنید. از پزشک یا داروساز خود در مورد شیوه صحیح دفع داروهایی که دیگر استفاده نمی‌کنید، بپرسید. این

اقدامـات بـه حفاظت از محیط زیسـت کمـک می‌کند.

فنوسـا® از چـه اجزایی تشـکیل شـده اسـت و بسـته‌بندی آن چگونه است؟

ماده مؤثره فنوسا®، رگورافنیب است.
هر قرص روکش‌دار فنوسا® حاوی ۴۰ میلی‌گرم رگورافنیب است.
سایر مواد تشکیل دهنده فنوسا® عبارتند از:
میکروکریستالین سلولز، کراس کارملوز سدیم، منیزیم استئارات، پوویدون و سیلیکا

هـر ۲۸ عـدد قـرص روکـش‌دار فنوسـا® داخـل یک قوطـی و هر ۳ عـدد قوطی بـه همراه یـک دفترچـه راهنمـا، داخـل یـک جعبه بسـته‌بندی می‌گـردد. هـر جعبه فنوسـا® حاوی ۸۴ عـدد قرص می‌باشـد.

تاریخ آخرین بازنگری:
آگوست ۲۰۲۱ برابر با مرداد ۱۴۰۰

ساخت شرکت نانوفناوران دارویی الوند (نانوالوند)

آدرس: ایران، البرز، کرج، شهرک صنعتی سیمین دشت، خیابان هفتم غربی
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پاسخگوی ۲۴ ساعته مرکز حمایت از بیماران: ۰۲۱-۴۲۵۹۳

11.08.00 05

Fenosa®

Regorafenib

Film-coated Tablet

1. NAME OF THE MEDICINAL PRODUCT

Fenosa® 40 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 40 mg of regorafenib.

Excipients with known effect

Each daily dose of 160 mg contains 2.427 mmol (or 55.8 mg) of sodium (see section 4.4).

Each daily dose of 160 mg contains 1.68 mg of lecithin (derived from soya) (see section 4.4). For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Regorafenib is indicated as monotherapy for the treatment of adult patients with

- metastatic colorectal cancer (CRC) who have been previously treated with, or are not considered candidates for, available therapies. These include fluoropyrimidine-based chemotherapy, an anti-VEGF therapy and an anti-

EGFR therapy (see section 5.1)

- unresectable or metastatic gastrointestinal stromal tumors (GIST) who progressed on or are intolerant to prior treatment with imatinib and sunitinib.
- hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

4.2. Posology and method of administration

Regorafenib should be prescribed by physicians

experienced in the administration of anticancer therapy.

Posology

The recommended dose of regorafenib is 160 mg (4 tablets of 40 mg) taken once daily for 3 weeks followed by 1 week off therapy. This 4-week period is considered a treatment cycle.

If a dose is missed, then it should be taken on the same day as soon as the patient remembers. The patient should not

take two doses on the same day to make up for a missed dose. In case of vomiting after regorafenib administration, the patient should not take additional tablets.

Treatment should continue as long as benefit is observed or until unacceptable toxicity occurs (see section 4.4).

Patients with performance status (PS) 2 or higher were excluded from clinical studies. There is limited data in patients with PS ≥2.

Posology adjustments

Dose interruptions and/or dose reductions may be required based on individual safety and tolerability. Dose modifications are to be applied in 40 mg (one tablet) steps. The lowest recommended daily dose is 80 mg. The maximum daily dose is 160 mg.

For recommended dose modifications and measures in case of hand-foot skin reaction (HFSR)/palmar-plantar erythrodysesthesia syndrome see Table 1.

Table 1: Recommended dose modifications and measures for HFSR

Skin toxicity grade	Occurrence	Recommended dose modification and measures
Grade 1	Any	Maintain dose level and immediately institute supportive measures for symptomatic relief.
Grade 2	1st occurrence	Decrease dose by 40 mg (one tablet) and immediately institute supportive measures. If no improvement occurs despite dose reduction, interrupt therapy for a minimum of 7 days, until toxicity resolves to Grade 0-1. A dose re-escalation is permitted at the discretion of the physician.
Grade 2	No improvement within 7 days or 2nd occurrence	Interrupt therapy until toxicity resolves to Grade 0-1. When re-starting treatment, decrease dose by 40 mg (one tablet). A dose re-escalation is permitted at the discretion of the physician.
Grade 2	3rd occurrence	Interrupt therapy until toxicity resolves to Grade 0-1. When re-starting treatment, decrease dose by 40 mg (one tablet). A dose re-escalation is permitted at the discretion of the physician.
Grade 2	4th occurrence	Discontinue treatment with regorafenib permanently.

Grade 3	1st occurrence	Institute supportive measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to Grade 0-1. When re-starting treatment, decrease dose by 40 mg (one tablet). A dose re-escalation is permitted at the discretion of the physician.
	2nd occurrence	Institute supportive measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to Grade 0-1. When re-starting treatment, decrease dose by 40 mg (one tablet).
	3rd occurrence	Discontinue treatment with regorafenib permanently.

For recommended measures and dose modifications in case of worsening of liver function tests considered related to treatment with regorafenib see Table 2 (see also section 4.4).

Table 2: Recommended measures and dose modifications in case of drug-related liver function test abnormalities

Observed elevations of ALT and/or AST	Occurrence	Recommended measures and dose modification
≤5 times upper limit of normal (ULN) (maximum Grade 2)	Any occurrence	Continue regorafenib treatment. Monitor liver function weekly until transaminases return to <3 times ULN (Grade 1) or baseline.
>5 times ULN ≤20 times ULN (Grade 3)	1st occurrence	Interrupt regorafenib treatment. Monitor transaminases weekly until return to <3 times ULN or baseline. Restart: If the potential benefit outweighs the risk of hepatotoxicity, re-start regorafenib treatment, reduce dose by 40 mg (one tablet), and monitor liver function weekly for at least 4 weeks.
	Re-occurrence	Discontinue treatment with regorafenib permanently.

>20 times ULN (Grade 4)	Any occurrence	Discontinue treatment with regorafenib permanently.
>3 times ULN (Grade 2 or higher) with concurrent bilirubin >2 times ULN	Any occurrence	Discontinue treatment with regorafenib permanently. Monitor liver function weekly until resolution or return to baseline. Exception: patients with Gilbert's syndrome who develop elevated transaminases should be managed as per the above outlined recommendations for the respective observed elevation of ALT and/or AST.

Hepatic impairment

Regorafenib is eliminated mainly via the hepatic route.

In clinical studies, no relevant differences in exposure, safety or efficacy were observed between patients with mild hepatic impairment (Child-Pugh A) and normal hepatic function. No dose adjustment is required in patients with mild hepatic impairment. Since only limited data are available for patients with moderate hepatic impairment (Child Pugh B), no dose recommendation can be provided.

Close monitoring of overall safety is recommended in these patients (see sections 4.4 and 5.2).

Regorafenib is not recommended for use in patients with severe hepatic impairment (Child-Pugh C) as regorafenib has not been studied in this population.

Renal impairment

Available clinical data indicate similar exposure of regorafenib and its metabolites M-2 and M-5 in patients

with mild, moderate or severe renal impairment compared to patients with normal renal function. No dose adjustment is required in patients with mild, moderate or severe renal impairment (see also section 5.2).

Elderly population

In clinical studies, no relevant differences in exposure, safety or efficacy were observed between elderly (aged 65 years and above) and younger patients (see also section 5.2).

Gender

In clinical studies, no relevant differences in exposure, safety or efficacy were observed between male and female patients. No dose adjustment is necessary based on gender (see also section 5.2).

Ethnic differences

In clinical studies, no relevant differences in exposure or efficacy were observed between patients of different

ethnic groups. A higher incidence of hand foot skin reaction (HFSR)/palmar-plantar erythrodysesthesia syndrome, severe liver function test abnormalities and hepatic dysfunction was observed in Asian (in particular Japanese) patients treated with regorafenib compared with Caucasians. The Asian patients treated with regorafenib in clinical studies were primarily from East Asia (~90%).

There is limited data on regorafenib in the black patient population. No dose adjustment is necessary based on

ethnicity (see section 5.2).

Pediatric population

There is no relevant use of regorafenib in the pediatric population in the indication of metastatic colorectal cancer.

The safety and efficacy of regorafenib in patients below 18 years of age in the indication gastrointestinal stromal tumors (GIST) have not been established. No data are available.

There is no relevant use of regorafenib in the pediatric

population in the indication of hepatocellular carcinoma.

Method of administration

Regorafenib is for oral use.

Regorafenib should be taken at the same time each day. The tablets should be swallowed whole with water after a light meal that contains less than 30% fat. An example of a light (low-fat) meal would include 1 portion of cereal (about 30 g), 1 glass of skimmed milk, 1 slice of toast with jam, 1 glass of

apple juice, and 1 cup of coffee or tea (520 calories, 2 g fat).

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4. Special warnings and precautions for use

Hepatic effects

Abnormalities of liver function tests (alanine

aminotransferase [ALT], aspartate aminotransferase [AST] and bilirubin) have been frequently observed in patients treated with regorafenib. Severe liver function test abnormalities (Grade 3 to 4) and hepatic dysfunction with clinical manifestations (including fatal outcomes) have been reported in a small proportion of patients (see section 4.8).

In clinical trials, a higher incidence of severe liver function test abnormalities and hepatic dysfunction was observed

in Asian (in particular Japanese) patients treated with regorafenib, compared with Caucasians (see section 4.2).

It is recommended to perform liver function tests (ALT, AST and bilirubin) before initiation of treatment with regorafenib and monitor closely (at least every two weeks) during the first 2 months of treatment. Thereafter, periodic monitoring should be continued at least monthly and as clinically indicated.

Regorafenib is a uridine diphosphate glucuronosyl

transferase (UGT) 1A1 inhibitor (see section 4.5). Mild, indirect (unconjugated) hyperbilirubinemia may occur in patients with Gilbert's syndrome.

For patients with observed worsening of liver function tests considered related to treatment with regorafenib (i.e. where no alternative cause is evident, such as post-hepatic cholestasis or disease progression), the dose modification and monitoring advice in Table 2 should be followed (see section 4.2).

Regorafenib is eliminated mainly via the hepatic route.

Close monitoring of the overall safety is recommended in patients with mild or moderate hepatic impairment (see also sections 4.2 and 5.2). Regorafenib is not recommended for use in patients with severe hepatic impairment (Child-Pugh C) as regorafenib has not been studied in this population and exposure might be increased in these patients.

Infections

Regorafenib has been associated with an increased incidence of infection events, some of which were fatal (see

section 4.8).

In cases of worsening infection events, interruption of regorafenib treatment should be considered.

Hemorrhage

Regorafenib has been associated with an increased incidence of hemorrhagic events, some of which were fatal (see section 4.8). Blood counts and coagulation parameters should be monitored in patients with

conditions predisposing to bleeding, and in those treated with anticoagulants (e.g. warfarin and phenprocoumon) or other concomitant medicinal products that increase the risk of bleeding. Screening for and subsequent treatment of esophageal varices in patients with liver cirrhosis should be performed as per standard of care before starting treatment with regorafenib. In the event of severe bleeding necessitating urgent medical intervention, permanent discontinuation of regorafenib should be considered.

Gastrointestinal perforation and fistula

Gastrointestinal perforation (including fatal outcome) and fistula have been reported in patients treated with regorafenib (see section 4.8). These events are also known to be common disease-related complications in patients with intra-abdominal malignancies. Discontinuation of regorafenib is recommended in patients developing gastrointestinal perforation or fistula.

Cardiac ischemia and infarction

Regorafenib has been associated with an increased incidence of myocardial ischemia and infarction (see section 4.8). Patients with unstable angina or new onset angina (within 3 months of starting regorafenib therapy), recent myocardial infarction (within 6 months of starting regorafenib therapy) and those with cardiac failure New York Heart Association (NYHA) Classification 2 or higher were excluded from the clinical studies.

Patients with a history of ischemic heart disease should be monitored for clinical signs and symptoms of myocardial ischemia. In patients who develop cardiac ischemia and/or infarction, interruption of regorafenib is recommended until resolution. The decision to re-start regorafenib therapy should be based on careful consideration of the potential benefits and risks of the individual patient. Regorafenib should be permanently discontinued if there is no resolution.

Posterior reversible encephalopathy syndrome (PRES)

PRES has been reported in association with regorafenib treatment (see section 4.8). Signs and symptoms of PRES include seizures, headache, altered mental status, visual disturbance or cortical blindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging. In patients developing PRES, discontinuation of regorafenib , along with control of hypertension and supportive medical management of

other symptoms is recommended.

Arterial hypertension

Regorafenib has been associated with an increased incidence of arterial hypertension (see section 4.8). Blood pressure should be controlled prior to initiation of treatment with regorafenib. It is recommended to monitor blood pressure and to treat hypertension in accordance with standard medical practice. In cases of severe or persistent hypertension despite adequate medical

management, treatment should be temporarily interrupted and/or the dose reduced at the discretion of the physician (see section 4.2). In case of hypertensive crisis, regorafenib should be discontinued.

Aneurysms and artery dissections

The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating regorafenib, this risk should be carefully considered in

patients with risk factors such as hypertension or history of aneurysm.

Wound healing complications

As medicinal products with anti-angiogenic properties may suppress or interfere with wound healing, temporary interruption of regorafenib is recommended for precautionary reasons in patients undergoing major surgical procedures. The decision to resume treatment with regorafenib following major surgical intervention should

be based on clinical judgment of adequate wound healing.

Dermatological toxicity

Hand-foot skin reaction (HFSR) or palmar-plantar erythrodysesthesia syndrome and rash represent the most frequently observed dermatological adverse reactions with regorafenib (see section 4.8). In clinical trials, a higher incidence of HFSR was observed in Asian (in particular Japanese) patients treated with regorafenib, compared with Caucasians (see section 4.2). Measures for the

prevention of HFSR include control of calluses and use of shoe cushions and gloves to prevent pressure stress to soles and palms. Management of HFSR may include the use of keratolytic creams (e.g. urea-, salicylic acid-, or alpha hydroxyl acid-based creams applied sparingly only on affected areas) and moisturizing creams (applied liberally) for symptomatic relief. Dose reduction and/or temporary interruption of regorafenib, or in severe or persistent cases, permanent discontinuation of regorafenib should be considered (see section 4.2).

Biochemical and metabolic laboratory test abnormalities

Regorafenib has been associated with an increased incidence of electrolyte abnormalities (including hypophosphatemia, hypocalcemia, hyponatremia and hypokalemia) and metabolic abnormalities (including increases in thyroid stimulating hormone, lipase and amylase). The abnormalities are generally of mild to moderate severity, not associated with clinical manifestations, and do not usually require dose

interruptions or reductions. It is recommended to monitor biochemical and metabolic parameters during regorafenib treatment and to institute appropriate replacement therapy according to standard clinical practice if required. Dose interruption or reduction, or permanent discontinuation of regorafenib should be considered in case of persistent or recurrent significant abnormalities (see section 4.2).

Important information about some of the ingredients

This medicinal product contains 55.8 mg sodium per

daily dose of 160 mg, equivalent to 3% of the WHO recommended maximum daily intake of 2 g sodium for an adult. Each daily dose of 160 mg contains 1.68 mg of lecithin (derived from soya).

Disease-specific precautions – Hepatocellular carcinoma (HCC)

In the pivotal placebo-controlled phase III study, patients received prior therapy with sorafenib.

There is insufficient data on patients who discontinued sorafenib therapy due to sorafenib-related toxicity or only tolerated a low dose (< 400 mg daily) of sorafenib. The tolerability of regorafenib in these patients has not been established.

4.5. Interaction with other medicinal products and other forms of interaction

Inhibitors of CYP3A4 and UGT1A9/inducers of CYP3A4

In vitro data indicate that regorafenib is metabolized by

cytochrome CYP3A4 and uridine diphosphate glucuronosyl transferase UGT1A9.

Administration of ketoconazole (400 mg for 18 days), a strong CYP3A4 inhibitor, with a single dose of regorafenib (160 mg on day 5) resulted in an increase in mean exposure (AUC) of regorafenib of approximately 33%, and a decrease in mean exposure of the active metabolites, M-2 (N-oxide) and M-5 (N-oxide and N-desmethyl), of approximately 90%. It is recommended to avoid concomitant use of

strong inhibitors of CYP3A4 activity (e.g. clarithromycin, grapefruit juice, itraconazole, ketoconazole, posaconazole, telithromycin and voriconazole) as their influence on the steady-state exposure of regorafenib and its metabolites has not been studied.

Co-administration of a strong UGT1A9 inhibitor (e.g. mefenamic acid, diflunisal, and niflumic acid) during regorafenib treatment should be avoided, as their influence on the steady-state exposure of regorafenib and

its metabolites has not been studied.

Administration of rifampicin (600 mg for 9 days), a strong CYP3A4 inducer, with a single dose of regorafenib (160 mg on day 7) resulted in a reduction in AUC of regorafenib of approximately 50%, a 3- to 4-fold increase in mean exposure of the active metabolite M-5, and no change in exposure of active metabolite M-2. Other strong CYP3A4 inducers (e.g. phenytoin, carbamazepine, phenobarbital and St. John's wort) may also increase metabolism of regorafenib. Strong

inducers of CYP3A4 should be avoided, or selection of an alternate concomitant medicinal product, with no or minimal potential to induce CYP3A4 should be considered.

UGT1A1 and UGT1A9 substrates

In vitro data indicate that regorafenib as well as its active metabolite M-2 inhibit glucuronidation mediated by UGT1A1 and UGT1A9 whereas M-5 only inhibits UGT1A1 at concentrations which are achieved *in vivo* at steady state. Administration of regorafenib with a 5-day break prior

to administration of irinotecan resulted in an increase of approximately 44% in AUC of SN-38, a substrate of UGT1A1 and an active metabolite of irinotecan. An increase in AUC of irinotecan of approximately 28% was also observed. This indicates that co-administration of regorafenib may increase systemic exposure to UGT1A1 and UGT1A9 substrates.

Breast cancer resistance protein (BCRP) and P-glycoprotein substrates

Administration of regorafenib (160 mg for 14 days) prior to

administration of a single dose of rosuvastatin (5 mg), a BCRP substrate, resulted in a 3.8-fold increase in mean exposure (AUC) of rosuvastatin and a 4.6-fold increase in C_{max}.

This indicates that co-administration of regorafenib may increase the plasma concentrations of other concomitant BCRP substrates (e.g. methotrexate, fluvastatin, atorvastatin). Therefore, it is recommended to monitor patients closely for signs and symptoms of increased exposure to BCRP substrates.

Clinical data indicate that regorafenib has no effect on digoxin pharmacokinetics, therefore can be given concomitantly with p-glycoprotein substrates, such as digoxin, without a clinically meaningful drug interaction.

Inhibitors of P-glycoprotein and BCRP/Inducers of P-glycoprotein and BCRP

In vitro studies indicate that the active metabolites M-2 and M-5 are substrates for P-glycoprotein and BCRP. Inhibitors and inducers of BCRP and P-glycoprotein may interfere

with the exposure of M-2 and M-5. The clinical significance of these findings is unknown (see also section 5.2).

CYP isoform-selective substrates

In vitro data indicate that regorafenib is a competitive inhibitor of the cytochromes CYP2C8 (K_i value of 0.6 micromolar), CYP2C9 (K_i value of 4.7 micromolar), CYP2B6 (K_i value of 5.2 micromolar) at concentrations which are achieved *In vitro* at steady state (peak plasma concentration of 8.1 micromolar). The *In vitro* inhibitory potency towards

CYP3A4 (K_i value of 11.1 micromolar) and CYP2C19 (K_i value of 16.4 micromolar) was less pronounced.

A clinical probe substrate study was performed to evaluate the effect of 14 days of dosing with 160 mg regorafenib on the pharmacokinetics of probe substrates of CYP2C8 (rosiglitazone), CYP2C9 (S-warfarin), CYP2C19 (omeprazole), and CYP3A4 (midazolam).

Pharmacokinetic data indicate that regorafenib may be given concomitantly with substrates of CYP2C8, CYP2C9,

CYP3A4, and CYP2C19 without a clinically meaningful drug interaction (see also section 4.4).

Antibiotics

The concentration-time profile indicates that regorafenib and its metabolites may undergo enterohepatic circulation (see section 5.2). Co-administration with neomycin, a poorly absorbed antimicrobial agent used for eradicating the gastrointestinal microflora (which may interfere with the enterohepatic circulation of regorafenib) had no effect on

the regorafenib exposure, but there was an approximately 80% decrease in the exposure of the active metabolites M-2 and M-5 which showed *In vitro* and *In vitro* comparable pharmacological activity as regorafenib. The clinical significance of this neomycin interaction is unknown, but may result in a decreased efficacy of regorafenib.

Pharmacokinetic interactions of other antibiotics have not been studied.

Bile salt-sequestering agents

Regorafenib, M-2 and M-5 are likely to undergo enterohepatic circulation (see section 5.2). Bile salt-sequestering agents such as cholestyramine and cholestagel may interact with regorafenib by forming insoluble complexes which may impact absorption (or reabsorption), thus resulting in potentially decreased exposure. The clinical significance of these potential interactions is unknown, but may result in a decreased

efficacy of regorafenib.

4.6. Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Women of childbearing potential must be informed that regorafenib may cause fetal harm.

Women of childbearing potential and men should ensure effective contraception during treatment and up to 8 weeks

after completion of therapy.

Pregnancy

There are no data on the use of regorafenib in pregnant women.

Based on its mechanism of action regorafenib is suspected to cause fetal harm when administered during pregnancy. Animal studies have shown reproductive toxicity (see section 5.3).

Regorafenib should not be used during pregnancy unless clearly necessary and after careful consideration of the benefits for the mother and the risk to the fetus.

Breast-feeding

It is unknown whether regorafenib or its metabolites are excreted in human milk.

In rats, regorafenib or its metabolites are excreted in milk. A risk to the breast-fed child cannot be excluded.

Regorafenib could harm infant growth and development (see section 5.3).

Breast-feeding must be discontinued during treatment with regorafenib.

Fertility

There are no data on the effect of regorafenib on human fertility. Results from animal studies indicate that regorafenib can impair male and female fertility (see section 5.3).

4.7.Effects on ability to drive and use machines

No studies on the effects of regorafenib on the ability to drive or use machines have been performed. If patients experience symptoms affecting their ability to concentrate and react during treatment with regorafenib, it is recommended that they do not drive or use machines until the effect subsides.

4.8. Undesirable effects

Summary of the safety profile

The overall safety profile of regorafenib is based on data from more than 4,800 treated patients in clinical trials including placebo-controlled phase III data for 636 patients with metastatic colorectal cancer (CRC), 132 patients with gastrointestinal stromal tumors (GIST) and 374 patients with hepatocellular carcinoma (HCC).

The safety profile of regorafenib in these studies was consistent with the safety results of a phase III B study conducted in 2872 patients with metastatic colorectal cancer whose disease had progressed after treatment with standard therapies.

The **most serious** adverse drug reactions in patients receiving regorafenib are severe liver injury, hemorrhage, gastrointestinal perforation and infection.

The **most frequently** observed adverse drug reactions

(≥30%) in patients receiving regorafenib are pain, hand foot skin reaction, asthenia/fatigue, diarrhea, decreased appetite and food intake, hypertension and infection.

Tabulated list of adverse reactions

The adverse drug reactions reported in clinical trials in patients treated with regorafenib are shown in Table 3. They are classified according to System Organ Class and the most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions.

Adverse drug reactions are grouped according to their frequencies. Frequency groups are defined by the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000) and not known (cannot be estimated from the available data).

Within each frequency group, undesirable effects are presented in order of decreasing seriousness.

Table 3: Adverse drug reactions (ADRs) reported in clinical trials in patients treated with regorafenib

System Organ Class (MedDRA)	Very common	Common	Uncommon	Rare	Not known
Infections and infestations	Infection*	–	–	–	–
Neoplasms benign, malignant and unspecified (including cysts and polyps)	–	–	–	Keratoacanthoma/ Squamous cell carcinoma of the skin	–

Blood and lymphatic system disorders	Thrombocytopenia Anemia	Leukopenia	–	–	–
Immune system disorders	–	–	Hypersensitivity reaction	–	–
Endocrine disorders	–	Hypothyroidism	–	–	–
Metabolism and nutrition disorders	Decreased appetite and food intake	Hypokalemia Hypophosphatemia Hypocalcemia Hyponatremia Hypomagnesemia Hyperuricemia Dehydration	–	–	–

Nervous system disorders	–	Headache Tremor Peripheral neuropathy	–	Posterior reversible encephalopathy syndrome (PRES)	–
Cardiac disorders	–	–	Myocardial infarction Myocardial ischemia	–	–
Vascular disorders	Hemorrhage* Hypertension	–	Hypertensive crisis	–	Aneurysms and artery dissections
Respiratory, thoracic and mediastinal disorders	Dysphonia	–	–	–	–

Gastrointestinal disorders	Diarrhea Stomatitis Vomiting Nausea	Taste disorders Dry mouth Gastro-esophageal reflux Gastro-enteritis	Gastrointestinal perforation* Gastrointestinal fistula Pancreatitis	–	–
Hepatobiliary disorders	Hyperbilirubinemia Increase in transaminases	–	Severe liver injury*#	–	–
Skin and subcutaneous tissue disorders	Hand-foot skin reaction** Rash	Alopecia Dry skin Exfoliative rash	Nail disorder Erythema multiforme	Stevens-Johnson syndrome Toxic epidermal necrolysis	–
Musculo-skeletal and connective tissue disorders	–	Muscle spasms	–	–	–

Renal and urinary disorders	–	Proteinuria	–	–	–
General disorders and administration site conditions	Asthenia/ fatigue Pain Fever Mucosal inflammation	–	–	–	–
Investigations	Weight loss	Increase in amylase Increase in lipase Abnormal international normalized ratio	–	–	–

* Fatal cases have been reported

** Palmar-plantar erythrodysesthesia syndrome in MedDRA terminology

According to drug-induced liver injury (DILI) criteria of the international DILI expert working group

Description of selected adverse reactions

In most cases of severe liver injury, liver dysfunction had an onset within the first 2 months of therapy, and was characterized by a hepatocellular pattern of injury with transaminase elevations >20xULN, followed by bilirubin increase. In clinical trials, a higher incidence of severe liver injury with fatal outcome was observed in Japanese

patients (~1.5%) treated with regorafenib, compared with non-Japanese patients (<0.1%).

In the placebo-controlled phase III trials, the overall incidence of hemorrhage was 18.2% in patients treated with regorafenib and 9.5% in patients receiving placebo. Most cases of bleeding events in patients treated with regorafenib were mild to moderate in severity (Grades 1 and 2: 15.2%), most notably epistaxis (6.1%). Fatal outcome in patients treated with regorafenib was uncommon (0.7%),

and included cerebral, respiratory, gastrointestinal and genitourinary events.

In the placebo-controlled phase III trials, infections were more often observed in patients treated with regorafenib, compared to patients receiving placebo (all grades: 31.6% vs. 17.2%). Most infections in patients treated with regorafenib were mild to moderate in severity (Grades 1 and 2: 23.0%), and included urinary tract infections (5.7%), nasopharyngitis (4.0%), mucocutaneous and systemic

fungal infections (3.3%) as well as pneumonia (2.6%). Fatal outcomes associated with infection were observed more often in patients treated with regorafenib (1.0%), compared to patients receiving placebo (0.3%), and were mainly respiratory events.

In the placebo-controlled phase III trials, the overall incidence of hand-foot skin reaction was higher in patients treated with regorafenib, compared to patients receiving placebo (all grades: 51.4% vs. 6.5% CRC, 66.7% vs. 15.2%

GIST and 51.6% vs. 7.3% HCC). Most cases of hand-foot skin reaction in patients treated with regorafenib appeared during the first cycle of treatment and were mild to moderate in severity (Grades 1 and 2: 34.3% CRC, 44.7% GIST, and 39.3% HCC). The incidence of Grade 3 hand-foot skin reaction was 17.1% (CRC), 22.0% (GIST) and 12.3% (HCC). The overall incidence of hand-foot skin reaction (74.8% CRC, 88.2% GIST, and 67.1%, HCC) was higher in regorafenib-treated Asian patients, compared to other ethnicities. The incidence of Grade 3 hand-foot

skin reaction in Asians was 20.5% (CRC), 23.5% (GIST) and 13.5% (HCC) (see sections 4.2 and 4.4).

In the placebo-controlled phase III trials, the overall incidence of hypertension was higher in patients treated with regorafenib, compared to patients receiving placebo (29.6% vs. 7.5% CRC, 60.6% vs. 25.8% GIST, and 31.0% vs. 6.2% HCC). Most cases of hypertension in patients treated with regorafenib appeared during the first cycle of treatment and were mild to moderate in severity (Grades

1 and 2: 20.9% CRC, 31.8% GIST, and 15.8% HCC). The incidence of Grade 3 hypertension was 8.7% (CRC), 28.0% (GIST) and 15.2% (HCC). One case of Grade 4 hypertension was reported in the GIST trial.

In the placebo-controlled phase III trials, the overall incidence of treatment emergent proteinuria was 9.1% in patients treated with regorafenib, compared to 1.9% in patients receiving placebo. Of these events, 35.6% in the regorafenib arm and 54.5% in the placebo arm have been

reported as not recovered/not resolved.

Across all clinical trials, cardiac disorder events (all grades) have been more often (13.7% vs. 6.5%) reported in regorafenib-treated patients aged 75 years or older (N=410), compared to regorafenib-treated patients below 75 years (N=4108).

Laboratory test abnormalities

Treatment-emergent laboratory abnormalities observed in

the placebo-controlled phase III trials are shown in Table 4 and Table 4a (see also section 4.4).

Table 4: Treatment-emergent laboratory test abnormalities reported in placebo-controlled phase III trials in patients with metastatic CRC (CORRECT), GIST (GRID) and HCC (RESORCE)

	mCRC (CORRECT)			
Laboratory Parameter (in % of samples investigated)	Regorafenib plus BSC (n= 500)	Placebo plus BSC (n=253)	Regorafenib plus BSC (n= 500)	Placebo plus BSC (n=253)
	Grade *			
	All Grades %		Grade 3/4 %	
Blood and lymphatic system disorders				
Hemoglobin decreased	78.5	66.3	5.3	2.8
Thrombocytopenia	40.5	16.8	2.8	0.4
Neutropenia	2.8	0	0.6	0
Lymphopenia	54.1	34.8	9.3	4.0

Laboratory Parameter (in % of samples investigated)	mCRC (CORRECT)			
	Regorafenib plus BSC (n= 500)	Placebo plus BSC (n=253)	Regorafenib plus BSC (n= 500)	Placebo plus BSC (n=253)
	Grade [a]			
	All Grades %		Grade 3/4 %	
Metabolism and nutrition disorders				
Hypocalcemia	59.3	18.3	1.2	1.2
Hypokalemia	25.7	8.3	4.3	0.4
Hypophosphatemia	57.4	11.1	31.1	3.6
Hepatobiliary disorders				
Hyperbilirubinemia	44.6	17.1	12.2	8.4
Increased AST	65.0	45.6	5.9	5.2
Increased ALT	45.2	29.8	5.5	3.2

Laboratory Parameter (in % of samples investigated)	mCRC (CORRECT)			
	Regorafenib plus BSC (n= 500)	Placebo plus BSC (n=253)	Regorafenib plus BSC (n= 500)	Placebo plus BSC (n=253)
	Grade [a]			
	All Grades %		Grade 3/4 %	
Renal and urinary disorders				
Proteinuria	83.6	61.0	1.8	0.8
Investigations				
Increased INR*	23.7	16.6	4.2	1.6
Increased Lipase	46.0	18.7	11.4	4.4
Increased Amylase	25.5	16.7	2.6	2.4

Laboratory Parameter (in % of samples investigated)	GIST (GRID)			
	Regorafenib plus BSC (n= 132)	Placebo plus BSC (n= 66)	Regorafenib plus BSC (n=132)	Placebo plus BSC (n= 66)
	Grade [b]			
	All Grades %		Grade 3/4 %	
Blood and lymphatic system disorders				
Hemoglobin decreased	75.0	72.7	3.0	1.5
Thrombocytopenia	12.9	1.5	0.8	1.5
Neutropenia	15.9	12.1	3.1	3.0
Lymphopenia	29.9	24.2	7.6	3.0

Laboratory Parameter (in % of samples investigated)	GIST (GRID)			
	Regorafenib plus BSC (n= 132)	Placebo plus BSC (n= 66)	Regorafenib plus BSC (n=132)	Placebo Plus BSC (n= 66)
	Grade [b]			
	All Grades %		Grade 3/4 %	
Metabolism and nutrition disorders				
Hypocalcemia	16.7	4.5	1.5	0
Hypokalemia	20.5	3.0	3.0	0
Hypophosphatemia	54.5	3.1	21.2	1.5
Hepatobiliary disorders				
Hyperbilirubinemia	33.3	12.1	3.8	1.5
Increased AST	58.3	47.0	3.8	3.0
Increased ALT	39.4	39.4	4.6	1.5

Laboratory Parameter (in % of samples investigated)	GIST (GRID)			
	Regorafenib plus BSC (n= 132)	Placebo plus BSC (n= 66)	Regorafenib plus BSC (n=132)	Placebo plus BSC (n= 66)
	Grade [b]			
	All Grades %		Grade 3/4 %	
Renal and urinary disorders				
Proteinuria	59.2	52.5	3.1	3.4
Investigations				
Increased INR*	9.3	12.5	1.6	4.7
Increased Lipase	14.4	4.6	0.8	0
Increased Amylase	-	-	-	-

Laboratory Parameter (in % of samples investigated)	HCC (RESORCE)			
	Regorafenib plus BSC (n= 374)	Placebo plus BSC (n=193)	Regorafenib plus BSC (n= 374)	Placebo plus BSC (n=193)
	Grade [b]			
	All Grades %		Grade 3/4 %	
Blood and lymphatic system disorders				
Hemoglobin decreased	72.5	71.3	6.0	4.8
Thrombocytopenia	63.1	50.0	5.4	0
Neutropenia	13.6	14.9	3.0	1.0
Lymphopenia	67.8	58.5	17.4	11.7

Laboratory Parameter (in % of samples investigated)	HCC (RESORCE)			
	Regorafenib plus BSC (n= 374)	Placebo plus BSC (n=193)	Regorafenib plus BSC (n= 374)	Placebo plus BSC (n=193)
	Grade [b]			
	All Grades %		Grade 3/4 %	
Metabolism and nutrition disorders				
Hypocalcemia	23.4	10.1	0.3	0
Hypokalemia	30.7	9.0	4.3	2.1
Hypophosphatemia	70.4	31.4	33.9	6.9
Hepatobiliary disorders				
Hyperbilirubinemia	78.2	54.5	15.9	15.7
Increased AST	92.7	84.3	17.8	19.9
Increased ALT	70.4	58.6	6.2	4.7

Laboratory Parameter (in % of samples investigated)	HCC (RESORCE)			
	Regorafenib plus BSC (n= 374)	Placebo plus BSC (n=193)	Regorafenib plus BSC (n= 374)	Placebo plus BSC (n=193)
	Grade [b]			
	All Grades %		Grade 3/4 %	
Renal and urinary disorders				
Proteinuria	51.0	36.5	16.7	3.1
Investigations				
Increased INR*	44.4	35.4	0.7	2.1
Increased Lipase	40.5	27.0	14.2	8.7
Increased Amylase	23.0	19.0	2.8	2.7

[a] Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0
[b] Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0
* International normalized ratio
BSC = Best Supportive Care

Compared to the global phase III CRC trial (CORRECT) with predominantly (~80%) Caucasian patients enrolled, a higher incidence of liver enzyme increases was observed in regorafenib-treated patients in the Asian phase III CRC trial (CONCUR) with predominantly (> 90%) East Asian patients enrolled.

Table 4a: Treatment emergent liver enzyme test abnormalities reported in placebo-controlled phase III trial in Asian patients with metastatic CRC (CONCUR)

Laboratory parameter, (in % of samples investigated)	Regorafenib plus BSC§ (N=136)			Placebo plus BSC§ (N=68)		
	All Grades*	Grade 3*	Grade 4*	All Grades*	Grade 3*	Grade 4*
Bilirubin increased	66.7	7.4	4.4	32.8	4.5	0.0
AST increased	69.6	10.4	0.7	47.8	3.0	0.0
ALT increased	54.1	8.9	0.0	29.9	1.5	0.0

§ Best Supportive Care

* Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0

In the placebo-controlled phase III trials, tests on thyroid stimulating hormone (TSH) showed post baseline >ULN in 34.6% of patients treated with regorafenib and in 17.2% of patients receiving placebo. TSH post baseline >4 times ULN was reported in 6.5% of patients treated with regorafenib and in 1.3% of patients receiving placebo. Concentration of free triiodothyronine (FT3) post baseline

below lower limit of normal (<LLN) was reported in 29.2% of patients treated with regorafenib and in 20.4% of patients receiving placebo. Concentration of free thyroxin (FT4) post baseline <LLN was reported in 8.1% of patients treated with regorafenib and 5.6% of patients receiving placebo. Overall approximately 4.6% of patients treated with regorafenib developed hypothyroidism requiring hormonal replacement treatment.

4.9. Overdose

The highest dose of regorafenib studied clinically was 220 mg per day. The most frequently observed adverse drug reactions at this dose were dermatological events, dysphonia, diarrhea, mucosal inflammation, dry mouth, decreased appetite, hypertension, and fatigue.

There is no specific antidote for regorafenib overdose. In the event of suspected overdose, regorafenib should be discontinued immediately, with best supportive care

initiated by a medical professional, and the patient should be observed until clinical stabilization.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitor;

ATC Code: L01XE21

Mechanism of action and pharmacodynamic effects

Regorafenib is an oral tumor deactivation agent that potently blocks multiple protein kinases, including kinases involved in tumor angiogenesis (VEGFR1, -2, -3, TIE2), oncogenesis (KIT, RET, RAF-1, BRAF, $BRAF^{V600E}$), metastasis (VEGFR3, PDGFR, FGFR) and tumor immunity (CSF1R). In particular, regorafenib inhibits mutated KIT, a major oncogenic driver in gastrointestinal stromal tumors, and thereby blocks tumor cell proliferation. In preclinical studies regorafenib has demonstrated potent antitumor activity in a broad spectrum of tumor models including colorectal, gastrointestinal stromal and hepatocellular tumor models which is likely mediated by its anti-angiogenic and anti-proliferative effects. In addition, regorafenib reduced the levels of tumor associated macrophages and has shown anti-metastatic effects *In vitro*. Major human metabolites (M-2 and M-5) exhibited similar efficacies, compared to regorafenib in *In vitro* and *In vivo* models.

Clinical efficacy and safety

Metastatic colorectal cancer (CRC)

The clinical efficacy and safety of regorafenib have been evaluated in an international, multi-center, randomized, double-blind, placebo-controlled phase III study (CORRECT) in patients with metastatic colorectal cancer who have progressed after failure of standard therapy.

The primary efficacy endpoint was Overall Survival (OS).

Secondary endpoints were Progression-Free Survival (PFS), Objective Tumor Response Rate (ORR) and Disease Control Rate (DCR).

In total, 760 patients were randomized 2:1 to receive 160 mg regorafenib (4 tablets regorafenib each containing 40 mg regorafenib) orally once daily (N=505) plus Best Supportive Care (BSC) or matching placebo (N=255) plus BSC for 3 weeks on therapy followed by 1 week off therapy. The mean daily regorafenib dose received was 147 mg.

Patients continued therapy until disease progression or unacceptable toxicity. A pre-planned interim analysis for efficacy was performed when 432 deaths had occurred. The study was un-blinded after this planned interim analysis of OS had crossed the pre-specified efficacy boundary.

Of the 760 randomized patients, the median age was 61 years, 61% were male, 78% were Caucasian, and all patients had baseline ECOG Performance Status (PS) of 0 or 1. PS ≥2 was reported during regorafenib treatment in 11.4% of

patients. The median treatment duration and daily dose, as well as the rate of dose modification and dose reduction were similar to those observed in patients with a reported PS ≥ 2 receiving placebo (8.3%). The majority of patients with PS ≥2 discontinued treatment for progressive disease. The primary site of disease was colon (65%), rectum (29%), or both (6%). A KRAS mutation was reported in 57% of patients at study entry.

Most patients (52%) received 3 or fewer previous lines

of treatment for metastatic disease. Therapies included treatment with fluoropyrimidine-based chemotherapy, an anti-VEGF therapy, and, if the patient was KRAS wild type, an anti-EGFR therapy.

The addition of regorafenib to BSC resulted in significantly longer survival, compared to placebo plus BSC with a p value of 0.005178 from stratified log rank test, a hazard ratio of 0.774 [95% CI 0.636, 0.942]) and a median OS of 6.4 months vs. 5.0 months (see Table 5 and Figure 1). PFS

was significantly longer in patients receiving regorafenib BSC (hazard ratio: 0.494, p<0.000001, see Table 5). The response rate (complete response or partial response) was 1% and 0.4% for regorafenib and placebo treated patients, respectively (p=0.188432, 1-sided). The DCR (complete response or partial response or stable disease) was significantly higher in patients treated with regorafenib (41.0% vs. 14.9%, p<0.000001, 1 sided).

Table 5: Efficacy results from the CORRECT study

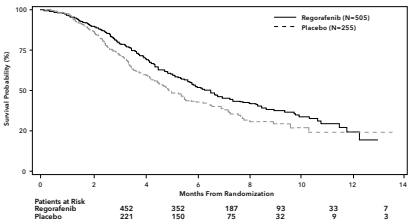
Efficacy parameter	Hazard ratio* (95% CI)	P-value (one-sided)	Median (95% CI)	
			Regorafenib plus BSC§ (N=505)	Placebo plus BSC§ (N=255)
OS	0.774 (0.636, 0.942)	0.005178	6.4 months (5.9, 7.3)	5.0 months (4.4, 5.8)
PFS**	0.494 (0.419, 0.582)	<0.000001	1.9 months (1.9, 2.1)	1.7 months (1.7, 1.7)

§ BSC Supportive Care

* Hazard ratio < 1 favors regorafenib

** Based on investigator's assessment of tumor response

Figure 1: Kaplan-Meier curve of OS



Subgroup analyses for OS and PFS according to age (<65; ≥65), gender, ECOG PS, primary site of disease, time from first diagnosis of metastatic disease, prior anticancer treatment, prior treatment lines for metastatic disease, and KRAS mutation status showed a treatment effect favoring the regorafenib regimen over the placebo regimen.

Subgroup analysis results by historical KRAS mutational status showed a treatment effect for OS in favor of regorafenib over placebo for patients with KRAS wild-type

tumors whereas a numerically lower effect was reported in patients with KRAS mutant tumors; the treatment effect for PFS favoring regorafenib was observed regardless of KRAS mutational status. The hazard ratio (95% CI) of OS was 0.653 (0.476 to 0.895) for patients with KRAS wild-type tumors and 0.867 (0.670 to 1.123) for patients with KRAS mutant tumors, with no evidence of heterogeneity in treatment effect (non-significant interaction test). The hazard ratio (95% CI) of PFS was 0.475 (0.362 to 0.623) for patients with KRAS wild-type tumors and 0.525 (0.425 to

0.649) for patients with KRAS mutant tumors.

A second phase III, international, multi-center, randomized, double blind, placebo-controlled study (CONCUR) evaluated the efficacy and safety of regorafenib in 204 pre-treated Asian patients (> 90% East Asian) with metastatic colorectal cancer who have progressed after failure of fluoropyrimidine-based chemotherapy. Only 59.5% of patients enrolled in the CONCUR study were also previously treated with VEGF- or EGFR-targeted agents. The primary

efficacy endpoint was OS. The addition of regorafenib to BSC resulted in a significantly longer survival, compared to placebo plus BSC with a hazard ratio of 0.550 (p= 0.000159 stratified log rank test) and a median OS of 8.8 months vs. 6.3 months [95% CI: 0.395, 0.765]. PFS was also significantly longer in patients receiving regorafenib plus BSC (hazard ratio: 0.311, p<0.000001), median PFS 3.2 months with regorafenib vs. 1.7 months with placebo. The safety profile of regorafenib plus BSC in the CONCUR study was consistent with the safety profile

observed in the CORRECT study.

Gastrointestinal stromal tumors (GIST)

The clinical efficacy and safety of regorafenib have been evaluated in an international, multi-center, randomized, double-blind, placebo-controlled phase III study (GRID) in patients with gastrointestinal stromal tumors (GIST) previously treated with 2 tyrosine kinase inhibitors (imatinib and sunitinib).

The analysis of the primary efficacy endpoint Progression-Free Survival (PFS) was conducted after 144 PFS events (central blinded assessment). Secondary endpoints including Time To Progression (TTP) and Overall Survival (OS) (interim analysis) were also assessed.

In total, 199 patients with GIST were randomized 2:1 to receive either 160 mg regorafenib plus Best Supportive Care (BSC) (N=133) orally once daily or matching placebo plus BSC (N=66) for 3 weeks on therapy followed by 1 week

off therapy. The mean daily regorafenib dose received was 140 mg.

Patients continued therapy until disease progression or unacceptable toxicity. Patients receiving placebo who experienced disease progression were offered open-label regorafenib (cross-over option). Patients receiving regorafenib who experienced disease progression and for whom in the investigator's opinion, treatment with regorafenib was providing clinical benefit, were offered the

opportunity to continue open-label regorafenib.

Of the 199 randomized patients, the mean age was 58 years, 64% were male, 68% were Caucasian, and all patients had baseline ECOG Performance Status (PS of 0 or 1). The overall median time since most recent progression or relapse to randomization was 6 weeks.

Regorafenib plus BSC resulted in significantly longer PFS, compared to placebo plus BSC with a hazard ratio of 0.268 [95% CI 0.185, 0.388] and a median PFS of 4.8 months

vs. 0.9 months ($p < 0.000001$). The relative risk of disease progression or death was reduced by approximately 73.2% in regorafenib-treated patients, compared to placebo treated patients (see Table 6, Figure 2). The increase in PFS was consistent independent of age, sex, geographic region, prior lines of treatment, ECOG PS.

TTP was significantly longer in patients receiving regorafenib plus BSC than in patients receiving placebo plus BSC with a hazard ratio of 0.248 [95% CI: 0.170, 0.364], and median TTP of 5.4 months vs. 0.9 months ($p<0.000001$) (see Table 6).

The HR for OS was 0.772 (95% CI, 0.423, 1.408; $p = 0.199$; median OS not reached in either arm); 85% of patients initially randomized to the placebo arm received post-progression treatment with regorafenib (see Table 6, Figure 3).

Table 6: Efficacy results from the GRID study

Efficacy parameter	Hazard ratio* (95% CI)	P-value (one-sided)	Median (95% CI)	
			Regorafenib plus BSC§ (N=133)	Placebo plus BSC§ (N=66)
PFS	0.268 (0.185, 0.388)	<0.000001	4.8 months (4.0, 5.7)	0.9 months (0.9, 1.1)
TTP	0.248 (0.170, 0.364)	<0.000001	5.4 months (4.1, 5.7)	0.9 months (0.9, 1.1)
OS	0.772 (0.423, 1.408)	0.199	NR**	NR**

§ Best Supportive Care

* Hazard ratio < 1 favors regorafenib

** NR: not reached

Figure 2: Kaplan-Meier curves of PFS

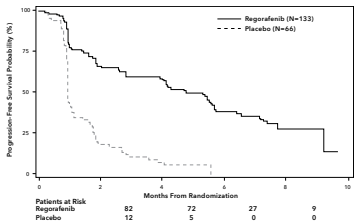
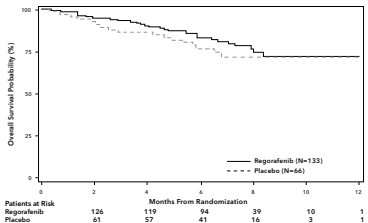


Figure 3: Kaplan-Meier curves of OS



In addition, 56 placebos plus BSC patients received open-label regorafenib after cross-over following disease progression and a total of 41 regorafenib plus BSC patients continued regorafenib treatment after disease progression. The median secondary PFS (as measured by the investigator's assessment) were 5.0 and 4.5 months, respectively.

Hepatocellular carcinoma (HCC)

The clinical efficacy and safety of regorafenib have been

evaluated in an international, multi-center, randomized, double-blind, placebo-controlled phase III study (RESORCE) in patients with hepatocellular carcinoma who have been previously treated with sorafenib.

The primary efficacy endpoint was Overall Survival (OS). Secondary endpoints were Progression-Free Survival (PFS), Time To Progression (TTP), Objective Tumor Response Rate (ORR) and Disease Control Rate (DCR).

In total, 573 patients with HCC were randomized 2:1

to receive either 160 mg regorafenib orally once daily (n=379) plus Best Supportive Care (BSC) or matching placebo (n=194) plus BSC for 3 weeks on therapy followed by 1 week off therapy. The mean daily regorafenib dose received was 144 mg.

Patients were eligible to participate in the study if they experienced radiological disease progression during treatment with sorafenib and if they had a liver function status of Child-Pugh class A. Patients who permanently

discontinued sorafenib therapy due to sorafenib-related toxicity or who tolerated less than 400 mg sorafenib once daily prior to withdrawal were excluded from the study. Randomization was performed within 10 weeks after the last treatment with sorafenib. Patients continued therapy with regorafenib until clinical or radiological disease progression or unacceptable toxicity. However, patients could continue regorafenib therapy past progression at the discretion of the investigator.

Demographics and baseline disease characteristics were comparable between the regorafenib- and placebo-treated groups and are shown below for all 573 randomized patients:

- Median age: 63 years
- Male: 88%
- Caucasian: 36%, Asian: 41%
- ECOG Performance Status (PS) of 0: 66% or ECOG PS of

1: 34%

- Child-Pugh A: 98%, Child-Pugh B: 2%
- Etiology included Hepatitis B (38%), Hepatitis C (21%), Non-Alcoholic Steato Hepatitis (NASH, 7%)
- Absence of both macroscopic vascular invasion and extra-hepatic tumor spread: 19%
- Barcelona Clinic Liver Cancer (BCLC) stage B: 13%; BCLC stage C: 87%

- Loco-regional trans arterial embolization or chem-infusion procedures: 61%
- Radiotherapy prior to regorafenib treatment: 15%
- Median duration of sorafenib treatment: 7.8 months

The addition of regorafenib to BSC resulted in a statistically significant improvement in OS compared to placebo plus BSC with a hazard ratio of 0.624 [95% CI: 0.498, 0.782], p=0.000017 stratified log rank test, and a median OS of

10.6 months vs. 7.8 months (see Table 7 and Figure 4).

Table 7: Efficacy results from the RESORCE study

Efficacy parameter	Hazard ratio* (95% CI)	P-value (one-sided)	Median (95% CI)	
			Regorafenib plus BSC§ (N=379)	Placebo plus BSC§ (N=194)
OS	0.624 (0.498, 0.782)	0.000017	10.6 months (9.1, 12.1)	7.8 months (6.3, 8.8)
PFS**	0.453 (0.369, 0.555)	<0.000001	3.1 months (2.8, 4.2)	1.5 months (1.4, 1.6)
TTP**	0.439 (0.355, 0.542)	<0.000001	3.2 months (2.9, 4.2)	1.5 months (1.4, 1.6)

			Percentages	
ORR**#	NA	0.003650	11%	4%
DCR **#	NA	<0.000001	65%	36%

§ Best Supportive Care

* Hazard ratio < 1 favors regorafenib

** Based on investigator's assessment of tumor response by modified RECIST

Response rate (complete or partial response), DCR (complete response, partial response and stable disease maintained for 6 weeks)

Figure 4: Kaplan-Meier curve of OS

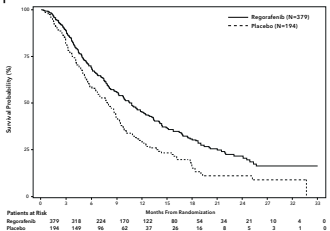
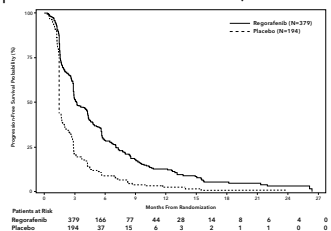


Figure 5: Kaplan-Meier curve of PFS (mRECIST)



Pediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with regorafenib in all subsets of the pediatric population in the treatment of adenocarcinoma of the colon and rectum (see section 4.2 for information on pediatric use).

The European Medicines Agency has deferred the obligation to submit the results of studies with regorafenib in one or more subsets of the pediatric population in the

treatment of solid malignant tumors (see section 4.2 for information on pediatric use).

The European Medicines Agency has waived the obligation to submit the results of studies with regorafenib in all subsets of the pediatric population in the treatment of hepatocellular carcinoma (see section 4.2 for information on pediatric use).

5.2. Pharmacokinetic properties

Absorption

Regorafenib reaches mean peak plasma levels of about 2.5 mg/l at about 3 to 4 hours after a single oral dose of 160 mg given as 4 tablets each containing 40 mg. Following single doses of 60 mg or 100 mg, the average relative bioavailability of tablets compared to an oral solution was 69% and 83%, respectively.

The concentrations of regorafenib and its major pharmacologically active metabolites (M-2 and M-5) were highest when given after a low-fat (light) breakfast, compared to either a high-fat breakfast or fasting condition. The exposure for regorafenib was increased by 48% when administered with a high-fat breakfast, and 36% when administered with a low-fat breakfast, compared to fasting. The exposure of metabolites M-2 (N-oxide) and M-5 (N-oxide and N-desmethyl) is higher when regorafenib is given with a low-fat breakfast, compared to fasting

condition and lower when given with a high fat meal, compared to fasting condition.

Distribution

Plasma concentration-time profiles for regorafenib as well as for the major circulating metabolites showed multiple peaks across the 24-hour dosing interval, which are attributed to enterohepatic circulation. *In vitro* protein binding of regorafenib to human plasma proteins is high (99.5%). *In vitro* protein binding of M-2

and M-5 is higher (99.8% and 99.95%, respectively) than that of regorafenib. Metabolites M-2 and M-5 are weak substrates of P-gp. Metabolite M-5 is a weak BCRP-substrate.

Biotransformation

Regorafenib is metabolized primarily in the liver by oxidative metabolism mediated by CYP3A4, as well as by glucuronidation mediated by UGT1A9. Two major and six minor metabolites of regorafenib have been identified in

plasma. The main circulating metabolites of regorafenib in human plasma are M-2 (N-oxide) and M-5 (N-oxide and N-desmethyl), which are pharmacologically active and have similar concentrations as regorafenib at steady state. M-2 is further metabolized by oxidative metabolism mediated by CYP3A4, as well as by glucuronidation mediated by UGT1A9.

Metabolites may be reduced or hydrolyzed in the gastrointestinal tract by microbial flora, allowing

reabsorption of the unconjugated active substance and metabolites (enterohepatic circulation).

Elimination

Following oral administration, mean elimination half-life for regorafenib and its metabolite M-2 in plasma ranges from 20 to 30 hours in different studies. The mean elimination half-life for the metabolite M-5 is approximately 60 hours (range from 40 to 100 hours).

Approximately 90% of the radioactive dose was recovered within 12 days after administration, with about 71% of the dose excreted in feces (47% as parent compound, 24% as metabolites), and about 19% of the dose excreted in urine as glucuronides. Urinary excretion of glucuronides decreased below 10% under steady-state conditions. Parent compound found in feces could be derived from intestinal degradation of glucuronides or reduction of metabolite M-2 (N-oxide), as well as unabsorbed regorafenib.

M-5 may be reduced to M-4 in the gastrointestinal tract by microbial flora, allowing reabsorption of M-4 (enterohepatic circulation). M-5 is finally excreted via M-4 as M-6 (carboxylic acid) in faeces.

Linearity/non-linearity

Systemic exposure of regorafenib at steady-state increases dose proportionally up to 60 mg and less than proportionally at doses greater than 60 mg. Accumulation of regorafenib at steady state results in

about a 2-fold increase in plasma concentrations, which is consistent with the elimination half-life and dosing frequency. At steady state, regorafenib reaches mean peak plasma levels of about 3.9 mg/l (8.1 micromolar) after oral administration of 160 mg regorafenib and the peak-to-trough ratio of mean plasma concentrations is less than 2.

Both metabolites, M-2 and M-5, exhibit non-linear accumulation, which might be caused by entero- hepatic

recycling or saturation of the UGT1A9 pathway. Whereas plasma concentrations of M-2 and M-5 after a single dose of regorafenib are much lower than those of parent compound, steady-state plasma concentrations of M-2 and M-5 are comparable to those of regorafenib.

Hepatic impairment

The exposure of regorafenib and its metabolites M-2 and M-5 is comparable in patients with mild hepatic impairment (Child-Pugh A) and patients with normal hepatic function.

Limited data in patients with moderate hepatic impairment (Child-Pugh B) indicate similar exposure, compared to patients with normal hepatic function after a single 100 mg dose of regorafenib. There are no data for patients with Child-Pugh C (severe) hepatic impairment. Regorafenib is mainly eliminated via the liver, and exposure might be increased in this patient population.

Renal impairment

Available clinical data and physiology-based

pharmacokinetic modelling indicate similar steady-state exposure of regorafenib and its metabolites M-2 and M-5 in patients with mild or moderate renal impairment, compared to patients with normal renal function. In patients with severe renal impairment compared to patients with normal renal function, regorafenib exposure was similar while exposure to M-2 and M-5 was decreased by about 30% under steady-state conditions, which is not considered clinically relevant.

The pharmacokinetics of regorafenib has not been studied in patients with end-stage renal disease. However, physiology-based pharmacokinetic modelling does not predict any relevant change in exposure in these patients.

Elderly

Age did not affect the regorafenib pharmacokinetics over the studied age range (29–85 years).

Gender

The pharmacokinetics of regorafenib is not influenced by gender.

Ethnic differences

The exposure of regorafenib in various Asian populations (Chinese, Japanese, Korean) is within the same range as seen in Caucasians.

Cardiac electrophysiology/QT prolongation

No QTc prolonging effects were observed after administration of 160 mg regorafenib at steady state in a dedicated QT study in male and female cancer patients.

5.3. Preclinical safety data

Systemic toxicity

After repeated dosing to mice, rats and dogs, adverse effects were observed in a number of organs, primarily in

the kidneys, liver, digestive tract, thyroid gland, lympho-/hematopoietic system, endocrine system, reproductive system and skin. A slightly increased incidence of thickening of the atrioventricular valves of the heart was seen in the 26-week repeat-dose toxicity study in rats. This may be due to acceleration of an age-related physiological process. These effects occurred at systemic exposures in the range of or below the anticipated human exposure (based on AUC comparison).

Alterations of teeth and bones and adverse effects in the reproductive system were more pronounced in young and growing animals as well as in juvenile rats and indicate a potential risk for children and adolescents.

Reproductive and developmental toxicity

Specific studies on fertility have not been performed. However, a potential of regorafenib to adversely affect male and female reproduction has to be considered based on morphological changes in the testes, ovaries, and the

uterus observed after repeated dosing in rats and dogs at exposures below the anticipated human exposure (based on AUC comparison). The observed changes were only partially reversible.

An effect of regorafenib on intrauterine development was shown in rabbits at exposures below the anticipated human exposure (based on AUC comparison). Main findings consisted of malformations of the urinary system, the heart and major vessels, and the skeleton.

Genotoxicity and carcinogenicity

There was no indication for a genotoxic potential of regorafenib tested in standard assays *in vitro* and *in vivo* in mice.

Studies on the carcinogenic potential of regorafenib have not been performed.

Environmental risk assessment (ERA)

Environmental risk assessment studies have shown that regorafenib has the potential to be persistent,

bioaccumulative and toxic to the environment and may pose a risk to the surface water and to the sediment compartment (see section 6.6).

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Cellulose microcrystalline

Croscarmellose sodium

Magnesium stearate

Povidone (K-25)

Silica, colloidal anhydrous

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

2 years

Once the bottle is opened the medicinal product has shown to be stable for 7 weeks. Thereafter, the medicinal product is to be discarded.

6.4. Special precautions for storage

Store below 30° C.

Store in the original package in order to protect from moisture.

Keep the bottle tightly closed.

6.5. Nature and contents of container

Each bottle contains 28 film-coated tablets.

3 bottles are packaged in one box with a leaflet.

6.6. Special precautions for disposal and other handling

This medicinal product may pose a risk to the environment (see section 5.3).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Last revision: August 2021

Manufactured by Nano Fanavaran Darouei Alvand (NanoAlvand)

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