مرتیسو®

اُسیمرتینیب

قرص روکش‌دار

پیش از شروع مصرف مرتیسو® محتوای دفترچه راهنما را به دقت مطالعه کنید. این دفترچه راهنما در برگیرنده پاسخ شایع‌ترین سؤالات در مورد داروی مرتیسو® است. درصورتی که پاسخ تمامی سؤالات 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 بر گیرنده 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 سؤالات زیر پاسخ داده می‌شود:

- مرتیسو® چیست و در چه مواردی تجویز می‌شود؟
- چه افرادی نباید مرتیسو® را دریافت کنند؟
- پیش از دریافت مرتیسو® یا در طول درمان با آن چه مواردی را حتماً باید به پزشک خود اطلاع دهید؟
- آیا مرتیسو® در کودکان و نوجوانان قابل تجویز است؟
- آیا مرتیسو® با سایر داروها تداخل دارد؟
- ایمنی مصرف مرتیسو® در دوران بارداری و شیردهی چگونه است؟

- آیا در طول مدت مصرف مرتیسو® رانندگی و کار با ماشین‌آلات مجاز است؟
- دوز، فواصل تجویز و طول دوره درمان با مرتیسو® چقدر است؟
- در صورت مصرف بیش از حد مرتیسو® چه باید کرد؟
- در صورت فراموشی مصرف مرتیسو® چه باید کرد؟
- مرتیسو® ممکن است چه اثرات نامطلوبی داشته باشد؟
- مرتیسو® را در چه شرایطی باید نگهداری کرد؟
- مرتیسو® از چه اجزایی تشکیل شده است و بسته‌بندی آن چگونه است؟

مرتیسو® چیست و در چه مواردی تجویز می‌شود؟

نـام اختصاصـی داروی شـما مرتیسـو® و نـام ژنریـک آن اُسـیمرتینیب اسـت. مرتیسـو® متعلـق بـه دسـته‌ای از داروهـا بـه نـام مهارکننده‌هـای پروتئیـن کینـاز اسـت و در درمان نوعـی سـرطان ریـه (NSCLC) در بزرگسـالان کاربـرد دارد. اگـر سـرطان با جهـش در ژن گیرنـده فاکتـور رشـد اپیدرمی (EGFR) همراه باشـد، احتمالاً به درمان با مرتیسـو® پاسـخ می‌دهـد. مرتیسـو® می‌توانـد در مـوارد زیـر تجویز شـود:

- به عنوان یک درمان کمکی پس از جراحی و برداشت کامل سلول‌های سرطانی
- بـه عنـوان نخسـتین درمـان دارویـی در مواردی که سـرطان به سـایر قسـمت‌های بدن

منتشر شـده باشد.

- در شـرایط خـاص، در بیمارانـی کـه قبـلاً تحـت درمـان بـا سـایر داروهـای مهارکننـده پروتئیـن کینـاز قـرار گرفته‌انـد.

نحوه عملکرد مرتیسو®

مرتیسـو® بـا مسـدود کـردن گیرنده‌هـای فاکتـور رشـد اپیدرمـی باعـث کاهش یـا توقف رشـد سـلول‌های سـرطانی ریـه می‌شـود. همچنین ممکن اسـت بـه کاهش انـدازه تومور و جلوگیـری از بازگشـت تومـور پـس از جراحـی کمک کند.

اگر مرتیسو® پس از برداشت کامل سلول‌های سرطانی، برای شما تجویز شده است و یا نخستین دارو از دسته مهارکننده‌های پروتئین کیناز است که برایتان تجویز شده است، به این معنی است که بیماری شما همراه با نقص‌هایی در ژن EGFR مانند "حذف اگزون ۱۹" یا "جهش جایگزینی اگزون ۲۱" می‌باشد.

اگر ضمن مصرف سایر داروهای مهارکننده پروتئین کیناز، سرطان شما پیشرفت کرده است، به این معنی است که بیماری شما همراه با یک نقص ژنی به نام «T790M» می‌باشد. به همین دلیل ممکن است سایر داروهای مهارکننده پروتئین کیناز نیز مؤثر نباشند.

همچنین این دارو ممکن است در مواردی که در این دفترچه راهنما ذکر نشده است، تجویز شود. در صورتی که در مورد علت تجویز این دارو و نحوه عملکرد آن سؤالی

دارید، از پزشک خود بپرسید.

چه افرادی نباید مرتیسو® را دریافت کنند؟

- اگر در گذشته سابقه واکنش حساسیتی به اُسیمرتینیب و یا مواد جانبی موجود در مرتیسو® را داشته‌اید. (لیست این مواد در قسمت آخر دفترچه راهنما آمده است.)
- اگر در حال مصرف فرآورده‌های حاوی گیاه علف چای (Hypericum perforatum) هستید.

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

پیش از مصرف مرتیسو® اگر هر یک از شرایط زیر را داشتید، به پزشک، پرستار یا داروساز خود اطلاع دهید:

- اگر مبتلا به التهاب ریوی هستید.
- اگر تاکنون مشکلات قلبی داشته‌اید؛ زیرا لازم است پزشک شرایط شما را به دقت پایش کند.
- اگر سابقه مشکلات چشمی دارید.

در طول درمان با مرتیسو® در صورت مواجهه با هر کدام از شرایط زیر، فوراً به پزشک خود اطلاع دهید:

- مشکل ناگهانی در نفس کشیدن همراه با سرفه یا تب
- جدا شدن لایه‌های سطح پوست
- ضربان سریع یا نامنظم قلب، سرگیجه، سبکی سر، تنگی نفس، احساس ناراحتی در قفسه سینه و غش کردن
- آبریزش، درد و قرمزی چشم‌ها، حساسیت به نور و تغییر در بینایی

آیا مرتیسو® در کودکان و نوجوانان قابل تجویز است؟

مصرف مرتیسو® در افراد کمتر از ۱۸ سال توصیه نمی‌شود؛ زیرا مطالعات کافی در خصوص مصرف آن در این گروه از بیماران وجود ندارد.

آیا مرتیسو® با سایر داروها تداخل دارد؟

بسیاری از داروها ممکن است با مرتیسو® 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.

داروهای زیر باعث کاهش اثربخشی مرتیسو® می‌شوند:

- فنی‌توئین، کاربامازپین، فنوباربیتال
- ریفابوتین، ریفامپیسین
- علف چای (Hypericum perforatum)

مرتیسو® باعث کاهش اثربخشی یا افزایش عوارض ناخواسته داروهای زیر می‌شود:

- رزوواستاتین
- قرص‌های هورمونی ضدبارداری خوراکی

- بوسنتان
- افاویرنز، اتراویرین
- مدافینیل
- دابیگاتران
- دیگوکسین
- آلیسکیرن

اگـر هـر یـک از داروهـای فـوق را اسـتفاده می‌کنیـد، پیـش از شـروع مصـرف مرتیسـو® بـه پزشـک خـود اطـلاع دهیـد. پزشـک در خصـوص گزینه‌هـای درمانی مناسـب شـما را

راهنمایـی خواهـد کرد.

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

پیشگیری از بارداری-خانم‌ها

اگـر در دوران بـارداری هسـتید یـا قصـد بـاردار شـدن داریـد، پیـش از مصـرف مرتیسـو® حتمـاً بـه پزشـک خـود اطـلاع دهیـد. در طـول درمـان بـا مرتیسـو® و حداقـل تـا ۲ ماه پـس از دریافـت آخریـن دوز دارو، بایـد از یـک روش پیشـگیری از بارداری مطمئن اسـتفاده کنیـد. در صورتـی کـه علی‌رغـم پیشـگیری از بـارداری، بـاردار شـدید حتمـاً بـه پزشـک

خـود اطـلاع دهیـد. پزشـک در مـورد ادامـه یا قطـع مصـرف مرتیسـو® شـما را راهنمایی خواهـد کرد.

اگـر از داروهـای خوراکـی هورمونـی بـرای پیشـگیری از بـارداری اسـتفاده می‌کنیـد، بـه پزشـک خـود اطـلاع دهید. زیرا مرتیسـو® می‌تواند اثربخشـی ایـن داروهـا را کاهش دهد. پزشـک در مـورد بهتریـن روش‌هـای پیشـگیری از بـارداری شـما را راهنمایـی می‌کند.

پیشگیری از بارداری-آقایان

مرتیسـو® داخـل مایـع منـی ترشـح می‌شـود؛ بنابرایـن آقایـان نیـز در طـول دوره درمان و حداقـل تـا ۴ مـاه پـس از دریافـت آخریـن دوز مرتیسـو® بایـد از یـک روش پیشـگیری از بـارداری مطمئـن اسـتفاده کننـد تـا از بارداری شـریک جنسـی خـود جلوگیـری کنند.

شیردهی

مرتیسـو® نباید در دوران شـیردهی مصرف شـود. در صورتی که پزشـک مصرف مرتیسـو® را بـرای شـما ضروری بدانـد، باید شـیردهی را متوقف کنید.

در خصـوص مـدت زمـان دقیـق مورد نیـاز برای عدم شـیردهی پس از مصـرف آخرین دوز دارو، با پزشـک خود مشـورت کنید.

آیـا در طـول مـدت مصـرف مرتیسـو® رانندگـی و کار با ماشـین‌آلات مجاز اسـت؟

مرتیسو® بر توانایی رانندگی و کار با ماشین‌آلات تأثیری نمی‌گذارد.

آیا مرتیسو® حاوی سدیم است؟

هر یک از قرص‌های ۴۰ میلی‌گرم و ۸۰ میلی‌گرم مرتیسو® حاوی کمتر از ۱ میلی‌مول (۲۳ میلی‌گرم) سدیم است، بنابراین می‌توان آن را فاقد سدیم در نظر گرفت.

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

مرتیسو® را دقیقاً مطابق دستور پزشک خود استفاده نمایید. در صورتی که سؤالی در مورد نحوه مصرف این دارو دارید، از پزشک یا داروساز خود بپرسید.

دوز پیشنهادی روزانه یک قرص ۸۰ میلی‌گرمی است. در صورت صلاحدید پزشک این

میزان ممکن است به ۴۰ میلی‌گرم کاهش یابد.

مرتیسو® را هر روز در زمان ثابتی با یا بدون غذا، همراه با یک لیوان آب مصرف نمایید. از خرد کردن، نصف کردن و یا جویدن قرص خودداری کنید.

اگر در بلع قرص مشکل دارید، می‌توانید طبق روش زیر آن را در آب حل کنید:

۱- قرص را داخل یک لیوان قرار دهید.

۲- ۵۰ میلی‌لیتر (حدود دو سوم لیوان) آب غیرگازدار به آن اضافه کنید. از سایر مایعات استفاده نکنید.

۳- تا زمانی که قرص به ذرات بسیار ریز تبدیل شود، محتویات لیوان را هم بزنید.

بـه خاطـر داشـته باشـید این قـرص به طـور کامل حل نمی‌شـود.

۴- بلافاصله محتویات لیوان را بنوشید.

۵- بـرای اطمینـان از مصـرف دوز کامـل، ۵۰ میلی‌لیتـر دیگـر آب به لیوان اضافـه کنید و پـس از چرخانـدن دور دیواره‌هـای لیوان، آن را بنوشـید.

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

اگـر دارو را بیشـتر از میـزان تجویـز شـده مصـرف کردید، بلافاصله به پزشـک خـود اطلاع دهیـد یـا بـه نزدیکترین مرکـز درمانی مراجعـه نمایید.

در صورت فراموشی مصرف مرتیسو® چه باید کرد؟

اگـر مصـرف یـک دوز از دارو را فرامـوش کردیـد، به محض یـادآوری آن را مصـرف نمایید. امـا اگـر کمتـر از ۱۲ سـاعت تـا زمان مصـرف دوز بعدی باقیمانـده بود، دوز فراموش شـده را مصـرف نکنیـد و بقیـه دوزهـا را طبق برنامه پیشـین مصـرف کنید.

اگر سؤال دیگری در مورد مصرف این دارو دارید، از پزشک یا داروساز خود بپرسید.

مرتیسو® ممکن است چه اثرات نامطلوبی داشته باشد؟

مرتیسـو® نیـز مانند سـایر داروهـا می‌تواند موجـب بروز عوارض ناخواسـته شـود. هر چند ایـن عـوارض در همـه افـراد مصرف‌کننده بـروز نخواهد کرد.

عوارض مهم و جدی

در صورتی که هر یک از عوارض زیر را تجربه کردید، بلافاصله به پزشک خود اطلاع دهید:

- بروز مشکل ناگهانی در نفس کشیدن همراه با سرفه یا تب. این علائم می‌تواند نشانه التهاب ریه باشد. هر چند بیشتر افرادی که دچار این عارضه می‌شوند، بهبود می‌یابند اما در مواردی ممکن است کشنده باشد. در صورت بروز این عارضه پزشک ممکن است مصرف مرتیسو® را قطع کند. میزان شیوع این عارضه ۱۰ درصد است.

- سندرم استیونس- جانسون. این عارضه غالباً با تب و علائم شبه آنفلوانزا شروع می‌شود و به دنبال آن ممکن است ضایعات پوستی قرمز رنگ همراه با تاول، جدا شدن لایه‌های سطح پوست، زخم در ناحیه دهان، گلو، بینی، چشم‌ها و ناحیه واژینال بروز کند. میزان شیوع این عارضه کمتر از ۰/۱ درصد است.
- تغییر در فعالیت الکتریکی قلب (طولانی شدن QTc) مانند ضربان قلب سریع یا نامنظم، سرگیجه، سبکی سر، تنگی نفس، احساس ناراحتی در قفسه سینه و غش کردن. میزان شیوع این عارضه کمتر از ۱ درصد است.

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

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

- اسهال. در صورت بروز اسهال شدید یا مداوم، به پزشک خود اطلاع دهید.
- مشکلات پوست و ناخن شامل درد، خشکی پوست، خارش، راش و قرمزی اطراف ناخن‌ها. این عوارض بیشتر در نواحی‌ای که در مواجهه با آفتاب قرار می‌گیرد، بروز می‌کند. مصرف منظم محصولات مرطوب‌کننده می‌تواند کمک‌کننده باشد. در صورت بدتر شدن علائم، به پزشک خود اطلاع دهید.
- استوماتیت (التهاب لایه داخلی دهان یا زخم‌های دهانی)

- کاهش اشتها
- کاهش تعداد گلبول‌های سفید خون
- کاهش تعداد پلاکت‌های خون

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

- خونریزی بینی
- نازک شدن مو
- کهیر

- سندرم دست و پا (Hand-foot syndrome)
- افزایش سطح کراتینین خون

عوارض غیر شایع (با شیوع کمتر از ۱٪) مرتیسو® عبارتند از:

- ضایعات پوستی شبیه حلقه یا به شکل حلقه (ممکن است نشانه اریتم مولتی فرم باشد.)
- التهاب عروق خونی پوست که می‌تواند به شکل کبودی یا قرمزی بروز کند.

عوارضی که در اینجا نام برده شده است شامل همه عوارض مرتیسو® نمی‌شوند. جهت کسب اطلاعات بیشتر در این زمینه از پزشک یا داروساز خود کمک

بگیرید. ضمناً عوارض جانبی دارو به طور کامل در قسمت انگلیسی دفترچه راهنما آورده شده است.

مرتیسو® را در چه شرایطی باید نگهداری کرد؟

دارو را دور از دید و دسترس کودکان نگهداری نمایید.

مرتیسو® نباید بعد از تاریخ انقضایی که بر روی آن درج شده است، مصرف شود.

جهت محافظت از رطوبت، مرتیسو® را تا زمان مصرف در بسته‌بندی اصلی نگهداری نمایید.

مرتیسو® را در دمای کمتر از ۳۰ درجه سانتی‌گراد نگهداری نمایید.

این دارو سایتوتوکسیک است. مطابق با دستورالعمل داروهای سایتوتوکسیک حمل، نگهداری و مصرف شود.

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، سؤال کنید. این اقدامات به حفاظت از محیط زیست کمک می‌کند.

مرتیسو® از چه اجزایی تشکیل شده است و بسته‌بندی آن چگونه است؟

ماده مؤثره مرتیسو®، اُسیمرتینیب (به صورت مزیلات) است.

هر قرص مرتیسو® ۴۰، حاوی ۴۰ میلی‌گرم اُسیمرتینیب (به صورت مزیلات) است.

هر قرص مرتیسو® ۸۰، حاوی ۸۰ میلی‌گرم اُسیمرتینیب (به صورت مزیلات) است.

سایر مواد تشکیل دهنده مرتیسو® عبارتند از:

مانیتول، میکروکریستالین سلولز، هیدروکسی پروپیل سلولز، سدیم استئاریل فومارات

۳۰ عدد قرص مرتیسو® به صورت ۳ بلیستر ۱۰ عددی به همراه یک دفترچه راهنما در یک جعبه بسته‌بندی می‌گردد.

تاریخ آخرین بازنگری: نوامبر ۲۰۲۱ برابر با آذر 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

01.07.25. 07

Mertisso®

Osimertinib

Film-coated Tablet

1. NAME OF THE MEDICINAL PRODUCT

Mertisso® 40 mg film-coated tablets

Mertisso® 80 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Mertisso® 40 mg tablets

Each tablet contains 40 mg osimertinib (as mesylate).

Mertisso® 80 mg tablets

Each tablet contains 80 mg osimertinib (as mesylate).

Excipient with known effect

This medicine contains 0.3 mg sodium per 40 mg tablet and 0.6 mg sodium per 80 mg tablet. For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Osimertinib as monotherapy is indicated for:

- the adjuvant treatment after complete tumor resection in

adult patients with stage IB-IIIA non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations.

- the first-line treatment of adult patients with locally advanced or metastatic NSCLC with activating EGFR mutations.
- the treatment of adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC.

4.2. Posology and method of administration

Treatment with osimertinib should be initiated by a physician experienced in the use of anticancer therapies.

When considering the use of osimertinib, EGFR mutation status (in tumor specimens for adjuvant treatment and tumor or plasma specimens for locally advanced or metastatic setting) should be determined using a validated test method (see section 4.4).

Posology

The recommended dose is 80 mg osimertinib once a day.

Patients in the adjuvant setting should receive treatment until disease recurrence or unacceptable toxicity. Treatment duration for more than 3 years was not studied.

Patients with locally advanced or metastatic lung cancer should receive treatment until disease progression or unacceptable toxicity.

If a dose of osimertinib is missed, the dose should be made up unless the next dose is due within 12 hours.

Osimertinib can be taken with or without food at the same time each day.

Dose adjustments

Dosing interruption and/or dose reduction may be required based on individual safety and tolerability. If dose reduction is necessary, then the dose should be reduced to

40 mg taken once daily.

Dose reduction guidelines for adverse reactions toxicities are provided in Table 1.

Table 1. Recommended dose modifications for osimertinib

Target organ	Adverse reaction[a]	Dose modification
Pulmonary	ILD/Pneumonitis	Discontinue osimertinib (see Section 4.4)
Cardiac	QTc interval greater than 500 msec on at least 2 separate ECGs	Withhold osimertinib until QTc interval is less than 481 msec or recovery to baseline if baseline QTc is greater than or equal to 481 msec, then restart at a reduced dose (40 mg)
	QTc interval prolongation with signs/symptoms of serious arrhythmia	Permanently discontinue osimertinib

Other	Grade 3 or higher adverse reaction	Withhold osimertinib for up to 3 weeks
	If Grade 3 or higher adverse reaction improves to Grade 0-2 after withholding of osimertinib for up to 3 weeks	Osimertinib may be restarted at the same dose (80 mg) or a lower dose (40 mg)
	Grade 3 or higher adverse reaction that does not improve to Grade 0-2 after withholding for up to 3 weeks	Permanently discontinue osimertinib

[a] Note: The intensity of clinical adverse events graded by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

ECGs: Electrocardiograms; QTc: QT interval corrected for heart rate

Special populations

No dosage adjustment is required due to patient age, body weight, gender, ethnicity and smoking status (see section 5.2).

Hepatic impairment

Based on clinical studies, no dose adjustments are necessary in patients with mild hepatic impairment (Child Pugh A) or moderate hepatic impairment (Child Pugh B). Similarly, based on population pharmacokinetic analysis, no dose adjustment is recommended in patients with mild hepatic impairment (total bilirubin ≤upper limit of normal (ULN) and aspartate aminotransferase (AST) >ULN or total bilirubin >1.0 to 1.5x ULN and any AST) or moderate

hepatic impairment (total bilirubin between 1.5 to 3 times ULN and any AST). The safety and efficacy of this medicinal product has not been established in patients with severe hepatic impairment. Until additional data become available, use in patients with severe hepatic impairment is not recommended (see section 5.2).

Renal impairment

Based on clinical studies and population PK analysis, no dose adjustments are necessary in patients with mild,

moderate, or severe renal impairment. The safety and efficacy of this medicinal product has not been established in patients with end-stage renal disease [creatinine clearance (CLcr) less than 15 ml/min, calculated by the Cockcroft and Gault equation], or on dialysis. Caution should be exercised when treating patients with severe and end-stage renal impairment (see section 5.2).

Pediatric population

The safety and efficacy of osimertinib in children or

adolescents aged less than 18 years have not been established. No data are available.

Method of administration

This medicinal product is for oral use. The tablet should be swallowed whole with water and it should not be crushed, split or chewed.

If the patient is unable to swallow the tablet, the tablet may first be dispersed in 50 ml of non-carbonated water.

It should be dropped in the water, without crushing, stirred until dispersed and immediately swallowed. An additional half a glass of water should be added to ensure that no residue remains and then immediately swallowed. No other liquids should be added.

If administration via naso-gastric tube is required, the same process as above should be followed but using volumes of 15 ml for the initial dispersion and 15 ml for the residue rinses. The resulting 30 ml of liquid should be

administered as per the naso-gastric tube manufacturer's instructions with appropriate water flushes. The dispersion and residues should be administered within 30 minutes of the addition of the tablets to water.

4.3. Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- St. John's Wort should not be used together with

osimertinib (see section 4.5).

4.4. Special warnings and precautions for use

Assessment of EGFR mutation status

When considering the use of osimertinib as adjuvant treatment after complete tumor resection in patients with NSCLC, it is important that the EGFR mutation positive status (exon 19 deletions (Ex19del) or exon 21 L858R substitution mutations (L858R)) indicates treatment eligibility. A validated

test should be performed in a clinical laboratory using tumor tissue DNA from biopsy or surgical specimen.

When considering the use of osimertinib as a treatment for locally advanced or metastatic NSCLC, it is important that the EGFR mutation positive status is determined. A validated test should be performed using either tumor DNA derived from a tissue sample or circulating tumor DNA (ctDNA) obtained from a plasma sample.

Positive determination of EGFR mutation status (activating

EGFR mutations for first-line treatment or T790M mutations following progression on or after EGFR TKI therapy) using either a tissue-based or plasma-based test indicates eligibility for treatment with osimertinib. However, if a plasma-based ctDNA test is used and the result is negative, it is advisable to follow-up with a tissue test wherever possible due to the potential for false negative results using a plasma-based test.

Only robust, reliable and sensitive tests with demonstrated

utility for the determination of EGFR mutation status should be used.

Interstitial Lung Disease (ILD)

Severe, life-threatening or fatal Interstitial Lung Disease (ILD) or ILD-like adverse reactions (e.g. pneumonitis) have been observed in patients treated with osimertinib in clinical studies. Most cases improved or resolved with interruption of treatment. Patients with a past medical history of ILD, drug-induced ILD, radiation pneumonitis that required

steroid treatment, or any evidence of clinically active ILD were excluded from clinical studies (see section 4.8).

ILD or ILD-like adverse reactions were reported in 3.7% of the 1479 patients who received osimertinib in the ADAURA, FLAURA and AURA studies. Five fatal cases were reported in the locally advanced or metastatic setting. No fatal cases were reported in the adjuvant setting. The incidence of ILD was 10.9% in patients of Japanese ethnicity, 1.6% in patients of Asian ethnicity and 2.5% in non-Asian patients (see section 4.8).

Careful assessment of all patients with an acute onset and/or unexplained worsening of pulmonary symptoms (dyspnea, cough, fever) should be performed to exclude ILD. Treatment with this medicinal product should be interrupted pending investigation of these symptoms. If ILD is diagnosed, osimertinib should be discontinued and appropriate treatment initiated as necessary. Reintroduction of osimertinib should be considered only after careful consideration of the individual patient's benefits and risk.

Stevens-Johnson syndrome

Case reports of Stevens-Johnson syndrome (SJS) have been reported rarely in association with osimertinib treatment. Before initiating treatment, patients should be advised of signs and symptoms of SJS. If signs and symptoms suggestive of SJS appear, osimertinib should be interrupted or discontinued immediately.

QTc interval prolongation

QTc interval prolongation occurs in patients treated with osimertinib. QTc interval prolongation may lead to an increased risk for ventricular tachyarrhythmias (e.g. torsade de pointes) or sudden death. No arrhythmic events were reported in ADAURA, FLAURA or AURA studies (see section 4.8). Patients with clinically important abnormalities in rhythm and conduction as measured by resting electrocardiogram (ECG) (e.g. QTc interval greater than 470 msec) were

excluded from these studies (see section 4.8).

When possible, the use of osimertinib in patients with congenital long QT syndrome should be avoided. Periodic monitoring with electrocardiograms (ECGs) and electrolytes should be considered in patients with congestive heart failure, electrolyte abnormalities, or those who are taking medicinal products that are known to prolong the QTc interval. Treatment should be withheld in patients who develop a QTc interval greater than 500 msec on at least 2 separate ECGs until the

QTc interval is less than 481 msec or recovery to baseline if the QTc interval is greater than or equal to 481 msec, then resume osimertinib at a reduced dose as described in Table 1. Osimertinib should be permanently discontinued in patients who develop QTc interval prolongation in combination with any of the following: Torsade de pointes, polymorphic ventricular tachycardia, signs/symptoms of serious arrhythmia.

Changes in cardiac contractility

Across clinical trials, Left Ventricular Ejection Fraction (LVEF)

decreases greater than or equal to 10 percentage points and a drop to less than 50% occurred in 3.2% (40/1233) of patients treated with osimertinib who had baseline and at least one follow-up LVEF assessment. In patients with cardiac risk factors and those with conditions that can affect LVEF, cardiac monitoring, including an assessment of LVEF at baseline and during treatment, should be considered. In patients who develop relevant cardiac signs/symptoms during treatment, cardiac monitoring including LVEF assessment should be considered. In an adjuvant placebo-

controlled trial (ADAURA), 1.6% (5/312) of patients treated with osimertinib and 1.5% (5/331) of patients treated with placebo experienced LVEF decreases greater than or equal to 10 percentage points and a drop to less than 50%.

Keratitis

Keratitis was reported in 0.7% (n=10) of the 1479 patients treated with osimertinib in the ADAURA, FLAURA and AURA studies. Patients presenting with signs and symptoms suggestive of keratitis such as acute or worsening: eye

inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmology specialist (see section 4.2 Table 1).

Age and body weight

Elderly patients (>65 years) or patients with low body weight (<50 kg) may be at increased risk of developing adverse events of Grade 3 or higher. Close monitoring is recommended in these patients (see section 4.8).

Sodium

This medicine contains <1 mmol sodium (23 mg) per 40 mg or 80 mg tablet, that is to say essentially "sodium-free".

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

Pharmacokinetic interactions

Strong CYP3A4 inducers can decrease the exposure of osimertinib. Osimertinib may increase the exposure of

breast cancer resistant protein (BCRP) and P-glycoprotein (P-gp) substrates.

Active substances that may increase osimertinib plasma concentrations

In vitro studies have demonstrated that the Phase I metabolism of osimertinib is predominantly via CYP3A4 and CYP3A5. In a clinical pharmacokinetic study in patients, co-administration with 200 mg itraconazole twice daily (a strong CYP3A4 inhibitor) had no clinically significant effect on the exposure

of osimertinib (area under the curve (AUC) increased by 24% and C_{max} decreased by 20%). Therefore, CYP3A4 inhibitors are not likely to affect the exposure of osimertinib. Further catalyzing enzymes have not been identified.

Active substances that may decrease osimertinib plasma concentrations

In a clinical pharmacokinetic study in patients, the steady-state AUC of osimertinib was reduced by 78% when co-administered with rifampicin (600 mg daily for

21 days). Similarly, the exposure to metabolite AZ5104 decreased by 82% for the AUC and 78% for C_{max}. It is recommended that concomitant use of strong CYP3A inducers (e.g. phenytoin, rifampicin and carbamazepine) with osimertinib should be avoided. Moderate CYP3A4 inducers (e.g. bosentan, efavirenz, etravirine, modafinil) may also decrease osimertinib exposure and should be used with caution, or avoided when possible. There are no clinical data available to recommend a dose adjustment of osimertinib. Concomitant use of St. John's Wort is

contraindicated (see section 4.3).

Effect of gastric acid reducing active substances on osimertinib

In a clinical pharmacokinetic study, co-administration of omeprazole did not result in clinically relevant changes in osimertinib exposures. Gastric pH modifying agents can be concomitantly used with osimertinib without any restrictions.

Active substances whose plasma concentrations may be altered by osimertinib

Based on *in vitro* studies, osimertinib is a competitive inhibitor of BCRP transporters.

In a clinical PK study, co-administration of osimertinib with rosuvastatin (sensitive BCRP substrate) increased the AUC and C_{max} of rosuvastatin by 35% and 72%, respectively. Patients taking concomitant medications with disposition dependent upon BCRP and with narrow therapeutic index

should be closely monitored for signs of changed tolerability of the concomitant medication as a result of increased exposure whilst receiving osimertinib (see section 5.2).

In a clinical PK study, co-administration of osimertinib with simvastatin (sensitive CYP3A4 substrate) decreased the AUC and C_{max} of simvastatin by 9% and 23% respectively. These changes are small and not likely to be of clinical significance. Clinical PK interactions with CYP3A4 substrates are unlikely. A risk for decreased exposure of

hormonal contraceptives cannot be excluded.

In a clinical Pregnane X Receptor (PXR) interaction study, co-administration of osimertinib with fexofenadine (P-gp substrate) increased the AUC and C_{max} of fexofenadine by 56% (90% CI 35, 79) and 76% (90% CI 49, 108) after a single dose and 27% (90% CI 11, 46) and 25% (90% CI 6, 48) at steady-state, respectively. Patients taking concomitant medications with disposition dependent upon P-gp and with narrow therapeutic index (e.g. digoxin, dabigatran, aliskiren)

should be closely monitored for signs of changed tolerability as a result of increased exposure of the concomitant medication whilst receiving osimertinib (see section 5.2).

4.6. Fertility, pregnancy and lactation

Contraception in males and females

Women of childbearing potential should be advised to avoid becoming pregnant while receiving osimertinib. Patients should be advised to use effective contraception

for the following periods after completion of treatment with this medicinal product: at least 2 months for females and 4 months for males. A risk for decreased exposure of hormonal contraceptives cannot be excluded.

Pregnancy

There are no or limited amount of data from the use of osimertinib in pregnant women. Studies in animals have shown reproductive toxicity (embryo lethality, reduced fetal growth, and neonatal death, see section 5.3). Based on its mechanism

of action and preclinical data, osimertinib may cause fetal harm when administered to a pregnant woman. Osimertinib should not be used during pregnancy unless the clinical condition of the woman requires treatment with osimertinib.

Breast-feeding

It is not known whether osimertinib or its metabolites are excreted in human milk. There is insufficient information on the excretion of osimertinib or its metabolites in animal milk. However, osimertinib and its metabolites were

detected in the suckling pups and there were adverse effects on pup growth and survival (see section 5.3). A risk to the suckling child cannot be excluded.

Breast-feeding should be discontinued during treatment with osimertinib.

Fertility

There are no data on the effect of osimertinib on human fertility. Results from animal studies have shown that

osimertinib has effects on male and female reproductive organs and could impair fertility (see section 5.3).

4.7. Effects on ability to drive and use machines

Osimertinib has no or negligible influence on the ability to drive and use machines.

4.8. Undesirable effects

Summary of the safety profile

Studies in EGFR mutation-positive NSCLC patients

The data described below reflect exposure to osimertinib in 1479 patients with EGFR mutation-positive non-small cell lung cancer. These patients received osimertinib at a dose of 80 mg daily in three randomized Phase 3 studies (ADAURA, adjuvant; FLAURA, first line and AURA3, second line only), two single-arm studies (AURAex and AURA2, second line or later) and one Phase 1 study (AURA1, first-line or later). Most adverse reactions were Grade 1 or 2 in severity. The most commonly reported adverse drug reactions (ADRs) were diarrhea (47%), rash (45%), paronychia (33%), dry skin (32%), and stomatitis (24%). Grade 3 and Grade 4 adverse reactions across the studies were 10% and 0.1%, respectively. In patients treated with osimertinib 80 mg once daily, dose reductions due to adverse reactions occurred in 3.4% of the patients. Discontinuation due to adverse reactions was 4.8%.

Patients with a medical history of ILD, drug-induced ILD, radiation pneumonitis that required steroid treatment, or any evidence of clinically active ILD were excluded from clinical studies. Patients with clinically important abnormalities in rhythm and conduction as measured by resting electrocardiogram (ECG) (e.g. QTc interval greater than 470 msec) were excluded from these studies. Patients were evaluated for LVEF at screening and every 12 weeks thereafter.

Tabulated list of adverse reactions

Adverse reactions have been assigned to the frequency categories in Table 2 where possible based on the incidence of comparable adverse event reports in a pooled dataset from the 1479 EGFR mutation positive NSCLC patients who received osimertinib at a dose of 80 mg daily in the ADAURA, FLAURA, AURA3, AURAex, AURA 2 and AURA1 studies.

Adverse reactions are listed according to system organ class (SOC) in MedDRA. 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 reaction is based on the CIOMS III convention and is defined as: 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); not known (cannot be estimated from available data).

Table 2. Adverse reactions reported in ADAURA, FLAURA and AURA studies[a]

MedDRA SOC	MedDRA term	CIOMS descriptor overall frequency (all CTCAE grades)[b]	Frequency of CTCAE grade 3 or higher [b]
Metabolism and nutrition disorders	Decreased appetite	Very common (19%)	1.1%

Respiratory, thoracic and mediastinal disorders	Epistaxis	Common (5%)	0
	Interstitial lung disease[c]	Common (3.7%)[d]	1.1%

Gastrointestinal disorders	Diarrhea	Very common (47%)	1.4%
	Stomatitis[e]	Very common (24%)	0.5%
Eye disorders	Keratitis[f]	Uncommon (0.7%)	0.1%

Skin and subcutaneous tissue disorders	Rash[g]	Very common (45%)	0.7%
	Paronychia[h]	Very common (33%)	0.4%
	Dry skin[i]	Very common (32%)	0.1%
	Pruritus[j]	Very common (17%)	0.1%

Skin and subcutaneous tissue disorders	Alopecia	Common (4.6%)	0
	Urticaria	Common (1.9%)	0.1%
	Palmar-plantar erythrodysaesthesia syndrome	Common (1.7%)	0

Skin and subcutaneous tissue disorders	Erythema multiforme[k]	Uncommon (0.3%)	0
	Cutaneous vasculitis[l]	Uncommon (0.3%)	0
	Stevens-Johnson syndrome[m]	Rare (0.02%)	

Investigations	QTc interval prolongation[n]	Uncommon (0.8%)	
Findings based on test results presented as CTCAE grade shifts	Leucocytes decreased[o]	Very common (65%)	1.2%
	Lymphocytes decreased[o]	Very common (62%)	6.1%

Findings based on test results presented as CTCAE grade shifts	Platelet count decreased°	Very common (53%)	1.2%
	Neutrophils decreased°	Very common (33%)	3.2%
	Blood creatinine increased°	Common (9%)	0

[a] Data is pooled from ADAURA, FLAURA and AURA (AURA3, AURAex, AURA 2 and AURA1) studies; only events for patients receiving at least one dose of osimertinib as their randomized treatment are summarized.

[b] National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

[c] Includes: interstitial lung disease, pneumonitis.

[d] 5 CTCAE grade 5 events (fatal) were reported.

[e] Includes: mouth ulceration, stomatitis.

[f] Includes: corneal epithelium defect, corneal erosion, keratitis, punctate keratitis.

[g] Includes: acne, dermatitis, dermatitis acneiform, drug eruption, erythema, folliculitis, pustule, rash, rash erythematous, rash follicular, rash generalized,

rash macular, rash maculo-papular, rash popular, rash pustular, rash pruritic, rash vesicular, skin erosion.

[h] Includes: nail bed disorder, nail bed infection, nail bed inflammation, nail discoloration, nail disorder, nail dystrophy, nail infection, nail pigmentation, nail ridging, nail toxicity, onychalgia, onycholysis, onychomadesis, onychomalacia, paronychia.

[i] Includes: dry skin, eczema, skin fissures, xeroderma, xerosis.

[j] Includes: eyelid pruritus, pruritus, pruritus generalized.

[k] Five of the 1479 patients in the ADAURA, AURA and FLAURA studies reported erythema multiforme. Post-marketing reports of erythema multiforme have also been received, including 7 reports from a post-marketing surveillance study (N=3578).

[l] Estimated frequency. The upper limit of the 95% CI for the point estimate is 3/1142 (0.3%).

[m] One event was reported in a post-marketing study, and the frequency has been derived from the ADAURA, FLAURA and AURA studies and the post-marketing study (N=5057).

[n] Represents the incidence of patients who had a QTcF prolongation >500 msec.

[o] Represents the incidence of laboratory findings, not of reported adverse events.

Description of selected adverse reactions

Interstitial lung disease (ILD)

In the ADAURA, FLAURA and AURA studies, the incidence of ILD was 11% in patients of Japanese ethnicity, 1.6% in patients of non-Japanese Asian ethnicity and 2.5% in non-Asian patients. The median time to onset of ILD or ILD-like adverse reactions was 84 days (see section 4.4).

QTc interval prolongation

Of the 1479 patients in ADAURA, FLAURA and AURA studies treated with osimertinib 80 mg, 0.8% of patients (n=12) were found to have a QTc greater than 500 msec, and 3.1% of patients (n=46) had an increase from baseline QTc greater than 60 msec. A pharmacokinetic/pharmacodynamic analysis with osimertinib predicted a concentration-dependent increase in QTc interval prolongation. No QTc-related arrhythmias were reported in the ADAURA, FLAURA or AURA

studies (see sections 4.4 and 5.1).

Gastrointestinal effects

In the ADAURA, FLAURA and AURA studies, diarrhea was reported in 47% of patients of which 38% were Grade 1 events, 7.9% Grade 2 and 1.4% were Grade 3; no Grade 4 or 5 events were reported. Dose reduction was required in 0.3% of patients and dose interruption in 2%. Four events (0.3%) led to discontinuation. In ADAURA, FLAURA and AURA3 the median time to onset was 22 days, 19 days and

22 days, respectively, and the median duration of the Grade 2 events was 11 days, 19 days and 6 days, respectively.

Hematological events

Early reductions in the median laboratory counts of leukocytes, lymphocytes, neutrophils and platelets have been observed in patients treated with osimertinib, which stabilized over time and then remained above the lower limit of normal. Adverse events of leukopenia, lymphopenia, neutropenia and thrombocytopenia have been reported,

most of which were mild or moderate in severity and did not lead to dose interruptions.

Elderly

In ADAURA, FLAURA and AURA3 (N=1479), 43% of patients were 65 years of age and older, and 12% were 75 years of age and older. Compared with younger subjects (<65), more subjects ≥65 years old had reported adverse reactions that led to study drug dose modifications (interruptions or reductions) (16% versus 9%). The types

of adverse events reported were similar regardless of age. Older patients reported more Grade 3 or higher adverse reactions compared to younger patients (13% versus 8%). No overall differences in efficacy were observed between these subjects and younger subjects. A consistent pattern in safety and efficacy results was observed in the analysis of AURA Phase 2 studies.

Low body weight

Patients receiving osimertinib 80 mg with low body weight

(<50 kg) reported higher frequencies of Grade ≥3 adverse events (46% versus 31%) and QTc prolongation (12% versus 5%) than patients with higher body weight (≥50 kg).

4.9. Overdose

In osimertinib clinical trials a limited number of patients were treated with daily doses of up to 240 mg without dose limiting toxicities. In these studies, patients who were treated with osimertinib daily doses of 160 mg and 240 mg experienced an increase in the frequency

and severity of a number of typical EGFR TKI-induced AEs (primarily diarrhea and skin rash) compared to the 80 mg dose. There is limited experience with accidental overdoses in humans. All cases were isolated incidents of patients taking an additional daily dose of osimertinib in error, without any resulting clinical consequences.

There is no specific treatment in the event of osimertinib overdose. In case of suspected overdose, osimertinib should be withheld and symptomatic treatment initiated.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, protein kinase inhibitors; ATC code: L01EB04.

Mechanism of action

Osimertinib is a Tyrosine Kinase Inhibitor (TKI). It is an irreversible inhibitor of Epidermal Growth Factor Receptors (EGFRs) harboring sensitizing-mutations

(EGFRm) and TKI-resistance mutation T790M.

Pharmacodynamic effects

In vitro studies have demonstrated that osimertinib has high potency and inhibitory activity against EGFR across a range of all clinically relevant EGFR sensitizing-mutant and T790M mutant non-small cell lung cancer (NSCLC) cell lines (apparent IC50s from 6 nM to 54 nM against phospho-EGFR). This leads to inhibition of cell growth, while showing significantly less activity against EGFR in wild-type

cell lines (apparent IC50s from 480 nM to 1.8 μM against phospho-EGFR). *In vivo* oral administration of osimertinib lead to tumor shrinkage in both EGFRm and T790M NSCLC xenograft and transgenic mouse lung tumor models.

Cardiac electrophysiology

The QTc interval prolongation potential of osimertinib was assessed in 210 patients who received osimertinib 80 mg daily in AURA2. Serial ECGs were collected following a single dose and at steady-state to

evaluate the effect of osimertinib on QTc intervals. A pharmacokinetic/pharmacodynamic analysis predicted a drug-related QTc interval prolongation at 80 mg of 14 msec with an upper bound of 16 msec (90% CI).

5.2 Pharmacokinetic properties

Osimertinib pharmacokinetic parameters have been characterized in healthy subjects and NSCLC patients. Based on population pharmacokinetic analysis, osimertinib apparent plasma clearance is 14.3 l/h, apparent volume of

distribution is 918 l and terminal half-life of approximately 44 hours. The AUC and Cmax increased dose proportionally over 20 to 240 mg dose range. Administration of osimertinib once daily results in approximately 3-fold accumulation with steady-state exposures achieved by 15 days of dosing. At steady-state, circulating plasma concentrations are typically maintained within a 1.6-fold range over the 24-hour dosing interval.

Absorption

Following oral administration of osimertinib, peak plasma concentrations of osimertinib were achieved with a median (min-max) t_{max} of 6 (3-24) hours, with several peaks observed over the first 24 hours in some patients. The absolute bioavailability of osimertinib is 70% (90% CI 67, 73). Based on a clinical pharmacokinetic study in patients at 80 mg, food does not alter osimertinib bioavailability to a clinically meaningful extent. (AUC increase by 6% (90% CI -5, 19) and

C_{max} decrease by 7% (90% CI -19, 6)). In healthy volunteers administered an 80 mg tablet where gastric pH was elevated by dosing of omeprazole for 5 days, osimertinib exposure was not affected (AUC and C_{max} increase by 7% and 2%, respectively) with the 90% CI for exposure ratio contained within the 80-125% limit.

Distribution

Population estimated mean volume of distribution at steady-state (V_{ss}/F) of osimertinib is 918 l indicating

extensive distribution into tissue. In vitro plasma protein binding of osimertinib is 94.7% (5.3% free). Osimertinib has also been demonstrated to bind covalently to rat and human plasma proteins, human serum albumin and rat and human hepatocytes.

Biotransformation

In vitro studies indicate that osimertinib is metabolized predominantly by CYP3A4, and CYP3A5. However, with current available data, alternative metabolic pathways

cannot be fully ruled out. Based on *in vitro* studies, 2 pharmacologically active metabolites (AZ7550 and AZ5104) have subsequently been identified in the plasma of preclinical species and in humans after oral dosing with osimertinib; AZ7550 showed a similar pharmacological profile to osimertinib while AZ5104 showed greater potency across both mutant and wild-type EGFR. Both metabolites appeared slowly in plasma after administration of osimertinib to patients, with a median (min-max) t_{max} of 24 (4-72) and 24 (6-72) hours, respectively. In human plasma, parent

osimertinib accounted for 0.8%, with the 2 metabolites contributing 0.08% and 0.07% of the total radioactivity with the majority of the radioactivity being covalently bound to plasma proteins. The geometric mean exposure of both AZ5104 and AZ7550, based on AUC, was approximately 10% each of the exposure of osimertinib at steady-state.

The main metabolic pathway of osimertinib was oxidation and dealkylation. At least 12 components were observed in the pooled urine and fecal samples in humans with

5 components accounting for >1% of the dose of which unchanged osimertinib, AZ5104 and AZ7550, accounted for approximately 1.9, 6.6 and 2.7% of the dose while a cysteinyl adduct (M21) and an unknown metabolite (M25) accounted for 1.5% and 1.9% of the dose, respectively.

Based on in vitro studies, osimertinib is a competitive inhibitor of CYP 3A4/5 but not CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, and 2E1 at clinically relevant concentrations. Based on in vitro studies, osimertinib is not an inhibitor of

UGT1A1 and UGT2B7 at clinically relevant concentrations hepatically. Intestinal inhibition of UGT1A1 is possible but the clinical impact is unknown.

Elimination

Following a single oral dose of 20 mg, 67.8% of the dose was recovered in feces (1.2% as parent) while 14.2% of the administered dose (0.8% as parent) was found in urine by 84 days of sample collection. Unchanged osimertinib accounted for approximately 2% of the elimination with

0.8% in urine and 1.2% in feces.

Interactions with transport proteins

In vitro studies have shown that osimertinib is not a substrate of OATP1B1 and OATP1B3. In vitro, osimertinib does not inhibit OAT1, OAT3, OATP1B1, OATP1B3, MATE1, OCT2, and MATE2K at clinically relevant concentrations.

Based on in vitro studies osimertinib is a substrate of P-gp and BCRP but at clinical doses, clinically relevant

interactions are unlikely. Based on in vitro data, osimertinib is an inhibitor of BCRP and P-gp (see section 4.5).

Special populations

In a population based pharmacokinetic analyses (n=1367), no clinically significant relationships were identified between predicted steady-state exposure (AUC_{ss}) and patient's age (range: 25 to 91 years), gender (65% female), ethnicity (including White, Asian, Japanese, Chinese and non-Asian-non-White patients), line of therapy and smoking

status (n=34 current smokers, n=419 former smokers).

Population PK analysis indicated that body weight was a significant covariate with a less than 20% change in osimertinib AUC_{ss} expected across a body weight range of 88 kg to 43 kg respectively (95% to 5% quantiles) when compared to the AUC_{ss} for the median body weight of 61 kg. Taking the extremes of body weight into consideration, from <43 kg to >88 kg, AZ5104 metabolite ratios ranged from 11.8% to 9.6% while for AZ7550 it ranged from 12.8% to 8.1%,

respectively. Based on population PK analysis, serum albumin was identified as a significant covariate with a <30% change in osimertinib AUC_{ss} expected across the albumin range of 29 to 46 g/l respectively (95% to 5% quantiles) when compared to the AUC_{ss} for the median baseline albumin of 39 g/l. These exposure changes due to body weight or baseline albumin differences are not considered clinically relevant.

Hepatic impairment

Osimertinib is eliminated mainly via the liver. In a clinical

trial, patients with different types of advanced solid tumors and with mild hepatic impairment (Child Pugh A, mean score=5.3, n=7) or moderate hepatic impairment (Child Pugh B, mean score=8.2, n=5) had no increase in exposure compared to patients with normal hepatic function (n=10) after a single 80 mg dose of osimertinib. The geometric mean ratio (90% CI) of osimertinib AUC and C_{max} was 63.3% (47.3, 84.5) and 51.4% (36.6, 72.3) in patients with mild hepatic impairment and 68.4% (49.6, 94.2) and 60.7% (41.6, 88.6) in patients with moderate hepatic impairment; for the

metabolite AZ5104 the AUC and C_{max} were 66.5% (43.4, 101.9) and 66.3% (45.3, 96.9) in patients with mild hepatic impairment and 50.9% (31.7, 81.6) and 44.0% (28.9, 67.1) in patients with moderate hepatic impairment, compared to the exposure in patients with normal hepatic function. Based on population PK analysis, there was no relationship between markers of hepatic function (ALT, AST, bilirubin) and osimertinib exposure. The hepatic impairment marker serum albumin showed an effect on the PK of osimertinib. Clinical studies that were conducted excluded patients

with AST or ALT >2.5x upper limit of normal (ULN), or if due to underlying malignancy, >5.0x ULN or with total bilirubin >1.5x ULN. Based on a pharmacokinetic analysis of 134 patients with mild hepatic impairment, 8 patients with moderate hepatic impairment and 1216 patients with normal hepatic function osimertinib exposures were similar. There are no data available on patients with severe hepatic impairment (see section 4.2).

Renal impairment

In a clinical trial, patients with severe renal impairment (CLcr 15 to less than 30 ml/min; n=7) compared to patients with normal renal function (CLcr greater than or equal to 90 ml/min; n=8) after a single 80 mg oral dose of osimertinib showed a 1.85-fold increase in AUC (90% CI; 0.94, 3.64) and a 1.19-fold increase in C_{max} (90% CI: 0.69, 2.07). Furthermore, based on a population pharmacokinetic analysis of 593 patients with mild renal impairment (CLcr 60

to less than 90 ml/min), 254 patients with moderate renal impairment (CLcr 30 to less than 60 ml/min), 5 patients with severe renal impairment (CLcr 15 to less than 30 ml/min) and 502 patients with normal renal function (CLcr greater than or equal to 90 ml/min), osimertinib exposures were similar. Patients with CLcr less than or equal to 10 ml/min were not included in the clinical trials.

5.3. Preclinical safety data

The main findings observed in repeat dose toxicity studies

in rats and dogs comprised atrophic, inflammatory and/or degenerative changes affecting the epithelia of the cornea (accompanied by corneal translucencies and opacities in dogs at ophthalmology examination), GI tract (including tongue), skin, and male and female reproductive tracts with secondary changes in spleen. These findings occurred at plasma concentrations that were below those seen in patients at the 80 mg therapeutic dose. The findings present following 1 month of dosing were largely reversible within 1 month of cessation of dosing with the exception of partial

recovery for some of the corneal changes.

Osimertinib penetrated the intact blood-brain barrier of the cynomolgus monkey (i.v. dosing), rat and mouse (oral administration).

Non-clinical data indicate that osimertinib and its metabolite (AZ5104) inhibit the h-ERG channel, and QTc prolonging effect cannot be excluded.

Osimertinib did not cause genetic damage in *in vitro* and *in vivo*

assays. Osimertinib showed no carcinogenic potential when administered orally to Tg rasH2 transgenic mice for 26 weeks.

Reproductive toxicity

Degenerative changes were present in the testes in rats and dogs exposed to osimertinib for ≥1 month and there was a reduction in male fertility in rats following exposure to osimertinib for 3 months. These findings were seen at clinically relevant plasma concentrations. Pathology findings in the testes seen following 1 month dosing

were reversible in rats; however, a definitive statement on reversibility of these lesions in dogs cannot be made.

Based on studies in animals, female fertility may be impaired by treatment with osimertinib. In repeat dose toxicity studies, an increased incidence of anestrus, corpora lutea degeneration in the ovaries and epithelial thinning in the uterus and vagina were seen in rats exposed to osimertinib for ≥1 month at clinically relevant plasma concentrations. Findings in the ovaries seen following 1

month dosing were reversible. In a female fertility study in rats, administration of osimertinib at 20 mg/kg/day (approximately equal to the recommended daily clinical dose of 80 mg) had no effects on estrus cycling or the number of females becoming pregnant, but caused early embryonic deaths. These findings showed evidence of reversibility following a 1 month off-dose.

In a modified embryofetal development study in the rat, osimertinib caused embryo lethality when administered

to pregnant rats prior to embryonic implantation. These effects were seen at a maternally tolerated dose of 20 mg/kg where exposure was equivalent to the human exposure at the recommended dose of 80 mg daily (based on total AUC). Exposure at doses of 20 mg/kg and above during organogenesis caused reduced fetal weights but no adverse effects on external or visceral fetal morphology. When osimertinib was administered to pregnant female rats throughout gestation and then through early lactation, there was demonstrable exposure to osimertinib and its

metabolites in suckling pups plus a reduction in pup survival and poor pup growth (at doses of 20 mg/kg and above).

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Mannitol

Microcrystalline cellulose

Low-substituted hydroxypropyl cellulose

Sodium stearyl fumarate

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

2 years.

6.4. Special precautions for storage

Store below 30°C.

Cytotoxic agent. Must be transported, stored, and used according to guidelines for handling of cytotoxic compounds.

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

6.5. Nature and contents of container

10 film-coated tablets are in a blister, and 3 blisters are

packaged in one box with a leaflet.

Not all doses may be marketed.

6.6. Special precautions for disposal

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

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