

# تریستال®

## آرسنیک تری اکساید

محلول غلیظ برای تهیه محلول جهت انفوزیون

پیش از شروع مصرف تریسنال® محتوای دفترچه راهنما را به دقت مطالعه کنید. این دفترچه راهنما در برگیرنده پاسخ شایع‌ترین سؤالات در مورد داروی تریسنال® است. در صورتی 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 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 نانوآلوند به آدرس [www.nanoalvand.com](http://www.nanoalvand.com) مراجعه فرمایید.

در این دفترچه به سوالات زیر پاسخ داده می‌شود:

- تریسنال® چیست و در چه مواردی تجویز می‌شود؟

- چه افرادی نباید تریسنال® را دریافت کنند؟

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

- آیا تریسنال® در کودکان و نوجوانان قابل تجویز است؟

- آیا تریسنال® با سایر داروها تداخل دارد؟

- آیا تریسنال® با غذا و نوشیدنی‌ها تداخل دارد؟

- ایمنی مصرف تریسنال® در دوران بارداری و شیردهی چگونه است؟

- آیا در طول مدت مصرف تریسنال® رانندگی و کار با ماشین آلات مجاز است؟

- آیا تریسنال® حاوی سدیم است؟

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

- تریسنال® چگونه تجویز می‌شود؟

- در صورت مصرف بیش از حد تریسنال® چه باید کرد؟

- تریسنال® ممکن است چه اثرات نامطلوبی داشته باشد؟

- تریسنال® را در چه شرایطی باید نگهداری کرد؟

- نحوه آماده‌سازی محلول تریسنال® برای تزریق وریدی به چه صورت است؟  
(ویژه کادر درمان)

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



تریسنال® چیست و در چه مواردی تجویز می‌شود؟

نام اختصاصی داروی شما تریسنال® و نام ژنریک آن آرسنیک تری‌اکساید است. تریسنال® یک داروی ضد سرطان است که برای درمان لوکمی پرومیلوسیتیک حاد در بزرگسالان استفاده می‌شود. لوکمی پرومیلوسیتیک حاد یک نوع خاص از لوکمی میلوئیدی است که در آن گلبول‌های سفید غیر طبیعی در خون ظاهر

می‌شوند و خون‌ریزی‌ها و کبودی‌های غیر عادی بروز می‌کند.  
تریسنال® باید توسط پزشک متخصص برای شما تجویز شود.



### چه افرادی نباید تریسنال® را دریافت کنند؟

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



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

- اگر مبتلا به اختلال عملکرد کلیه هستید.

- اگر مبتلا به مشکلات کبدی هستید.

پزشک ممکن است برای شما اقدامات احتیاطی زیر را انجام دهد:

- آزمایش‌هایی برای اندازه‌گیری میزان پتاسیم، منیزیم، کلسیم و کراتینین

خون قبل از مصرف اولین دوز تریسنال® و به صورت دوره‌ای در طول درمان با آن، تجویز خواهد کرد.

- تست نوار قلب قبل از مصرف اولین دوز دارو و همچنین دوبار در هفته در طول درمان با تریسنال® انجام خواهد شد.

- اگر در معرض ابتلا به نوع خاصی از آریتمی قلبی (مانند torsade de pointes یا طولانی شدن QT) هستید، قلب شما به طور مداوم چک خواهد شد.

- آرسنیک تری اکساید، ماده فعال موجود در تریسنال®، ممکن است باعث بروز سرطان‌های دیگر شود. در هر نوبت مراجعه به پزشک، علائم و شرایط جدید و خاص را به وی اطلاع دهید.

- اگر در معرض کمبود ویتامین B1 هستید، عملکرد مکانیسم‌های شناختی و حرکتی شما به طور مرتب مورد ارزیابی قرار خواهد گرفت.



آیا تریسنال® در کودکان و نوجوانان قابل تجویز است؟

مصرف تریسنال® در کودکان و افراد کمتر از ۱۸ سال توصیه نمی‌شود.



آیا تریسنال® با سایر داروها تداخل دارد؟

بسیاری از داروها ممکن است با تریسنال® 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 باعث تغییر در ریتم ضربان قلب می‌شوند؛ شامل:

- داروهایی که برای اصلاح ریتم ضربان قلب مصرف می‌شوند؛ مانند کینیدین، آمیودارون، سوتالول، دوفتیلید
- داروهای درمان سایکوز مانند تیوریدازین

• داروهای ضد افسردگی مانند آمی‌تریپتیلین

• بعضی از آنتی‌بیوتیک‌ها مانند اریترومایسین و اسپارفلوکساسین

• بعضی از داروهای ضد حساسیت مانند ترفنادین

• داروهایی که باعث کاهش سطح منیزیم یا پتاسیم خون می‌شوند؛ مانند آمفوتریسین B

• سیزاپراید

مصرف همزمان تریسنال® و داروهای فوق ممکن است اثر این داروها بر ضربان قلب

را تشدید کند. حتماً پزشک خود را در جریان تمامی داروهای مصرفی‌تان قرار دهید.

اگر در حال مصرف دارویی هستید که کبد را تحت تأثیر قرار می‌دهد یا قصد مصرف آن را دارید، حتماً به پزشک خود اطلاع دهید. اگر از اثر داروی خود بر کبد مطمئن نیستید، با پزشک خود مشورت کنید.

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





**نہا** آیا تریسنال® با غذا و نوشیدنی‌ها تداخل دارد؟

هیچ محدودیت غذایی همراه با مصرف تریسنال® وجود ندارد.



**ایمنی مصرف تریسنال® در دوران بارداری و شیردهی چگونه است؟**

مصرف تریسنال® می‌تواند باعث آسیب به جنین شود. قبل از شروع مصرف دارو باید تست بارداری انجام شود. از مصرف این دارو در دوران بارداری خودداری نمایید.

در صورتی که شما یا شریک جنسی‌تان در سن باروری قرار دارید، حین مصرف این دارو از روش‌های مطمئن برای جلوگیری از بارداری استفاده کنید. چنانچه علی‌رغم آنچه گفته شد بارداری اتفاق افتاد، فوراً به پزشک خود اطلاع دهید.

آرسنیک موجود در تریسنال® در شیر مادر ترشح می‌شود. از آنجا که احتمال آسیب به نوزاد شیرخوار وجود دارد، در حین مصرف این دارو نباید شیردهی صورت گیرد.

در خصوص مدت زمان دقیق مورد نیاز برای پیشگیری از بارداری و شیردهی پس از مصرف آخرین دوز دارو با پزشک خود مشورت کنید.

**آیا در طول مدت مصرف تریسنال® رانندگی و کار با ماشین آلات مجاز است؟**

به نظر می‌رسد اثر تریسنال® بر هوشیاری و توانایی کار با ماشین‌آلات ناچیز باشد. در صورتی که بعد از تزریق تریسنال® احساس ناراحتی داشتید، باید تا

زمان رفع علائم صبر کنید و از رانندگی و کار با ماشین‌آلات خودداری نمایید.

**آیا تریسنال® حاوی سدیم است؟**

تریسنال® حاوی کمتر از ۱ میلی‌مول سدیم در هر دوز است و می‌توان آن را فاقد سدیم در نظر گرفت.



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

پزشک شما براساس نوع بیماری و پاسخ به درمان، دوز، فواصل تجویز و طول دوره درمان با تریسنال® را تعیین می‌کند.

**لوکمی پرومیلوسیتیک حاد که به تازگی تشخیص داده شده است:**

تریسنال® معمولاً یک بار در روز به صورت انفوزیون تزریق می‌گردد. طول اولین دوره درمان بر اساس نظر پزشک تعیین می‌شود و حداکثر ۶۰ روز است. اگر

بیماری شما به تریسنال® پاسخ دهد، ۴ دوره دیگر به رژیم درمانی تان اضافه می‌شود؛ هر دوره شامل ۲۰ دوز است که به صورت ۵ روز در هفته (و به دنبال آن ۲ روز عدم تزریق دارو) به مدت ۴ هفته تزریق می‌شود. پس از هر دوره، ۴ هفته وقفه در تزریق در نظر گرفته می‌شود.

**لوکمی پرومیلوسیتیک حاد که به سایر درمان‌ها مقاوم است:**

تریسنال® معمولاً یک بار در روز به صورت انفوزیون تزریق می‌گردد. طول اولین دوره درمان بر اساس نظر پزشک تعیین می‌شود و حداکثر تا ۵۰ روز



## تریسنال® چگونه تجویز می‌شود؟

تریسنال® باید توسط پزشک متخصص تجویز و توسط پزشک یا پرستار تزریق شود.

تریسنال® باید فقط در محلول‌های حاوی گلوکز یا سدیم کلراید رقیق شود.

تریسنال® به صورت انفوزیون وریدی طی ۱-۲ ساعت تزریق می‌شود. در صورت بروز عوارضی مانند گر گرفتگی یا سرگیجه، ممکن است پزشک مدت زمان انفوزیون دارو را طولانی‌تر کند.

ادامه می‌باید. اگر بیماری شما به تریسنال® پاسخ دهد، یک دوره دیگر به رژیم درمانی اضافه می‌شود. این دوره شامل ۲۵ دوز است که به صورت ۵ روز در هفته (و به دنبال آن ۲ روز عدم تزریق دارو) و به مدت ۵ هفته تزریق می‌شود. پزشک شما مدت زمان دقیق ادامه درمان با تریسنال® را تعیین می‌کند.

تریسنال® نباید با سایر داروها ترکیب، یا از مسیر یکسان تزریق شود.



**در صورت مصرف بیش از حد تریسنال® چه باید کرد؟**

در صورت مصرف بیش از حد تریسنال®، ممکن است دچار تشنج، ضعف عضلانی و گیجی شوید. اگر این اتفاق رخ دهد، درمان با تریسنال® باید بلافاصله متوقف شود و پزشک معالج اقدامات درمانی لازم را آغاز کند.



**تریسنال® ممکن است چه اثرات نامطلوبی داشته باشد؟**

تریسنال® نیز مانند سایر داروها می‌تواند موجب بروز عوارض ناخواسته شود. هر چند این عوارض در همه افراد مصرف‌کننده بروز نخواهد کرد.

- در صورت مشاهده عوارض جانبی مانند سختی در تنفس، سرفه، درد قفسه سینه و تب، فوراً به پزشک یا پرستار خود اطلاع دهید؛ زیرا این علائم ممکن است ناشی از یک بیماری خطرناک به نام "سندرم تمایز" باشد.

- در صورت مشاهده سختی در تنفس، تب، افزایش وزن ناگهانی، احتباس مایعات، از هوش رفتن و تپش قلب، بلافاصله به پزشک یا پرستار خود اطلاع دهید؛ زیرا این علائم ممکن است ناشی از واکنش‌های حساسیتی باشد.

هم‌چنین در طول درمان با تریسنال®، ممکن است برخی از علائم زیر را تجربه کنید:

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

- خستگی، درد، تب، سردرد

- تهوع، استفراغ، اسهال

- سرگیجه، درد عضلانی، بی‌حسی یا مور مور شدن

- جوش یا خارش، افزایش قند خون، اِدم

- تنگی نفس، افزایش ضربان قلب، نوار قلب غیر طبیعی

- کاهش پتاسیم یا منیزیم خون، افزایش بیلی‌روبین؛ یا گاماگلوتامیل ترانسفراز خون که نشانه عملکرد غیر طبیعی کبد است.

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

- کاهش سلول‌های خون (پلاکت‌ها، گلبول‌های سفید، گلبول‌های قرمز)، افزایش گلبول‌های سفید خون
- لرز، افزایش وزن
- تب به دنبال عفونت و کاهش تعداد گلبول‌های سفید، ابتلا به عفونت هرپس زوستر
- درد قفسه سینه، خونریزی ریه، کاهش سطح اکسیژن خون، تجمع مایع اطراف قلب یا ریه، کاهش فشار خون، ضربان قلب غیر طبیعی

- درد مفاصل یا استخوان‌ها، التهاب عروق

- افزایش سدیم یا منیزیم، کتواسیدوز، عملکرد غیر طبیعی کلیه، نارسایی کلیه
- درد شکمی

- قرمزی پوست، تورم صورت، تاری دید

عوارض تریسنال® با شیوع نامشخص عبارتند از:

- عفونت ریه، عفونت خون

- التهاب ریه که منجر به درد قفسه سینه و تنگی نفس می‌شود، نارسایی قلب
- کمبود آب بدن، اضطراب
- مشکلات مغزی (انسفالوپاتی، انسفالوپاتی ورنیک) با تظاهرات مختلف از جمله اختلالات حرکتی، اختلالات گفتاری و گیجی



### تریسنال® را در چه شرایطی باید نگهداری کرد؟

- دارو را دور از دید و دسترس کودکان نگهداری نمایید.
- تریسنال® نباید بعد از تاریخ انقضایی که بر روی آن درج شده است، مصرف شود.
- تریسنال® را در دمای کمتر از ۳۰ درجه سانتی‌گراد نگهداری و از یخ‌زدگی محافظت نمایید.
- جهت محافظت از نور، دارو را تا زمان مصرف در بسته بندی اصلی نگهداری نمایید.



- تریسنال® به صورت محلول غلیظ، شفاف، بی‌رنگ و فاقد ذره است. در غیر این صورت از مصرف آن خودداری کنید.

- ویال تریسنال® فاقد مواد نگهدارنده ضد میکروبی بوده و لذا بلافاصله پس از رقیق‌سازی باید مورد مصرف قرار گیرد. احتیاطات لازم در خصوص آماده‌سازی محلول تزریقی به صورت استریل باید صورت گیرد. محلول تزریقی می‌بایست از جهت عدم وجود ذرات معلق و تغییر رنگ مورد بررسی قرار گیرد.

- این دارو سایتوتوکسیک است. آن را مطابق با دستورالعمل داروهای سایتوتوکسیک

حمل، نگهداری و مصرف کنید.

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



**نحوه آماده‌سازی محلول تریسنال® برای تزریق وریدی به چه صورت است؟ (ویژه کادر درمان)**

داروی تریسنال® فاقد مواد نگهدارنده ضد میکروبی است؛ بنابراین آماده‌سازی آن باید حتما در شرایط آسپتیک انجام شود.

#### رقیق‌سازی

به آرامی سوزن را وارد ویال کنید و حجم مورد نیاز را به داخل سرنگ بکشید. تریسنال® باید بلافاصله با ۲۵۰-۱۰۰ میلی‌لیتر محلول قابل تزریق دکستروز ۵

درصد یا محلول تزریقی سدیم کلراید ۰/۹ درصد رقیق شود.

#### باقیمانده دارو در ویال

باقیمانده محلول در ویال را دور بریزید. هرگز بیش از یک بار از هر ویال استفاده نکنید.

#### نحوه مصرف تریسنال®

تریسنال® فقط برای یک‌بار استفاده است. محلول رقیق‌شده تریسنال® نباید همراه با داروهای دیگر یا از طریق مسیر مشترک با داروهای دیگر تزریق گردد.

تریسنال® باید به صورت وریدی طی ۱-۲ ساعت انفوزیون شود. در صورت مشاهده واکنش‌های وازوموتور مدت زمان انفوزیون ممکن است تا ۴ ساعت افزایش یابد. برای تزریق تریسنال® نیازی به کاتتر ورید مرکزی نیست.

محلول رقیق‌شده باید شفاف و بی‌رنگ باشد. همه محلول‌های تزریقی باید قبل از تزریق از نظر عدم وجود ذرات معلق و تغییر رنگ مورد بررسی قرار گیرند. در صورت مشاهده ذره یا تغییر رنگ محلول از مصرف آن خودداری نمایید.

ویال تریسنال® فاقد مواد نگهدارنده ضد میکروبی بوده و لذا بلافاصله پس از

رقیق‌سازی باید مورد مصرف قرار گیرد.



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

- در این فرآورده از آرسنیک تری‌اکساید به عنوان ماده مؤثره و از سدیم هیدروکساید، هیدروکلریک اسید غلیظ و آب قابل تزریق به عنوان مواد جانبی استفاده شده است.



تاریخ آخرین بازننگری:  
مه ۲۰۲۱ برابر با اردیبهشت ۱۴۰۰

ساخت شرکت نانوفناوران دارویی الوند (نانوالوند)

آدرس: ایران، تهران، خیابان کارگر شمالی، پارک ملی زیست فناوری بوعلی سینا، مرکز رشد واحدهای  
فناوری فرآورده‌های دارویی دانشگاه علوم پزشکی تهران، پلاک ۱۴۶۲  
کدپستی: ۱۴۳۹۹۵۵۹۹۱  
تلفن: ۰۲۱-۸۸۰۲۰۵۷۹  
فاکس: ۰۲۱-۸۸۰۲۰۵۹۷  
پست الکترونیکی: info@nanoalvand.com  
وبسایت: www.nanoalvand.com  
پاسخگوی ۲۴ ساعته مرکز حمایت از بیماران: ۰۲۱-۴۲۵۹۳

- تریسنال® به شکل محلول غلیظ استریل، شفاف، بی‌رنگ و فاقد ذره بوده  
و به صورت بسته بندی ۱۰ عددی (۱۰ ویال در یک جعبه)، با دوز ۱۰  
میلی گرم در ۱۰ میلی لیتر به همراه یک دفترچه راهنما موجود است.

**Trisenal<sup>®</sup>**  
**Arsenic trioxide**

**Concentrate for Solution for Infusion**

## **1. Name of the medicinal product**

Trisenal® 1 mg/ml concentrate for solution for infusion

## **2. Qualitative and quantitative composition**

Each ml of concentrate contains 1 mg of arsenic trioxide.

Each vial of 10 ml contains 10 mg of arsenic trioxide.

For the full list of excipients, see section 6.1

### **3. Pharmaceutical form**

Concentrate for solution for infusion.

Sterile, clear, colorless, aqueous solution, free from particles having a pH range of 7.7 - 8.3.

### **4. Clinical particulars**

#### **4.1 Therapeutic indications**

Arsenic trioxide is indicated for induction of remission, and

consolidation in adult patients with:

- Newly diagnosed low-to-intermediate risk acute promyelocytic leukemia (APL) (white blood cell count,  $\leq 10 \times 10^3/\mu\text{l}$ ) in combination with all-trans-retinoic acid (ATRA)
- Relapsed/refractory acute promyelocytic leukemia (APL) (previous treatment should have included a retinoid and chemotherapy) characterized by the

presence of the t (15;17) translocation and/or the presence of the promyelocytic leukemia/retinoic-acid-receptor-alpha (PML/RAR-alpha) gene.

The response rate of other acute myelogenous leukemia subtypes to arsenic trioxide has not been examined.

#### **4.2 Posology and method of administration**

Arsenic trioxide must be administered under the supervision of a physician who is experienced in the management of

acute leukemias, and the special monitoring procedures described in section 4.4 must be followed.

#### Posology

The same dose is recommended for adults and elderly.

*Newly diagnosed low-to-intermediate risk acute promyelocytic leukemia (APL)*



### *Induction treatment schedule*

Arsenic trioxide must be administered intravenously at a dose of 0.15 mg/kg/day, given daily until complete remission is achieved. If complete remission has not occurred by day 60, dosing must be discontinued.

### *Consolidation schedule*

Arsenic trioxide must be administered intravenously at a dose of 0.15 mg/kg/day, 5 days per week. Treatment

should be continued for 4 weeks on and 4 weeks off, for a total of 4 cycles.

### *Relapsed/refractory acute promyelocytic leukemia (APL)*

#### *Induction treatment schedule*

Arsenic trioxide must be administered intravenously at a fixed dose of 0.15 mg/kg/day given daily until complete remission is achieved (less than 5% blasts present in cellular bone marrow with no evidence of leukemic cells).

If complete remission has not occurred by day 50, dosing must be discontinued.

#### *Consolidation schedule*

Consolidation treatment must begin 3 to 4 weeks after completion of induction therapy. Arsenic trioxide is to be administered intravenously at a dose of 0.15 mg/kg/day for 25 doses given 5 days per week, followed by 2 days interruption, repeated for 5 weeks.

#### Dose delay, modification and reinitiation

Treatment with arsenic trioxide must be temporarily interrupted before the scheduled end of therapy at any time that a toxicity grade 3 or greater on the National Cancer Institute Common Toxicity Criteria is observed and judged to be possibly related to arsenic trioxide treatment. Patients who experience such reactions that are considered arsenic trioxide related must resume treatment only after resolution of the toxic event

or after recovery to baseline status of the abnormality that prompted the interruption. In such cases, treatment must resume at 50% of the preceding daily dose. If the toxic event does not recur within 7 days of restarting treatment at the reduced dose, the daily dose can be escalated back to 100% of the original dose. Patients who experience a recurrence of toxicity must be removed from treatment. For ECG, electrolytes abnormalities and hepatotoxicity see

section 4.4.

### Special populations

#### Hepatic impairment

Since no data are available across all hepatic impairment groups and hepatotoxic effects may occur during the treatment with arsenic trioxide, caution is advised in the use of arsenic trioxide in patients with hepatic impairment (see section 4.4 and 4.8).

### Renal impairment

Since no data are available across all renal impairment groups, caution is advised in the use of arsenic trioxide in patients with renal impairment.

### Pediatric population

The safety and efficacy of arsenic trioxide in children aged up to 17 years has not been established. Currently available data for children aged 5 to 16 years are described

in section 5.1 but no recommendation on a posology can be made. No data are available for children under 5 years.

### Method of administration

Arsenic trioxide must be administered intravenously over 1-2 hours. The infusion duration may be extended up to 4 hours if vasomotor reactions are observed. A central venous catheter is not required. Patients must be hospitalized at the beginning of treatment due to symptoms of disease and to

ensure adequate monitoring.

For instructions on preparation of the medicinal product before administration, see section 6.6.

### **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**

Clinically unstable APL patients are especially at risk and will require more frequent monitoring of electrolyte and glycemia levels as well as more frequent hematologic, hepatic, renal and coagulation parameter tests.

Leukocyte activation syndrome (APL differentiation syndrome)

27% of patients with APL, in the relapsed/refractory setting, treated with arsenic trioxide have experienced symptoms

similar to a syndrome called the retinoic-acid-acute promyelocytic leukemia (RA-APL) or APL differentiation syndrome, characterized by fever, dyspnea, weight gain, pulmonary infiltrates and pleural or pericardial effusions, with or without leukocytosis. This syndrome can be fatal. In newly diagnosed APL patients treated with arsenic trioxide and all-trans-retinoic acid (ATRA), APL differentiation syndrome was observed in 19% including 5 severe cases. At the first signs that could suggest the syndrome

(unexplained fever, dyspnea and/or weight gain, abnormal chest auscultatory findings or radiographic abnormalities), treatment with arsenic trioxide must be temporarily discontinued and high-dose steroids (dexamethasone 10 mg intravenously twice a day) must be immediately initiated, irrespective of the leukocyte count and continued for at least 3 days or longer until signs and symptoms have abated. If clinically justified/required, concomitant diuretic therapy is also recommended. The majority of

patients do not require permanent termination of arsenic trioxide therapy during treatment of the APL differentiation syndrome. As soon as signs and symptoms have subsided, treatment with arsenic trioxide can be resumed at 50% of the previous dose during the first 7 days. Thereafter, in the absence of worsening of the previous toxicity, arsenic trioxide might be resumed at full dosage. In the case of the reappearance of symptoms arsenic trioxide should be reduced to the previous dosage. In order to prevent

the development of the APL differentiation syndrome during induction treatment, prednisone (0.5 mg/kg body weight per day throughout induction treatment) may be administered from day 1 of arsenic trioxide application to the end of induction therapy in APL patients. It is recommended that chemotherapy not be added to treatment with steroids since there is no experience with administration of both steroids and chemotherapy during treatment of the leukocyte activation syndrome due to

arsenic trioxide. Post-marketing experience suggests that a similar syndrome may occur in patients with other types of malignancy. Monitoring and management for these patients should be as described above.

#### Electrocardiogram (ECG) abnormalities

Arsenic trioxide can cause QT interval prolongation and complete atrioventricular block. QT prolongation can lead to a torsade de pointes-type ventricular arrhythmia, which

can be fatal. Previous treatment with anthracyclines may increase the risk of QT prolongation. The risk of torsade de pointes is related to the extent of QT prolongation, concomitant administration of QT prolonging medicinal products (such as class Ia and III antiarrhythmics (e.g. quinidine, amiodarone, sotalol, dofetilide), antipsychotics (e.g. thioridazine), antidepressants (e.g. amitriptyline), some macrolides (e.g. erythromycin), some antihistamines (e.g. terfenadine and astemizole), some quinolone antibiotics



(e.g. sparfloxacin), and other individual medicinal products known to increase QT interval (e.g. cisapride), a history of torsade de pointes, pre-existing QT interval prolongation, congestive heart failure, administration of potassium-wasting diuretics, amphotericin B or other conditions that result in hypokalemia or hypomagnesemia. In clinical trials, in the relapsed/refractory setting, 40% of patients treated with arsenic trioxide experienced at least one QT corrected (QTc) interval prolongation greater than 500 msec. Prolongation of

the QTc was observed between 1 and 5 weeks after arsenic trioxide infusion, and then returned to baseline by the end of 8 weeks after arsenic trioxide infusion. One patient (receiving multiple, concomitant medicinal products, including amphotericin B) had asymptomatic torsade de pointes during induction therapy for relapsed APL with arsenic trioxide. In newly diagnosed APL patients 15.6% showed QTc prolongation with arsenic trioxide in combination with ATRA (see section 4.8). In one newly diagnosed patient induction

treatment was terminated because of severe prolongation of the QTc interval and electrolyte abnormalities on day 3 of induction treatment.

#### ECG and electrolyte monitoring recommendations

Prior to initiating therapy with arsenic trioxide, a 12-lead ECG must be performed and serum electrolytes (potassium, calcium, and magnesium) and creatinine must be assessed; pre-existing electrolyte abnormalities must

be corrected and, if possible, medicinal products that are known to prolong the QT interval must be discontinued. Patients with risk factors of QTc prolongation or risk factors of torsade de pointes should be monitored with continuous cardiac monitoring (ECG). For QTc greater than 500 msec, corrective measures must be completed and the QTc reassessed with serial ECGs and, if available, a specialist advice could be sought prior to considering using arsenic trioxide. During therapy with arsenic trioxide.

Potassium concentrations must be kept above 4 mEq/l and magnesium concentrations must be kept above 1.8 mg/dl. Patients who reach an absolute QT interval value > 500 msec must be reassessed and immediate action must be taken to correct concomitant risk factors, if any, while the risk/benefit of continuing versus suspending arsenic trioxide therapy must be considered. If syncope, rapid or irregular heartbeat develops, the patient must be hospitalized and monitored continuously, serum electrolytes must be

assessed, arsenic trioxide therapy must be temporarily discontinued until the QTc interval regresses to below 460 msec, electrolyte abnormalities are corrected, and the syncope and irregular heartbeat cease. After recovery, treatment should be resumed at 50% of the preceding daily dose. If QTc prolongation does not recur within 7 days of restarting treatment at the reduced dose, treatment with arsenic trioxide can be resumed at 0.11 mg/kg body weight per day for a second week. The daily dose can be escalated

back to 100% of the original dose if no prolongation occurs. There are no data on the effect of arsenic trioxide on the QTc interval during the infusion. Electrocardiograms must be obtained twice weekly, and more frequently for clinically unstable patients, during induction and consolidation.

#### Hepatotoxicity (grade 3 or greater)

In newly diagnosed patients with low to intermediate risk APL 63.2% developed grade 3 or 4 hepatic toxic effects

during induction or consolidation treatment with arsenic trioxide in combination with ATRA (see section 4.8). However, toxic effects resolved with temporary discontinuation of either arsenic trioxide, ATRA or both. Treatment with arsenic trioxide must be discontinued before the scheduled end of therapy at any time that a hepatotoxicity grade 3 or greater on the National Cancer Institute Common Toxicity Criteria is observed. As soon as bilirubin and/or SGOT and/or alkaline phosphatase are decreased to below 4 times the

normal upper level, treatment with arsenic trioxide should be resumed at 50% of the previous dose during the first 7 days. Thereafter, in absence of worsening of the previous toxicity, arsenic trioxide should be resumed at full dosage. In case of reappearance of hepatotoxicity, arsenic trioxide must be permanently discontinued.

#### Dose delay and modification

Treatment with arsenic trioxide must be temporarily interrupted

before the scheduled end of therapy at any time that a toxicity grade 3 or greater on the National Cancer Institute Common Toxicity Criteria is observed and judged to be possibly related to arsenic trioxide treatment. (see section 4.2)

#### Laboratory tests

The patient's electrolyte and glycemia levels, as well as hematologic, hepatic, renal and coagulation parameter tests must be monitored at least twice weekly, and more frequently

for clinically unstable patients during the induction phase and at least weekly during the consolidation phase.

#### Renal impairment

Since no data are available across all renal impairment groups, caution is advised in the use of arsenic trioxide in patients with renal impairment. The experience in patients with severe renal impairment is insufficient to determine if dose adjustment is required.

The use of arsenic trioxide in patients on dialysis has not been studied.

#### Hepatic impairment

Since no data are available across all hepatic impairment groups and hepatotoxic effects may occur during the treatment with arsenic trioxide, caution is advised in the use of arsenic trioxide in patients with hepatic impairment (see section 4.4 on hepatotoxicity and section 4.8). The

experience in patients with severe hepatic impairment is insufficient to determine if dose adjustment is required.

#### Elderly

There is limited clinical data on the use of arsenic trioxide in the elderly population. Caution is needed in these patients.

#### Hyperleukocytosis

Treatment with arsenic trioxide has been associated with the

development of hyperleukocytosis ( $\geq 10 \times 10^3/\mu\text{l}$ ) in some relapsed/refractory APL patients. There did not appear to be a relationship between baseline white blood cell (WBC) counts and development of hyperleukocytosis nor did there appear to be a correlation between baseline WBC count and peak WBC counts. Hyperleukocytosis was never treated with additional chemotherapy and resolved on continuation of arsenic trioxide. WBC counts during consolidation were not as high as during induction treatment and were

<  $10 \times 10^3/\mu\text{l}$ , except in one patient who had a WBC count of  $22 \times 10^3/\mu\text{l}$  during consolidation. Twenty relapsed/refractory APL patients (50%) experienced leukocytosis; however, in all these patients, the WBC count was declining or had normalized by the time of bone marrow remission and cytotoxic chemotherapy or leukapheresis was not required. In newly diagnosed patients with low to intermediate risk APL leukocytosis developed during induction therapy in 35 of 74 (47%) patients (see section 4.8). However, all cases

were successfully managed with hydroxyurea therapy. In newly diagnosed and relapsed/refractory APL patients who develop sustained leukocytosis after initiation of therapy, hydroxyurea should be administered. Hydroxyurea should be continued at a given dose to keep the white blood cell count  $\leq 10 \times 10^3/\mu\text{l}$  and subsequently tapered.



Table 1: Recommendation for initiation of hydroxyurea

WBC	Hydroxyurea
10-50 x 10 <sup>3</sup> /μl	500 mg four times a day
>50 x 10 <sup>3</sup> /μl	1000 mg four times a day

#### Development of second primary malignancies

The active ingredient of Trisenal®, arsenic trioxide, is a human carcinogen. Monitor patients for the development of second primary malignancies.

#### *Encephalopathy*

Cases of encephalopathy were reported with treatment with arsenic trioxide. Wernicke encephalopathy after arsenic trioxide treatment was reported in patients with vitamin B1 deficiency. Patients at risk of B1 deficiency should be closely monitored for signs and symptoms of encephalopathy after arsenic trioxide initiation. Some cases recovered with vitamin B1 supplementation.

#### *Excipient with known effect*

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

No formal assessments of pharmacokinetic interactions between arsenic trioxide and other therapeutic medicinal products have been conducted.

#### Medicinal products known to cause QT/QTc interval prolongation, hypokalemia or hypomagnesemia

QT/QTc prolongation is expected during treatment with arsenic trioxide, and torsade de pointes and complete heart block have been reported. Patients who are receiving, or who have received, medicinal products known to cause hypokalemia or hypomagnesemia, such as diuretics or amphotericin B, may be at higher risk for torsade de pointes.

Caution is advised when arsenic trioxide is co-administered with other medicinal products known to cause QT/QTc interval prolongation such as macrolide antibiotics, the antipsychotic thioridazine, or medicinal products known to cause hypokalemia or hypomagnesemia. Additional information about QT prolonging medicinal agents, is provided in section 4.4.

#### Medicinal products known to cause hepatotoxic effects

Hepatotoxic effects may occur during the treatment with arsenic trioxide, caution is advised when arsenic trioxide is co-administered with other medicinal products known to cause hepatotoxic effects.

#### Other antileukemic medicinal products

The influence of arsenic trioxide on the efficacy of other antileukemic medicinal products is unknown.

## **4.6 Fertility, pregnancy and lactation**

### Contraception in males and females

Women of childbearing potential and men must use effective contraception during treatment with arsenic trioxide.

Ask your doctor about the exact time required to use contraception after stopping treatment with arsenic trioxide.

### Pregnancy

Arsenic trioxide has been shown to be embryotoxic and teratogenic in animal studies (see section 5.3). There are no studies in pregnant women using arsenic trioxide. If this medicinal product is used during pregnancy or if the patient becomes pregnant while taking this product, the patient must be informed of the potential harm to the fetus.

### Breast-feeding

Arsenic is excreted in human milk. Because of the potential for serious adverse reactions in breast-feeding infants and children from arsenic trioxide, breast-feeding must be discontinued prior to and throughout administration. Ask your doctor about the exact time required to avoid breastfeeding after stopping treatment with arsenic trioxide.

### Fertility

No clinical or non-clinical fertility studies have been conducted with arsenic trioxide.

### **4.7 Effects on ability to drive and use machines**

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

## 4.8 Undesirable effects

### Summary of the safety profile

Related adverse reactions of CTC grade 3 and 4 occurred in 37% of relapsed/refractory APL patients in clinical trials. The most commonly reported reactions were hyperglycemia, hypokalemia, neutropenia, and increased alanine amino transferase (ALT). Leukocytosis occurred in 50% of patients with relapsed/refractory APL, as determined by

hematology assessments.

Serious adverse reactions were common (1-10 %) and not unexpected in the relapsed/refractory population. Those serious adverse reactions attributed to arsenic trioxide included APL differentiation syndrome (3), leukocytosis (3), prolonged QT interval (4, 1 with torsade de pointes), atrial fibrillation/atrial flutter (1), hyperglycemia (2) and a variety of serious adverse reactions related to hemorrhage,

infections, pain, diarrhea, nausea.

In general, treatment-emergent adverse events tended to decrease over time, in relapsed/refractory APL patients perhaps accounted for by amelioration of the underlying disease process. Patients tended to tolerate consolidation and maintenance treatment with less toxicity than in induction. This is probably due to the confounding of adverse events by the uncontrolled disease process early on in the

treatment course and the myriad concomitant medicinal products required to control symptoms and morbidity.

In a phase 3, multicenter, non-inferiority trial comparing all-trans-retinoic acid (ATRA) plus chemotherapy with ATRA plus arsenic trioxide in newly diagnosed low-to-intermediate risk APL patients (Study APL0406; see also section 5.1), serious adverse reactions including hepatic toxicity, thrombocytopenia, neutropenia and QTc prolongation were

observed in patients treated with arsenic trioxide.

#### Tabulated list of adverse reactions

The following undesirable effects have been reported in the APL0406 study in newly diagnosed patients and in clinical trials and/or post-marketing experience in relapsed/refractory APL patients. Undesirable effects are listed in table 2 below as MedDRA preferred term by system organ class and frequencies observed during

arsenic trioxide clinical trials in 52 patients with refractory/relapsed APL. Frequencies are defined as: (very common  $\geq 1/10$ ), (common  $\geq 1/100$  to  $< 1/10$ ), (uncommon  $\geq 1/1,000$  to  $< 1/100$ ), not known (cannot be estimated from available data).

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



Table 2

	All grades	Grades $\geq 3$
<b>Infections and infestations</b>		
Herpes zoster	Common	Not known
Sepsis	Not known	Not known
Pneumonia	Not known	Not known
<b>Blood and lymphatic system disorders</b>		
Febrile neutropenia	Common	Common
Leukocytosis	Common	Common
Neutropenia	Common	Common

Pancytopenia	Common	Common
Thrombocytopenia	Common	Common
Anemia	Common	Not known
Leukopenia	Not known	Not known
Lymphopenia	Not known	Not known
<b>Metabolism and nutrition disorders</b>		
Hyperglycemia	Very Common	Very Common
Hypokalemia	Very Common	Very Common
Hypomagnesemia	Very Common	Common
Hypernatremia	Common	Common
Ketoacidosis	Common	Common

Hypermagnesemia	Common	Not known
Dehydration	Not known	Not known
Fluid retention	Not known	Not known
<b>Psychiatric disorders</b>		
Confusional state	Not known	Not known
<b>Nervous system disorders</b>		
Paresthesia	Very Common	Common
Dizziness	Very Common	Not known
Headache	Very Common	Not known
Convulsion	Common	Not known

Encephalopathy, Wernicke encephalopathy	Not known	Not known
<b>Eye disorders</b>		
Vision blurred	Common	Not known
<b>Cardiac disorders</b>		
Tachycardia	Very Common	Common
Pericardial effusion	Common	Common
Ventricular extrasystoles	Common	Not known
Cardiac failure	Not known	Not known
Ventricular tachycardia	Not known	Not known

<b>Vascular disorders</b>		
Vasculitis	Common	Common
Hypotension	Common	Not known
<b>Respiratory, thoracic and mediastinal disorders</b>		
Differentiation syndrome	Very Common	Very Common
Dyspnea	Very Common	Common
Hypoxia	Common	Common
Pleural effusion	Common	Common
Pleuritic pain	Common	Common
Pulmonary alveolar hemorrhage	Common	Common

Pneumonitis	Not known	Not known
<b>Gastrointestinal disorders</b>		
Diarrhea	Very Common	Common
Vomiting	Very Common	Not known
Nausea	Very Common	Common
Abdominal pain	Common	Common
<b>Skin and subcutaneous tissue disorders</b>		
Pruritus	Very Common	Not known
Rash	Very Common	Not known
Erythema	Common	Common
Face edema	Common	Not known

<b>Musculoskeletal and connective tissue disorders</b>		
Myalgia	Very Common	Common
Arthralgia	Common	Common
Bone pain	Common	Common
<b>Renal and urinary disorders</b>		
Renal failure	Common	Not known
<b>General disorders and administration site conditions</b>		
Pyrexia	Very Common	Common
Pain	Very Common	Common
Fatigue	Very Common	Not known
Edema	Very Common	Not known

Chest pain	Common	Common
Chills	Common	Not known
<b>Investigations</b>		
Alanine amino transferase increased	Very Common	Common
Aspartate amino transferase increased	Very Common	Common
Electrocardiogram QT prolonged	Very Common	Common
Hyperbilirubinemia	Common	Common
Blood creatinine increased	Common	Not known

Weight increased	Common	Not known
Gamma-glutamyl transferase increased*	Not known*	Not known*

\*In the CALGB study C9710, 2 cases of grade  $\geq 3$  increased GGT were reported out of the 200 patients who received arsenic trioxide consolidation cycles (cycle 1 and cycle 2) versus none in the control arm.

### Description of selected adverse reactions

#### Differentiation syndrome

During arsenic trioxide treatment, 14 of the 52 patients in

the APL studies in the relapsed setting had one or more symptoms of APL differentiation syndrome, characterized by fever, dyspnea, weight gain, pulmonary infiltrates and pleural or pericardial effusions, with or without leukocytosis (see section 4.4). Twenty-seven patients had leukocytosis (WBC  $\geq 10 \times 10^3/\mu\text{l}$ ) during induction, 4 of whom had values above 100,000/ $\mu\text{l}$ . Baseline white blood cell (WBC) counts did not correlate with development of leukocytosis on study, and WBC counts during consolidation therapy were not as

high as during induction. In these studies, leukocytosis was not treated with chemotherapeutic medicinal products. Medicinal products that are used to lower the white blood cell count often exacerbate the toxicities associated with leukocytosis, and no standard approach has proven effective. One patient treated under a compassionate use program died from cerebral infarct due to leukocytosis, following treatment with chemotherapeutic medicinal products to lower WBC count. Observation is the recommended

approach with intervention only in selected cases.

Mortality in the pivotal studies in the relapsed setting from disseminated intravascular coagulation (DIC associated hemorrhage was very common (> 10 %), which is consistent with the early mortality reported in the literature. In newly diagnosed patients with low to intermediate risk APL, differentiation syndrome was observed in 19% including 5 severe cases. In post marketing experience, a differentiation

syndrome, like retinoic acid syndrome, has also been reported for the treatment of malignancies other than APL with arsenic trioxide.

#### QT interval prolongation

Arsenic trioxide can cause QT interval prolongation (see section 4.4). QT prolongation can lead to a torsade de pointes type ventricular arrhythmia, which can be fatal. The risk of torsade de pointes is related to the extent

of QT prolongation, concomitant administration of QT prolonging medicinal products, a history of torsade de pointes, pre-existing QT interval prolongation, congestive heart failure, administration of potassium-wasting diuretics, or other conditions that result in hypokalemia or hypomagnesemia. One patient (receiving multiple, concomitant medicinal products, including amphotericin B) had asymptomatic torsade de pointes during induction therapy for relapsed APL with arsenic trioxide. She went onto

consolidation without further evidence of QT prolongation. In newly diagnosed patients, with low to intermediate risk APL, QTc prolongation was observed in 15.6%. In one patient induction treatment was terminated because of severe prolongation of the QTc interval and electrolyte abnormalities on day 3.

#### Peripheral neuropathy

Peripheral neuropathy, characterized by paresthesia/

dysesthesia, is a common and well-known effect of environmental arsenic. Only 2 relapsed/refractory APL patients discontinued treatment early due to this adverse event and one went on to receive additional arsenic trioxide on a subsequent protocol. Forty-four percent of relapsed/refractory APL patients experienced symptoms that could be associated with neuropathy; most were mild to moderate and were reversible upon cessation of treatment with arsenic trioxide.



### Hepatotoxicity (grade 3-4)

In newly diagnosed patients with low to intermediate risk APL 63.2% developed grade 3 or 4 hepatic toxic effects during induction or consolidation treatment with arsenic trioxide in combination with ATRA. However, toxic effects resolved with temporary discontinuation of either arsenic trioxide, ATRA or both (see section 4.4).

### Hematological and gastrointestinal toxicity

In newly diagnosed patients with low to intermediate risk APL, gastrointestinal toxicity, grade 3-4 neutropenia and grade 3 or 4 thrombocytopenia occurred, however these were 2.2 times less frequent in patients treated with arsenic trioxide in combination with ATRA compared to patients treated with ATRA + chemotherapy.

## 4.9 Overdose

If symptoms suggestive of serious acute arsenic toxicity (e.g. convulsions, muscle weakness and confusion) appear, arsenic trioxide must be immediately discontinued and chelating therapy with penicillamine at a daily dose  $\leq 1$  g per day may be considered. The duration of treatment with penicillamine must be evaluated taking into account the urinary arsenic laboratory values. For patients who cannot

take oral medicinal product, dimercaprol administered at a dose of 3 mg/kg intramuscularly every 4 hours until any immediately life-threatening toxicity has subsided may be considered. Thereafter, penicillamine at a daily dose  $\leq 1$  g per day may be given. In the presence of coagulopathy, the oral administration of the chelating agent Dimercaptosuccinic Acid Succimer (DCI) 10 mg/kg or 350 mg/m<sup>2</sup> every 8 hours during 5 days and then every 12 hours during 2 weeks is recommended. For patients

with severe, acute arsenic overdose, dialysis should be considered.

## **5. Pharmacological properties**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: antineoplastic agents

ATC code: L01XX27

### Mechanism of action

The mechanism of action of arsenic trioxide is not completely understood. Arsenic trioxide causes morphological changes and deoxyribonucleic acid (DNA) fragmentation characteristic of apoptosis in NB4 human promyelocytic leukemia cells *in vitro*. Arsenic trioxide also causes damage or degradation of the fusion protein promyelocytic leukemia/retinoic acid receptor-alpha (PML/RAR alpha).

## Clinical efficacy and safety

### Newly diagnosed non-high-risk APL patients

Arsenic trioxide has been investigated in 77 newly diagnosed patients with low to intermediate risk APL, in a controlled, randomized, non-inferiority Phase 3 clinical study comparing the efficacy and safety of arsenic trioxide combined with all trans-retinoic acid (ATRA) with those of ATRA + chemotherapy (eg, idarubicin and mitoxantrone) (Study APL0406). Patients

with newly diagnosed APL confirmed by the presence of t(15; 17) or PML-RAR $\alpha$  by RT-PCR or micro speckled PML nuclear distribution in leukemic cells were included. No data are available on patient with variant translocations like (11;17) (PLZF/RAR $\alpha$ ). Patients with significant arrhythmias, EKG abnormalities (congenital long QT syndrome, history or presence of significant ventricular or atrial tachyarrhythmia, clinically significant resting bradycardia (< 50 beats per minute), QTc > 450 msec on screening EKG,

right bundle branch block plus left anterior hemiblock, (bifascicular block) or neuropathy were excluded from the study. Patients in the ATRA + arsenic trioxide treatment group received oral ATRA at 45 mg/m<sup>2</sup> daily and IV arsenic trioxide at 0.15 mg/kg daily until CR. During consolidation, ATRA was given at the same dose for periods of 2 weeks on and 2 weeks off for a total of 7 courses, and arsenic trioxide was given at the same dose 5 days per week, 4 weeks on and 4 weeks off, for a total of 4 courses. Patients in the ATRA

+ chemotherapy treatment group received IV idarubicin at 12 mg/m<sup>2</sup> on days 2, 4, 6, and 8 and oral ATRA at 45 mg/m<sup>2</sup> daily until CR. During consolidation, patients received idarubicin at 5 mg/m<sup>2</sup> on days 1 to 4 and ATRA at 45 mg/m<sup>2</sup> daily for 15 days, then IV mitoxantrone at 10 mg/m<sup>2</sup> on days 1 to 5 and ATRA again at 45 mg/m<sup>2</sup> daily for 15 days, and finally a single dose of idarubicin at 12 mg/m<sup>2</sup> and ATRA at 45 mg/m<sup>2</sup> daily for 15 days. Each course of consolidation was initiated at hematological recovery

from the previous course defined as absolute neutrophil count  $> 1.5 \times 10^9/l$  and platelets  $> 100 \times 10^9/l$ . Patients in the ATRA + chemotherapy treatment group also received maintenance treatment for up to 2 years, consisting of oral 6 mercaptopurine at  $50 \text{ mg/m}^2$  daily, intramuscular methotrexate at  $15 \text{ mg/m}^2$  weekly, and ATRA at  $45 \text{ mg/m}^2$  daily for 15 days every 3 months.

The key efficacy results are summarized in table 3 below:

Table 3

Endpoint	ATRA + Arsenic trioxide (n = 77) [%]	ATRA + Chemotherapy (n = 79) [%]	Confidence interval (CI)	P-value
2-Year event-free survival (EFS)	97	86	95 % CI for the difference, 2-22 percentage points	p < 0.001 for non inferiority p = 0.02 for superiority of ATRA + arsenic trioxide

Hematologic complete remission (HCR)	100	95		p = 0.12
2-Year overall survival (OS)	99	91		p = 0.02
2-Year disease-free survival (DFS)	97	90		p = 0.11
2-Year cumulative incidence of relapse (CIR)	1	6		p = 0.24

APL = acute promyelocytic leukemia; ATRA = all-trans-retinoic acid

### Relapsed/refractory APL

Arsenic trioxide has been investigated in 52 APL patients, previously treated with an anthracycline and a retinoid regimen, in two open-label, single-arm, non-comparative studies. One was a single investigator clinical study (n=12) and the other was a multicenter, 9-institution study (n=40). Patients in the first study received a median dose of 0.16 mg/kg/day of arsenic trioxide (range 0.06 to 0.20 mg/kg/day) and patients in the multicenter study received a fixed dose of 0.15 mg/kg/

day. Arsenic trioxide was administered intravenously over 1 to 2 hours until the bone marrow was free of leukemic cells, up to a maximum of 60 days. Patients with complete remission received consolidation therapy with arsenic trioxide for 25 additional doses over a 5-week period. Consolidation therapy began 6 weeks (range, 3-8) after induction in the single institution study and 4 weeks (range, 3-6) in the multicenter study. Complete remission (CR) was defined as the absence of visible leukemic cells in the bone marrow and peripheral

recovery of platelets and white blood cells. Patients in the single center study had relapsed following 1-6 prior therapy regimens and 2 patients had relapsed following stem cell transplantation. Patients in the multicenter study had relapsed following 1-4 prior therapy regimens and 5 patients had relapsed following stem cell transplantation. The median age in the single center study was 33 years (age range 9 to 75). The median age in the multicenter study was 40 years (age range 5 to 73).



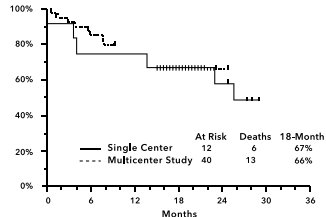
The results are summarized in the table 4 below:

Table 4

	Single center trial N=12	Multicenter trial N=40
Arsenic trioxide dose, mg/kg/day (median, range)	0.16 (0.06 - 0.20)	0.15
Complete remission	11 (92 %)	34 (85 %)
<b>Time to bone marrow remission (median)</b>	32 days	35 days
<b>Time to CR (median)</b>	54 days	59 days
18-Month survival	67 %	66 %

The single institution study included 2 pediatric patients (< 18 years old), both of whom achieved CR. The multicenter trial included 5 pediatric patients (< 18 years old), 3 of whom achieved CR. No children of less than 5 years of age were treated. In a follow-up treatment after consolidation, 7 patients in the single institution study and 18 patients in the multicenter study received further maintenance therapy with arsenic trioxide. Three patients from the single institution study and 15 patients from the multicenter study had stem cell

transplants after completing arsenic trioxide. The Kaplan-Meier median CR duration for the single institution study is 14 months and has not been reached for the multicenter study. At last follow-up, 6 of 12 patients in the single institution study were alive with a median follow-up time of 28 months (range 25 to 29). In the multicenter study 27 of 40 patients were alive with a median follow-up time of 16 months (range 9 to 25). Kaplan Meier estimates of 18-month survival for each study are shown below.



Cytogenetic confirmation of conversion to a normal genotype and reverse transcriptase - polymerase chain reaction (RTPCR) detection of PML/RAR $\alpha$  conversion to normal are shown in table 5 below.

### Cytogenetics after arsenic trioxide therapy

Table 5

	Single center pilot trial N with CR = 11	Multicenter trial N with CR = 34
Conventional Cytogenetics [t(15;17)]		
<b>Absent</b>	8 (73 %)	31 (91 %)
<b>Present</b>	1 (9 %)	0 %
<b>Not evaluable</b>	2 (18 %)	3 (9 %)

RT-PCR for PML/ RAR $\alpha$		
<b>Negative</b>	8 (73 %)	27 (79 %)
<b>Positive</b>	3 (27 %)	4 (12 %)
<b>Not evaluable</b>	0	3 (9 %)

Responses were seen across all age groups tested, ranging from 6 to 75 years. The response rate was similar for both genders. There is no experience on the effect of arsenic trioxide on the variant APL containing the t (11;17) and t (5;17) chromosomal translocations.

### Pediatric population

The experience in children is limited. Of 7 patients under 18 years of age (range 5 to 16 years) treated with arsenic trioxide at the recommended dose of 0.15 mg/kg/day, 5 patients achieved a complete response (see section 4.2).

### **5.2 Pharmacokinetic properties**

The inorganic, lyophilized form of arsenic trioxide, when placed into solution, immediately forms the hydrolysis

product arsenious acid ( $\text{As}^{\text{III}}$ ).  $\text{As}^{\text{III}}$  is the pharmacologically active species of arsenic trioxide.

### Distribution

The volume of distribution ( $V_d$ ) for  $\text{As}^{\text{III}}$  is large ( $> 400 \text{ l}$ ) indicating significant distribution into the tissues with negligible protein binding.  $V_d$  is also weight dependent, increasing with increasing body weight. Total arsenic accumulates mainly in the liver, kidney, and heart and, to a

lesser extent, in the lung, hair, and nails.

### Biotransformation

The metabolism of arsenic trioxide involves oxidation of arsenious acid ( $\text{As}^{\text{III}}$ ), the active species of arsenic trioxide, to arsenic acid ( $\text{As}^{\text{V}}$ ), as well as oxidative methylation to monomethylarsonic acid ( $\text{MMA}^{\text{V}}$ ) and dimethylarsinic acid ( $\text{DMA}^{\text{V}}$ ) by methyltransferases, primarily in the liver. The pentavalent metabolites,  $\text{MMA}^{\text{V}}$  and  $\text{DMA}^{\text{V}}$ , are slow to

appear in plasma (approximately 10-24 hours after first administration of arsenic trioxide), but due to their longer half-life, accumulate more upon multiple dosing than does As<sup>III</sup>. The extent of accumulation of these metabolites is dependent on the dosing regimen. Approximate accumulation ranged from 1.4- to 8-fold following multiple as compared to single dose administration. As<sup>V</sup> is present in plasma only at relatively low levels.

In vitro enzymatic studies with human liver microsomes revealed that arsenic trioxide has no inhibitory activity on substrates of the major cytochrome P450 enzymes such as 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4/5, 4A9/11. Substances that are substrates for these P450 enzymes are not expected to interact with arsenic trioxide.

#### Elimination

Approximately 15% of the administered arsenic trioxide

dose is excreted in the urine as unchanged  $As^{III}$ . The methylated metabolites of  $As^{III}$  ( $MMA^V$  and  $DMA^V$ ) are primarily excreted in the urine. The plasma concentration of  $As^{III}$  declines from peak plasma concentration in a biphasic manner with a mean terminal elimination half-life of 10 to 14 hours. The total clearance of  $As^{III}$  over the single-dose range of 7-32 mg (administered as 0.15 mg/kg) is 49 l/h and the renal clearance is 9 l/h. Clearance is not dependent on the weight of the subject or the dose administered

over the dose range studied. The mean estimated terminal elimination half-lives of the metabolites  $MMA^V$  and  $DMA^V$  are 32 hours and 70 hours, respectively.

#### Renal impairment

Plasma clearance of  $As^{III}$  was not altered in patients with mild renal impairment (creatinine clearance of 50-80 ml/min) or moderate renal impairment (creatinine clearance of 30-49 ml/min). The plasma clearance of  $As^{III}$  in patients

with severe renal impairment (creatinine clearance less than 30 ml/min) was 40% lower when compared with patients with normal renal function (see section 4.4). Systemic exposure to MMA<sup>V</sup> and DMA<sup>V</sup> tended to be larger in patients with renal impairment; the clinical consequence of this is unknown but no increased toxicity was noted.

#### Hepatic impairment

Pharmacokinetic data from patients with hepatocellular

carcinoma having mild to moderate hepatic impairment indicate that As<sup>III</sup> or As<sup>V</sup> do not accumulate following twice-weekly infusions. No clear trend toward an increase in systemic exposure to As<sup>III</sup>, As<sup>V</sup>, MMA<sup>V</sup> and DMA<sup>V</sup> was observed with decreasing level of hepatic function as assessed by dose normalized (per mg dose) AUC.

#### Linearity/non-linearity

In the total single dose range of 7 to 32 mg (administered



as 0.15 mg/kg), systemic exposure (AUC) appears to be linear. The decline from peak plasma concentration of As<sup>III</sup> occurs in a biphasic manner and is characterized by an initial rapid distribution phase followed by a slower terminal elimination phase. After administration at 0.15 mg/kg on a daily (n=6) or twice-weekly (n=3) regimen, an approximate 2-fold accumulation of As<sup>III</sup> was observed as compared to a single infusion. This accumulation was slightly more than expected based on single-dose results.

### **5.3 Preclinical safety data**

Limited reproductive toxicity studies of arsenic trioxide in animals indicate embryotoxicity and teratogenicity (neural tube defects, anophthalmia and microphthalmia) at administration of 1-10 times the recommended clinical dose (mg/m<sup>2</sup>). Fertility studies have not been conducted with arsenic trioxide. Arsenic compounds induce chromosomal aberrations and morphological transformations of mammalian cells in vitro and in vivo. No

formal carcinogenicity studies of arsenic trioxide have been performed. However, arsenic trioxide and other inorganic arsenic compounds are recognized as human carcinogens.

## **6. Pharmaceutical particulars**

### **6.1 List of excipients**

Sodium hydroxide

Hydrochloric acid, concentrated

Water for injections

### **6.2 Incompatibilities**

In the absence of incompatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

### **6.3 Shelf life**

Unopened vial

2 years

#### After opening and dilution

Once opened the product should be used immediately.

#### **6.4 Special precautions for storage**

- Store below 30°C. Do not freeze.
- Keep vials in the original package in order to protect from light.
- Cytotoxic agent. Must be transported, stored, and used according to guidelines for handling of cytotoxic compounds.

#### **6.5 Nature and contents of container**

Transparent colorless glass vial sealed with rubber and cap containing 10 ml arsenic trioxide concentrate. Each pack contains 10 vials.

#### **6.6 Special precautions for disposal and other handling**

##### Preparation of Trisenal®

Aseptic technique must be strictly observed throughout

handling of Trisenal® since no preservative is present.

Trisenal® must be diluted with 100 to 250 ml of dextrose 50 mg/ml (5%) solution for injection or sodium chloride 9 mg/ml (0.9%) solution for injection immediately after withdrawal from the vial. PVC free plastic bags should be used. It is for single use only, and any unused portions of each vial must be discarded properly. Do not save any unused portions for later administration.

Trisenal® must not be mixed with or concomitantly administered in the same intravenous line with other medicinal products.

Trisenal® must be administered intravenously over 1-2 hours. The infusion duration may be extended up to 4 hours if vasomotor reactions are observed. A central venous catheter is not required.

The diluted solution must be clear and colorless. All

parenteral solutions must be inspected visually for particulate matter and discoloration prior to administration. Do not use the preparation if foreign particulate matter is present.

#### Procedure for proper disposal

Any unused medicinal product, any items that come into contact with the product or waste material must be disposed of in accordance with local requirements.

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**Manufactured by Nano Fanavaran Darouei Alvand (NanoAlvand)**

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