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Re: Expediente No. 04-052.110

Solicitud de patente de invención titulada: "COMPOSICIONES
FARMACÉUTICAS SOLIDAS RECUBIERTAS QUE COMPRENDEN
SUMATRIPTAN"

Solicitante: GLAXO GROUP LIMITED

Nuestra Ref.: P2004/00065

RESPUESTA AL OFICIO No.11255 NOTIFICADO POR FIJACIÓN EN LISTA No. 309,
DE FECHA 03 DE SEPTIEMBRE DE 2010
(TERCER EXAMEN DE FONDO)

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, identificado tal como aparece al pie de mi firma, en mi carácter de apoderado de la sociedad solicitante, me permito manifestar lo siguiente ante el auto emanado por ese Despacho, dentro del plazo legal previsto en el artículo 45 de la Decisión 486, en los siguientes términos:

1. En primer lugar y con el ánimo de brindar mayor claridad a la materia reivindicada, me permito presentar un **Capítulo Reivindicatorio Modificado**, que reemplaza en su totalidad al Capítulo Reivindicatorio presentado en mi memorial de respuesta al segundo examen de fondo, de fecha 27 de abril de 2009.

Así entonces, el Capítulo Reivindicatorio Modificado adjunto contiene los siguientes cambios:

- En la Reivindicación 1 se ha limitado la cantidad del componente básico a 8-15%, cuyo soporte se encuentra en el Capítulo Descriptivo, página 13, líneas 5 y 6;
- La Reivindicación 1 se ha limitado al incluir la cantidad de sumatriptan o una sal farmacéuticamente aceptable del mismo, expresado en porcentaje en peso con base en el peso seco de la forma de dosificación; soporte de lo anterior se encuentra en el Capítulo Descriptivo, página 16, línea 1;
- Se ha limitado la cantidad del agente de absorción (que facilita el efecto capilar y en adelante se refiere como agente de acción capilar), específicamente a 12-55%, basado en el peso seco de la forma de dosificación. Lo anterior encuentra soporte en el Capítulo Descriptivo, página 14 línea 24, y página 15, líneas 1 a 5;
- Se ha eliminado la Reivindicación 3, y las reivindicaciones restantes se han reenumerado.

Valga anotar que la anterior modificación cumple a cabalidad con lo estipulado en el Artículo 34 de la Decisión 486, ya que ésta de ninguna manera implica una ampliación de la protección correspondiente a la divulgación contenida en la solicitud inicial.

2. a- El Examinador señala que las patentes WO 92/15295 (D1) y WO98/38983 (D2), afectan el nivel inventivo de la presente invención.

El Examinador argumenta que D1 divulga una composición farmacéutica sólida recubierta con una película que elimina el sabor desagradable del fármaco, para administrar oralmente sumatriptan, útil en el tratamiento de condiciones asociadas con el dolor cefálico, particularmente, migraña. Así, la composición farmacéutica divulgada en D1 contiene sumatriptan (25-200mg) en base libre, excipientes farmacéuticamente aceptables, tales como: agentes de relleno, desintegrantes y lubricantes. El Examinador concluye que la única diferencia entre D1 y la presente invención es el componente básico de un par efervescente. Sobre este punto, el Examinador acepta que dicha diferencia proporciona una forma farmacéutica agradable al gusto y deglutible, que permite una rápida absorción del fármaco logrando una velocidad de acción mayor que la que se obtiene con formas de dosificación sólidas convencionales.

Sin embargo, el Examinador señala que D2 enseña que tal componente básico de un par efervescente (bicarbonato de sodio) en composiciones sólidas deglutibles de un fármaco (que para el caso de D2 es paracetamol), permite una rápida absorción del fármaco, logrando una velocidad de acción mayor que la obtenida con formas de dosificación convencional sólida.

El Examinador concluye que una persona medianamente versada en la materia habría incluido las enseñanzas de D2 en las composiciones desarrolladas en D1, con la expectativa de alcanzar una

rápida absorción del fármaco y lograr una velocidad de acción mayor al comparar con formas de dosificación sólida convencional.

b- i) En primer lugar, aparentemente el Examinador no ha comprendido claramente la naturaleza de la presente invención, en qué consiste la composición farmacéutica reivindicada, ni sus diferencias con las composiciones del arte previo.

Me permito aclarar respetuosamente que la presente invención proporciona una forma de dosificación sólida que puede ser digerida completamente, con la ventaja de una rápida absorción lograda por las propiedades efervescente una vez está en el estómago. La composición aquí reivindicada alcanza el estómago sustancialmente intacta, para rápidamente desintegrarse y disolverse en el mismo. Así, la rápida dispersión y absorción del sumatriptan se alcanza gracias a la combinación de una cantidad definida del componente básico de una pareja efervescente y una cantidad definida de un relleno insoluble que contiene un agente de acción capilar.

Por lo tanto, las formas de dosificación sólidas reivindicadas en la presente invención representan una aproximación muy diferente a las enseñanzas de D1 y/o D2. La presente invención se fundamenta en la naturaleza insoluble del relleno que comprende un agente de acción capilar, con el fin de asegurar que el fluido gástrico penetre a través de todo el recubrimiento, de forma inmediata. Lo anterior resulta en que el gas efervescente se produce a través de todo el recubrimiento de forma casi simultánea, produciendo una fuerza de empuje en contra de los excipientes insolubles, y logrando que la tableta se desintegre en el estómago rápidamente. Gracias a este mecanismo, es posible utilizar una baja cantidad del componente básico en la formulación (tanto en términos absolutos como en porcentaje), para alcanzar un efecto máximo en el recubrimiento de la tableta.

ii) Ahora bien, como se describe claramente en el Capítulo Descriptivo de la presente invención, las diferencias entre las composiciones de D1 y la presente invención proporcionan ventajas sorprendentes e inesperadas en términos de características farmacocinéticas, como se ilustra en las Tablas 1A, 1B, 3, 4, 5 y 6, y en las Figuras 1 a 3, donde se enseña comparativamente el perfil de disolución y las características farmacocinéticas de ambas invenciones.

D1 se refiere a una formulación convencional sólida de sumatriptan, en donde el recubrimiento se usa simplemente para enmascarar el sabor desagradable del ingrediente activo y para reducir la formación de polvo durante el embalaje o administración. D1 no se refiere a la necesidad de desarrollar formas farmacéuticas con un rápido comienzo en la acción, y menos aún sugiere el uso de una pareja efervescente para producir los cambios farmacocinéticos necesarios.



El Examinador sugiere que la única diferencia entre las composiciones de la presente invención y lo divulgado en D1 es el uso de un componente básico de una pareja efervescente, sin embargo, difiere respetuosamente de esa posición. Al examinar lo divulgado en D1, es fácil inferir que la persona medianamente versada en la materia no habría podido modificar las composiciones de D1 (como lo sugiere el Examinador) para llegar de manera obvia a la presente invención. Por ejemplo, si al único ejemplo ilustrado en D1, tan solo se adicionara una pareja efervescente (en las cantidades ilustradas en los ejemplos de la presente invención), resultaría una tableta que no exhibiría una rápida disolución al exponerse a los fluidos gástricos, en su lugar, la tableta se desintegraría por un proceso de erosión de la superficie como resultado del relleno (lactosa), que es predominantemente soluble. Aunque D1 también contiene referencias a otros posibles rellenos, incluyendo algunos insolubles, la presente invención requiere necesariamente que el relleno sea insoluble, lo que de ninguna manera es sugerido en D1. Claramente, la decisión de incluir específicamente el relleno insoluble es una elección creativa de los inventores en el presente caso. El único ejemplo de D1 incluye un relleno soluble, en donde no se especifica una cantidad adecuada del mismo en la tableta. Lo anterior aleja inevitablemente al técnico medio de la decisión de seleccionar un único relleno insoluble, en una cantidad específica, tal y como se realiza en la presente invención.

iii) De otra parte, D2 revela una formulación de paracetamol de rápida acción que contiene bicarbonato de sodio, en la forma de una cápsula o tableta digerible.

Para empezar, D2 divulga formulaciones farmacéuticas de un ingrediente activo completamente diferente al sumatriptán. El paracetamol y el sumatriptán no son químicamente similares, por lo tanto, las enseñanzas de D2 no pueden simplemente trasladarse a otro ingrediente activo sin el despliegue de actividad inventiva. Esto se ilustra claramente al reconocer las diferencias entre la presente invención y las formulaciones enseñadas en D2:

- El efecto efervescente del bicarbonato de sodio es significativamente mayor que el producido por el carbonato de calcio. D2 explica este fenómeno como una interacción favorable del bicarbonato de sodio y el paracetamol, por lo que ningún técnico medio en la materia podría esperar, de manera previsible, que tal interacción y sus ventajas podrían ocurrir con todos los otros ingredientes activos, incluyendo el sumatriptán;
- La presente invención utiliza una baja cantidad del componente básico (8-15% en peso), mientras que en D2 se ilustran composiciones con 300mg, y una relación bicarbonato de sodio:paracetamol de, por lo menos, 0.74:1. Lo anterior se evidencia en los ejemplos de D2 que ilustran tabletas con un exceso de 400mg,

mientras que en los ejemplos de la presente invención, la cantidad de bicarbonato de sodio se encuentra en el rango de los 40mg. Ahora bien, teniendo en cuenta las limitaciones incluidas en el Capítulo Reivindicatorio Modificado adjunto, en cuanto a las cantidades del componente básico y el sumatriptan, la relación entre dichos componentes (8-15% y 20-35% en peso, respectivamente) se opone a lo enseñado en D2;

- La presente invención permite una dispersión y absorción *in vivo* más rápida para una composición que usa una cantidad considerablemente menor de componente básico;
- La naturaleza de los materiales de relleno, como se ha mencionado anteriormente, es fundamental en la presente invención. En D2 no se hace referencia alguna a la importancia de que el relleno sea insoluble y contenga un agente de acción capilar, y menos aún, se especifican las cantidades en las que se deben encontrar en la formulación farmacéutica.

La anteriores diferencias resultan de crucial importancia en la presente invención, ya que precisamente es el uso de una cantidad significativa del relleno insoluble (que incluye un agente de acción capilar), la que permite usar el componente básico del par efervescente en pequeñas cantidades, y sin embargo, alcanzar una rápida dispersión y absorción de la tableta. Como resultado, las tabletas de la presente invención se desintegran por un mecanismo diferente al enseñado para las tabletas efervescentes tradicionales de D2.

En conclusión, de ninguna manera, la persona medianamente versada en la materia encontraría motivación alguna en D2 para reducir la cantidad del componente básico y además introducir la cantidad necesaria de relleno insoluble (incluyendo un agente de acción capilar) con el propósito de lograr una rápida desintegración de la tableta en el estómago, mediante la acción específica de la producción de gas efervescente a través de todo el recubrimiento, al producir una fuerza de empuje en contra de los excipientes insolubles.

iv) Adicionalmente, es importante señalar que no existe motivación alguna en el arte previo para combinar las enseñanzas de D1 y D2, y esperar los resultados alcanzados. Nada en D1 y/o D2 enseña o incluso sugiere que, con el fin de proporcionar una formulación de sumatriptan con una biodisponibilidad mejorada y un rápido inicio de acción, la forma de dosificación sólida debía encontrarse recubierta con una capa que se desintegra y dispersa en el estómago, y que adicionalmente contiene un relleno insoluble y una menor cantidad de componente. En conclusión, el arte previo no proporciona información alguna sobre cómo formular una forma de dosificación sólida que libere el sumatriptan sólo una vez ha llegado a

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estómago, y en donde el recubrimiento se desintegra y dispersa rápidamente facilitando la absorción inmediata de una dosis completa.

Según la aproximación del Examinador, es claro que después de desarrollar la formulación de la presente invención con las propiedades y efectos sorprendentes deseados, la misma resulta obvia después de preparada. Sin embargo, el análisis en retrospectiva como el anterior, o tipo “hindsight”, debe evitarse estrictamente en el análisis de patentabilidad de una invención, ya que, en el presente caso, antes que la invención fuera desarrollada, el arte previo existente no había considerado una formulación de sumatriptan con una pareja efervescente, que contiene una menor cantidad de componente básico y un relleno insoluble. Es más, para efectuar el análisis de patentabilidad, tal como lo menciona el Manual Andino de Patentes (MAP) “toda objeción respecto a la falta de nivel inventivo de una invención debe probarse a partir del estado de la técnica” (mi subrayado).

El análisis de nivel inventivo no puede estar basado en si es o no posible obtener la invención reclamada, pues claramente era posible, toda vez que la composición reivindicada existe. Esta aproximación conllevaría a que ninguna invención sería patentable, volviendo así inoperante el sistema de patentes. De igual manera, el criterio no puede involucrar la cuestión de si las técnicas aplicadas en el desarrollo de la invención son comunes u obvias, sino más bien si la sal podía derivarse de manera evidente del arte previo. El hecho de implementar herramientas conocidas en el estado de la técnica como las divulgadas en D2 no desvirtúa automáticamente el nivel inventivo de una invención. El Examinador parece desatender la jurisprudencia establecida por el Tribunal de Justicia Andino, que con relación al nivel inventivo en el área de los inventos químicos y biotecnológicos ha manifestado que frecuentemente “...**aplicando procedimientos conocidos** pueden obtenerse resultados inesperados para una persona normalmente versada en la materia...”, pero que “...por ello, el juicio del nivel inventivo no puede ser elaborado con criterios generales, sino que dependerá de las especiales circunstancias de cada caso.”¹

Así las cosas, solicito respetosamente al examinador explicar de manera detallada las enseñanzas de D1 y/o D2 que conduzcan a la persona medianamente versada en la materia a esperar inequívocamente que la materia revelada en D2, con los cambios introducidos en la presente invención, podría aplicarse en las formulaciones de D1, y proporcionaría los resultados ventajosos en las características farmacocinéticas y de disolución que se ilustran en el Capítulo Descriptivo, sin necesidad de realizar experimentación adicional alguna.

En este punto debo subrayar que el MAP establece que resultados y mejoras sorprendentes constituyen indicios de no obviedad, de tal manera que propiedades ventajosas constituyen

¹ Proceso 105-IP-2000, página 7, líneas 45 a 50.

indicios aceptables de nivel inventivo.² Como evidencia de tales ventajas, adjunto a este memorial como Anexo 1, el artículo de Sheftell et al, en donde se evidencian los resultados de dos estudios que comparan el tiempo de inicio del alivio del dolor de migraña moderada a severa, al administrarse una formulación en tabletas de rápida desintegración y liberación de sumatriptan de 50 y 100mg y placebo.

Adicionalmente, no puede olvidarse que como lo ha determinado el Tribunal Andino de Justicia, “lo obvio es aquello que salta a la vista de manera clara y directa; lo “que se encuentra o pone delante de los ojos, muy claro o que no tiene dificultad”. Lo evidente consiste en la “certeza clara y manifiesta de la que no se puede dudar, cierto, claro, patente y sin la menor duda”. Continúa el Tribunal diciendo que “una invención goza de nivel inventivo cuando a los ojos de un experto medio en el asunto de que se trate, se necesita algo más que la simple aplicación de los conocimientos técnicos en la materia para llegar a ella, es decir, que de conformidad con el estado de la técnica el invento no es consecuencia clara y directa de dicho estado.”³ En el presente caso, queda demostrado que las composiciones de sumatriptan de la presente solicitud son inventivas, ya que no hay enseñanzas directas en el arte previo para su preparación, ni sugerencias de los resultados superiores obtenidos.

3. Finalmente, me permito reiterar que para el concepto inventivo comprendido en la presente solicitud, además de Europa (EP1284974), Estados Unidos (US6667314), Australia (AU20011252482) y Canadá (CA2408909), ha sido otorgado hasta el momento el privilegio de patente en Austria, Bélgica, Bulgaria, Canadá, China, Chipre, República Checa, Dinamarca, Estonia, Finlandia, Francia, Alemania, Inglaterra, Grecia, Hong Kong, India, Irlanda, Israel, Italia, Japón, Corea del Sur, Latvia, Lituania, Luxemburgo, Malasia, México, Mónaco, Holanda, Nueva Zelanda, Pakistán, Filipinas, Polonia, Portugal, Rumania, Rusia, Singapur, República eslovaca, Eslovenia, Sudáfrica, España, Suecia, Suiza, Taiwán y Turquía.

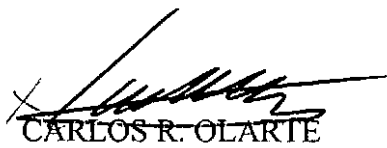
Si bien es cierto que las concesiones de patentes en oficinas de otros países no son vinculantes en el sentido que obliguen a la SIC a tomar una decisión en el mismo sentido, considero que dichas concesiones sugieren el cumplimiento de los requisitos de patentabilidad de la materia reivindicada, ya que los criterios de evaluación y estudio aplicados para concluir la aceptación de dichas patentes resultan equivalentes a los que la SIC debe emplear.

² Manual Andino de Patentes. OMPI, EPO, Secretaría de la Comunidad Andina. 2004. ISBN9978-43-855-6. Sección 4.6.1.

³ Proceso 10-IP-2009, página 12, párrafos 5 y 6.

4. Por todo lo anterior, considero que las objeciones presentadas por el Examinador en su examen de fondo 2751 han sido resueltas y por consiguiente solicito respetuosamente que se tengan por cumplidos los requisitos de patentabilidad, y se proceda con la concesión de la patente.

Atentamente,


CARLOS R. OLARTE

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T.P. 74.295

Anexos:

- Capítulo Reivindicatorio Modificado.
- Anexo 1: Sheftell F., et al, "Two replicated randomized, double-blind, placebo-controlled trials of the time to onset of pain relief in the acute treatment of migraine with a Fast-disintegrating/rapid-release formulation of Sumatriptan tablets". Clinical Therapeutics Vol. 27, Number 4 (2005).

CAPITULO REIVINDICATORIO MODIFICADO
(Tercer Examen de Fondo)

1. Una composición farmacéutica en forma de dosificación sólida recubierta con película para administración oral, y la cual al administrarse se desintegra y se dispersa en el estómago, que comprende sumatriptan o una sal farmacéuticamente aceptable o solvato del mismo como ingrediente activo, donde la cantidad de sumatriptan, expresado como el peso de base libre, está en el rango de 20 mg a 150 mg; y en donde el sumatriptan o de una sal farmacéuticamente aceptable del mismo comprende entre un 20% y 35% en peso, basado en el peso seco de la forma de dosificación;

la cual comprende el componente básico de un par efervescente, un desintegrante y un relleno insoluble, donde el componente básico comprende de 8 a 15% en peso basado en el peso seco de la forma de dosificación, el desintegrante comprende de 0.5 a 10% en peso, basado en el peso seco de la forma de dosificación, y el relleno insoluble comprende de 35 a 80% en peso, basado en el peso seco de la forma de dosificación, dicho relleno insoluble incluye un agente de acción capilar el cual comprende de 12 a 55% en peso basado en el peso seco de la forma de dosificación, todos los porcentajes con base en el peso en seco de la forma de dosificación; y

donde más del 70% del ingrediente activo se disuelve en un fluido gástrico simulado durante cinco minutos en un aparato USP II a una velocidad de paletas de 10 r.p.m.

2. Una composición según lo reclamado en la Reivindicación 1 donde el sumatriptán está presente como sal farmacéuticamente aceptable la cual provee un componente con carácter ácido en un ambiente acuso.

3. Una composición según lo reclamado en cualquiera de las Reivindicaciones 1 o 2 la cual adicionalmente comprende un componente ácido de un par efervescente, donde dicho componente ácido (incluyendo la sal farmacéuticamente aceptable de sumatriptan cuando esta funciona como tal) comprende de 5 a 50% en peso, con base en el peso en seco de la forma de dosificación.

4. Una composición según lo reclamado en cualquiera de las Reivindicaciones 1 a 3 donde el componente básico del par efervescente comprende bicarbonato de sodio, el desintegrante comprende croscarmelosa sódica, y el relleno insoluble comprende celulosa microcristalina o una mezcla de fosfato de calcio dibásico anhidro y celulosa microcristalina.

5. Una composición según lo reclamado en cualquiera de las Reivindicaciones 1 a 4, donde el sumatriptan está presente en la forma de su sal succinato (1:1).

6. Una composición según lo reclamado en cualquiera de las Reivindicaciones 1 a 6 en forma de una tableta.

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Two Replicate Randomized, Double-Blind, Placebo-Controlled Trials of the Time to Onset of Pain Relief in the Acute Treatment of Migraine with a Fast-Disintegrating/Rapid-Release Formulation of Sumatriptan Tablets

Fred D. Sheftell, MD¹; Carl G.H. Dahlöf, MD, PhD²; Jan Lewis Brandes, MD³; Reto Agosti, MD⁴; Martin W. Jones, PhD⁵; and Pamela S. Barrett, PharmD⁶

¹New England Center for Headache, Stamford, Connecticut; ²Gothenburg Migraine Clinic, Gothenburg, Sweden; ³Nashville Neuroscience Group, Nashville, Tennessee; ⁴Headache Center Hirslanden Zürich, Zürich, Switzerland; ⁵GlaxoSmithKline, Greenford, United Kingdom; and ⁶GlaxoSmithKline, Research Triangle Park, North Carolina

ABSTRACT

Background: The gastric stasis that commonly accompanies migraine headache may impair absorption of conventional oral tablets in the stomach. A fast-disintegrating/rapid-release formulation of sumatriptan has been developed to enhance tablet disintegration and drug dispersion and potentially improve absorption.

Objective: Two studies were conducted comparing the time to onset of relief from moderate or severe migraine pain with the fast-disintegrating/rapid-release formulation of sumatriptan tablets 50 and 100 mg and placebo.

Methods: These were 2 identically designed randomized, double-blind, parallel-group studies. Sumatriptan 50 or 100 mg or placebo was taken on an outpatient basis to treat a single moderate or severe migraine attack. Using a personal digital assistant, patients recorded the time of dosing and the time at which pain severity reached none or mild (ie, pain relief) or none (ie, pain free) in real time so that the time to onset of relief could be measured as a continuous variable. Onset of relief was defined as the earliest time point at which a statistically significant difference in pain relief compared with placebo was achieved and maintained through 2 hours after dosing. Before dosing and at predetermined time points after dosing, patients also provided an assessment of migraine pain as none, mild, moderate, or severe. At a clinic visit within 1 week after treatment of the migraine attack, patients were queried about adverse events. For each adverse event, investigators recorded whether study medication was considered the cause. Data analyses were undertaken for each study individually and, in post hoc analyses of the pri-

mary and key secondary end points, on pooled data from both studies.

Results: The 2 studies comprised 2696 patients: 902 received sumatriptan 50 mg, 902 received sumatriptan 100 mg, and 892 received placebo. Patients' mean age ranged from 40.2 to 40.8 years across treatment groups, and most patients were female (83%–87%) and white (92%–93%). In the analysis of pooled data, sumatriptan tablets provided significantly more effective pain relief compared with placebo as early as 20 minutes after dosing with the 100-mg dose and as early as 30 minutes after dosing with the 50-mg dose ($P \leq 0.05$). Similar results were observed for the individual studies: in study 1, sumatriptan tablets were significantly more effective than placebo at 25 minutes with the 100-mg dose and at 50 minutes with the 50-mg dose; in study 2, sumatriptan tablets were significantly more effective than placebo at 17 minutes for the 100-mg dose and at 30 minutes for the 50-mg dose ($P \leq 0.05$). In the pooled data, the cumulative percentages of patients with pain relief by 2 hours after dosing were 72% for the 100-mg dose and 67% for the 50-mg dose, compared with 42% for placebo ($P \leq 0.001$, both sumatriptan doses vs placebo). The cumulative percentages of patients with a pain-free response by 2 hours were 47% for the 100-mg dose,

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40% for the 50-mg dose, and 15% for placebo ($P \leq 0.001$, both sumatriptan doses vs placebo). In the individual studies, significantly more patients receiving either sumatriptan dose were migraine free 2 hours after dosing and had sustained pain relief and a sustained pain-free response over 24 hours compared with placebo ($P \leq 0.001$, both sumatriptan doses vs placebo). The only drug-related adverse events reported in $>2\%$ of patients in any treatment group in either study were nausea (both studies: 3% sumatriptan 100 mg, 2% sumatriptan 50 mg, 1% placebo) and paresthesia (study 1: $<1\%$ sumatriptan 100 mg, $<1\%$ sumatriptan 50 mg, 0% placebo; study 2: 3% sumatriptan 100 mg, 1% sumatriptan 50 mg, $<1\%$ placebo).

Conclusions: In these studies, sumatriptan tablets in a fast-disintegrating/rapid-release formulation were effective for the acute treatment of moderate to severe migraine pain, were generally well tolerated, and achieved an onset of pain relief as early as 20 minutes for 100 mg and as early as 30 minutes for 50 mg. (*Clin Ther.* 2005;27:407-417) Copyright © 2005 Excerpta Medica, Inc.

Key words: migraine, sumatriptan, fast-disintegrating/rapid-release formulation.

INTRODUCTION

To facilitate customization of migraine therapy to patients' needs, triptans are available in several formulations, including oral tablets to be swallowed with liquid, orally dissolving tablets to be taken without liquid, subcutaneous injection, nasal sprays, and, in some countries, a suppository.¹ Overall, those with migraine prefer oral tablets to other forms of migraine medication for such reasons as convenience, familiarity, and ease of use.²⁻⁴ Given a choice of formulations, patients generally prefer to use tablets for the initial treatment of migraine attacks compared with all other forms.² When they do choose an injectable or nasal spray form over tablets, it is often for speed of action, which is cited by migraineurs as a principal important attribute of migraine medication and a key determinant of their satisfaction with therapy.^{2,5-9} In some patients, the onset of pain relief has been shown to differ significantly from placebo, occurring as early as 10 minutes after dosing with the injectable form, as early as 15 minutes after dosing with the nasal spray form, and as early as 30 minutes after dosing with oral tablets (including conventional tablets swallowed

with liquid and orally dissolving tablets taken without liquid).¹⁰⁻¹⁵

A fast-disintegrating/rapid-release form of sumatriptan tablets has been developed to facilitate tablet disintegration and dispersion and potentially improve absorption. This form employs RT Technology™ (GlaxoSmithKline, Research Triangle Park, North Carolina), which draws water into the tablet to cause it to swell and break apart. This creates the potential for early absorption into the bloodstream. Hence, the fast-disintegrating/rapid-release formulation of sumatriptan may be better absorbed than conventional tablets in the context of the gastric stasis that can accompany migraine. In an in vitro study under conditions simulating gastric stasis, the fast-disintegrating/rapid-release tablet dissolved 5 times faster than the conventional tablet.¹⁶ Additionally, a pharmacokinetic study in healthy volunteers showed quicker absorption 0 to 2 hours after dosing with the reformulated tablet.¹⁶ Compared with the conventional tablet, the AUC_{0-2} of the fast-disintegrating/rapid-release tablet was, on average, 1% (50 mg) and 8% greater (100 mg) and maximal sumatriptan levels were attained, on average, 10 minutes earlier (50 mg) and 15 minutes earlier (100 mg). Although the fast-disintegrating/rapid-release form appears to be absorbed more quickly than the conventional tablets, the reformulated tablet is considered bioequivalent to the conventional tablets in terms of C_{max} and overall 24-hour exposure (AUC_{0-24}) in healthy volunteers,¹⁶ in accordance with US and European Union regulatory definitions of bioequivalence.^{17,18} In a randomized, double-blind, placebo-controlled trial in patients treating a migraine attack when pain was mild, the fast-disintegrating/rapid-release tablet was more effective than placebo with respect to pain-free response and migraine-free results (no pain and no associated symptoms) 2 hours after dosing and sustained pain-free response from 2 through 24 hours after dosing.¹⁹ In addition, the tolerability profile of the reformulated tablet appeared not to differ from that of the conventional tablet.

This article describes the results of 2 identically designed studies of the time to onset of pain relief with the fast-disintegrating/rapid-release form of sumatriptan tablets 50 and 100 mg in patients with moderate or severe migraine pain. The studies employed a personal digital assistant (PDA) and survival analysis methodology to assess the onset of pain relief. Use of the PDA, which was programmed to record the time to

pain relief and pain-free response in real time, permitted measurement of time to the onset of pain relief as a continuous variable and thereby provided a more accurate assessment of the onset of therapeutic efficacy in migraine compared with previous migraine studies.¹⁰⁻¹⁵ Previous studies have measured pain relief as a discrete variable at certain time points (eg, 30 minutes, 1 hour, and 2 hours after dosing), a method that addresses efficacy at the specific time points but does not provide a sensitive estimate of the onset of pain relief.

PATIENTS AND METHODS

Inclusion and Exclusion Criteria

Eligible men and women were aged between 18 and 65 years, had a ≥ 6 -month history of migraine with or without aura as defined in the 1988 International Headache Society criteria,²⁰ had 1 to 6 migraines per month during the 3 months before the screening visit, and had a history of moderate to severe pain during migraine attacks. Women could not be pregnant and were required to be using adequate contraception.

Patients were excluded if they had uncontrolled hypertension (sitting diastolic blood pressure >95 mm Hg or systolic blood pressure >160 mm Hg) at screening; a history of epilepsy or seizures within 5 years before screening; confirmed or suspected cardiovascular or cerebrovascular disease; basilar or hemiplegic migraine; or headache on ≥ 15 days per month in any of the 3 months before screening. Other exclusion criteria included the use of migraine prophylactic medication containing ergotamine, an ergot derivative, or methysergide; use of a monoamine oxidase inhibitor within 2 weeks before screening; and, in countries where the combination of a selective serotonin reuptake inhibitor and a triptan is not allowed, the need for a selective serotonin reuptake inhibitor. Previous experience with triptan therapy was not an exclusion criterion.

Study Procedures

The 2 trials were identically designed randomized, double-blind, placebo-controlled studies. The protocols were approved by ethics committees or institutional review boards for each study site. Study 1 (GlaxoSmithKline protocol SUM30047) was conducted at 153 centers in the United States and Canada. Study 2 (GlaxoSmithKline protocol SUM30053) was conducted at 119 centers in Europe. All patients provided written informed consent.

Patients meeting the eligibility criteria were randomized in a 1:1:1 ratio to receive the fast-disintegrating/rapid-release form of sumatriptan tablets 50 or 100 mg or placebo for the outpatient treatment of a single migraine attack characterized by moderate or severe pain. The randomization code was generated by the study sponsor and was not accessible to investigators. Each investigator was provided with a unique set of numbers to be assigned to patients. On study entry, patients who had given their informed consent were assigned the lowest available number based on the chronological order of their presentation at the study site. When a patient became eligible for randomization, study personnel phoned an automated registration and medication ordering system and received a randomization number corresponding to 1 of the 3 blinded treatments.

Prohibited medications included ergotamine-containing and ergot-type medications and triptans (other than study medication) within 24 hours of the use of study medication; analgesics, antiemetics, and nontriptan acute migraine medications from 6 hours before through 2 hours after the use of study medication; and monoamine oxidase inhibitors throughout the study. Patients experiencing a recurrence of headache (ie, a return of moderate or severe pain after having mild or no pain 2 hours after the initial dose of study medication) could take a second dose of study medication or a nonprohibited acute migraine medication between 2 and 24 hours after dosing. Patients whose pain was not reduced to mild or none within 2 hours of the first dose of study medication could take a nonprohibited acute migraine medication (ie, rescue medication) from 2 through 24 hours after dosing.

Study Assessments

Patients were trained in the use of a handheld PDA as an electronic diary for recording data. The PDA operated as a study tool only, and no other functions were available to patients. The device was programmed to record in real time the time to the onset of pain relief and to pain-free response. The data collection and management system was extensively tested, cross-checked, and verified before the studies to ensure accuracy, consistency, completeness, and reliability of the data. Research staff at the study sites were trained and certified in the use of the PDA to ensure standardization of methods and quality assurance procedures.

For the continuous measurement of pain, the patient tapped the PDA screen to record the time of dosing and tapped it again when pain severity reached none or mild (ie, pain relief) or none (ie, pain free). In addition, at predetermined discrete time points, pain was rated on the 4-point scale (ie, none, mild, moderate, severe) used in previous migraine trials to measure a medication's effects on pain severity.¹⁰⁻¹⁵

The PDA dated and time-stamped all entries. Electronic diary assessments included the time and date of onset of the treated migraine attack; the time and date of dosing with study medication; the severity of migraine pain (mild, moderate, or severe) at the onset of the attack and immediately before dosing; the time elapsed from dosing to mild pain and no pain; pain severity and the presence or absence of nausea, vomiting, photophobia, and phonophobia 2 and 4 hours after dosing; use of a second dose of study medication; and headache recurrence.

Patients returned the electronic diary and a paper record of their use of rescue medication to the clinic at a visit within 1 week after treatment of the migraine attack. At this visit, patients were queried about adverse events, defined as any untoward medical occurrences experienced at any time during the study, regardless of suspected cause. For each adverse event, investigators recorded whether it was considered related to study medication.

Efficacy End Points

The primary efficacy end point was the time to onset of pain relief, defined as the earliest time at which sumatriptan 100 mg was significantly effective in reducing moderate or severe predose pain to mild or no pain compared with placebo and efficacy was sustained through 2 hours after dosing. Key secondary efficacy end points included the time to onset of pain relief for sumatriptan 50 mg compared with placebo and the time to onset of pain-free response for sumatriptan 50 and 100 mg compared with placebo. Pain-free response was defined as a reduction in moderate or severe predose pain to no pain.

Other efficacy end points included the following categorical measures: the percentage of patients who were migraine free (ie, no pain and no associated symptoms of nausea, vomiting, photophobia, or phonophobia) 2 hours after dosing; the percentage of patients with sustained pain relief and sustained pain-free response (ie, pain relief or pain-free response from

2 through 24 hours after dosing with no use of a second dose of study medication or rescue medication); the percentage of patients taking rescue medication or a second dose of study medication during the 24-hour period after dosing; and the percentage of patients with a recurrence (ie, return of moderate or severe pain in the 24 hours after dosing in patients who had experienced pain relief 2 hours after dosing).

Statistical Methods

Kaplan-Meier survival analysis techniques²¹ were used to derive time-to-event curves for sumatriptan tablets 50 and 100 mg and placebo for the cumulative percentages of patients with pain relief and pain-free response through 2 hours after dosing. Differences between each active treatment and placebo in the time-to-event curves for pain relief and pain-free response were tested with 2-sided log-rank tests.²¹ In the analyses of pooled data, the log-rank tests were stratified by study.

P values ≤ 0.05 were considered statistically significant. If a significant difference was observed between an active treatment and placebo in the time-to-pain-relief or time-to-pain-free curves for 0 to 2 hours, the time to the onset of pain relief or to pain-free response was identified by evaluating the differences in the curves using various time points in a fixed sequence. The times to onset of pain relief and onset of pain-free response were defined as the earliest times at which the respective time-to-event curves for sumatriptan differed significantly from those for placebo. Once statistical significance was lost, earlier time points were not considered statistically significant with respect to the onset of pain relief.

To control for type I error at 0.05 for all primary and key secondary comparisons, a testing method was employed with the following fixed sequence: (1) time to pain relief for sumatriptan tablets 100 mg versus placebo (the primary end point); (2) time to pain-free response for sumatriptan tablets 100 mg versus placebo and time to pain relief for sumatriptan tablets 50 mg versus placebo (key secondary end points); and (3) time to pain-free response for sumatriptan tablets 50 mg versus placebo (key secondary end point). The previous comparison in the sequence must have been statistically significant for the next comparison in the sequence to be tested. For all categorical end points except headache recurrence, the Fisher exact test was used to compare each active treatment with placebo in the individual studies.

Efficacy data were analyzed for the intent-to-treat (ITT) population, defined as patients who treated a migraine attack and provided ≥ 1 postdose efficacy assessment. The studies were designed to compare both sumatriptan doses with placebo but not to compare the 2 sumatriptan doses. Sample-size calculations revealed that in each study, ~457 patients in each group needed to treat a migraine attack for the study to have 90% power to detect a difference at time t between a 12% incidence of pain relief for an active treatment and a 7% incidence of pain relief for placebo (ie, a 5% difference at $t < 30$ minutes). The 5% difference between an active treatment and placebo was used in the sample-size calculations on the basis of previous data suggesting that this amount of difference could be detected within 30 minutes after dosing.^{22,23} The primary and key secondary end points were analyzed both for the individual studies and using pooled data from both studies. The analyses of pooled data were considered post hoc.

The main objective of the individual studies was to evaluate the speed of onset of efficacy of sumatriptan fast-disintegrating/rapid-release tablets compared with placebo. Because the 2 studies had identical designs and were conducted simultaneously, the data could be combined to obtain a single time to onset of pain relief and time to onset of pain-free response for sumatriptan tablets 50 mg and 100 mg. Although the pooled data analyses were post hoc, results from these analyses, along with the results from the individual studies, can be expected to provide an accurate description of the efficacy of both sumatriptan doses from the onset of a migraine attack through 2 hours after dosing for use in the clinical setting.

Adverse-event data were summarized for the safety population, defined as all patients who treated a migraine attack with study medication. The incidence of specific drug-related adverse events was calculated. Inferential statistical analyses were not performed on the adverse-event data, as there were no predetermined adverse events of special interest.

RESULTS

Patient Populations

In study 1, 1665 patients were randomized to treatment (556 sumatriptan 50 mg, 551 sumatriptan 100 mg, 558 placebo); 1477 patients treated a migraine attack with study medication and were included in the safety population (494 sumatriptan 50 mg, 488 sumatrip-

tan 100 mg, 495 placebo); and 1366 treated a migraine attack and provided ≥ 1 postdose efficacy assessment and were included in the ITT population (448 sumatriptan 50 mg, 462 sumatriptan 100 mg, 456 placebo). Comparable numbers of patients were included in study 2 (1475 in the safety population, 1330 in the ITT population). Among randomized patients, the primary reason for exclusion from the safety and ITT populations was not having the occasion to treat a migraine attack during the study (study 1: 7%, 7%, and 8% for sumatriptan 50 mg, 100 mg, and placebo, respectively; study 2: 9%, 10%, and 9%), followed by loss to follow-up (study 1: 2%, 1%, and 2%; study 2: 1%, <1%, and <1%). Comparable proportions of patients across groups withdrew prematurely from the studies (Table I).

Demographic and baseline clinical characteristics were comparable among treatment groups and between studies. Using the pooled data, patients' mean age ranged from 40.2 to 40.8 years across treatment groups, and most patients were female (83%–87%) and white (92%–93%). In the individual studies, the majority of patients (65%–72%) had a history of migraine without aura. Across treatment groups and studies, most patients (77%–84%) were using triptans at study entry or had a history of triptan use (Table I).

Time to Onset of Pain Relief

Pain intensity immediately before treatment was moderate or severe in all patients in both studies. Using pooled data, the cumulative percentages of patients with pain relief by 2 hours after dosing were 67% for sumatriptan tablets 50 mg and 72% for sumatriptan tablets 100 mg, compared with 42% for placebo ($P \leq 0.001$, both sumatriptan doses vs placebo) (Figure 1). A similar pattern of results was observed in the individual studies (Table II).

In the analysis of the individual studies, the time to onset of pain relief for sumatriptan 100 mg was 25 minutes in study 1 and 17 minutes in study 2 (Table II). In the analysis of pooled data, the time to onset of pain relief with the 100-mg dose was 20 minutes (6% of patients reported pain relief vs 4% with placebo; $P \leq 0.05$) (Figure 2).

For sumatriptan 50 mg, the time to onset of pain relief was 50 minutes in study 1 and 30 minutes in study 2 (Table II). In the analysis of pooled data, the time to onset of pain relief was 30 minutes (19% of patients re-

Table I. Patient disposition and demographic and clinical characteristics.

	Sumatriptan 50 mg	Sumatriptan 100 mg	Placebo
Patient disposition			
Randomized, no.			
Study 1	556	551	558
Study 2	561	550	555
Pooled studies	1117	1101	1113
Safety population, no.			
Study 1	494	488	495
Study 2	496	485	494
Pooled studies	990	973	989
Intent-to-treat population, n/N (%)			
Study 1	448/494 (91)	462/488 (95)	456/495 (92)
Study 2	454/496 (92)	440/485 (91)	436/494 (88)
Pooled studies	902/990 (91)	902/973 (93)	892/989 (90)
Premature withdrawals, n/N (%)			
Study 1	72/556 (13)	67/551 (12)	75/558 (13)
Study 2	66/561 (12)	65/550 (12)	61/555 (11)
Demographic characteristics			
Mean (SD) age, y			
Study 1	41.6 (10.8)	41.5 (11.2)	41.2 (10.8)
Study 2	39.9 (10.8)	40.2 (10.8)	39.2 (10.5)
Pooled studies	40.7 (10.8)	40.8 (11.0)	40.2 (10.7)
Women, n/N (%)			
Study 1	380/448 (85)	389/462 (84)	401/456 (88)
Study 2	387/454 (85)	361/440 (82)	378/436 (87)
Pooled studies	767/902 (85)	750/902 (83)	779/892 (87)
White, n/N (%)			
Study 1	387/448 (86)	399/462 (86)	403/456 (88)
Study 2	444/454 (98)	436/440 (99)	428/436 (98)
Pooled studies	831/902 (92)	835/902 (93)	831/892 (93)
Clinical characteristics			
History of triptan use, n/N (%)			
Study 1	343/448 (77)	364/462 (79)	355/456 (78)
Study 2	380/454 (84)	368/440 (84)	367/436 (84)
History of migraine without aura only, n/N (%)			
Study 1	321/448 (72)	315/462 (68)	325/456 (71)
Study 2	296/454 (65)	309/440 (70)	290/436 (67)

ported pain relief vs 14% with placebo; $P \leq 0.05$) (Figure 2).

Other Efficacy Results

Using pooled data, the cumulative percentages of patients with a pain-free response by 2 hours after dosing were 40% for sumatriptan tablets 50 mg and

47% for sumatriptan tablets 100 mg, compared with 15% for placebo ($P \leq 0.001$, both sumatriptan doses vs placebo). A similar pattern of results was observed in the individual studies (Table II).

In the individual studies, significantly more patients taking either sumatriptan dose were migraine free 2 hours after dosing compared with those taking

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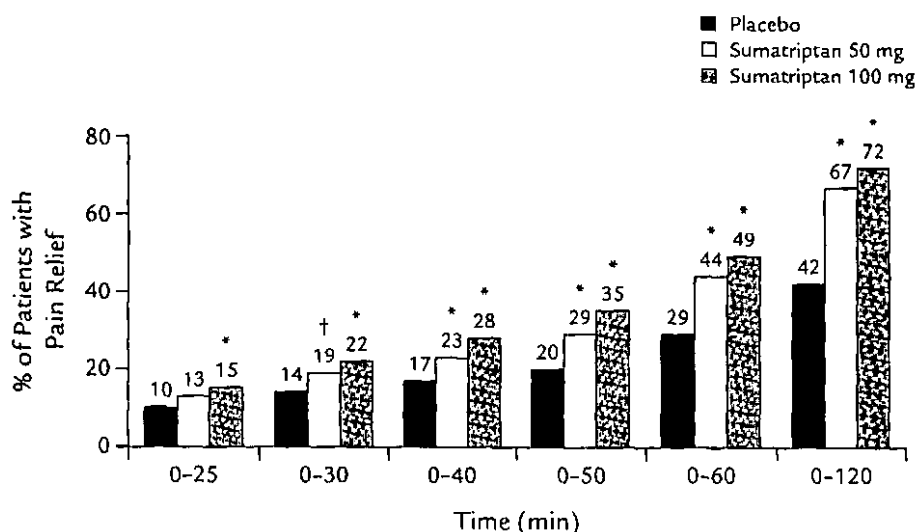


Figure 1. Cumulative percentage of patients with pain relief after treating a single migraine attack with sumatriptan tablets 50 or 100 mg in a fast-disintegrating/rapid-release formulation or placebo (pooled data from 2 studies). * $P \leq 0.001$ versus placebo; † $P \leq 0.05$ versus placebo.

placebo ($P \leq 0.001$, both sumatriptan doses vs placebo) (Table II). The percentages of patients with sustained pain relief and sustained pain-free response in the individual studies were also significantly higher with both doses of sumatriptan compared with placebo ($P \leq 0.001$).

In the individual studies, significantly fewer patients who took either dose of sumatriptan used rescue medication or a second dose of study medication during the 24 hours after dosing compared with those who took placebo ($P \leq 0.001$) (Table II). The percentage of patients with a recurrence in the individual studies ranged from 26% to 28% with sumatriptan 50 mg, from 28% to 30% with sumatriptan 100 mg, and from 43% to 50% with placebo.

Adverse Events

Both sumatriptan doses were generally well tolerated. The percentages of patients with ≥ 1 drug-related adverse event were 8% with sumatriptan 50 mg, 12% with sumatriptan 100 mg, and 3% with placebo in study 1 and a corresponding 12%, 19%, and 5% in study 2 (Table III). The only drug-related adverse events reported in $>2\%$ of patients in any treatment group in either study were nausea (2%, 3%, and 1%, respectively, in both studies) and paresthesia (study 1: $<1\%$, $<1\%$, and 0%; study 2: 1%, 3%, and $<1\%$). No serious drug-related adverse events were reported.

No patient withdrew from either study because of adverse events.

DISCUSSION

The gastric stasis that commonly accompanies migraine headache may impair absorption of conventional oral tablets in the stomach.^{24,25} Therefore, a fast-disintegrating/rapid-release formulation of sumatriptan was developed to enhance tablet disintegration and drug dispersion and potentially improve absorption. Reports of faster in vitro dissolution of sumatriptan in the fast-disintegrating/rapid-release tablet compared with the conventional tablet and slightly faster absorption during the early period after dosing (0–2 hours) in healthy volunteers¹⁶ suggested that this formulation may have a rapid onset of action. An earlier clinical trial of the fast-disintegrating/rapid-release formulation evaluated its efficacy and tolerability in the early-intervention treatment paradigm¹⁹; however, before the present studies, the efficacy and onset of pain relief with this formulation had not been evaluated in patients with moderate or severe migraine pain.

With respect to the onset of pain relief, previous migraine studies have assessed pain relief as a discrete variable at specific time points after dosing (eg, 30 minutes, 1 hour, and 2 hours),^{10–15} a method that addresses efficacy at the specific time points but does not provide a sen-

Table II. Efficacy data for study 1 and study 2.

	Sumatriptan 50 mg	Sumatriptan 100 mg	Placebo
Time to significant difference in onset of pain relief vs placebo, min			
Study 1	50*	25*	NA
Study 2	30*	17*	NA
Pooled studies	30*	20*	NA
Cumulative incidence of pain relief 2 hours after dosing, n/N (%)			
Study 1	310/448 (69) [†]	331/462 (72) [†]	208/456 (46)
Study 2	293/454 (65) [†]	318/440 (72) [†]	167/436 (38)
Pooled studies	603/902 (67) [†]	649/902 (72) [†]	375/892 (42)
Time to significant difference in onset of pain-free response vs placebo, min			
Study 1	47*	29*	NA
Study 2	49*	39*	NA
Cumulative incidence of pain-free response 2 hours after dosing, n/N (%)			
Study 1	180/448 (40) [†]	219/462 (47) [†]	84/456 (18)
Study 2	178/454 (39) [†]	207/440 (47) [†]	53/436 (12)
Migraine-free response 2 hours after dosing, n/N (%)			
Study 1	139/442 (31) [†]	179/455 (39) [†]	69/455 (15)
Study 2	140/449 (31) [†]	155/437 (35) [†]	41/435 (9)
Sustained pain relief, n/N (%)			
Study 1	154/405 (38) [†]	163/420 (39) [†]	92/446 (21)
Study 2	173/437 (40) [†]	181/421 (43) [†]	69/429 (16)
Sustained pain-free response, n/N (%)			
Study 1	85/419 (20) [†]	107/426 (25) [†]	46/449 (10)
Study 2	96/442 (22) [†]	108/424 (25) [†]	21/430 (5)
Recurrence, n/N (%) [‡]			
Study 1	81/310 (26)	93/331 (28)	89/209 (43)
Study 2	81/293 (28)	95/319 (30)	84/167 (50)
Use of rescue medication or second dose of study medication, n/N (%)			
Study 1	192/448 (43) [†]	180/462 (39) [†]	257/456 (56)
Study 2	187/454 (41) [†]	162/440 (37) [†]	272/436 (62)

NA = not applicable.

* $P \leq 0.05$ versus placebo.[†] $P \leq 0.001$ versus placebo.

[‡]Based on number of patients reporting pain relief 2 hours after dosing (discrete time-point data). The difference in the numbers of patients reporting pain relief using the personal digital assistant (PDA) and the numbers for the cumulative incidence of pain relief 2 hours after dosing is explained by 2 patients who reported pain relief at the 2-hour discrete time point, but not using the PDA. No statistical analysis of recurrence was planned or performed.

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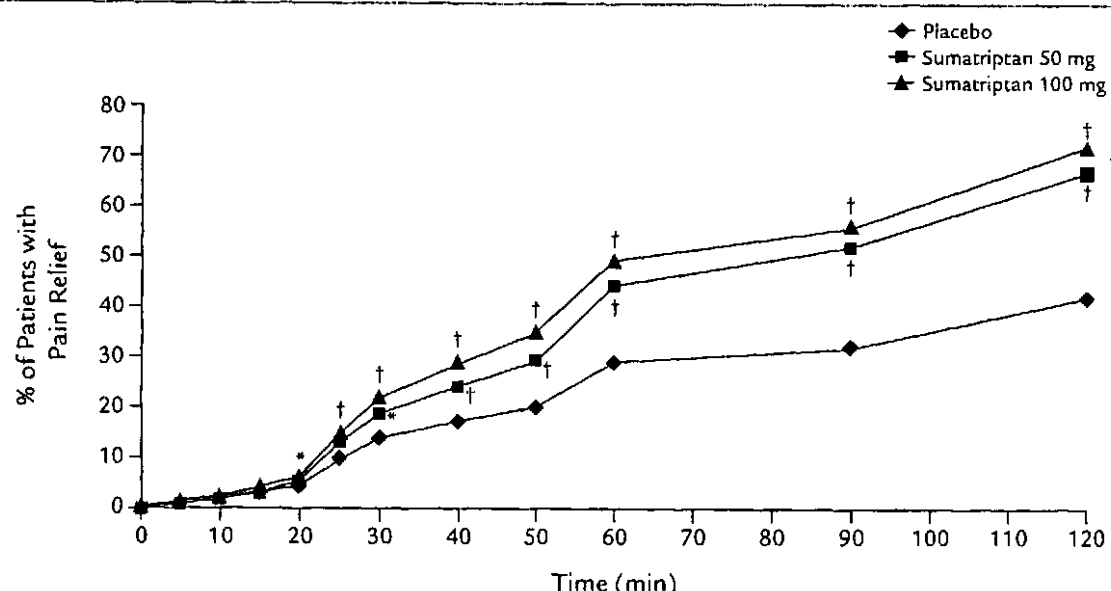


Figure 2. Time to onset of pain relief in patients treating a single migraine attack with sumatriptan tablets 50 or 100 mg in a fast-disintegrating/rapid-release formulation or placebo (pooled data from 2 studies). Onset of pain relief was defined as the earliest time point at which pain relief was achieved (ie, showed a statistically significant difference compared with placebo) and was maintained through 2 hours after dosing. * $P \leq 0.05$ versus placebo; † $P \leq 0.001$ versus placebo.

sitive estimate of the onset of pain relief. In contrast, patients in the present studies recorded the time elapsed to mild or no pain in real time, which permitted measurement of time to the onset of pain relief as a continuous variable, providing a more accurate assessment of the onset of therapeutic efficacy. Use of the PDA to measure elapsed time to mild or no pain and use of survival

analysis methodology to analyze the onset of pain relief and pain-free response may have broad applications in migraine research.

In the pooled results from these randomized, double-blind, placebo-controlled studies, the time at which the onset of pain relief differed significantly from placebo occurred as early as 20 minutes after dosing with suma-

Table III. Adverse events (no. [%]) reported in >2% of patients in any treatment group in either study.

	Sumatriptan 50 mg	Sumatriptan 100 mg	Placebo
No. in safety population			
Study 1	494	488	495
Study 2	496	485	494
Any drug-related adverse event			
Study 1	40 (8)	57 (12)	17 (3)
Study 2	58 (12)	94 (19)	25 (5)
Nausea (drug-related)			
Study 1	11 (2)	13 (3)	5 (1)
Study 2	10 (2)	16 (3)	5 (1)
Paresthesia (drug-related)			
Study 1	4 (<1)	3 (<1)	0 (0)
Study 2	5 (1)	14 (3)	1 (<1)

triptan 100 mg and as early as 30 minutes after dosing with sumatriptan 50 mg. In the individual studies, the time to onset of pain relief ranged from 17 to 25 minutes for the 100-mg dose and from 30 to 50 minutes for the 50-mg dose. The cumulative percentage of patients with pain relief 2 hours after dosing was 67% for sumatriptan 50 mg and 72% for sumatriptan 100 mg, compared with 42% for placebo. An onset of pain relief as early as 30 minutes after dosing has been documented for oral tablet formulations of other triptans.^{14,15,22} However, firm conclusions about the comparative onset of pain relief with the fast-disintegrating/rapid-release formulation of sumatriptan and other triptan tablets cannot be drawn, as no head-to-head clinical trials have been conducted. In addition, the design and methods of the present studies differed from those of past migraine trials in that the time to onset of pain relief was assessed as a continuous variable, survival analysis methodology was used, and cumulative percentages of patients with pain relief and pain-free response were calculated. These differences render comparisons between these and other studies difficult.

In assessing the profile of patient response over time, the data show the single time point at which active treatment and placebo separate and maintain their separation over the 2-hour period after dosing. By definition, this point of separation applies to a small proportion of patients. However, in these studies, after the initial point of separation at which the active treatments became significantly superior to placebo, the difference was not only maintained but continued to expand relative to placebo over the 2-hour interval after dosing. Thus, pain relief with sumatriptan 100 mg began in a small proportion of patients as early as 20 minutes after dosing, and up to 72% of patients achieved pain relief by 2 hours.

In addition to providing rapid pain relief, the fast-disintegrating/rapid-release form of sumatriptan was associated with sustained pain relief. Across sumatriptan doses and studies, up to 2 times more sumatriptan recipients reported sustained pain relief compared with placebo recipients (38%–43% vs 16%–21%, respectively) and 2 to 5 times more reported sustained freedom from pain (20%–25% vs 5%–10%). In addition, use of rescue medication or a second dose of study medication during the 24-hour period after dosing was significantly less frequent with both sumatriptan doses compared with placebo ($P \leq 0.001$).

Both doses of sumatriptan tablets were generally well tolerated. Nausea and paresthesia were the only

drug-related adverse events reported in >2% of patients in any treatment group in either study. The safety profile of the fast-disintegrating/rapid-release formulation of sumatriptan tablets appears comparable to that of the conventional form²² in terms of both the type and frequency of adverse events.

The exclusion criteria used in these studies, which are typical for migraine studies, may somewhat limit the extent to which the data can be generalized to all patients with migraine. Patients were excluded who had basilar or hemiplegic migraine or who had headache on ≥ 15 days per month in any of the 3 months before screening, as were patients residing in countries where the combination of a selective serotonin reuptake inhibitor and a triptan is not allowed who required a selective serotonin reuptake inhibitor. Also excluded were those using migraine prophylactic medication containing ergotamine, an ergot derivative, or methysergide, and those who had used a monoamine oxidase inhibitor within 2 weeks before screening.

CONCLUSIONS

In these 2 identical randomized, double-blind, placebo-controlled studies, a fast-disintegrating/rapid-release formulation of sumatriptan tablets was effective, was generally well tolerated, and provided a rapid onset of pain relief in the acute treatment of moderate or severe migraine pain. Onset of pain relief was detected as early as 20 minutes after dosing with the 100-mg dose of sumatriptan and 30 minutes after dosing with the 50-mg dose. Sumatriptan tablets in this formulation provided rapid pain relief and a rapid pain-free response in the acute treatment of migraine.

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Ortho-McNeil Pharmaceutical, Inc., Pierre Fabre, Pfizer Inc., and Pharmacia & Upjohn; and Dr. Brandes has served in similar capacities for Allergan, Inc., AZ, BMS, Eli Lilly and Company, GSK, MedPointe Pharmaceuticals, Merck & Co., Inc., Novartis Pharmaceuticals Corporation, Ortho-McNeil Pharmaceutical, Inc., and Pfizer Inc.

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