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Sumatriptan Fast-Disintegrating/ Rapid-Release Tablets

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Contents

Abstract

▲ Sumatriptan is a serotonin 5-$HT_{1B/1D}$ receptor agonist that is used for the acute treatment of migraine attacks. A new fast-disintegrating/rapid-release sumatriptan tablet (sumatriptan FDT/RRT) has been developed with the goal of speeding absorption and onset of effect compared with standard sumatriptan tablets.

▲ Bioequivalence of sumatriptan FDT/RRT tablets to standard sumatriptan tablets was established in healthy volunteers. Initial data suggest that sumatriptan FDT/RRT tablets may disintegrate faster and get emptied from the stomach faster than standard sumatriptan tablets.

▲ In a randomised, double-blind, multicentre, early intervention trial in adults with mild migraine, significantly more sumatriptan FDT/RRT 50 and 100mg recipients than placebo recipients were pain free or migraine free 2 hours after receiving study medication.

▲ Compared with placebo, pain relief was significantly greater with sumatriptan FDT/RRT 100mg at 25 and 17 minutes following administration, and with sumatriptan FDT/RRT 50mg at 50 and 30 minutes following administration, in two randomised, double-blind, multicentre trials in adults with moderate to severe migraine.

▲ Sumatriptan FDT/RRT tablets were generally well tolerated; the tolerability profile was similar to that reported for standard sumatriptan tablets in other studies.

Features and properties of sumatriptan fast-disintegrating/rapid-release tablets	
Indication	
Acute relief of migraine with or without aura in adults	
Mechanism of action	
Serotonin 5-$HT_{1B/1D}$ agonist	Constricts cranial arteries and inhibits neurogenic inflammation
Dosage and administration	
Dose	50mg (or 100mg if required)
Route of administration	Oral
Frequency of administration	Single dose as early as possible after the onset of the migraine attack. If the symptoms recur following response, a second dose may be taken ≥2h following the first dose
Pharmacokinetic profile after a single 50 or 100mg dose	
Mean peak plasma concentration	50mg: 30.0 ng/mL 100mg: 52.2 ng/mL
Median time to peak plasma concentration	50mg: 0.83h 100mg: 1.00h
Mean area under the plasma concentration-time curve	50mg: 103 ng • h/mL 100mg: 199 ng • h/mL
Mean elimination half-life	50mg: 2.78h 100mg: 3.07h
Drug-related adverse events	
Most common	Nausea and/or vomiting, paraesthesia, chest symptoms, malaise and fatigue

Migraine is characterised by episodes of moderate to severe head pain, which may be accompanied by nausea, vomiting, photophobia or phonophobia, and can occur with or without aura.[1] Approximately 10% of the population suffers from migraine.[2] Migraine prevalence is at its highest between the ages of 25 and 55 years, and it affects more adult women (3.3–21.9%) than men (0.7–16.1%) [reviewed by Lipton and Bigal[3]]. The severity and frequency of migraine attacks vary between patients and between attacks in the same patient. Because attacks can be extremely disabling, this can result in reduced or lost productivity and a lower overall quality of life.[3]

Migraine attacks were originally thought to begin with vasoconstriction of cranial blood vessels, which was followed by vasodilation of meningeal blood vessels and then activation of trigeminal sensory nerves (reviewed by Silberstein[4]). A more recent neurovascular theory suggests that migraine may originate from neuronal dysfunction (reviewed by Silberstein,[4] Nissan and Diamond,[5] and Landy et al.[6]). This theory proposes that when an attack is triggered, a wave of depressed neural function spreads across the cortex (cortical spreading depression), causing migraine aura.[4,5] This leads to peripheral sensitisation of the trigeminal vascular system and subsequent vasodilation and plasma protein extravasation (neurogenic inflammation).[4] Central neurones are also activated and may later in the attack become sensitised (central sensitisation) leading to cutaneous allodynia.[4]

Management of migraine requires the use of abortive treatments. Generally, aspirin and NSAIDs (in high doses) or combination analgesics are recommended for acute treatment of mild to moderate migraine attacks.[2,7] The efficacy of the group of migraine-specific triptan drugs, which includes sumatriptan, is well established.[8] Triptans are recommended for first-line treatment of moderate to severe migraine attacks, and also in patients with mild to moderate migraine who do not respond to the recommended therapies.[2,7]

Sumatriptan is a selective serotonin 5-HT receptor agonist that has been available for the treatment of migraine since the early 1990s. It is already available as standard oral tablets, subcutaneous injection, nasal spray and, in some countries, as suppositories. Early treatment of migraine attacks and use of drug formulations associated with rapid absorption and prompt drug delivery to the site of action are strategies for preventing or minimising central sensitisation.[9] Migraine is often accompanied by gastric stasis, which may impair the absorption of conventional tablet formulations.[10]

Recently, a new fast-disintegrating/rapid-release tablet, sumatriptan FDT/RRT[1], has been designed using RT Technology™, which draws water into the sumatriptan tablet, causing it to swell and break apart.[10] These tablets were designed with the intention of speeding the absorption of sumatriptan and its onset of effect, potentially preventing or minimising central sensitisation. This new formulation is the focus of this article.

1. Pharmacodynamic Profile

The pharmacodynamic properties of sumatriptan have been reviewed previously;[1] this section provides an overview of the pharmacodynamics of the drug.

- Sumatriptan is a selective agonist at serotonin 5-$HT_{1B/1D}$ receptor subtypes.[1] Vascular 5-HT_{1B} receptors are located mainly in cerebral and dural vessels in the cranial vasculature and 5-HT_{1D} receptors are located in nervous tissue. These receptor subtypes mediate constriction of cranial arteries and arteriovenous anastomoses and inhibition of neurogenic inflammation.[1]
- Administration of sumatriptan causes constriction of large cerebral blood vessels and increases blood flow velocity.[1] It also reduces neurogenic inflammation via the activation of 5-HT receptors

1 Trade names include Imitrex®, Imitrex DF®, Imigran Radis®, Imigran FDT®, Imigran Sprint®, Imigran Neo®, Imigran Novum®, Imigran T® and Imigran Ftab®. The use of trade names is for product identification purposes only and does not imply endorsement.

on trigeminal perivascular nerve fibres. These effects are believed to be responsible for the therapeutic effects of sumatriptan on migraine. Sumatriptan also causes moderate constriction of coronary arteries and nonsignificant vasoconstriction of peripheral veins.[1]

- The efficacy of sumatriptan may be affected by the presence of cutaneous allodynia.[11] It has been suggested that if central sensitisation occurs before a triptan is administered, although the throbbing of the migraine will be relieved, the pain will continue and cutaneous allodynia will still develop.[4] In a small study (n = 31) in patients with migraine, 25 of 27 (93%) migraine attacks that were not associated with cutaneous allodynia were effectively treated (patients pain free within 2 hours) with subcutaneous sumatriptan 6mg, compared with only 5 of 34 (15%) attacks where allodynia was present (determined by skin sensitivity tests).[11] It has therefore been suggested that triptans should be administered early in a migraine attack to prevent the development of cutaneous allodynia.[5,6]

2. Pharmacokinetic Profile

This section is based primarily on a randomised, nonblind, crossover, bioequivalence study in healthy volunteers that compared the pharmacokinetics of sumatriptan FDT/RRT tablets with standard sumatriptan tablets.[9] Participants received single doses of sumatriptan FDT/RRT 50 and 100mg and standard sumatriptan 50 and 100mg tablets (n = 32).[9]

A small gamma scintigraphy study (n = 5) that assessed disintegration and gastric emptying of the sumatriptan FDT/RRT tablets (available as an abstract and poster only)[12] is discussed briefly. Data from the UK[13] prescribing information are also included.

- Sumatriptan reached a mean peak plasma concentration (C_{max}) of 30.0 ng/mL at a median of 0.83 hours (t_{max}) after a single dose of sumatriptan FDT/RRT 50mg.[9] The corresponding values following administration of a standard sumatriptan 50mg tablet were 29.1 ng/mL and 1.00 hours.[9] The mean area under the plasma concentration-time curve from time zero to infinity (AUC_∞) for sumatriptan FDT/RRT 50mg was 103 ng • h/mL and for standard sumatriptan 50mg was 105 ng • h/mL.[9]

- For the 100mg dose, C_{max} values were 52.2 and 53.2 ng/mL for sumatriptan FDT/RRT and standard sumatriptan tablets.[9] C_{max} occurred at 1.00 hour for both formulations. The corresponding AUC_∞ values were 199 and 167 ng • h/mL.

- Sumatriptan FDT/RRT tablets were found to be bioequivalent to standard sumatriptan tablets.[9] The test for bioequivalence was if the geometric mean ratio (sumatriptan FDT/RRT **:** standard sumatriptan tablet) 90% confidence intervals for C_{max} and AUC_∞ were between 0.8 and 1.25.[9] The geometric mean ratios for AUC_∞ were 0.97 (90% CI 0.91, 1.04) for the 50mg tablets and 1.05 (90% CI 0.98, 1.12) for the 100mg tablets. For C_{max}, the ratios were 1.03 (90% CI 0.93, 1.15) and 1.01 (90% CI 0.91, 1.12) for the 50 and 100mg tablets.[9]

- In five patients who experienced migraines, but did not have a migraine at the time of the study, the mean time to initial disintegration of sumatriptan FDT/RRT 100mg tablets was 1.4 minutes compared with 19.8 minutes for standard sumatriptan tablets.[12] The times to complete disintegration were 6.2 versus 38.8 minutes. Sumatriptan FDT/RRT tablets were 50% emptied from the stomach after 57.9 minutes compared with 94.2 minutes for standard sumatriptan tablets.[12] Data from the same five patients during a migraine attack have not yet been obtained.[12]

- Sumatriptan is ≈14–21% bound to plasma proteins and has a bioavailability of ≈14%.[13] The mean volume of distribution of sumatriptan is 170L.[13]

- After oral administration, sumatriptan is metabolised to an indoleacetic acid analogue.[1] This inactive metabolite is excreted mainly in the urine and also in the faeces. Some of the sumatriptan oral dose is excreted unchanged in the urine (3%) and the faeces (9%).[1] The mean elimination half-life was 2.78 and 3.07 hours for the sumatriptan FDT/RRT 50 and 100mg tablets and 2.90 and 2.86 hours for the standard sumatriptan 50 and 100mg tablets.[9]

3. Therapeutic Efficacy

Early Intervention

The efficacy of sumatriptan FDT/RRT tablets in the early treatment of migraine has been evaluated in a randomised, double-blind, parallel-group, placebo-controlled, multicentre, phase III trial (n = 432).[14] The trial also assessed the effects of sumatriptan FDT/RRT tablets on functional ability as a secondary endpoint; these outcomes were reported separately.[15]

Patients were eligible for the study if they were aged between 18 and 65 years, had a ≥1-year history of migraine with or without aura, and had experienced 1–6 migraines per month during the 2 months prior to the screening visit.[14] Inclusion criteria also included a history of moderate to severe migraine attacks with an initial mild-pain phase.

Eligible patients were randomised to receive sumatriptan FDT/RRT 50 or 100mg or placebo to treat a single migraine attack on an outpatient basis.[14] Patients were instructed to treat the migraine within 1 hour of the onset of mild pain while the pain was still mild (early intervention).

The primary endpoint was the percentage of patients who had no pain at 2 hours following drug administration.[14] Pain severity was assessed at various timepoints following drug administration and recorded using a 4-point scale (none, mild, moderate or severe) using a diary card.

Secondary endpoints included the percentage of pain-free patients at 30 minutes, 45 minutes and 1 hour after drug administration; the percentage of migraine-free patients through 2 hours after drug administration; and the percentage of patients with sustained pain relief not requiring additional study medication or rescue medication (i.e. the sustained pain-free response rate 2–24 hours after taking study medication).[14]

Patients were also asked to record their functional ability immediately before taking the study medication and at 30 minutes, 45 minutes, 1 hour and 2 hours after drug administration.[15] Data on the number of hours missed from work and non-work activities; the number of hours working or taking part in other activities with migraine symptoms; and the effectiveness while continuing work or other activities with migraine symptoms in the 24 hours following drug administration were combined to calculate lost time equivalents.[15]

The intent-to-treat population included those patients who treated a migraine attack and recorded at least one efficacy assessment.[14] The study compared sumatriptan FDT/RRT 50 or 100mg tablets with placebo and was not designed to detect differences between the two sumatriptan doses.[14]

The mean patient age ranged between 39.7 and 41.5 years across the treatment groups.[14] Most patients were female (80–86%), White (99–100%), had a history of migraine without aura (75–80%) and were using a triptan when they entered the study (71–80%).

Effects on Pain Relief

- Sumatriptan FDT/RRT tablets were more effective than placebo for eliminating migraine pain 2 hours after treatment.[14] A significantly greater proportion of sumatriptan FDT/RRT recipients than placebo recipients were pain free 2 hours after receiving study medication (figure 1). Moreover, significantly more sumatriptan FDT/RRT 100 than 50mg recipients were pain free 2 hours after treatment ($p = 0.007$), although the study was not designed to compare the two sumatriptan doses.
- Significantly more sumatriptan FDT/RRT 100mg recipients were pain free compared with placebo recipients at 30 minutes (10.6% vs 1.9%; $p < 0.01$), 45 minutes (24.6% vs 9.1%; $p < 0.001$) and 1 hour (44.4% vs 18.9%; $p < 0.001$) after study drug administration.[14] The differences between sumatriptan FDT/RRT 50mg and placebo recipients were significant at 45 minutes (18.2% vs 9.1%; $p < 0.05$) and 1 hour (36.5% vs 18.9%; $p < 0.01$) after administration.
- The percentage of migraine-free patients 2 hours after study drug administration was also significantly higher in both sumatriptan FDT/RRT groups than in the placebo group (figure 1).[14]
- Significantly more sumatriptan FDT/RRT 50 and 100mg recipients than placebo recipients exper-

ienced a sustained pain-free response 2–24 hours after taking study medication (figure 1).[14]

Effects on Functional Ability

- Significantly more patients in the sumatriptan FDT/RRT groups experienced a return to normal functional ability after treatment of the migraine attack compared with those in the placebo group.[15] The percentage of patients with normal functional ability was significantly greater in sumatriptan FDT/RRT 100mg recipients than in placebo recipients 45 minutes after drug administration (29% vs 18%; $p < 0.05$), and significantly greater in sumatriptan FDT/RRT 50mg recipients than in placebo recipients 1 hour after drug administration (41% vs 25%; $p < 0.05$). Before study drug administration, 13%, 16% and 15% of patients receiving sumatriptan FDT/RRT 100 or 50mg or placebo, respectively, had normal functional ability.
- The number of lost time equivalents in the 24 hours following study drug administration was significantly lower for recipients of sumatriptan FDT/RRT tablets than for placebo recipients.[15] Mean lost time equivalents (for paid work and other activities) were 2.5 and 1.9 hours with sumatriptan FDT/RRT 50 and 100mg compared with 3.5 hours with placebo (both sumatriptan doses $p < 0.05$ vs placebo).
- The difference in lost time equivalents was driven by significantly lower lost time equivalent values for activities outside paid work in sumatriptan compared with placebo recipients (2.5 and 2 hours for sumatriptan FDT/RRT 50 and 100mg vs 3.6 hours for placebo; $p < 0.05$ for both sumatriptan doses); the between-group differences were not significant for lost time equivalents during paid work.[15]

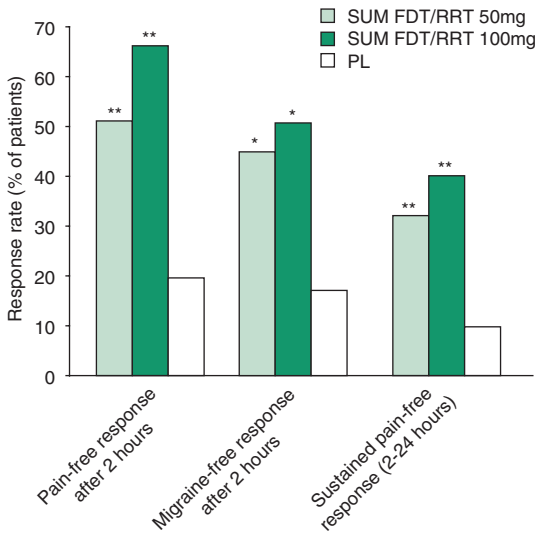

Fig. 1. Efficacy of sumatriptan fast-disintegrating/rapid-release (SUM FDT/RRT) tablets in the treatment of migraine (early intervention).[14] In a randomised, double-blind, parallel-group, placebo-controlled, multicentre study, patients received SUM FDT/RRT 50 or 100mg or placebo (PL) to treat a single migraine attack on an outpatient basis (n = 432). Patients were instructed to treat the migraine within 1 hour of the onset of mild pain while the pain was still mild.[14] * $p < 0.05$, ** $p < 0.001$ vs PL.

Late Intervention

Two randomised, double-blind, parallel-group, placebo-controlled, multicentre, phase III trials assessed the efficacy of late intervention with sumatriptan FDT/RRT.[10] These two large trials were identical in design and took place in the US and Canada (n = 1366) and in Europe (n = 1330). The results from both trials were published together.[10]

Inclusion criteria included an age of 18–65 years, a ≥6-month history of migraine with or without aura, a history of 1–6 migraines per month during the 3 months prior to the screening visit, and a history of migraine attacks with moderate to severe pain.[10]

Patients were randomised to receive sumatriptan FDT/RRT 50 or 100mg tablets or placebo to treat a single migraine attack on an outpatient basis.[10] Treatment was for a migraine characterised by moderate or severe pain (late intervention).

The primary endpoint of both studies was the time to onset of pain relief following administration of a sumatriptan FDT/RRT 100mg tablet.[10] This was defined as the time at which the proportion of sumatriptan FDT/RRT 100mg recipients achieving pain relief (defined as a reduction from moderate or severe pain to mild or no pain that was sustained for 2 hours) was significantly greater than the proportion of placebo recipients achieving pain relief. Pain severity was recorded on a personal digital assistant using a 4-point scale (none, mild, moderate or severe).

Key secondary endpoints included the time to onset of pain relief in sumatriptan FDT/RRT 50mg recipients, and the time to onset of a pain-free response (i.e. the time at which the proportion of sumatriptan FDT/RRT 50 or 100mg recipients achieving a pain-free response [defined as a reduction in pain from moderate or severe to none] was significantly greater than the proportion of placebo recipients achieving a pain-free response).

Other efficacy endpoints included the percentage of migraine-free (no pain, nausea, vomiting, photophobia or phonophobia) patients 2 hours after study drug administration; the percentage of patients with pain relief and pain-free response from 2 to 24 hours after a single dose of sumatriptan FDT/RRT; the percentage of patients who took rescue medication or an additional dose of study medication; and the percentage of patients with a recurrence of migraine within 24 hours following pain relief at 2 hours after drug administration.[10]

The studies compared sumatriptan FDT/RRT 50 or 100mg tablets with placebo.[10] Data from the two large, identical studies were reported for each trial separately and were also pooled in a *post hoc* analysis, which is discussed briefly. Outcomes were analysed using an intent-to-treat approach.

Across the treatment groups from both studies, the mean patient age ranged between 39.2 and 41.6 years.[10] Most patients were female (82–88%), White (86–99%), had a history of migraine without aura (65–72%) and had a history of triptan use (77–84%).

Effects on Pain Relief

- The time to onset of pain relief (from moderate or severe to mild or no pain) in the two studies was 25 and 17 minutes following administration of sumatriptan FDT/RRT 100mg, and 50 and 30 minutes following sumatriptan FDT/RRT 50mg (all $p \leq 0.05$ vs placebo) [figure 2].[10] In the *post hoc* pooled analysis, pain relief started 20 minutes after administration of sumatriptan FDT/RRT 100mg and 30 minutes after administration of sumatriptan FDT/RRT 50mg (both $p \leq 0.05$ vs placebo).
- The proportion of sumatriptan recipients who experienced a pain-free response was significantly greater than placebo recipients by 29 and 39 minutes following administration of sumatriptan FDT/RRT 100mg, and by 47 and 49 minutes after sumatriptan FDT/RRT 50mg (all $p \leq 0.05$ vs placebo) [figure 2].[10]
- Significantly more sumatriptan FDT/RRT 50 or 100mg recipients than placebo recipients experienced pain relief or were pain- or migraine-free 2 hours after receiving study medication (figure 3). In

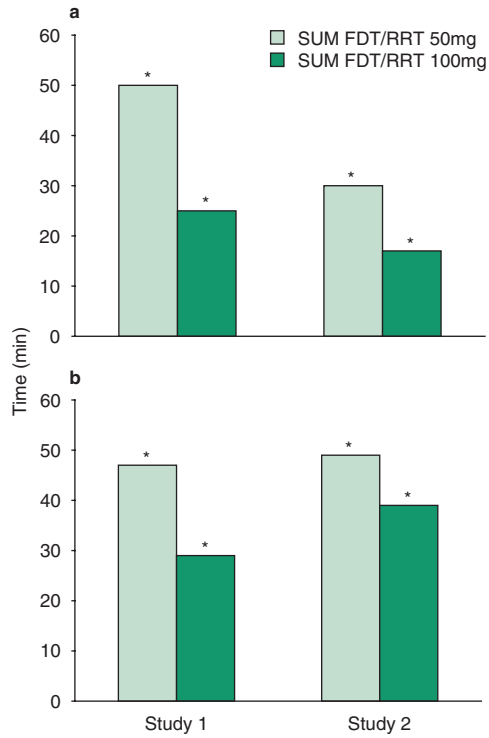

Fig. 2. Primary and key secondary endpoints in two late intervention studies of sumatriptan fast-disintegrating/rapid-release (SUM FDT/RRT) tablets in the treatment of migraine.[10] Shown are the times from study drug administration to when the proportion of SUM FDT/RRT 50 or 100mg recipients achieving (**a**) pain relief or (**b**) a pain-free response was significantly greater than the proportion of placebo (PL) recipients achieving pain relief or a pain-free response. The primary endpoint of both studies was the time to onset of pain relief following administration of a SUM FDT/RRT 100mg tablet. In the randomised, double-blind, parallel-group, PL-controlled, multicentre studies, patients received SUM FDT/RRT 50 or 100mg or PL to treat a single migraine attack on an outpatient basis. Patients were instructed to treat a migraine characterised by moderate or severe pain. The studies took place in the US and Canada (study 1; n = 1366) and in Europe (study 2; n = 1330).[10] * $p \leq 0.05$ vs PL.

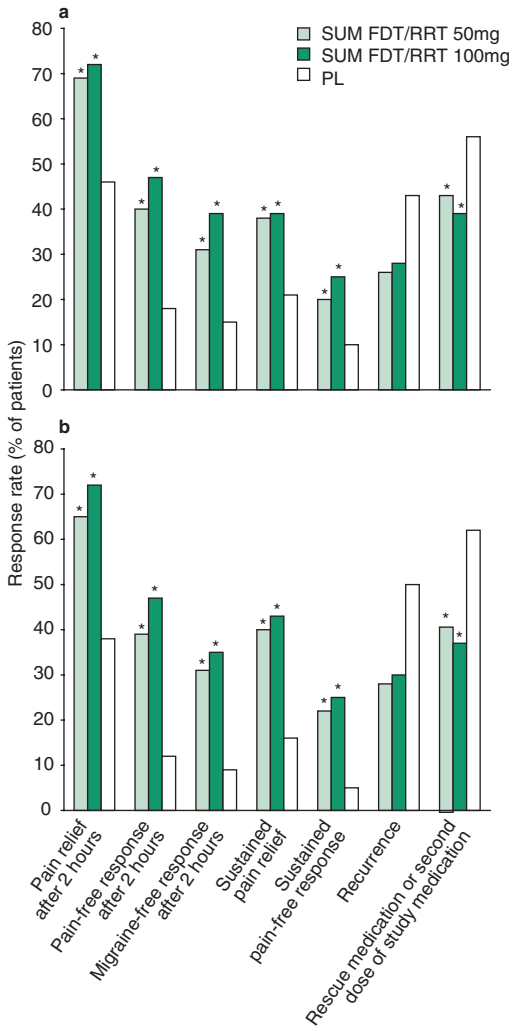

Fig. 3. Secondary endpoints in two late intervention studies of sumatriptan fast-disintegrating/rapid-release (SUM FDT/RRT) tablets in the treatment of migraine.[10] In the randomised, double-blind, parallel-group, placebo (PL)-controlled, multicentre studies, patients received SUM FDT/RRT 50 or 100mg or PL to treat a single migraine attack on an outpatient basis. Patients were instructed to treat a migraine characterised by moderate or severe pain. The studies took place in (**a**) the US and Canada (n = 1366) and (**b**) in Europe (n = 1330).[10] * $p \leq 0.001$ vs PL; statistical analysis was not performed for recurrence.

addition, the proportion of patients with sustained pain relief and the sustained pain-free response rate 2–24 hours after taking study medication were significantly higher with sumatriptan FDT/RRT 50 or 100mg than with placebo (figure 3). The rate of recurrence was numerically lower with sumatriptan FDT/RRT 50 or 100mg than with placebo (figure 3), although statistical analysis was not performed.

- Significantly fewer sumatriptan FDT/RRT recipients than placebo recipients required rescue medication or a second dose of study medication (figure 3).[10]

4. Tolerability

- Sumatriptan FDT/RRT tablets were generally well tolerated in the three phase III trials[10,14] (see section 3 for study design details); the tolerability profile was similar to that reported for standard sumatriptan tablets in other studies. Nausea was the most common drug-related adverse event in the late intervention trials with an incidence of 2% and 3% in sumatriptan FDT/RRT 50 and 100mg recipients, respectively, versus 1% in placebo recipients.[10] Nausea and vomiting occurred in <1% and 5% of sumatriptan FDT/RRT 50 and 100mg recipients and 2% of placebo recipients in the early intervention study.[14]
- The only other drug-related adverse event reported in the late intervention studies (that occurred in >2% of patients in any treatment arm) was paraesthesia which was reported by ≤1% of sumatriptan FDT/RRT 50mg recipients and <1–3% of sumatriptan FDT/RRT 100mg recipients compared with <1% of placebo recipients.[10] In the early intervention study, other drug-related adverse events were chest symptoms (2% and 3% of sumatriptan FDT/RRT 50 and 100mg recipients vs 0% of placebo recipients) and malaise and fatigue (1% and 3% vs <1%).[14]
- Drug-related adverse events were experienced by 8–12% of sumatriptan FDT/RRT 50mg recipients, 12–19% of sumatriptan FDT/RRT 100mg recipients and 3–5% of placebo recipients.[10,14] No patients in any of the studies reported any serious drug-related adverse events and no patients withdrew from the studies because of drug-related adverse events.[10,14]

5. Dosage and Administration

The recommended dose for sumatriptan FDT/RRT tablets in adults is a single oral 50mg dose administered as early as possible after the onset of the migraine attack.[13,16] Some patients may require 100mg. The tablet should be swallowed whole with water. A second dose may be taken ≥2 hours following the first dose if symptoms recur following response to the first dose. If the patient does not respond to sumatriptan FDT/RRT, a second dose should not be given for the same attack; however, sumatriptan FDT/RRT can be used for subsequent attacks.[13] The maximum total daily dose of sumatriptan is 300mg.[13]

Sumatriptan FDT/RRT is for the acute relief of migraine attacks and should not be used prophylactically.[13,16] It is not recommended for use in elderly patients (aged >65 years) and efficacy and safety in paediatric patients (aged <18 years) have not been established.

Local prescribing information should be consulted for detailed information, including contraindications, precautions, drug interactions and use in special patient populations.

6. Sumatriptan Fast-Disintegrating/ Rapid-Release Tablets: Current Status

Sumatriptan FDT/RRT tablets[2] are approved in the US, the UK, some other European countries, and several other countries around the world for the acute treatment of migraine with or without aura in adults. This new formulation of sumatriptan has shown clinical efficacy compared with placebo in one early and two late intervention phase III trials and was generally well tolerated.

Disclosure

During the peer review process, the manufacturer of the agent under review was also offered an opportunity to comment on this article; changes based on any comments received were made on the basis of scientific and editorial merit.

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2 For a full list of trade names, please refer to footnote 1.