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REVIEW ARTICLES

Bioavailability File: Rufinamide

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SUMMARY

Rufinamide is a third-generation, a triazole derivative drug. Rufinamide is indicated for treatment of seizures associated with Lennox-Gastaut syndrome (LGS). LGS is one of the most severe forms of childhood epilepsy and responsible of approximately 1to 4% of all childhood epilepsy cases, especially between 3 and 5 years. The etiology of LGS is frequently unknown which makes it difficult to control. The condition is characterized by a triad of symptoms, including impairment of cognitive function, slow spike-and-wave complexes on electroencephalogram (EEG) recordings, and multiple seizure types.

Rufinamide is a lipophilic compound. Water solubility is very low and similar across pH values ranging from 1 to 10. Rufinamide is highly absorbed after oral administration. Food increases the exposure to rufinamide. On single and multiple dosing, rufinamide exhibited nonlinear pharmacokinetics in the dose range from 200 mg to 1200 mg, which may be attributed to saturable absorption or limited solubility at higher doses. The drug is bound to plasma proteins in low amount (26 to 34 %). Rufinamide is extensively metabolized but has no active metabolites. The primary biotransformation pathway is carboxylesterase mediated hydrolysis of the carboxylamide group. Renal excretion is the predominant route of elimination for drug related material.

In this paper, the physicochemical and pharmacokinetic properties, analytical determination methods and pharmacological properties of rufinamide are reviewed.

Key Words: *Rufinamide, pharmacokinetics, bioavailability, orphan drug, lennox-gastaut syndrome, 3rd generation*

Biyoyararlanım Dosyası: Rufinamit

ÖZ

Rufinamit üçüncü jenerasyon, triazole türevi bir ilaçtır. Lennox-Gastaut sendromunda (LGS) meydana gelen krizlerin tedavisinde kullanılır.

LGS, çocukluk tipi epilepsi türevleri arasında en şiddetli gözlenen türlerden biridir, çocukluk epilepsi vakalarının yaklaşık %1 - 4'ü arasında, özellikle 3-5 yaşları arasında daha yoğun olarak gözlenir. Etiyolojisi tam olarak aydınlatılamamış olmakla birlikte, LGS bilişsel bozukluklar, düşük elektroensefalogram dalgalanması ve çoklu krizler ile karakterizedir ve kontrol altına alınması zordur.

Rufinamit lipofilik bir bileşiktir. Sudaki çözünürlüğü düşüktür ve pH 1 ile 10 arasında benzerdir. Oral alımın ardından yüksek oranda emilir. Yiyecekler rufinamide maruziyetini artırır. Tekli ve çoklu dozlamalarda, yüksek dozlarda düşük çözünürlük nedeniyle doygunluğa ulaşması sonucunda, 200 mg ve 1200 mg arasında non-lineer farmakokinetik gösterir. Plazma proteinlerine bağlanma oranı %26-34 arasıdır ve düşük bağlanır. Metabolize olur ve aktif metaboliti yoktur. Ana biyotranformasyon yolu karboksilamid grubundan karboksilesteraz aracılı hidrolizdir. Renal atılım ana atılım yoludur.

Bu yayında Rufinamit'e ait fizikokimyasal ve farmakokinetik özellikler, analitik tayin yöntemleri ve farmakolojik özellikleri derlenmiştir.

Anahtar kelimeler: *Rufinamit, farmakokinetik, biyoyararlanım, yetim ilaç, lennox-gastaut sendromu, 3. jenerasyon*

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INTRODUCTION

Lennox-Gastaut syndrome (LGS) is rare and one of the most severe forms of childhood epilepsy. LGS usually affects children between the ages of typically between 3 and 5 years. LGS has a significant morbidity and mortality, including multiple seizure types, mental retardation or a learning disability, generalized discharges with slow spike-and-wave complexes in the EEG (EMA, 2017). Therefore, childhood treatment of LGS is important and treatment success is uncommon or limited in this condition (Kim et al., 2018)(EMA, 2007a).

Current management of LGS is not satisfactory because the seizures associated with LGS are frequently unresponsive to standard anticonvulsants, in particular carbamazepine, phenytoin, and barbiturates. The treatment of patients with LGS often involves poly-therapy due to the lack of full response to any single antiepileptic drug (AED). Even when a drug is initially effective, this may not persist long term. Patients usually benefit only minor improvements in seizure frequency and severity (EMA, 2007a).

Rufinamide is a triazole derivative used as an AED, structurally unrelated to currently marketed AEDs, which was designated as Orphan for Lennox-Gastaut syndrome by the Committee on Orphan Medicinal Products (COMP) (EMEA/OD/047/04) on 9th September 2004(EMA, 2011), adopted by the European Commission on 20th October 2004 (EU/3/04/240) (EMA, 2007b) and approved from FDA on 10th August 2004 (EMA, 2007b). The earliest clinical studies has been started by Ciba-Geigy in Europe in 1987. Novartis, (merging of Ciba-Geigy and Sandoz), continued the development until 2001. Eisai Company, acquired the worldwide development rights to rufinamide from Novartis on 6 February 2004 for the submitted indication and further development work since this date has been carried out by Eisai (EMA, 2007a).

In this paper, the physicochemical and pharmacokinetic properties, analytical determination methods and pharmacological properties of rufinamide are reviewed.

PHYSICOCHEMICAL PROPERTIES

Rufinamide is a lipophilic compound with low LogP value between 0.65-0.88 (EMA, 2007a)(Wandera, 2013)(Perucca et al., 2008)(Mazzucchelli et al., 2011)(Cardot et al., 1998) with > 10 pKa value (Dalvi et al., 2018). The compound has no ionizable functionality. The increasing order of solubility was as follows: Water (0.642 mg/ml)< isopropyl alcohol < ethanol <methanol < chloroform < DMSO (48 mg/ml) (Wandera, 2013) Water solubility is similar across pH values ranging from 1 to 10 (EMA, 2007a)(Perucca et al., 2008)(Mazzucchelli et al., 2011). Solubility in 0.1 N HCl is 63 mg/mL and simulated intestinal fluid is 59 mg/mL (Mazzucchelli et al., 2011)(Cheung et al., 1995) (Cardot et al., 1998). The drug is highly resistant towards acidic and thermal degradations in comparison to alkaline and oxidation degradations (Portmann et al., 2010). Mehta et al. (Mehta et al., 2013) reported that solid sample is stable at 100°C for 24 hours. Molecular structure is schematized in Figure 1. Physicochemical properties are summarized in Table 1.

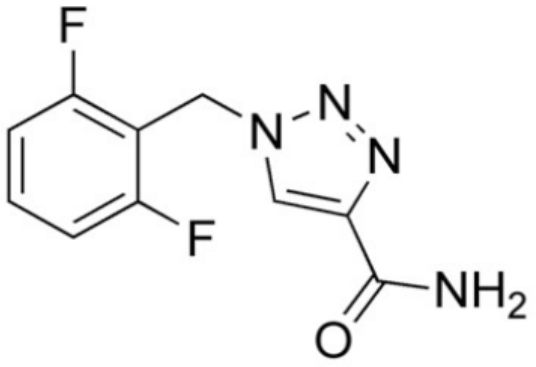

Figure 1. Rufinamide molecular structure

Table 1. Physicochemical properties of rufinamide

	Property	Reference
CAS No	106308-44-5	(EMA, 2007a)
Molecular formula	$C_{10}H_8F_2N_4O$	(EMA, 2007a)
Molecular weight	238.2 g/mol	(EMA, 2007a)
Chemical name	1-[(2,6-difluoro-phenyl) methyl]-1H-1,2,3-triazole-4 carboxamide [INN]	(Wheless & Vazquez, 2010)(Wandera, 2013)
Solubility	Practically insoluble in water (40 mg/L). Partially soluble in methanol, slightly soluble in ethanol.	(Mazzucchelli et al., 2011)
Melting temperature	230-240˚C	(Mehta et al., 2013)

Polymorphism

Rufinamide shows polymorphism. "Crystal modifications A, A', B and C" of the compound have been described in US Patents US8076362 B2(Portmann et al., 2011),US 6740669 Bl (Portmann et al., 2004) and US 7750028 B2 (Portmann et al., 2010). It has been found that choice of the solvent for the recrystallization or recrystallization process can effect the formation of different polymorphs (A, A', B, C).

Accordingly, the crystal modification A or A' fulfils the preconditions for being a pharmaceutical active ingredient with high stability for oral or parenteral administration, together with inorganic or organic, solid or liquid, pharmaceutically suitable diluents (Portmann et al., 2011)(Portmann et al., 2004)(Portmann et al., 2010).

QUANTIFICATION METHODS

There are publications regarding the quantification of rufinamide in pharmaceutical dosage forms or in biological media. Most recent HPLC-UV analytical methods are summarized in Table 2.

Table 2. Quantification methods of Rufinamide

Column	Detection Wavelength	Mobile Phase	Flow Rate	Column Temperature	Injection Volume	Diluent	RT	Ref.
C18, 5 µm, 250 x 4.60 mm	215 nm	10mM ammonium acetate buffer (pH 4.7 ± 0.1, adjusted with glacial acetic acid) : ACN (84.7:15.3)	1.0 mL/min	40 ˚C	50µL	Mobile phase	~15min	(Dalvi et al., 2018)
C18, 5 µm, 250 x 4.60 mm	293 nm	Buffer: ACN (60:40) (6.08 g/L KH_2PO_4 in water)	1.0 mL/min	25˚C	20 µL	Mobile phase	~ 5 min	(Mehta et al., 2013)
C18, 5 µm, 250 x 4.60 mm	215 nm	Tetrabutyl ammonium hydrogen sulphate: ACN (50:50)	1.0 mL/min	30 ˚C	20 µL	ACN	~ 4 min	(Annapurna et al., 2012)
C18, 5 µm, 125 x 4.60 mm	220 nm	MeOH : THF : Water (12:5:83)	1.0 mL/min	25˚C	20 µL	MeOH: THF (50:50)	~ 7 min	(USP, 2017a)
C18, 5 µm, 125 x 4.60 mm	210 nm	MeOH : THF : Buffer (15:5:80) (2.7 g/L KH_2PO_4 in water)	1.0 mL/min	25˚C	25 µL	ACN: MeOH: Water (40:50:10)	~ 7 min	(USP, 2017b)
C18, 5 µm, 250 x 4.60 mm	215 nm	Water: ACN (40:60)	0.8 mL/min	25˚C	20 µL	Mobile phase	~ 4 min	(Kumar et al., 2013)
C18, 5 µm, 125 x 4.60 mm (100A)	210 nm	Water: ACN (40:60)	1.0 mL/min	25˚C	20 µL	ACN	~ 4 min	(Patel et al., 2014)
ODS C18,5 µm, 250 x 4.60 mm	210 nm	ACN: Buffer (KH_2PO_4) (30:70) (pH 4.5, ortho phosphoric acid)	1.0 mL/min	25˚C	20 µL	Mobile phase	~ 3 min	(Harisudha et al., 2013)
C18, 3.5 µm, 150 x 4.60 mm	230 nm	MeOH : Water (35:65) with 1 mL/L TFA	0.5 mL/min	40 ˚C	10µL	MeOH: Water (80:20)	-	(Hutchinson et al., 2010)

KH_2PO_4: Potassium dihydrogen phosphate; ACN: Acetonitrile; MeOH: Methanol; THF: Tetrahydrofuran; TFA: Trifluoroacetic acid;

RT: Retention time of Rufinamide

CLINICAL PHARMACOLOGY

Lennox–Gastaut syndrome (LGS) is one of the most severe forms of childhood-onset epilepsy. LGS is responsible of approximately 1 to 4% of all childhood epilepsy cases, with peak onset occurring between the ages of 3 and 5 years. The etiology of LGS is frequently unknown. The condition is characterized by a triad of symptoms, including impairment of cognitive function, slow spike-and-wave complexes on electroencephalogram (EEG) recordings. Multiple seizure types making it particularly difficult to control (Kothare et al., 2017). Furthermore it is a well-known phenomenon that some antiepileptic drugs (AED) have a worsening effect on some seizure types, especially in the generalized epilepsies of childhood (Atmaca et al., 2012).

Epidemiology and Orphan Status

Although the incidence of LGS is estimated to 0.1 in 100.000 inhabitants per year (0.2–2.8/10,000 births in European countries (Rijckevorsel, 2008), the prevalence is high (5-10% of epileptic patients), representing 1-2% of all childhood epilepsies because of its refractory characteristics. The onset occurs between 2 and 7 years. Males seem to be more frequently affected (Campos-Castelló, 2004). Approximately 70% of LGS cases have an encephalopathy etiology, while about 30% are cryptogenic, with no known cause(McCormack, 2012).

In a US epidemiological study, the prevalence of LGS was 0.26 per 1000 children aged 10 years, which amounted to approximately 4% of all epilepsies (6.0 per 1000) among 10-year-olds in the study. LGS was more prevalent in males (0.37 per 1000) than in females (0.14 per 1000). While children with LGS accounted for 4% of 10-year- olds with epilepsy in the study, they accounted for 17% of 10-year-olds with profound mental retardation (IQ <20). Most children with LGS in the study had additional disabilities (mental retardation, cerebral palsy, and blindness or hearing impairment) and a high proportion had multiple disabilities. Overall, many patients with LGS are unable to live independent lives(McCormack, 2012).

The European Commission and the US FDA approved rufinamide as an orphan drug in 2007 and 2008, respectively, for adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in children 4 years of age or older and adults (Wier et al., 2011).

Mechanism of Action

Rufinamide is a triazole derivative which has a different structure from currently available antiepileptic drugs (Wier et al., 2011). Rufinamide is indicated for treatment of seizures associated with LGS in pediatric patients 1 year of age and older (Vendrame et al., 2010), and in adults (Arzimanoglou et al., 2016).

The principal mechanism of action is thought to be the prolongation of the inactive state of voltage gated sodium channels, which limits the sustained repetitive firing of sodium dependent action potentials in neurons (Joseph et al., 2011).

Efficacy

The efficacy of oral rufinamide was demonstrated in a pivotal, 12-week, randomized, double-blind trial. Rufinamide significantly reduced the 28-day frequency of both drop attacks and total seizures compared with placebo, and significantly increased the proportions of patients experiencing a ≥ 50% reduction in each seizure frequency. A significantly higher proportion of rufinamide than placebo recipients recorded an improvement in seizure severity at the end of treatment. Reductions in the frequency of drop attacks and total seizures were maintained in a long-term (up to 3 years), open-label extension study (McCormack, 2012).

In animal studies, oral rufinamide suppressed pentylene-tetrazol-induced seizures in mice (ED50 45.8 mg/kg) but not rats, and was active against MES-induced tonic seizures in mice (ED50 23.9 mg/kg) and rats (ED50 6.1 mg/kg). Intraperitoneal rufinamide suppressed pentylenetetrazol-, bicuculline-, and picrotoxin-induced clonus in mice (ED50 54.0, 50.5, and 76.3 mg/kg, respectively) (White et al., 2008).

Ohtsuka et al. demonstrated that the frequency of epileptic seizures was significantly decreased in the rufinamide group than in the placebo group; the median percent change in frequency of tonic—atonic seizures was −24.2% and −3.3%, respectively, ($p = 0.003$) and that of total seizures was −32.9 % and −3.1%, respectively ($p < 0.001$) (Ohtsuka et al., 2014).

Rufinamide efficacy and safety in children aged 1–4 years with Lennox–Gastaut syndrome was evaluated. 46.67% of patients were responders and four patients were seizure-free. The responder rate was increased to 69.23% by long-term treatment of rufinamide. Rufinamide tablets were found to be efficacious and well tolerated in LGS patients aged 1–4 years, at doses up to 1000 mg per day (Kim et al., 2018).

Tolerability

The behavioral toxicity of rufinamide was similar to or better than established AEDs tested in studies (White et al., 2008). LD50 value for rats and mouse's is > 5000mg/kg(USP, 2011).

Oral rufinamide was generally well tolerated in patients with LGS. Adverse events were usually of mild to moderate severity in patients with LGS. The most common adverse events occur in ≥10% of rufi-

namide treated patients were somnolence and vomiting occurred with a numerically higher incidence in rufinamide than placebo recipients(McCormack, 2012) (Deeks & Scott, 2006). The other adverse effects being dizziness, fatigue, nausea, vomiting, diplopia, and somnolence (Electronic medicines compendium, 2017b)(EMA, n.d.)(Brodie et al., 2009).

Cognitive function often becomes impaired in patients with epilepsy, partly as consequence of AED therapy; however, patients with partial seizures (189 of 647 patients evaluated) treated with rufinamide dosages ranging from 200 to 1600 mg/day demonstrated no worsening of cognitive ability from baseline compared with placebo after 12 weeks of treatment(Deeks & Scott, 2006).

In pre-licensure clinical trials, addition of rufinamide to standard anticonvulsant therapy was reported to be associated with only rare elevations in ALT above 3 times the upper limit of normal (ULN). Rufinamide was not linked to instances of clinically apparent liver injury, but a pooled analysis of more than 200 children mentioned that two patients needed to discontinue therapy early because of liver related adverse events, one of which was described as "toxic hepatitis". Rufinamide has been linked to instances of severe cutaneous reactions, including Stevens Johnson syndrome which often has some degree of associated liver injury. Thus, rufinamide may cause liver injury, but it is rare (NIH, 2017).

Dosing

Slow titration in dosing is recommended in literature(Kothare et al., 2017). Rufinamide is usually started orally at 10mg/kg/day for pediatric patients 1 year and older, titrating up by 10mg/kg/day every 2 days to a target dosage of 45mg/kg/day(Deeks & Scott, 2006) divided twice daily (maximum dosage of 3200mg/day) (FDA, 2008b)(Di & Obach, 2015). Regarding to adult dosing, Rufinamide is usually started orally at 400-800 mg /day, titrating up by 400-800 mg every other day, divided twice daily (maximum dosage of 3200mg/day) (FDA, 2008b).

PHARMACOKINETIC PROPERTIES

Pharmacokinetic properties of rufinamide is summarized in Table 3.

Table 3. Pharmacokinetic properties of rufinamide

	Property	Reference
Oral Bioavailability	70 % - 85 % (fed)	(Coppola et al., 2014)
	48.7 % (fasted)	(Szabo et al., 2017)
C_{max}	1.81 µg/mL (200 mg, Oral)	(Xu et al., 2016)
	2.0-4.0 µg/mL (400 mg, Oral)	(Xu et al., 2016)
	3.72 µg/mL (800 mg, Oral)	(Xu et al., 2016)
	10mg/kg/day: 4.01mg/mL 30mg/kg/day:8.68mg/mL	(Wier et al., 2011)
AUC	34.57 µg.hr/mL (200 mg, Oral)	(Xu et al., 2016)
	49-57 µg.hr/mL (400 mg, Oral)	(Xu et al., 2016)
	89.02 µg.hr/mL (800 mg, Oral)	(Xu et al., 2016)
	10mg/kg/day: 37.8 ±47 mg.h/mL 30mg/kg/day: 89.3 ±58mg h/mL ($AUC_{0\text{-}12h}$)	(Wier et al., 2011)
T_{max}	3-8 hours	(Kothare et al., 2017)
	Fasted: 8 hours ; Fed: 6 hours	(Cardot et al., 1998)
$T_{1/2}$	6-13 hours	(Kothare et al., 2017)
$T_{Steady\text{-}state}$	3-8 days	(Xu et al., 2016)
Food effect	Increase on C_{max} about 56 % - 50 % ; Increase on AUC about 34 %	(Coppola et al., 2014)
Vd	97.2 L (200 mg, Oral), 122.5 L (400 mg, Oral), 174.2 L (800 mg, Oral),	(Xu et al., 2016)
	0.8–1.2L/kg (Children = Adults)	(Wier et al., 2011)

CL	5.9 L/h (200 mg, Oral), 7.5 L/h (400 mg, Oral), 9.5 L/h (800 mg, Oral), (Low Clearance)	(Xu et al., 2016)
Protein binding	26 %- 34 % (poor)	(Coppola et al., 2014)
Transport effect	No effect of P-glycoprotein.	(Asconapé, 2018)
Metabolism	Extensively metabolized in hepatic circulation, with no active metabolites. No involvement of cytochrome P450	(Wheless & Vazquez, 2010) (Coppola et al., 2014)
Excretion	Renal excretion between 80 % - 90 %	(Di & Obach, 2015)
Pharmacokinetic	Non-linear	(Electronic medicines compendium, 2017b)
BCS	Class II	(Szabo et al., 2017)

Absorption

Rufinamide is highly absorbed (85%) after oral administration (Wheless & Vazquez, 2010)(Bialer et al., 1999)(Coppola et al., 2014) (La Marca et al., 2013). However, the rate of absorption was relatively slow (t_{max} > 3h) (Xu et al., 2016). Plasma levels peak 4-6 h after oral administration(Kothare et al., 2017) (Wheless & Vazquez, 2010)(Bialer et al., 1999)(Coppola et al., 2014) (La Marca et al., 2013) and then decline with a terminal half-life reported in various studies in the range 6–12 h (Kothare et al., 2017) (Wheless & Vazquez, 2010)(Bialer et al., 1999)(Coppola et al., 2014).

Food increases the exposure to rufinamide by about 50-56 % of C_{max} and about 34% of AUC (Coppola et al., 2014) (Wheless & Vazquez, 2010), (La Marca et al., 2013). Cardot et al. demonstrated the influence of food on the disposition of rufinamide in healthy volunteers with single per-oral doses of 600 mg of rufinamide after overnight fasting or a fat and protein rich breakfast. The average AUC was increased by 44% when rufinamide was given with food and the maximum concentration (C_{max}) by about 100%. The terminal half-life was not influenced by concomitant intake of food indicating unchanged elimination kinetics(Cardot et al., 1998).

The increase in rufinamide AUCs when administered with food is presumably due to a change in the GI absorption or dissolution of the drug. The physicochemical characteristics of the drug reinforce the hypothesis of a modified solubility in the presence of food possibly due to a larger volume of liquid and stimulated biliary secretion (Cardot et al., 1998).

The influence of food during chronic treatment was estimated by simulation. Simulation was performed using the superposition rule based on two administrations of per day (12 h interval) (600 mg b.i.d). Three cases were investigated: either both doses in fasted state or the first in fasted and the second in fed condition or both of them in fed condition. Statistical evaluations (ANOVA, procedure GLM, general linear model, of SAS®) was performed on the logarithmically transformed values of AUC and Cmax and the 90% confidence intervals were calculated (using the Estimate function of GLM), taking fasted conditions as standard.The predictions showed that at steady state the maximum concentrations in fasted subjects would be equal to the minimum concentrations in fed subjects. The fluctuation index was the lowest in fasted subjects. The highest fluctuations were predicted when one of the two daily doses was administered with food and the other one without food. This type of administration should be avoided (Table 4) (Cardot et al., 1998).

Table 4. Steady-state parameters obtained after three different simulation conditions, 600 mg b.i.d. (Cardot et al., 1998)

Predicted	Simulation 1	Simulation 2	Simulation 3	
	All doses fasted	All doses fed	First dose fasted	Second dose fed
C_{maxss}	5.24	7.62	5.96	7.15
C_{minss}	4.05	5.24	4.05	5.00
FI	0.25	0.35		0.54

FI, fluctuation index; C_{maxss} maximum concentration at steady state (μg/mL); C_{minss} minimum concentration at steady state (μg/mL).

At higher doses, the oral bioavailability of rufinamide decreases with increasing doses. Increments in Rufinamide dose within the recommended dose range may produce a less than proportional increase in plasma drug concentration(La Marca et al., 2013). The oral bioavailability is dependent mainly on absorption, which in turn is limited by the low, pH independent solubility of the drug in aqueous media: higher doses showing lower bioavailability(Szabo et al., 2017). On single and multiple dosing, rufinamide exhibited nonlinear pharmacokinetics in the dose range from 200 mg to 1200 mg (Xu et al., 2016), which may be attributed to saturable absorption or limited solubility at higher doses (Inmed-inserm et al., 1999)(Douroumis et al., 2007). Chan et al. demonstrated that Rufinamide is not a substrate of human P-gp, which suggests that resistance to rufinamide may not be attributed to increased P-gp activity in resistant patients (Chan et al., 2014).

Evaluation of the effects of gender on the pharmacokinetic profile of rufinamide found no significant differences in AUC, C_{max}, $T_{1/2}$ or CL between male and female(Xu et al., 2016). The pharmacokinetics of Rufinamide are not affected by impaired renal function(Perucca et al., 2008). Arzimanoglou et al. also demonstrated that CL/F was not significantly affected by other concomitant AEDs, age, gender, race, hepatic function, or renal function(Arzimanoglou et al., 2016).

The overall variabilities in absorption kinetics of rufinamide in healthy subjects were small with CV's of the population mean values for AUC and C_{max} less than 26% for both tablets and suspension. Contribution of intra-subject variability to the overall variability was also small (20%)(Cardot et al., 1998). Both the overall and intra-subject variabilities of AUC and C_{max} after suspension were larger than after the tablets (Cheung et al., 1995).

Distribution

Volume of distribution have been estimated at 50-80 L (Coppola et al., 2014) (Wheless & Vazquez, 2010); the drug is bound to plasma proteins in low amount (26 to 34 %) (Bialer et al., 1999), (Coppola et al., 2014) (Wheless & Vazquez, 2010)

Metabolism and Elimination

Rufinamide is extensively metabolized but has no active metabolites. The primary biotransformation pathway is carboxylesterase(s) mediated hydrolysis of the carboxylamide group to the acid derivative CGP 47292 (Bialer et al., 1999), (Coppola et al., 2014) (Di & Obach, 2015), (Wheless & Vazquez, 2010), (La Marca et al., 2013). Rufinamide has demonstrated little or no significant capacity in-vitro to act as a competitive or mechanism-based inhibitor of the following human P450 enzymes: CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5 or CYP4A9/11-2(EMA, n.d.). Rufinamide has low protein binding (about 34%), suggesting that competition for protein binding would not be a source of drug interaction (La Marca et al., 2013). Renal excretion is the predominant route of elimination for drug related material, accounting for 85% of the dose based on a radiolabeled study. Following a radiolabeled dose of rufinamide, less than 2% of the dose was recovered unchanged in urine (Bialer et al., 1999), (Coppola et al., 2014).

Rufinamide has a low clearance, which is frequently the goal of drug discovery projects in order to reduce dose, enhance exposure, and prolong half-life(Di & Obach, 2015), which means rufinamide has a low first-pass effect. Rufinamide does not affect the plasma concentration of other antiepileptics, but phenytoin, phenobarbital, valproate, and pyrimidone affect the clearance of rufinamide(Di & Obach, 2015).

Drug Interactions

Based on in vitro studies, rufinamide shows little or no inhibition of most cytochrome P450 enzymes at clinically relevant concentrations, with weak inhibition of CYP2E1. Drugs that are substrates of CYP2E1 (e.g. chlorzoxazone) may have increased plasma levels in the presence of rufinamide, but this has not been studied. Based on in vivo drug interaction studies with triazolam and oral contraceptives, rufinamide is a weak inducer of the CYP3A4 enzyme and can decrease exposure of drugs that are substrates of CYP3A4. Rufinamide is metabolized by carboxylesterases. Drugs that may induce the activity of carboxylesterases may increase the clearance of rufinamide. Broad-spectrum inducers such as carbamazepine and phenobarbital may have minor effects on rufinamide metabolism via this mechanism. Drugs that are inhibitors of carboxylesterases may decrease metabolism of rufinamide (FDA, 2008a).

Gall et al. has conducted a pharmacokinetic study at three different doses of 1 mg/kg body weight (bw), 5 mg/kg bw, and 20 mg/kg bw in adult Wistar male rats. Furthermore, total brain concentrations of the drug were determined in order to characterize its brain-to-plasma partition coefficient. The mean half-life was between 7 and 13 h, depending on route of administration – intravenously administered drug was eliminated faster than orally administered drug. Mean (S.E.M.) total plasma clearance was 84.01 ± 3.80 ml/h/kg for intravenous administration, while the apparent plasma clearance for oral administration was 95.52

± 39.45 ml/h/kg. The mean (S.E.M.) maximum plasma concentration reached after oral administration of 1 mg/kg bw and 5 mg/kg bw was 0.89 ± 0.09 μg/ml and 3.188 ± 0.71 μg/ml, respectively. The median (range) time to reach maximum plasma concentration (t_{max}) was 4 (2–8) h. Mean (S.E.M.) brain-to-plasma concentration ratio of rufinamide was 0.514 ± 0.036, consistent with the brain-to-plasma ratio calculated from the area under curves (AUC_{0-t}) of 0.441 ± 0.047. No influence of dose, route of administration, or post-dosing time was observed on brain-to-plasma ratio(Gáll et al., 2015).

FORMULATION TYPES

Rufinamide is presented as film-coated tablets containing 100, 200 or 400 mg rufinamide under tradename of Inovelon® or Banzel®. Inactive ingredients are lactose monohydrate, microcrystalline cellulose, maize starch, croscarmellose sodium, hypromellose, magnesium stearate, sodium lauryl sulphate and silica colloidal anhydrous. The film coating contains hypromellose, macrogols (8000), titanium dioxide (E171), talc and ferric oxide red (E172) (Electronic medicines compendium, 2017b). Each 100 mg film coated tablet contains 20 mg lactose monohydrate (EMA, n.d.).

In the Novartis patent, pharmaceutical composition is presented as Table 5. The active ingredient is granulated with water. Milled lactose, maize starch, microcrystalline cellulose PH 102, cellulose HP-M-603 and sodium lauryl sulfate are added to the above mixture and granulated with water. The moist material is dried and milled. After the addition of the remaining ingredients, the homogeneous mixture is compressed to give tablet cores. The tablet cores are coated with the film coat which is formed from the appropriate ingredients (Portmann et al., 2011);

In addition, rufinamide is presented as suspension, which is interchangeable with tablet formulations at equal doses, containing 40 mg/mL rufinamide(Critchley et al., 2011) Inactive ingredients are microcrystalline cellulose, carmellose sodium, hydroxyethyl cellulose, citric acid anhydrous, poloxamer 188, methyl parahydroxybenzoate, propyl parahydroxybenzoate, propylene glycol, potassium sorbate, sorbitol liquid non crystallizing, orange flavor, simeticone emulsion 30% (containing benzoic acid, cyclotetrasiloxane, dimethicone, glycol stearate and glyceryl distearate, methylcellulose, PEG-40 stearate, Polysorbate 65, silica gel, sorbic acid, sulphuric acid and water), and water(Electronic medicines compendium, 2017a).

Table 5. Qualitative and quantitative composition of Innovator product (Portmann et al., 2011)

	mg	mg	mg
Core material			
Rufinamide	100.00	200.00	400.00
Anhydrous, colloidal silica	0.88	1.75	3.50
Microcrystalline cellulose	36.62	73.25	146.50
Hydroxypropyl methylcellulose	5.00	10.00	20.00
Lactose	20.00	40.00	80.00
Magnesium stearate	2.00	4.00	8.00
Maize starch	10.00	20.00	40.00
Sodium carboxymethylcellulose	5.00	10.00	20.00
Sodium lauryl sulfate	0.50	1.00	2.00
Film coat			
Hydroxypropyl methylcellulose	3.22	6.43	12.87
Red iron oxide	0.04	0.09	0.18
Polyethylene glycol 8000, flakes	0.58	1.16	2.32
Talc	2.33	4.66	9.31
Titanium dioxide	0.83	1.66	3.32
TOTAL (mg)	187.00	374.00	748.00

Douroumis et al. have investigated the solid dispersion and dissolution profiles of rufinamide, prepared by the solvent evaporation method. Solid dispersion of the hydroxypropyl methylcellulose (HPMC), with drug: polymer ratios of 1:4, were prepared. The drugs and the polymer were dissolved in minimum chloroform–methanol volumes. A rotary evaporation system was used to remove the solvent at 40˚C. Solid dispersions of rufinamide showed modest enhancement of dissolution, suggesting negligible drug–polymer interactions. The different dissolution behavior is attributed to the extent of interactions between the polymer hydroxyl group and the drug amide groups (Douroumis et al., 2007).

Chatakonda et al., demonstrated a solid dispersion formulation of rufinamide with various fillers such as lactose, mannitol and urea to improve its dissolution rate. The solvent evaporation method was used. Rufinamide and filler is dispersed in methanol solution, then the dispersion was evaporated to dryness. In-vitro release indicated that the solid dispersion containing mannitol had shown better dissolution rate when compared with other two carriers, while pure drug dissolution rate was found to be 79.1% after 8 hours, mannitol solid dispersion dissolution rate was found to be 99.6 % after 8 hours (Chatakonda et al., 2012).

Another rufinamide solid dispersion formulation has been described in US 20150182458 A1 patent by solvent evaporation method. Researchers have evaluated different solid dispersions with various carriers as copovidone, span 20, ethyl cellulose, hydroxypropyl methylcellulose, polyethylene gycol or soluplus in a suitable solvent (dimethyl sulfoxide, dimethylacetamide, dimethylformamide, methanol, ethanol, isopropanol, n-butanol and n-pentanol). The solvent may be removed from the solution with distillation, freeze-drying or spray drying. Drug: carrier ratios are at1:08 to 1:20. The solid dispersion of rufinamide is stable, reproducible and amicable for large-scale preparation (Reddy et al., 2015).

PHARMACOECONOMIC ANALYSES

In 1993, it was estimated that the total burden of epilepsy in the UK was £1930 million per year, over two-thirds of which was the result of indirect costs. The cost-effectiveness analysis suggested that rufinamide would be associated with incremental costs of £62 (drop attacks) or £2151 (total seizures) per 1% increase in the number of patients achieving a >50% reduction in seizure frequency over 3 years (McCormack, 2012).

The available pharmacoeconomic data indicate that rufinamide is more effective, but more expensive, than alternative adjunctive therapies. Although rufinamide exceeds conventional cost-effectiveness thresholds when compared with lamotrigine, it may still be considered a valuable treatment option for a devastating orphan disease such as LGS (McCormack, 2012).

CONCLUSION

Rufinamide is a third generation, a triazole derivative that is structurally different from currently available antiepileptic drugs, is indicated for treatment of seizures associated with Lennox-Gastaut syndrome (LGS), an orphan disease, in pediatric patients 1 year of age and older, and in adults. Intra-subject variabilities of AUC and C_{max} after suspension were larger than after the tablets, which concludes the tablet dosage form is more appropriate for a stable serum plasma concentration.

On single and multiple dosing, rufinamide exhibited nonlinear pharmacokinetics in the dose range from 200 mg to 1200 mg, which may be attributed to saturable absorption or limited solubility at higher doses. Given that the therapeutic dose can reach up to 3200 mg/ day, non-linear pharmacokinetic behavior becomes a problem. Improving pharmacokinetic behavior of rufinamide from non-linear pharmacokinetic to linear pharmacokinetic thanks to increasing solubility would be a beneficial approach to achieve higher efficiency with lower doses, and decrease side effects. Food increases the exposure to rufinamide by about 50 - 56% of C_{max} and about 34% of AUC, which means the bioavailability is highly dependent to meals. In order to achieve desired and stable bioavailability, a food-independent formulation would be beneficial on LGS treatment.

Dissolution of drugs with poor aqueous solubility is the rate-limiting factor of absorption. Thus, formulations, which confer improved solubility and/or dissolution rate are therefore especially important to enhance bioavailability.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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