"To be sold by retail on the prescription of Neurologists/ Geriatricians only"

ZAFIMOVE

1. Generic Name

Safinamide Tablets 50mg

Safinamide Tablets 100mg

2. Qualitative and quantitative composition

ZAFIMOVE 50mg

Each film coated tablet contains:
Safinamide Methane Sulphonate IP eq. to Safinamide….50 mg
Colours: Red Oxide of Iron, Yellow Oxide of Iron and Titanium Dioxide I.P.

The other excipients are Silicified Microcrystalline Cellulose, Crospovidone, Magnesium Stearate, Colliodal Silicon Dioxide, Insta coat universal (contains: Hypromellose, polyethylene glycol, talc, Titanium Dioxide, Red oxide of Iron , Yellow oxide of iron.

ZAFIMOVE 100mg

Each film coated tablet contains:
Safinamide Methane sulfonate I.P equivalent to Safinamide.100 mg
Excipients ……. q.s
Colour: Titanium Dioxide I.P., Red oxide of Iron and Yellow oxide of Iron

The other excipients are Silicified Microcrystalline Cellulose, Crospovidone, Magnesium Stearate, Colliodal Silicon Dioxide, Insta coat universal (contains: Hypromellose, polyethylene glycol, talc, Titanium Dioxide, Red oxide of Iron , Yellow oxide of iron).

3. Dosage form and strength

Dosage Form: Film coated tablets

Strength: 50mg, 100mg

4. Clinical particulars

4.1 Therapeutic indication

For the treatment of adult patients with idiopathic Parkinson's disease (PD) as add-on therapy to a stable dose of Levodopa (L-dopa) alone or in combination with other Parkinson's disease (PD) medicinal products in mid to late stage fluctuating patients.

4.2 Posology and method of administration

Posology

Treatment with safinamide should be started at 50 mg per day. This daily dose may be increased to 100 mg/day on the basis of individual clinical need.

If a dose is missed the next dose should be taken at the usual time the next day.

Elderly

No change in dose is required for elderly patients.

Experience of use of safinamide in patients over 75 years of age is limited.

Hepatic impairment

Safinamide use in patients with severe hepatic impairment is contraindicated. No dose adjustment is required in patients with mild hepatic impairment. The lower dose of 50 mg/day is recommended for patients with moderate hepatic impairment. If patients progress from moderate to severe hepatic impairment safinamide should be stopped.

Renal impairment

No change in dose is required for patients with renal impairment.

Paediatric population

The safety and efficacy of safinamide in children and adolescents under 18 years of age have not been established. No data are available.

Method of administration

For oral use.

Safinamide should be taken with water.

Safinamide may be taken with or without food.

4.3 Contraindications

- Concomitant use of the other drugs in the monoamine oxidase inhibitors [MAO] or other drugs that are potent inhibitors of monoamine oxidase (e.g., linezolid). The combination may result in increased blood pressure, including hypertensive crisis.
- Concomitant use of Opioid drugs (e.g., tramadol, meperidine and it's derivatives, methadone or propoxyphene); serotonin-norepinephrine reuptake inhibitors (SNRIs); tri- or tetra-cyclic or triazolopyridine antidepressants; cyclobenzaprine; methylphenidate, amphetamine, and their derivatives; St. John's wort. Concomitant use could result in life-threatening serotonin syndrome.
- Concomitant use of Dextromethorphan. The combination of MAO inhibitors and dextromethorphan has been reported to cause episodes of psychosis or abnormal behaviour.
    - A history of a hypersensitivity to safinamide
    - Severe hepatic impairment (Child-Pugh)
- Hypersensitivity to the active substance or to any of the excipients.
- Concomitant treatment with pethidine.
- Use in patients with albinism, retinal degeneration, uveitis, inherited retinopathy or severe progressive diabetic retinopathy.

4.4 Special warnings and precautions for use

- May cause or exacerbate hypertension
- May cause serotonin syndrome when used with MAO inhibitors, antidepressants, or opioid drugs
- May cause falling asleep during activities of daily living
- May cause or exacerbate dyskinesia; consider levodopa dose reduction
- May cause hallucinations and psychotic behavior
- May cause problems with impulse control/compulsive behaviors
- May cause withdrawal-emergent hyperpyrexia and confusion

4.5 Drugs interactions

In vivo and *in vitro* pharmacodynamic drug interactions

MAO inhibitors and pethidine

Safinamide must not be administered along with other MAO inhibitors (including moclobemide) as there may be a risk of non-selective MAO inhibition that may lead to a hypertensive crisis.

Serious adverse reactions have been reported with the concomitant use of pethidine and MAO inhibitors. As this may be a class-effect, the concomitant administration of safinamide and pethidine is contraindicated.

There have been reports of medicinal product interactions with the concomitant use of MAO inhibitors and sympathomimetic medicinal products. In view of the MAO inhibitory activity of safinamide, concomitant administration of safinamide and sympathomimetics, such as those present in nasal and oral decongestants or cold medicinal products containing ephedrine or pseudoephedrine, requires caution.

Dextromethorphan

There have been reports of medicinal product interactions with the concomitant use of dextromethorphan and nonselective MAO inhibitors. In view of the MAO inhibitory activity of safinamide, the concomitant administration of safinamide and dextromethorphan is not recommended, or if concomitant treatment is necessary, it should be used with caution.

Antidepressants

The concomitant use of safinamide and fluoxetine or fluvoxamine should be avoided, this precaution is based on the occurrence of serious adverse reactions (e.g. serotonin syndrome), although rare, that have occurred when SSRIs and dextromethorphan have been used with MAO inhibitors. If necessary, the concomitant use of these medicinal products should be at the lowest effective dose. A washout period corresponding to 5 half-lives of the SSRI used previously should be considered prior to initiating treatment with safinamide.

Serious adverse reactions have been reported with the concomitant use of selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic/tetracyclic antidepressants and MAO inhibitors. In view of the selective and reversible MAO-B inhibitory activity of safinamide, antidepressants may be administered but used at the lowest doses necessary.

In vivo and *in vitro* pharmacokinetic drug interactions

Safinamide may transiently inhibit BCRP *in vitro*. In reported drug-drug-interaction studies in human, a weak interaction was observed with rosuvastatin (AUC increase between 1.25 and 2.00 fold) but no significant interaction was found with diclofenac.

It is recommended to monitor patients when safinamide is taken with medicinal products that are BCRP substrates (e.g., rosuvastatin, pitavastatin, pravastatin, ciprofloxacin, methotrexate, topotecan, diclofenac or glyburide) and to determine if a dose adjustment is needed.

Safinamide is almost exclusively eliminated via metabolism, largely by high capacity amidases that have not yet been characterized. Safinamide is eliminated mainly in the urine. In human liver microsomes (HLM), the N-dealkylation step appears to be catalysed by CYP3A4, as safinamide clearance in HLM was inhibited by ketoconazole by 90%.

Safinamide inhibits OCT1 *in vitro* at clinically relevant portal vein concentrations. Therefore, caution is necessary when safinamide is taken concomitantly with medicinal products that are

OCT1 substrates and have a t_{max} similar to safinamide (2 hours) (e.g. metformin, aciclovir, ganciclovir) as exposure to these substrates might be increased as a consequence.

The metabolite NW-1153 is a substrate for OAT3 at clinically relevant concentrations.

Medicinal products that are inhibitors of OAT3 given concomitantly with safinamide may reduce clearance of NW-1153, i.e., and thus may increase its systemic exposure. The systemic exposure of NW-1153 is low (1/10 of parent safinamide). This potential increase is most likely of no clinical relevance as NW-1153, the first product in the metabolic pathway, is further transformed to secondary and tertiary metabolites.

Paediatric population

Reportedly, interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Safinamide should not be given to women of childbearing potential unless adequate contraception is practiced.

Pregnancy

There are no or limited amount of data from the use of safinamide in pregnant women. Reported studies in animals have shown reproductive toxicity. Safinamide is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

Available pharmacodynamic/toxicological data in animals have shown excretion of safinamide in milk.

A risk for the breast-fed child cannot be excluded. Safinamide should not be used during breast-feeding.

Fertility

Reported animal studies indicate that safinamide treatment is associated with adverse reactions on female rat reproductive performance and sperm quality. Male rat fertility is not affected.

4.7 Effects on ability to drive and use machines

Somnolence and dizziness may occur during safinamide treatment, therefore patients should be cautioned about using hazardous machines, including motor vehicles, until they are reasonably certain that safinamide does not affect them adversely.

4.8 Undesirable effects

Summary of the safety profile

Dyskinesia was the most common adverse reaction reported in safinamide patients when used in combination with L-dopa alone or in combination with other PD treatments.

Serious adverse reactions are known to occur with the concomitant use of SSRIs, SNRIs, tricyclic/tetracyclic antidepressants and MAO inhibitors, such as hypertensive crisis (high blood pressure, collapse), neuroleptic malignant syndrome (confusion, sweating, muscle rigidity, hyperthermia, CPK increase), serotonin syndrome (confusion, hypertension, muscle stiffness, hallucinations), and hypotension. With MAO-inhibitors there have been reports of drug interactions with concomitant use of sympathomimetic medicinal products.

Impulse control disorders; pathological gambling, increased libido, hypersexuality, compulsive

spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists and/or other dopaminergic treatments.

Tabulated list of adverse reactions

The tabulation below includes all adverse reactions in reported clinical trials where adverse reactions were considered related.

Adverse reactions are ranked under headings of frequency using the following conventions: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000) and not known (cannot be estimated from the available data).

System Organ Class	Very Common	Common	Uncommon	Rare
Infections and Infestations			Urinary tract infection	Bronchopneumonia, furuncle, nasopharyngitis, pyoderma, rhinitis, tooth infection, viral infection
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			Basal cell carcinoma	Acrochordon, melanocytic naevus, seborrhoeic keratosis, skin papilloma
Blood and lymphatic system disorders			Anaemia, leukopenia, red blood cell abnormality	Eosinophilia, Lymphopenia
Metabolism and nutrition disorders			Decreased appetite, hypertriglyceridaemia, increased appetite, hypercholesterolaemia, hyperglycaemia,	Cachexia, Hyperkalaemia

Psychiatric disorders		Insomnia	Hallucination, depression, abnormal dreams, anxiety, confusional state, affect lability, libido increased, psychotic disorder, restlessness, sleep disorder	Compulsions, delirium, disorientation, illusion, impulsive behaviour, loss of libido, obsessive thoughts, paranoia, premature ejaculation, sleep attacks, social phobia, suicidal ideation
Nervous system Disorders		Dyskinesia somnolence, dizziness, headache, Parkinson's Disease	Paraesthesia, balance disorder, hypoaesthesia, dystonia, head discomfort, dysarthria, syncope, cognitive disorder	Coordination abnormal, disturbance in attention, dysgeusia, hyporeflexia, radicular pain, Restless Legs Syndrome, Sedation
Eye disorders		Cataract	Vision blurred, scotoma, diplopia, photophobia, retinal disorder, conjunctivitis, glaucoma	Amblyopia, chromatopsia, diabetic retinopathy, erythropsia, eye haemorrhage, eye pain, eyelid oedema, hypermetropia, keratitis, lacrimation increased, night blindness,

				papilloedema, presbyopia, strabismus
Ear and labyrinth Disorders			Vertigo	
Cardiac disorders			Palpitations, tachycardia, sinus bradycardia, arrhythmia	Myocardial infarction
Vascular disorders		Orthostatic Hypotension	Hypertension, hypotension, varicose vein	Arterial spasm, arteriosclerosis, hypertensive crisis
Respiratory, thoracic and mediastinal disorders			Cough, dyspnoea, rhinorrhoea	Bronchospasm, dysphonia, oropharyngeal pain, oropharyngeal spasm
Gastrointestinal Disorders		Nausea	Constipation, dyspepsia, vomiting, dry mouth, diarrhoea, abdominal pain, gastritis, flatulence, abdominal distension, salivary hypersecretion, gastrooesophageal reflux disease, aphthous stomatitis	Peptic ulcer, retching, upper gastrointestinal haemorrhage

Hepatobiliary Disorders				Hyperbilirubinaemia
Skin and subcutaneous tissue disorders			Hyperhidrosis, pruritus generalised, photosensitivity reaction, erythema	Alopecia, blister, dermatitis contact, dermatosis, ecchymosis, lichenoid keratosis, night sweats, pain of skin, pigmentation disorder, psoriasis, seborrhoeic dermatitis
Musculoskeletal and connective tissue disorders			Back pain, arthralgia, muscle spasms, muscle rigidity, pain in extremity, muscular weakness, sensation of heaviness	Ankylosing spondylitis, flank pain, joint swelling, musculoskeletal pain, myalgia, neck pain, osteoarthritis, synovial cyst
Renal and urinary Disorders			Nocturia, Dysuria	Micturition urgency, polyuria, pyuria, urinary hesitation
Reproductive system and breast disorders			Erectile dysfunction	Benign prostatic hyperplasia, breast disorder, breast pain
General disorders and			Fatigue, asthenia,	Drug effect decreased, drug intolerance,

administration site conditions			gait disturbance, oedema peripheral, pain, feeling hot	feeling cold, malaise, pyrexia, xerosis
Investigations			Weight decreased, weight increased, blood creatine phosphokinase increased, blood triglycerides increased, blood glucose increased, blood urea increased, blood alkaline phosphatase increased, blood bicarbonate increased, blood creatinine increased, electrocardiogram QT prolonged, liver function test abnormal, urine analysis abnormal, blood pressure increased, blood pressure decreased, ophthalmic diagnostic procedures abnormal	Blood calcium decreased, blood potassium decreased, blood cholesterol decreased, body temperature increased, cardiac murmur, cardiac stress test abnormal, haematocrit decreased, haemoglobin decreased, international normalised ratio decreased, lymphocyte count decreased, platelet count decreased, very low density lipoprotein increased
Injury, poisoning and		Fall	Foot fracture	Contusion,

procedural complications				fat embolism, head injury, mouth injury, skeletal injury
Social circumstances				Gambling

Description of selected adverse reactions

Dyskinesia occurred early in treatment, was rated "severe", led to discontinuation in very few patients (approx. 1.5%), and did not require reduction of dose in any patient.

- **Reporting of suspected adverse reactions**

If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

4.9 Overdose

In one patient suspected of consuming more than the daily prescribed dose of 100 mg for one month, symptoms of confusion, sleepiness, forgetfulness and dilated pupils were reported. These symptoms resolved on discontinuing the medicinal product, without sequelae.

The expected pattern of events or symptoms following intentional or accidental overdose with Safinamide would be those related to its pharmacodynamic profile: MAO-B inhibition with activity-dependent inhibition of Na+ channels. The symptoms of an excessive MAO-B inhibition (increase in dopamine level) could include hypertension, postural hypotension, hallucinations, agitation, nausea, vomiting, and dyskinesia.

There is no known antidote to safinamide or any specific treatment for safinamide overdose. If an important overdose occurs, safinamide treatment should be discontinued and supportive treatment should be administered as clinically indicated.

5. Pharmacological properties

Pharmacotherapeutic group: Anti-Parkinson-Drugs, monoamine oxidase -B inhibitors

ATC code: N04BD03

5.1 Mechanism of Action

Safinamide acts through both dopaminergic and non-dopaminergic mechanisms of action. Safinamide is a highly selective and reversible MAO-B inhibitor causing an increase in extracellular levels of dopamine in the striatum. Safinamide is associated with state-dependent inhibition of voltage-gated sodium ($Na^{+)}$ channels, and modulation of stimulated release of glutamate. To what extent the non-dopaminergic effects contribute to the overall effect has not been established.

5.2 Pharmacodynamic properties

Mechanism of action

Safinamide acts through both dopaminergic and non-dopaminergic mechanisms of action. Safinamide is a highly selective and reversible MAO-B inhibitor causing an increase in

extracellular levels of dopamine in the striatum. Safinamide is associated with state-dependent inhibition of voltage-gated sodium (Na^+) channels, and modulation of stimulated release of glutamate. To what extent the non-dopaminergic effects contribute to the overall effect has not been established.

Pharmacodynamic effects

Reportedly, population PK models developed from studies in patients with Parkinson's disease indicate that the pharmacokinetic and pharmacodynamics effects of safinamide were not dependent on age, gender, weight, renal function and exposure to levodopa, indicating that dose adjustments will not be required based on these variables.

Reported pooled analyses of adverse event data from placebo controlled studies in Parkinson's disease patients indicate that the concomitant administration of safinamide together with a broad category of commonly used medicinal products in this patient population (antihypertensive, beta-blockers cholesterol lowering, non-steroidal anti-inflammatory medicinal products, proton pump inhibitors, antidepressants, etc.) was not associated with an increased risk for adverse events. Studies were not stratified for co-medication, and no randomized interaction studies were performed for these medicinal products.

Clinical efficacy

Studies in mid- to late-stage PD patients

The efficacy of safinamide as add-on treatment in mid-to late-stage PD (LSPD) patients with motor fluctuations, currently receiving L-dopa alone or in combination with other PD medicinal products, was evaluated in two reported double-blind, placebo controlled studies: Study SETTLE (Study 27919; 50-100 mg/day; 24 weeks), and Study 016/018 (50 and 100 mg/day; 2- year, double-blind, placebo-controlled study).

The primary efficacy parameter was the change from baseline to endpoint in 'ON Time without troublesome dyskinesia'.

Secondary efficacy parameters included OFF Time, UPDRS II and III (Unified Parkinson's Disease Rating Scale – sections II and III), and CGI-C (Clinical Global Impression of Change)

Both the SETTLE and 016/018 studies indicated significant superiority of safinamide, compared to placebo, at the target doses of 50 and 100 mg/day for the primary, and selected secondary, efficacy variables, as summarized in the table below. The effect on ON Time was maintained at the end of the 24-month double-blind treatment period for both safinamide doses as compared to placebo.

Study	**016 (24 Weeks)**			**016/018 (2 Years)**			**27919 (SETTLE) (24 weeks)**	
Dose (mg/day) (a)	**Placebo**	**Safinamide**		**Placebo**	**Safinamide**		**Placebo**	**Safinamide**
		50	**100**		**50**	**100**		**50-100 (d)**
Randomized	222	223	224	222	223	224	275	274

Age (years) (b)	59.4 (9.5)	60.1 (9.7)	60.1 (9.2)	59.4 (9.5)	60.1 (9.7)	60.1 (9.2)	62.1 (9.0)	61.7 (9.0)
PD Duration (years) (b)	8.4 (3.8)	7.9 (3.9)	8.2 (3.8)	8.4 (3.8)	7.9 (3.9)	8.2 (3.8)	9.0 (4.9)	8.9 (4.4)
ON time without troublesome dyskinesia (hrs) (c)								
Baseline (b)	9.3 (2.2)	9.4 (2.2)	9.6 (2.5)	9.3 (2.2)	9.4 (2.2)	9.6 (2.5)	9.1 (2.5)	9.3 (2.4)
Change LSM (SE)	0.5 (0.2)	1.0 (0.2)	1.2 (0.2)	0.8 (0.2)	1.4 (0.2)	1.5 (0.2)	0.6 (0.1)	1.4 (0.1)
LS Diff vs Placebo		0.5	0.6		0.6	0.7		0.9
95% CI		[0.1, 0.9]	[0.3, 1.0]		[0.1, 1.0]	[0.2, 1.1]		[0.6, 1.2]
p-value		0.0054	0.0002		0.0110	0.0028		<0.0001
OFF time (hrs) (c)								
Baseline (b)	5.3 (2.1)	5.2 (2.0)	5.2 (2.2)	5.3 (2.1)	5.2 (2.2)	5.2 (2.1)	5.4 (2.0)	5.3 (2.0)
Change LSM (SE)	-0.8 (0.20)	-1.4 (0.20)	-1.5 (0.20)	-1.0 (0.20)	-1.5 (0.19)	-1.6 (0.19)	-0.5 (0.10)	-1.5 (0.10)
LS Diff vs Placebo		-0.6	-0.7		-0.5	-0.6		-1.0
95% CI		[-0.9, -0.3]	[-1.0, -0.4]		[-0.8, -0.2]	[-0.9, -0.3]		[-1.3, -0.7]
p-value		0.0002	<0.0001		0.0028	0.0003		<0.0001
UPDRS III (c)								
Baseline (b)	28.6 (12.0)	27.3 (12.8)	28.4 (13.5)	28.6 (12.0)	27.3 (12.8)	28.4 (13.5)	23.0 (12.8)	22.3 (11.8)
Change LSM (SE)	-4.5 (0.83)	-6.1 (0.82)	-6.8 (0.82)	-4.4 (0.85)	-5.6 (0.84)	-6.5 (0.84)	-2.6 (0.34)	-3.5 (0.34)

LS Diff vs Placebo		-1.6	-2.3		-1.2	-2.1		-0.9
95% CI		[-3.0, -0.2]	[-3.7, -0.9]		[-2.6, 0.2]	[-3.5, -0.6]		[-1.8, 0.0]
p-value		0.0207	0.0010		0.0939	0.0047		0.0514
UPDRS II (c)								
Baseline (b)	12.2 (5.9)	11.8 (5.7)	12.1 (5.9)	12.2 (5.9)	11.8 (5.7)	12.1 (5.9)	10.4 (6.3)	10.0 (5.6)
Change LSM (SE)	-1.2 (0.4)	-1.9 (0.4)	-2.3 (0.4)	-1.4 (0.3)	-2.0 (0.3)	-2.5 (0.3)	-0.8 (0.2)	-1.2 (0.2)
LS Diff vs Placebo		-0.7	-1.1		-0.6	-1.1		-0.4
95% CI		[-1.3, -0.0]	[-1.7, -0.5]		[-1.3, 0.0]	[-1.8, -0.4]		[-0.9, 0.0]
p-value		0.0367	0.0007		0.0676	0.0010		0.0564
Responder analyses (post-hoc) (e) n(%)								
ON time increase ≥60 Minutes	93 (43.9)	119 (54.8)	121 (56.0)	100 (47.2)	125 (57.6)	117 (54.2)	116 (42.5)	152 (56.3)
p-value		0.0233	0.0122		0.0308	0.1481		0.0013
≥60 minutes increase ON time and decrease in OFF time and ≥ 30% improvement UPDRS III	32 (15.1)	52 (24.0)	56 (25.9)	28 (13.2)	43 (19.8)	42 (19.4)	24 (8.8)	49 (18.1)

p-value		0.0216	0.0061		0.0671	0.0827		0.0017
CGI-C: patients who were much/very much improved	42 (19.8)	72 (33.2)	78 (36.1)	46 (21.7)	62 (28.6)	64 (29.6)	26 (9.5)	66 (24.4)
p-value (f)		0.0017	0.0002		0.0962	0.0575		<0.0001

(a) Daily targeted dose, (b) Mean (SD), (c) analysis population (mITT); MMRM model for change from Baseline to Endpoint includes treatment, region, and visit as fixed effects, and baseline value as a covariate; (d) target dose of 100 mg/day; (e) analysis population (mITT); data are presented as the number (percentage) of patients in each group meeting the responder definition (f) chi-square test of the odds ratio of the treatment groups compared to placebo using a logistic regression model, with fixed effects for treatment and country.

SE Standard Error, SD Standard deviation, LSM Least Square Mean, LS Diff. Least Square Difference vs Placebo mITT Population: Study 016/018 - Placebo (n=212), safinamide 50 mg/day (n=217) and 100 mg/day (n=216), and SETTLE - Placebo (n=270), safinamide 50-100 mg/day (n=273).

Paediatric population

The pharmacodynamic effects of safinamide have not been assessed in children and adolescents.

5.3 Pharmacokinetic properties

Absorption

Safinamide absorption is rapid after single and multiple oral dosing, reaching T_{max} in the time range 1.8-2.8 h after dosing under fasting conditions. Absolute bioavailability is high (95%), showing that safinamide is almost completely absorbed after oral administration and first pass metabolism is negligible. The high absorption classifies safinamide as a highly permeable substance.

Distribution

The volume of distribution (V_{ss}) is approximately 165 L which is 2.5-fold of body volume indicating extensive extravascular distribution of safinamide. Total clearance was determined to be 4.6 L/h classifying safinamide as a low clearance substance.

Plasma protein binding of safinamide is 88-90%.

Biotransformation

In humans, safinamide is almost exclusively eliminated via metabolism (urinary excretion of unchanged safinamide was <10%) mediated principally through high capacity amidases, that

have not yet been characterized. Reportedly, in vitro experiments indicated that inhibition of amidases in human hepatocytes led to complete suppression of the NW-1153 formation.

Amidase present in blood, plasma, serum, simulated gastric fluid and simulated intestinal fluid as well as human carboxylesterases hCE-1 and hCE-2 are not responsible for the biotransformation of safinamide to NW-1153. The amidase FAAH was able to catalyse the formation of NW-1153 at low rates only. Therefore, other amidases are likely to be involved in the conversion to NW-1153. Safinamide's metabolism is not dependent on Cytochrome P450 (CYP) based enzymes.

Metabolite structure elucidation revealed three metabolic pathways of safinamide. The principal pathway involves hydrolytic oxidation of the amide moiety leading to the primary metabolite 'safinamide acid' (NW-1153). Another pathway involves oxidative cleavage of the ether bond forming 'O-debenzylated safinamide' (NW-1199). Finally the 'N-dealkylated acid' (NW-1689) is formed by oxidative cleavage of the amine bond of either safinamide (minor) or the primary safinamide acid metabolite (NW-1153) (major). The 'N-dealkylated acid' (NW-1689) undergoes conjugation with glucuronic acid yielding its acyl glucuronide. None of these metabolites are pharmacologically active.

Safinamide does not appear to significantly induce or inhibit enzymes at clinically relevant systemic concentrations. Reported in vitro metabolism studies have indicated that there is no meaningful induction or inhibition of cytochrome P450, CYP2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A3/5 at concentrations which are relevant (C_{max} of free safinamide 0.4 μM at 100 mg/day) in man. Dedicated drug-drug interaction studies performed with ketoconazole, L-dopa and CYP1A2 and CYP3A4 substrates (caffeine and midazolam), did not detect any clinically significant effects on the pharmacokinetics of safinamide, or L-dopa, caffeine and midazolam.

A mass balance study showed that the plasma AUC0-24h of the unchanged 14C-safinamide accounted for approximately 30% of the total radioactivity AUC0-24h, indicative of an extensive metabolism.

Transporters

Reported preliminary in vitro studies have shown that safinamide is not a substrate for the transporters P-gp, BCRP, OAT1B1, OAT1B3, OATP1A2 or OAT2P1. Metabolite NW-1153 is not a substrate for OCT2, or OAT1, but it is substrate for OAT3.

This interaction has the potential to reduce the clearance of NW-1153 and increase its exposure; however the systemic exposure of NW-1153 is low (1/10 of parent safinamide), and as it is metabolised to secondary and tertiary metabolites, it is unlikely to be of any clinical relevance.

Safinamide transiently inhibits BCRP in the small intestine. At concentrations of 50μM, safinamide inhibited OATP1A2 and OATP2P1. The relevant plasma concentrations of safinamide are substantially lower, therefore a clinically relevant interaction with co-administered substrates of these transporters is unlikely. NW-1153 is not an inhibitor of OCT2, MATE1, or MATE2-K up to concentrations of 5μM.

Linearity/non-linearity

The pharmacokinetics of safinamide are linear after single and repeated doses. No time-dependency was observed.

Elimination

Safinamide undergoes almost complete metabolic transformation (<10% of the administered dose was found unchanged in urine). Substance-related radioactivity was largely excreted in

urine (76%) and only to a low extent in faeces (1.5%) after 192 hours. The terminal elimination half-life of total radioactivity was approximately 80 hours.

The elimination half-life of safinamide is 20-30 hours. Steady-state is reached within one week.

Patients with hepatic impairment

Safinamide exposure in patients with mild hepatic disease increased marginally (30% in AUC), while in patients with moderate hepatic impairment exposure increased by approximately 80%.

Patients with renal impairment

Moderate or severe renal impairment did not alter the exposure to safinamide, compared to healthy subjects.

6. Nonclinical properties

Retinal degeneration was observed in rodents after repeated safinamide dosing resulting in systemic exposure below the anticipated systemic exposure in patients given the maximal therapeutic dose. No retinal degeneration was noted in monkeys despite higher systemic exposure than in rodents or in patients at the maximum human dose.

As per reported data, long-term studies in animals have shown convulsions (1.6 to 12.8 times human clinical exposure, based on plasma AUC). Liver hypertrophy and fatty changes were seen only in rodent livers at exposures similar to humans.

Phospholipidosis was seen mainly in the lungs in rodents (at exposures similar to humans) and monkeys (at exposures greater than 12 fold higher than human).

Safinamide did not present genotoxic potential in in vivo and in several in vitro systems using bacteria or mammalian cells.

The results obtained from reported carcinogenicity studies in mice and rats showed no evidence of tumorigenic potential related to safinamide at systemic exposures up to 2.3 to 4.0 times respectively, the anticipated systemic exposure in patients given the maximal therapeutic dose.

Reported fertility studies in female rats showed reduced number of implantations and corpora lutea at exposures in excess of 3 times the anticipated human exposure. Male rats showed minor abnormal morphology and reduced speed of sperm cells at exposures in excess of 1.4 times the anticipated human exposure. Male rat fertility was not affected.

In reported embryo-foetal developmental studies in rats and rabbits malformations were induced at safinamide exposures 2 and 3-fold above human clinical exposure, respectively. The combination of safinamide with levodopa/carbidopa resulted in additive effects in the embryo-foetal development studies with a higher incidence of foetal skeletal abnormalities than seen with either treatment alone.

In a reported pre- and postnatal developmental rat study, pup mortality, absence of milk in the stomach and neonatal hepatotoxicity were observed at dose levels similar to the anticipated clinical exposure. Toxic effects on the liver and accompanying symptoms as yellow/orange skin and skull, in pups exposed to safinamide during lactation are mediated mainly via in utero exposure, whereas exposure via the mother's milk had only a minor influence.

7. Description

ZAFIMOVE 50

- Safinamide 50mg Tablets: Orange to copper colored, round film-coated, biconcave shaped tablet, debossed with ‘‘50’’ on one side and plain on other side.

ZAFIMOVE 100

- Safinamide 100mg Tablets: Orange to copper colored, round film-coated, biconcave shaped tablet, debossed with "100'' on one side and plain on other side.

8. Pharmaceutical particulars

8.1 Incompatibilities

Not applicable

8.2 Shelf-life

Do not use later than date of Expiry

8.3 Packaging information

Available in blister pack of 10 Tablets

8.4 Storage and handing instructions

- Store at a temperature not exceeding 30°C, protected from light and moisture.
- Keep all medicine out of reach of children.

9. Patient counselling information

Package leaflet information

ZAFIMOVE

SAFINAMIDE

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

• Keep this leaflet. You may need to read it again.

• If you have any further questions, ask your doctor or pharmacist.

• This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.

• If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet?

9.1 What ZAFIMOVE Tablets are and what they are used for

ZAFIMOVE contains Safinamide/ Safinamide Tablets are medicine that contains the active substance safinamide. It acts to increase the level of a substance called dopamine in the brain, which is involved in the control of movement and is present in reduced amounts in the brain of

patients with Parkinson's disease. ZAFIMOVE is used for the treatment of Parkinson's disease in adults.

In mid- to late-stage patients experiencing sudden switches between being "ON" and able to move and being "OFF" and having difficulties moving about, ZAFIMOVE is added to a stable dose of the medicine called levodopa alone or in combination with other medicines for Parkinson's disease.

9.2 What you need to know before you take ZAFIMOVE

Do not take ZAFIMOVE

- If you are allergic to safinamide or any of the other ingredients of this medicine.

- If you are taking any of the following medicines:

- Monoamine oxidase (MAO) inhibitors such as selegiline, rasagiline, moclobemide, phenelzine, isocarboxazid, tranylcypromine (e.g. for treatment of Parkinson's disease or depression, or used for any other condition).

- Pethidine (a strong pain killer).

You must wait at least 7 days after stopping ZAFIMOVE treatment before starting treatment with MAO inhibitors or pethidine.

- If you have been told that you have severe liver problems

- If you have an eye condition which might put you at risk of potential damage to your retina (the light sensitive layers at the back of your eyes), e.g. albinism (lack of pigment in your skin and eyes), retinal degeneration (loss of cells from light sensitive layer at the back of the eye), or uveitis (inflammation inside of the eye), inherited retinopathy (inherited disorders of the vision), or severe progressive diabetic retinopathy (a progressive decrease of the vision due to diabetes).

Warnings and precautions

Talk to your doctor before taking ZAFIMOVE

- If you have liver problems

- Patients and carers should be made aware that certain compulsive behaviours such as compulsions, obsessive thoughts, pathological gambling, increased libido, hypersexuality, impulsive behaviour and compulsive spending or buying have been reported with other medicines for Parkinson's disease.

- Uncontrollable jerky movements may occur or worsen when ZAFIMOVE is used together with levodopa.

Children and adolescents

ZAFIMOVE is not recommended for use in children and adolescents, below 18 years old due to the lack of data on safety and efficacy in this population.

Other medicines and ZAFIMOVE

Tell your doctor or pharmacist if you are taking or have recently taken or might take any other medicines. Ask your doctor for advice before taking any of the following medicines together with ZAFIMOVE:

- Cold or cough remedies containing dextromethorphan, ephedrine or pseudoephedrine

- Medicines called selective serotonin reuptake inhibitors (SSRIs) typically used to treat

anxiety disorders, and some personality disorders (e.g. fluoxetine or fluvoxamine)

- Medicines called serotonin–norepinephrine reuptake inhibitors (SNRIs), used in the treatment of major depression and other mood disorders, such as venlafaxine

- Medicines for high cholesterol such as rosuvastatin, pitavastatin, pravastatin

- Fluoroquinolone antibiotic such as ciprofloxacin

- Medicines that affect the immune system such as methotrexate

- Medicines to treat metastatic carcinoma such as topotecan

- Medicine to treat pain and inflammation such as diclofenac

- Medicines to treat type 2 diabetes such as glyburide, metformin

- Medicines to treat virus infection such as aciclovir, ganciclovir

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Pregnancy

ZAFIMOVE should not be used during pregnancy or by women of childbearing potential not practicing adequate contraception.

Breast Feeding

ZAFIMOVE is likely to be excreted in breast milk. ZAFIMOVE should not be used during breast-feeding.

Driving and using machines

Somnolence and dizziness may occur during ZAFIMOV treatment; you should be cautious about operating hazardous machines or driving, until you are reasonably certain that ZAFIMOV does not affect you in any way.

Ask your doctor for advice prior to driving or using machines.

9.3 How to take ZAFIMOVE

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

The recommended starting dose of ZAFIMOV is one 50 mg tablet that may be increased to one 100 mg tablet, taken once daily preferably in the morning by mouth with water. ZAFIMOV may be taken with or without food.

If you suffer from moderately reduced liver function, you should not take more than 50 mg a day; your doctor will advise if this applies to you.

If you take more ZAFIMOVE than you should

If you have taken too many ZAFIMOV tablets, you may develop raised blood pressure, anxiety, confusion, forgetfulness, sleepiness, lightheadedness; feel sick or be sick; dilated pupils or develop involuntary jerky movements. Contact your doctor immediately and take the **ZAFIMOVE** pack with you.

If you forget to take ZAFIMOVE

Do not take a double dose to make up for a forgotten dose. Skip the missed dose and take the

next dose at the time you normally take it.

If you stop taking ZAFIMOVE

Do not stop taking **ZAFIMOVE** without first talking to your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

9.4 Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Seek medical advice in case of hypertensive crisis (very high blood pressure, collapse), neuroleptic malignant syndrome (confusion, sweating, muscle rigidity, hyperthermia, increase level of enzyme creatine kinase in your blood), serotonin syndrome (confusion, hypertension, muscle stiffness, hallucinations), and hypotension.

The following side effects have been reported in patients at a mid- to late-stage of Parkinson's disease (patients taking ZAFIMOV as add-on to levodopa alone or in combination with other medicines for Parkinson's disease):

Common: insomnia, difficulty in performing voluntary movements, feeling sleepy, dizziness, headache, worsening of Parkinson's disease, clouding of the lens of the eye, fall in blood pressure when rising to a standing position, nausea, falling.

Uncommon: urine infection, skin cancer, low iron in your blood, low white cell count, red blood cell abnormality, decreased appetite, high fat in blood, increased appetite, high blood sugar, seeing things that are not there, feeling sad, abnormal dreams, fear and worry, confusional state, mood swings , increased interest in sex, abnormal thinking and perception, restlessness, sleep disorder, numbness, unsteadiness, loss of sensation, sustained abnormal muscle contraction, head discomfort, difficulty in speaking, fainting, memory impairment, blurring of vision, blind spot, double vision, aversion to light, disorders of the light sensitive layer at the back of your eye, redness of the eyes, increased pressure in the eye, sensation of room spinning, feeling of heart beating, fast heartbeat, irregular heartbeat, slowed heartbeat , high blood pressure, low blood pressure, veins that have become large and twisted, cough, difficult breathing, runny nose, constipation, heartburn, vomiting, dry mouth, diarrhoea, abdominal pain, burning stomach, wind, feeling full, drooling, mouth ulcer, sweating, itching, sensitive to light, redness of the skin, back pain, joint pain, cramps, stiffness, pain in legs or arms, muscle weakness, sensation of heaviness, increased urination at night, pain upon urination, difficulty in having sex in males, fatigue, feeling weak, unsteady walking, swelling of your feet, pain, feeling hot, weight loss, weight gain, abnormal blood tests, high fat in your blood, increased sugar in your blood, abnormal ECG, liver function test abnormal, abnormal urine tests, blood pressure decreased, blood pressure increased, abnormal eye test, fracture of your foot.

Rare: pneumonia, skin infection, sore throat, nasal allergy, tooth infection, viral infection, non-cancerous skin conditions/growth, white blood cell abnormalities, severe loss of weight and weakness, increased potassium in blood, uncontrollable urges, clouding of consciousness, disorientation, wrong perception of images, reduced interest in sex, thoughts that you cannot get rid of, feeling that someone is out to get you, premature ejaculation, uncontrollable urge to sleep, fear of social situations, thoughts of suicide, clumsiness, easily distracted, loss of taste, weak/slow reflexes, radiating pain in the legs, continuous desire to move your legs, feeling sleepy, eye abnormalities, progressive diminution of vision due to diabetes, increased tears, night blindness, cross eyed, heart attack, tightening/ narrowing of blood vessel, severe high blood pressure, tightening of the chest, difficulty in speaking, difficulty in/painful swallowing, peptic ulcer, retching, stomach bleeding, jaundice, loss of hair, blister, skin allergy, skin

conditions, bruising, scaly skin, night sweats, pain of skin, discolouration of the skin, psoriasis, flaky skin, inflammation of spinal joints due to an autoimmune disorder, pain in your sides, swelling of joints, musculoskeletal pain, muscular pain, neck pain, joint pain, cyst in the joint, uncontrollable urge to urinate, increased urination, passing of pus cells in urine, urinary hesitation, prostate problem, breast pain, drug effect decreased, drug intolerance, feeling cold, feeling unwell, fever, dryness of skin, eye and mouth, abnormal blood tests, heart murmur, abnormal heart tests, bruising/swelling after injury, blood vessel blockage due to fat, head injury, mouth injury, skeletal injury, gambling.

Reporting of suspected adverse reactions

If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

9.5 How to store ZAFIMOVE

- Store at a temperature not exceeding 30°C, protected from light and moisture.
- Keep all medicine out of reach of children.

9.6 Contents of the pack and other information

What ZAFIMOVE contain

The active substance in these tablets is ZAFIMOV

The other ingredients used are Siilicified Microcrystalline Cellulose, Crospovidone, Magnesium Stearate, Colliodal Silicon Dioxide, Insta coat universal (contains: Hypromellose, polyethylene glycol, talc, Titanium Dioxide, Red oxide of Iron , Yellow oxide of iron).

10. Details of manufacturer

Torrent Pharmaceuticals Ltd.

32 No, Middle Camp, NH-10,

East District, Gangtok, Sikkim-737 135

11. Details of permission or licence number with date

M/563/2010. 03.08.2020

12. Date of revision

JAN-2022

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/ ZAFIMOVE 50, 100 mg/JAN-22/02/PI