SCHEDULING STATUS S3

1. NAME OF THE MEDICINE

GRALISE 300 prolonged-release tablets

GRALISE 600 prolonged-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

GRALISE 300: Each prolonged-release tablet contains 300 mg gabapentin.

GRALISE 600: Each prolonged-release tablet contains 600 mg gabapentin.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablets.

GRALISE 300: White to off-white, oval shaped tablets, debossed with ‘SLV’ on one side and ‘300’ on the other side.

GRALISE 600: Beige, oval shaped tablets, debossed with ‘SLV’ on one side and ‘600’ on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

GRALISE is indicated for the treatment of post-herpetic neuralgia in adults.

4.2 Posology and method of administration

Posology

GRALISE should be titrated to an 1800 mg dose taken orally, once daily, with the evening meal.

In adults with post-herpetic neuralgia, GRALISE therapy should be initiated and titrated as indicated in Table 1.

Table 1: Gabapentin prolonged-release dose titration

	Day 1	Day 2	Days 3 - 6	Days 7 - 10	Days 11 - 14	Day 15
Daily dose	300 mg	600 mg	900 mg	1200 mg	1500 mg	1800 mg

Dosing should begin at 300 mg once daily and increased to 1500 mg once daily within two weeks based on individual patient response and tolerability followed by the recommended treatment duration of 8 weeks of stable dose after two weeks of titration. The maximum total daily dose is 1800 mg given once daily with an evening meal. Discontinue treatment after 10 weeks, if there is no symptom improvement since initiation of therapy with GRALISE.

Discontinuation of GRALISE

If the dose of GRALISE is reduced, discontinued, or substituted with an alternative medicine, this should be done gradually over a minimum of one week or longer (at the discretion of the healthcare provider).

Special populations

Elderly patients (over 65 years of age)

Although age is expected to have a minimal effect on GRALISE pharmacokinetics, elderly patients may require dosage adjustment because of declining renal function with age (see Table 2). Somnolence, peripheral oedema and asthenia may be more frequent in elderly patients (see section 4.4 and 4.8).

Renal impairment

Treatment with GRALISE in patients with severe renal impairment (CRCL < 30 mL/min) is contraindicated (see section 4.3). The dose of GRALISE should be adjusted in patients with reduced renal function based on creatinine clearance (CL_{CR}). Patients with mild and moderate renal impairment (CRCL ≥ 30 mL/min and < 90 mL/min) should initiate GRALISE at a daily dose of 300 mg. In these patients, GRALISE should be titrated following the schedule outlined in Table 1 up to the corresponding maintenance dose according to Table 2. Daily dosing in patients with reduced renal function must be individualised based on tolerability and desired clinical benefit.

Table 2: Maintenance dose recommendations for renal impairment categories

CL_{CR} categories	**GRALISE dosing regimen (once daily)**
CL_{CR} ≥ 90 mL/min	No dose adjustment is required
CL_{CR} ≥ 60 mL/min and <90 mL/min	1 200 mg
CL_{CR} ≥ 30 mL/min and < 60 mL/min	300 – 600 mg
CL_{CR} < 30 mL/min	Contraindicated (section 4.3)

Paediatric population

The safety and efficacy of GRALISE in the paediatric population have not been established. No data are available.

Method of administration

For oral use.

The tablets should be swallowed whole with water. The tablets must not be broken, crushed or chewed as this impairs the prolonged-release of gabapentin, the active ingredient in GRALISE. GRALISE should be taken with evening meals. If it is taken on an empty stomach, the bioavailability will be substantially lower (see section 4.5)

4.3 Contraindications

- Hypersensitivity to gabapentin or to any of the excipients listed in section 6.1.
- Patients receiving haemodialysis and patients with creatinine clearance < 30 mL/min should not take GRALISE.

GRALISE 300 contain lecithin (soya) (see section 6.1). Patients who are allergic to peanut or soya should not use GRALISE 300.

4.4 Special warnings and precautions for use

Important differences in posology between GRALISE and immediate release gabapentin medicines:

GRALISE is a prolonged-release formulation and has different pharmacokinetic characteristics compared with gabapentin immediate release medicine, which results in a different frequency of administration and maximum daily dose. Therefore, different gabapentin formulations should not be switched on a milligram-to-milligram basis. GRALISE is not interchangeable with other gabapentin medicines because of differing pharmacokinetic profiles that may affect the frequency of administration. No data to support switching between formulations has been generated. If no clinical benefit is observed during this period, particularly after 10 weeks at a stable dose, then gradual dose reduction and discontinuation should be considered (see section 4.2). Since there is no interchangeability between different formulations, treatment alternatives should be carefully considered by the treating healthcare provider, considering a different pharmacological approach. The safety and effectiveness of GRALISE in patients with epilepsy has not been studied.

Drug reaction with eosinophilia and systemic symptoms (DRESS)/ multiorgan hypersensitivity

Drug reaction with eosinophilia and systemic symptoms (DRESS), also known as multiorgan hypersensitivity, has been reported in patients taking antiepileptic medicines, including GRALISE (see section 4.8). Some of these events have been fatal or life- threatening. DRESS typically, although not exclusively, presents with fever, rash, and/or lymphadenopathy in association with other organ system involvement, such as hepatitis, nephritis, haematological abnormalities,

myocarditis, or myositis sometimes resembling an acute viral infection. Eosinophilia is often present.

Because this disorder is variable in its expression, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. GRALISE should be discontinued if an alternative aetiology for the signs or symptoms cannot be established.

Anaphylaxis

GRALISE can cause anaphylaxis. Signs and symptoms in reported cases have included difficulty breathing, swelling of the lips, throat, and tongue, and hypotension requiring emergency treatment. Patients should be instructed to discontinue GRALISE and seek immediate medical care should they experience signs or symptoms of anaphylaxis (see section 4.8).

Suicidal ideation and behaviour

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic medicines like GRALISE. A meta-analysis of randomised placebo controlled trials of antiepileptic medicines has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known. Cases of suicidal ideation and behaviour have been observed in patients treated with gabapentin, as in GRALISE, in the post marketing experience.

An epidemiological study using a self-controlled study design (comparing treatment periods with non-treatment periods within an individual) showed evidence of an increased risk of new onset of suicidal behaviour and death by suicide in patients treated with gabapentin, as in GRALISE. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge. Patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Discontinuation of GRALISE treatment should be considered in case of suicidal ideation and behaviour.

Acute pancreatitis

If a patient develops acute pancreatitis under treatment with GRALISE, discontinuation of GRALISE should be considered (see section 4.8).

Respiratory depression

GRALISE has been associated with severe respiratory depression. Patients with compromised respiratory function, respiratory or neurological disease, renal impairment, concomitant use of central nervous system (CNS) depressants and elderly patients might be at higher risk of experiencing this severe adverse reaction. Dose adjustments might be necessary in these patients.

Elderly patients (over 65 years of age)

No systematic studies in patients 65 years or older have been conducted with GRALISE. In one double blind study in patients with neuropathic pain, somnolence, peripheral oedema and asthenia occurred in a somewhat higher percentage in patients aged 65 years or above, than in younger patients. Apart from these findings, clinical investigations in this age group do not indicate an adverse event profile different from that observed in younger patients.

Abuse and dependence

Cases of abuse and dependence have been reported in the post-marketing database. Carefully evaluate patients for a history of medicine abuse and observe them for possible signs of GRALISE abuse e.g. drug-seeking behaviour, dose escalation, development of tolerance. Although gabapentin is prone to misuse, abuse, withdrawal and dependence, the abuse and dependence potential of GRALISE has not been evaluated in human studies.

Laboratory tests

False positive readings may be obtained in the semi-quantitative determination of total urine protein by dipstick tests. It is therefore recommended to verify such a positive dipstick test result by methods based on a different analytical principle such as the Biuret method, turbidimetric or dye-binding methods, or to use these alternative methods from the beginning.

Withdrawal of GRALISE

GRALISE should be withdrawn gradually. If GRALISE is discontinued, this should be done gradually over a minimum of 1 week or longer.

Concomitant use with opioids and other CNS depressants

Patients who require concomitant treatment with central nervous system (CNS) depressants, including opioids, should be carefully observed for signs of CNS depression, such as somnolence, sedation, and respiratory depression. Patients who use GRALISE and morphine concomitantly may experience increases in gabapentin concentrations. The dose of GRALISE, or concomitant treatment with CNS depressants including opioids, should be reduced appropriately (see section 4.5). Caution is advised when prescribing GRALISE concomitantly with opioids due to risk of CNS depression. In a population-based, observational, nested case-control study of opioid users, co prescription of opioids and gabapentin, as in GRALISE was associated with an increased risk for opioid-related death compared to opioid prescription use alone (adjusted odds ratio (aOR), 1.49 (95 % CI, 1,18 to 1,88, p < 0,001)).

4.5 Interaction with other medicines and other forms of interaction

Effects of other medicines on gabapentin

Morphine has been reported to reduce the clearance of gabapentin, as in GRALISE. Patients receiving both medicines should be monitored for signs of CNS depression and doses should be reduced accordingly. Serious, life-threatening, or fatal respiratory depression has been reported in patients receiving gabapentinoids (i.e., gabapentin and pregabalin). In the majority of cases, the

medicines were used in combination with an opiate analgesic (or other CNS depressant), in patients with pre-existing respiratory risk factors (e.g., COPD), or in elderly patients.

In a study involving healthy volunteers (N = 12), when a 60 mg controlled-release morphine capsule was administered 2 hours prior to a 600 mg gabapentin immediate-release capsule, mean gabapentin AUC increased by 44 % compared to gabapentin administered without morphine. Therefore, patients who require concomitant treatment with opioids should be carefully observed for signs of CNS depression, such as somnolence, sedation and respiratory depression and the dose of GRALISE or opioid should be reduced appropriately.

No interaction between GRALISE and phenobarbital, phenytoin, valproic acid or carbamazepine has been observed. GRALISE steady-state pharmacokinetics are similar for healthy subjects and patients with epilepsy receiving these antiepileptic medicines.

The absorption of GRALISE from the gastrointestinal tract is reduced by antacids containing aluminium or magnesium up to 24 %. It is recommended that GRALISE is taken at least 2 hours after any such antacid. Proton pump inhibitors did not influence the absorption and can be administered at anytime.

A slight decrease in renal excretion of GRALISE that is observed when it is co-administered with cimetidine is not expected to be of clinical importance. On the contrary, renal excretion of GRALISE is unaltered by probenecid.

Effect of gabapentin on other medicines

GRALISE is conspicuous among anticonvulsant medicines for its lack of clinically relevant medicine interactions, because of the lack of hepatic metabolism and ability to induce or inhibit hepatic microsomal enzymes and low protein binding. The active substance, at concentrations equal to or greater than those observed at efficacious dosages, does not inhibit the major

cytochrome P450 (CYP) enzymes (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4) that mediate xenobiotic metabolism in humans.

Effect of food on GRALISE

Administration of GRALISE with food increases the rate and extent of absorption of gabapentin compared to the fasted state. C_{max} of gabapentin increases 33 – 84 % and AUC of gabapentin increases 33 – 118 % with food depending on the fat content of the meal. GRALISE should be taken with food (refer to section 5.2).

Use with alcohol

GRALISE acts on the central nervous system and may cause drowsiness, dizziness or other related symptoms. Use with alcohol should be, therefore avoided, as it is expected to worsen the symptoms.

4.6 Fertility, pregnancy and lactation

Pregnancy

GRALISE crosses the human placenta. There are no or limited amount of data from the use of GRALISE in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. No definite conclusion can be made as to whether gabapentin is associated with an increased risk of congenital malformations when taken during pregnancy. Because animal reproduction studies are not always predictive of human response, GRALISE should not be used during pregnancy.

Breastfeeding

GRALISE is excreted in human milk. Because the effect on the breast-fed infant is unknown, caution should be exercised when GRALISE is administered to a breast-feeding mother.

Fertility

There is no effect on fertility in animal studies.

4.7 Effects on ability to drive and use machines

GRALISE may have minor or moderate influence on the ability to drive a vehicle and use machines. Gabapentin acts on the central nervous system and may cause drowsiness, dizziness or other related symptoms. Even, if they were only of mild or moderate degree, these undesirable effects could be potentially dangerous in patients driving or operating machinery. This is especially true at the beginning of the treatment and after increase in dose.

4.8 Undesirable effects

A total of 359 patients with neuropathic pain associated with post-herpetic neuralgia have received gabapentin prolonged-release at doses up to 1800 mg daily during placebo-controlled clinical studies. In clinical trials in patients with post-herpetic neuralgia, 9,7 % of the 359 patients treated with gabapentin prolonged-release and 6,9 % of 364 patients treated with placebo discontinued prematurely due to adverse reactions. In the gabapentin treatment group, the most common reason for discontinuation due to adverse reactions was dizziness. In gabapentin-treated patients who experienced adverse reactions in clinical studies, the majority of those adverse reactions were either "mild" or "moderate".

Tabulated summary of adverse reactions

System organ class	**Adverse drug reactions**
Infections and infestations	
Very Common	Viral infection
Common	Pneumonia, respiratory infection, urinary tract infection, infection, otitis media
Blood and the lymphatic system disorders	

Common	Leukopenia
Not known	Thrombocytopenia
Immune system disorders	
Uncommon	Allergic reactions (e.g. urticaria)
Not known	Hypersensitivity syndrome (a systemic reaction with a variable presentation that can include fever, rash, hepatitis, lymphadenopathy, eosinophilia, and sometimes other signs and symptoms), anaphylaxis (see section 4.4)
Metabolism and nutrition disorders	
Common	Anorexia, increased appetite
Uncommon	Hyperglycaemia (most often observed in patients with diabetes)
Rare	Hypoglycaemia (most often observed in patients with diabetes)
Non known	Hyponatraemia
Psychiatric disorders	
Common	Hostility, confusion and emotional lability, depression, anxiety, nervousness, thinking abnormal
Uncommon	Agitation
Not known	Hallucinations, suicidal ideation
Nervous system disorders	
Very Common	Somnolence, dizziness, ataxia
Common	Convulsions, hyperkinesia, dysarthria, amnesia, tremor, insomnia, headache, sensations such as paraesthesia, hypaesthesia, coordination abnormal, nystagmus, increased, decreased, or absent reflexes
Uncommon	Hypokinesia, mental impairment
Rare	Loss of consciousness
Not known	Movement disorders (e.g. choreoathetosis, dyskinesia, and dystonia)
Eye disorders	

Common	Visual disturbances such as amblyopia, diplopia
Ear and labyrinth disorders	
Common	Vertigo
Not known	Tinnitus
Cardiac disorders	
Uncommon	Palpitations
Vascular disorder	
Common	Hypertension, vasodilatation
Respiratory, thoracic and mediastinal disorders	
Common	Dyspnoea, bronchitis, pharyngitis, cough, rhinitis
Rare	Respiratory depression (see section 4.4)
Gastrointestinal disorders	
Common	Vomiting, nausea, dental abnormalities, gingivitis, diarrhoea, abdominal pain, dyspepsia, constipation, dry mouth or throat, flatulence
Uncommon	Dysphagia
Not known	Pancreatitis
Hepatobiliary disorders	
Not known	Hepatitis, jaundice
Skin and subcutaneous tissue disorders	
Common	Facial oedema, purpura most often described as bruises resulting from physical trauma, rash, pruritus, acne
Not known	Stevens-Johnson syndrome, angioedema, erythema multiforme, alopecia, drug rash with eosinophilia and systemic symptoms (see section 4.4)
Musculoskeletal, connective tissue and bone disorders	
Common	Arthralgia, myalgia, back pain, twitching
Not known	Rhabdomyolysis, myoclonus

Renal and urinary disorders	
Common	Incontinence
Not known	Acute renal failure
Reproductive system and breast disorders	
Common	Impotence
Not known	Breast hypertrophy, gynecomastia, sexual dysfunction (including changes in libido, ejaculation disorders and anorgasmia)
General disorders and administration site conditions	
Very Common	Fatigue, fever
Common	Peripheral oedema, abnormal gait, asthenia, pain, malaise, flu syndrome
Uncommon	Generalised oedema
Not known	Withdrawal reactions (mostly anxiety, insomnia, nausea, pains, sweating), chest pain. Sudden unexplained deaths have been reported where a causal relationship to treatment with gabapentin has not been established.
Investigations	
Common	Decreased white blood cell count, weight gain
Uncommon	Blood glucose fluctuations in patients with diabetes, elevated liver function tests, SGOT (AST), SGPT (ALT) and bilirubin
Not known	Blood creatine phosphokinase increased
Injury, poisoning and procedural complications	
Common	Accidental injury, fracture, abrasion
Uncommon	Fall

Under treatment with GRALISE cases of acute pancreatitis were reported.

Causality with GRALISE is unclear (see section 4.4).

In patients on haemodialysis due to end-stage renal failure, myopathy with elevated creatine

kinase levels has been reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any
suspected adverse drug reactions to SAHPRA via the Med Safety APP
(Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.
Alternatively side effects can be reported to Adcock Ingram Pharmacovigilance department by e-mail to Adcock.Aereports@adcock.com, call 011 635 0134.

4.9 Overdose

Acute, life-threatening toxicity has not been observed with GRALISE
overdoses of up to 49 g. Symptoms of the overdoses included dizziness,
double vision, slurred speech, drowsiness, loss of consciousness,
lethargy and mild diarrhoea.
All patients recovered fully with supportive care. Reduced absorption of
GRALISE at higher doses may limit drug absorption at the time of
overdosing and, hence, minimise toxicity from overdoses.
Although GRALISE can be removed by haemodialysis, based on prior
experience it is usually not required.
However, in patients with severe renal impairment, haemodialysis may
be indicated.
Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 2.5 Anticonvulsants, including anti-epileptics

Pharmacotherapeutic groups: Other antiepileptics

ATC code: N03AX12

Mechanism of action

The precise mechanism of action of gabapentin is not known. Gabapentin is structurally related to the neurotransmitter GABA (gamma-aminobutyric acid) but its mechanism of action is different from that of several other active substances that interact with GABA synapses including valproate, barbiturates, benzodiazepines, GABA transaminase inhibitors, GABA uptake inhibitors, GABA agonists, and GABA prodrugs. *In vitro* studies with radiolabelled gabapentin have characterised a novel peptide binding site in rat brain tissues including neocortex and hippocampus that may relate to anticonvulsant and analgesic activity of gabapentin and its structural derivatives. The binding site for gabapentin has been identified as the alpha2-delta subunit of voltage gated calcium channels. Gabapentin at relevant clinical concentrations does not bind to other common medicine or neurotransmitter receptors of the brain
including $GABA_A$, $GABA_B$, benzodiazepine, glutamate, glycine or
N-methyl-d-aspartate receptors.
The mechanism of action by which gabapentin exerts its analgesic action is unknown but in animal models of analgesia, gabapentin prevents allodynia (pain-related behaviour in response to a normally innocuous stimulus) and hyperalgesia (exaggerated response to painful stimuli). Gabapentin prevents pain-related responses in several models of neuropathic pain in rats and mice (e.g., spinal nerve ligation models, spinal cord injury model, acute herpes zoster infection model).
Gabapentin also decreases pain-related responses after peripheral inflammation (carrageenan footpad test, late phase of formalin test), but does not alter immediate pain-related behaviours (rat-tail flick test, formalin footpad acute phase). The relevance of these models to human pain is not known.

Pharmacodynamic effects

No pharmacodynamic studies have been conducted with gabapentin prolonged-release.

Clinical efficacy and safety

The efficacy of gabapentin prolonged-release for the management of post-herpetic neuralgia was established in a double-blind, placebo-controlled, multicentre study. This study enrolled patients between the age of 21 to 89 with post-herpetic neuralgia persisting for at least 6 months following healing of herpes zoster rash and a minimum baseline pain intensity score of at least 4 on an 11-point numerical pain rating scale ranging from 0 (no pain) to 10 (worst possible pain). This 11-week study compared gabapentin prolonged-release 1800 mg once daily with placebo. A total of 221 and 231 patients were treated with gabapentin or placebo, respectively. The study treatment including titration for all patients comprised a 10-week treatment period followed by 1-week of dose tapering. Double-blind treatment began with titration starting at 300 mg/day and titrated up to a total daily dose of 1800 mg over 2 weeks, followed by 8 weeks fixed dosing at 1800 mg once daily, and then 1 week of dose tapering. During the 8-week stable dosing period, patients took 3 active or placebo tablets each night with the evening meal. During baseline and treatment, patients recorded their pain in a daily diary using an 11-point numeric pain rating scale. After 10 weeks of treatment, there was statistically significantly greater reduction from baseline in average daily pain score when the gabapentin prolonged-release group was compared to placebo. The least squares mean difference in average daily pain score of gabapentin prolonged-release vs. placebo was -0,49 with p-value of 0,0125. The proportions of patients who were much or very much improved in the PGIC and the CGIC were greater in the Gabapentin prolonged-release 1800 mg daily group than in the placebo group, supporting the clinical significance of the primary endpoint result.

Treatment with gabapentin prolonged-release statistically significantly improved the endpoint mean pain score from baseline. For various degrees of improvement in pain from baseline to study endpoint, Figure 1 shows the fraction of patients achieving that degree of improvement. The figure is cumulative, so that patients whose change from baseline is, for example, 50 %, are also included at every level of improvement below 50 %. Patients who did not complete the study were assigned 0 % improvement.

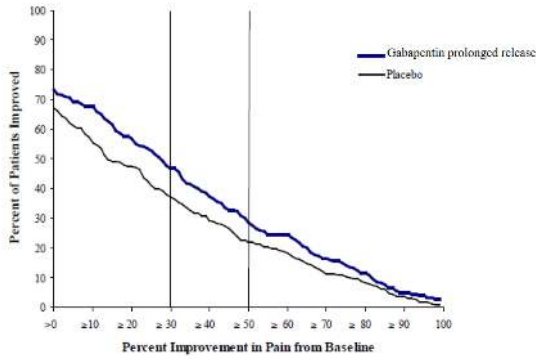

Figure 1: Percent of patients achieving various levels of pain relief

5.2 Pharmacokinetic properties

Absorption

Gabapentin is water-soluble and GI tract absorption occurs via the leucine amino acid transport system in the proximal small bowel. A two-compartment disposition model with first-order absorption and linear

clearance fits the data well. Pharmacokinetics of gabapentin following single- and multiple-dose administration was well characterised by a 2-compartment model with lag time and first-order absorption and elimination. Absorption is not influenced by genotypes for the main genetic polymorphisms of SLC22A2 (rs316019) and SLC22A4 (rs1050152), the genes encoding the transporters for organic cations

OCT2 and OCTN1.

Gabapentin is structurally similar to L-carnitine, which is a natural substrate of the OCTN1 transporter. Gabapentin has reported as substrate of, OCTN1 at the apical membrane of the enterocytes. Time to reach maximum plasma concentration (T_{max}) for gabapentin prolonged-release is 8 hours. Administration of GRALISE with food increases the rate and extent of absorption of gabapentin compared to the fasted state. C_{max} of gabapentin increases 33 – 84 % and AUC of gabapentin increases 33 – 118 % with food depending on the fat content of the meal. The relative bioavailability decreases with increasing doses. Compared with the 600 mg dose, bioavailability is 86 – 88 %, and 75 % for the 1 200 mg/day, and 1 800 mg/day.

Distribution

Gabapentin is not bound to plasma proteins. Plasma gabapentin concentrations are similar to the whole-blood concentrations, indicating that gabapentin penetrates red blood cells. Its extensive distribution is reflected in a volume of distribution of ≈ 3,31 L/kg. Cerebrospinal fluid (CSF) concentrations are 20 % of plasma concentrations. Brain tissue concentrations are 80 % the plasma level. Pancreatic accumulation of gabapentin does not occur in humans as it exists in a highly ionised state at physiological pH and concentrations in adipose tissue are low. Gabapentin has been found in human breast milk at concentrations similar to those in plasma.

Elimination

Gabapentin is not metabolised in humans and is eliminated unchanged in the urine. The total clearance is dependent on estimated glomerular filtration rate. Estimates (between-subject variability in percentage) for lag time, first-order absorption rate, and total apparent clearance were 0,316 h (10, 6 %), 1,12 h-1 (10,7 %) and 32,2 L/h (11 %) respectively. No

significant association was observed with hyperglycaemia, glycated haemoglobin, diabetes diagnosis, age, sex, weight, body mass index, and main genetic polymorphisms of SLC22A2 or SLC22A4 genotypes.
Gabapentin is removed by haemodialysis. The mean elimination half-life Of gabapentin prolonged release is 6 – 9 hours.

Biotransformation

Gabapentin is not metabolised in humans.

Linearity/non-linearity

Gabapentin exposure is not dose proportional as the dose is increased, bioavailability decreases.
Gabapentin prolonged-release tablets, 300 mg and 600 mg, the two strengths are not compositionally proportional.
Single oral doses of Gabapentin prolonged-release tablets from 600 mg to 2 400 mg resulted in less than proportional increases in both AUC and C_{max}. The intra-subject variability of gabapentin is small enough that
plasma medicine monitoring may be used to assess GBP absorption for a given subject and the benefit of dose individualisation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core (300 mg)

Cellulose, microcrystalline
Copovidone
Hypromellose
Macrogol (high-molecular-mass (polyethylene oxide))
Magnesium stearate

Coating (300 mg)

Opadry II 85g18490 White containing:

Lecithin (soya) (E322)

Macrogol 4000 (Polyethylene glycol) (E1521)

Polyvinyl alcohol (E1203)

Talc (E553b)

Titanium dioxide (E171)

Tablet core (600 mg)

Copovidone

Hypromellose

Macrogol (high-molecular-mass (polyethylene oxide))

Magnesium stearate

Coating 600 mg

Opadry II 85F91355 Beige containing:

Iron oxide red (E173)

Iron oxide yellow (E172)

Macrogol 4000 (Polyethylene glycol) (E1521)

Polyvinyl alcohol (E1203)

Talc (E553b)

Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

Store at or below 30 °C.

6.4 Special precautions for storage

GRALISE does not require any special storage conditions.

6.5 Nature and contents of container

GRALISE is packed in:

Starting (titration) pack

Carton tri-fold card containing 33 tablets (with both strengths) for 15 days of treatment, arranged in a single PVC/PCTFE aluminium blister strip.

Each day of treatment is marked from day 1 to day 15 and each daily dose is on its own row. The starting pack contains:

- 9 tablets of GRALISE 300 and
- 24 tablets of GRALISE 600.

Maintenance packs

Carton boxes containing 30 or 90 tablets in PVC/PCTFE aluminium blister strips (standard blister strips or unit dose perforated blister strips) of 10 tablets each.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicine should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Limited

1 New Road

Erand Gardens

Midrand 1685

Private Bax X69

Bryanston 2021

www.adcock.com

8. REGISTRATION NUMBERS

GRALISE 300: 57/2.5/0472

GRALISE 600: 57/2.5/0473

9. DATE OF FIRST AUTHORISATION

12 August 2025

10. DATE OF REVISION OF THE TEXT