La Renon

RISE
ABOVE PAIN

LAREGAB
Gabapentine 300 mg & 100 mg Capsules

LAREGAB-AT
Gabapentine 300 mg & Amitriptyline 10 mg Tablets

LAREGAB-AT-LS
Gabapentine 100 mg & Amitriptyline 10 mg Tablets

Background:

According to IASP, neuropathic pain (NP) is defined as "pain caused by a lesion or disease of the somatosensory system". NP develops as a consequence of a lesion or disease affecting the somatosensory pathways in the peripheral or central nervous system, and occurs in many neurological diseases (eg, peripheral neuropathy, radiculopathy, spinal cord injury, stroke and multiple sclerosis).

A peculiar feature of NP is the coexistence of negative and positive symptoms and signs, reflecting loss-of-function and gain-of-function of the somatosensory system, respectively.

Clinical Presentation of Neuropathic Pain:

POSITIVE SYMPTOMS AND SIGNS

SYMPTOMS	PHYSIOPATHOLOGICAL MECHANISMS
Paroxysmal pain	Spontaneous activity in c-fibres
Superficial pain	Spontaneous activity in a^{δ}- and c-fibres
Deep Pain	Spontaneous activity in articular / muscular nociceptors
Paraesthesia	Spontaneous activity in Aβ- fibres
SIGNS (EVOKED PAIN)	**PHYSIOPATHOLOGICAL MECHANISMS**
Cold hyperalgesia	Central sensitization/loss of central inhibition
Heat hyperalgesia	Peripheral sensitization
Punctate hyperalgesia	Central sensitization mediated by A^{δ}- fibres
Mechanical allodynia	Heterosynaptic central sensitization
Temporal summation of pain	Homosynaptic central sensitization
After – sensations	Homosynaptic central sensitization

NEUROPATHIC PAIN SYNDROMES

Coexistence of negative symptoms/signs (loss-of-function of the somatosensory system) and positive symptoms/signs (Gain-of-function of the somatosensory system)

SYMPTOMS	PHYSIOPATHOLOGICAL MECHANISMS
Hypalgesia	A^{δ}- fibres lesion
SIGNS	**PHYSIOPATHOLOGICAL MECHANISMS**
Tactile hypesthesia	Aβ- fibres lesion
Hypopallesthesia	Aβ- fibres lesion
Thermal hypesthesia	A^{δ}- and C-fibres lesion
Punctate hypesthesia	A^{δ}- fibres lesion

NEGATIVE SYMPTOMS AND SIGNS

How common is Neuropathic Pain??:

- General population studies, around 7–8% of adults currently have chronic pain with neuropathic characteristics.[1]
- 371 million people diagnosed with diabetes mellitus worldwide and a prevalence of 8.3% as per the Diabetes Atlas2012, diabetes mellitus and approximately 40–50% of the patients developing DPN further develop painful DPN.[2]
- Approximately 20% (18.7–21.4%) of people with cancer have cancer-related neuropathic pain, as a result of either the disease or its treatment.[3]
- 33 million people infected with HIV across the world, around 35% have neuropathic pain, which does not respond well to standard treatments.[3]
- In the India, studies in 2,006 patients with diabetes, 29.2% (586) of people with diabetes were found to have DPN.[2]

References:

1. International Association for the Study of Pain; 2014-2015 available at http://iasp.files.cms-plus.com/AM/Images/GVAP/Epidemiology%20of%20Neuropathic%20Pain.pdf

2. Diabetes Invest; 5: 714-721; 2014

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Clinical Effectiveness:

Clinical Efficacy and Safety of Gabapentin verses Placebo in Neuropathic Pain

Canadian Agency for Drugs and Technologies in Health; 2015:

- Pooled analysis of 15 clinical trials for clinical efficacy and safety of gabapentin verses placebo for adults with neuropathic pain:
- Assessment Criteria: At least 50% reduction in pain intensity.

Result:

Efficacy of gabapentin in a variety of conditions (such as PHN, DPN, SCI, and peripheral nerve injury [PNI]) is expressed in the number needed to treat to benefit (NNT) was 7.2 and the corresponding 95% CI was 5.9 to 9.1.

Safety of gabapentin is expressed in terms of the number needed to be treated to harm (NNH) was 25.6 and corresponding 95% CI was15.3 to 78.6.

Condition	No. of RCTs	No. of patients	Patients with substantial benefit (%) G vs plb	RR (95% CI)	NNT (95% CI)% CI)
PHN	6	1816	34 vs 21	1.6 (1.3 to 1.9)	8.0 (6.0 to 12)
DPN	6	1277	38 vs 21	1.9 (1.5 to 2.3)	5.9 (4.6 to 8.3)
Mixed NP	1	305	21 vs 14	1.5 (0.9 to 2.4)	NC
NIP	1	98	13 vs 92	1.4 (0.7 to 3.2)	NC
Small fiber sensory neuropathy	1	18	2 vs 6	5 (0.65 to 38.65)	NC

CI = confidence interval, DPN = diabetic peripheral neuropathy, G = gabapentin, NC = not calculated, NIP = nerve injury pain, NNT = number needed to treat to benefit, NP = neuropathic pain, PHN = postherpetic neuralgia, plb = placebo, RCT = randomized controlled trial, RR = risk ratio, vs = versus

Conclusion:

First-line treatment in neuropathic pain effective in treating various neuropathic pain disorders.

Clinical Effectiveness of Amitriptyline in Neuropathic Pain :

1. Amitriptyline recommended as a first line drug for pain in diabetic neuropathy by NICE [2013], EFNS [2010] and NeuPSIG IASP [2010].[1]
2. Number needed to treat (NNT) for at least 50% pain relief from Cochrane Collaboration reviews is 1.3. [1]
3. The Canadian Pain Society (CPS) recommends TCAs as first-line treatment for neuropathic pain due to diabetes, herpes zoster, and traumatic nerve injury or stroke.[2]
4. The typical starting dose of any TCA for the treatment of neuropathic pain is 10 to 25 mg nightly.[3]

Reference:

1. *Ther Adv Chronic Dis*; 6(1): 15-28: 2015
2. *Pain Res Manag*; 12(1):13-21: 2007
3. *Am J Med*; 122(10, Suppl):S22-S32: 2009

Description:

Laregab contains Gabapentin as capsules, a medication originally developed for the treatment of epilepsy. Presently, gabapentin is widely used to relieve pain, especially neuropathic pain. The molecular formula of gabapentin is C9H17NO2 and the molecular weight is 171.24.

Laregab-AT is a combination of gabapentin (300 mg) with amitriptyline (10mg), anti-epileptic and tricyclic anti-depressant are often widely used for various types of neuropathic pain or multiple sclerosis.

Laregab-AT LS is a combination of gabapentin (100 mg) with amitriptyline (10mg) in the lower strength.

Mechanism of Action:

Gabapentin: The precise mechanisms by which gabapentin produces its analgesic and antiepileptic actions are unknown. Gabapentin is structurally related to the neurotransmitter gamma-aminobutyric acid (GABA) but has no effect on GABA binding, uptake, or degradation. In vitro studies have shown that gabapentin binds with high-affinity to the α2δ subunit of voltage-activated calcium channels; however, the relationship of this binding to the therapeutic effects of gabapentin is unknown.

Amitriptyline is a dibenzocycloheptadiene tricyclic antidepressant. It increases synaptic concentration of serotonin and/or norepinephrine in the CNS by blocking the neuronal reuptake of norepinephrine and serotonin.

Amitriptyline is metabolized to nortriptyline which inhibits the reuptake of norepinephrine and serotonin almost equally. Amitriptyline inhibits the membrane pump mechanism responsible for uptake of norepinephrine and serotonin in adrenergic and serotonergic neurons.

Pharmacologically this action may potentiate or prolong neuronal activity since reuptake of these biogenic amines is important physiologically in terminating transmitting activity. This interference with the reuptake of norepinephrine and/or serotonin is believed by some to underlie the antidepressant activity of amitriptyline.

Indication:

For the management of Neuropathic pain

Dosage:

Neuropathic Pain -

Laregab therapy may be initiated at dosage of 100-300 mg at bedtime or 100-300 mg thrice a day. Maximum tolerable dose 3600 mg/day 1 Or as prescribed by the Registered Medical Practitioner.

Post herpetic Neuralgia:

Laregab therapy may be initiated as a single 300-mg dose on Day 1, 600 mg/day on Day 2 (divided BID), and 900 mg/day on Day 3 (divided TID). The dose can subsequently be titrated up as needed for pain relief to a daily dose of 1800 mg (divided TID) 2 Or as prescribed by the Registered Medical Practitioner.

Administration:

Laregab is given orally with or without food.

1 R.H. Dworkin et al. / Pain 132 (2007) 237-251
2 Acta Anaesthesiol Taiwan. 2005 Jun;43(2):73-7.

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