



## PURPOSE

Pregabalin is an analogue of GABA useful for the treatment of neuropathic pain, post hepatic neuralgia, partial onset seizure and fibromyalgia. Marketed immediate release (IR) capsule is administered in 2 or 3 divided doses per day. Controlled release (CR) formulation for once-a-day administration may be appropriate in order to enhance quality of sleep at night and reduce adverse events such as dizziness as well as improve patient's compliance.

GLARS platform comprising triple layers is able to be one of possibilities for controlling release and absorption through gastrointestinal tract of Pregabalin.

The aim of this study was to evaluate the comparative pharmacokinetics of triple layered CR tablet (GLARS platform) and commercial IR capsule (Lyrica®, Pfizer) containing 150mg and 75mg of Pregabalin respectively.

## METHODS

### Preparation of CR tablets and In vitro diffusion test

Pregabalin CR tablets comprising upper/lower layer with highly swelling polymer and hydrophilic middle layer were prepared by wet granulating, compressing triple layer tablet and film coating. In vitro diffusion test was performed by USP dissolution method 2 at 50rpm of paddle speed in 500mL of 0.06N HCl using Pregabalin CR tablet containing pigment in the middle layer.

### Comparative pharmacokinetic studies

#### Preclinical study

Randomized, open-label, 2-way crossover trial was performed in 8 beagle dogs. After oral administration of CR tablet qd and IR capsule bid respectively under fed state.

#### Phase I trial

Randomized, open-label, 3-period, 6-sequence crossover phase I trial was performed in 27 healthy volunteers. Each subject received single dose of CR tablet or twice-a-day dose of IR capsule with high fat meal.

Serial blood samples were collected and plasma concentration of Pregabalin was determined by LC-MS/MS analysis. Pharmacokinetic parameters and their equivalence between CR tablet and IR capsule were calculated using WinNonlin and K-BE softwares.

## RESULTS

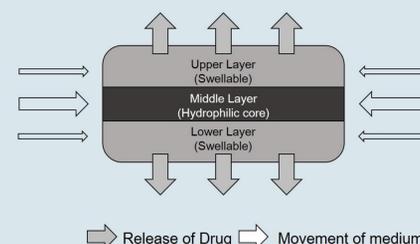


Fig 1. Schematic diagram of triple layer tablet (GLARS platform).

### In vitro diffusion test



Fig 2. Diffusion of pigment in middle layer of triple layer tablet.

### Preclinical study in beagle dogs

Treatment A : Lyrica capsule 75 mg bid

Treatment B : Pregabalin CR tablet 150mg qd

Table 1. Pharmacokinetic parameters of Pregabalin CR tablet qd and Lyrica capsule 75mg bid under fed state in beagle dogs (N=8).

Parameter (Unit)	Lyrica capsule 75 mg bid	Pregabalin CR tablet 150mg qd	Point Estimate [T/R]	Confidence Interval [90%]
$C_{max}$ ( $\mu\text{g/mL}$ )	15.75	13.34	0.85	0.74-0.97
$AUC_{(0-24)}$ ( $\text{h}\cdot\mu\text{g/mL}$ )	162.59	169.87	1.04	0.91-1.20

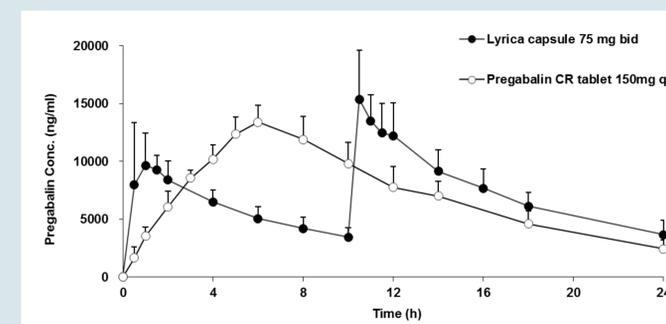


Fig 3. Mean plasma pregabalin concentration-time profiles of Pregabalin CR tablet qd and Lyrica capsule 75mg bid under fed state in beagle dogs (N=8).

### Phase I trial in healthy volunteers

Treatment A : Lyrica capsule 75 mg bid

Treatment B : Pregabalin CR tablet 150mg qd

Table 2. Pharmacokinetic parameters of Pregabalin CR tablet qd and Lyrica capsule 75mg bid under fed state in healthy volunteers (N=27).

Parameter (Unit)	Lyrica capsule 75 mg bid	Pregabalin CR tablet 150mg qd	Point Estimate [T/R]	Confidence Interval [90%]
$C_{max}$ ( $\mu\text{g/mL}$ )	1.62	1.70	1.05	0.97-1.13
$AUC_{last}$ ( $\text{h}\cdot\mu\text{g/mL}$ )	24.06	18.14	0.75	0.70-0.82
$t_{1/2}$ (hr)	5.71	6.31	—	—
$T_{max}$ (hr)	2.23	4.75	—	—

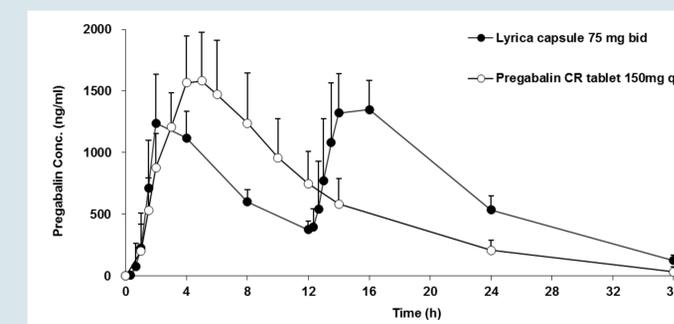


Fig 4. Mean plasma pregabalin concentration-time profiles of Pregabalin CR tablet qd and Lyrica capsule 75mg bid under fed state in healthy volunteers (N=27).

## CONCLUSIONS

- As a result of in vitro diffusion test, it was found that pigment from middle layer effectively diffused to upper and lower layer and hydrophilic middle layer played important role in promoting swelling of matrix by effective absorption of medium.
- The results of comparative pharmacokinetic studies in beagle dogs and healthy volunteers between CR tablet and IR capsule highlighted the potential of Pregabalin CR formulation using triple layered GLARS platform despite of lower AUC.