Developed Process Validation Method of Lamotrigine Extended Release Tablets for Pharmaceutical Manufacturing

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Abstract

Validation is integral part of cGMP, and assured production of quality based pharmaceutical products special reference to extended release tablets. The quality of pharmaceutical dosage form can be achieved by performing finished product testing and in-process monitoring. Hence, the present study was planned to developed process validation protocol and perform process validation for extended release tablets of Lamotrigine. The three different batches X, Y and Z of Lamotrigine extended release (Lamotrigine XR) tablets were manufactured with identified equipments and control parameters. The appearance, average weight, individual weight variation, thickness, hardness, assay, uniformity content and dissolution of blend stage, compression stage and coating stage of Lamotrigine XR were evaluated. Sampling, testing plan and acceptance criteria for each step were monitored. The findings exhibited that the values of all stages were found to be within the acceptable limit. Consequently, it can be concluded that the process stands validated and the data can be used in regulatory submission for obtaining marketing authorization of Lamotrigine XR tablets.

Keywords:
Lamotrigine, Process validation, Manufacturing, Extended release tablets

1 Introduction

Validation is defined as process of establishing through a documented program, which provides a high degree of assurance that a specific process will consistently produce, a product meeting its pre-determined specifications and critical quality attributes. The validated protocols means the manufacturing units producing quality based dosage forms with full assurance. Validation incorporated with qualification of materials, equipment, system, buildings and personnel. The process validation established the developed design stage throughout production, and it provides consistently delivering quality products with drug product will meet standards for quality, purity, identity, strength, effectiveness, stability, evaluation safety and efficacy. Further, process validation is documentary evidence that delivers a high degree of assurance for product meeting at predetermined specifications and quality characteristics. Process validation and process control provide a certain assurance of batch uniformity and integrity of the product manufactured.3

The extended release formulation are fabricated is such away to release drug in a controlled manner, at a predetermined rate, duration, and location to achieve and maintain optimum therapeutic blood levels of drug. These dosage forms allow at least a twofold reduction in dosage frequency as compared to that drug presented as an immediate-release (conventional) dosage form. The controlled-release, sustained-release, and long-acting drug products are the examples of extended-release dosage.

Lamotrigine is a worthy antiepileptic medicines to control seizures and bipolar disorder. Lamotrigine is a sodium channel-blocking antiepileptic, which restrains voltage-dependent sodium channels and reduces the release of the glutamate and aspartate to bring brain back to orderliness.3

It is available as immediate release and sustained release formulations in the market with different strengths such as 25 mg, 50 mg and 100 mg. In 2009 GSK received FDA approval for extended release version of Lamotrigine (Lamictal-XR). The validation is a Fundamental segment that supports to a
commitment of company towards quality assurance. It also assures that product meets its predetermined quality specification and quality characteristics. Hence aim of the present study was to designed the process validation protocol and perform process validation for extended release tablets of Lamotrigine to enhance the quality of drug.

2 Materials and Methods

2.1 Formulation of Lamotrigine XR tablets

Process validation was performed on the three batches of Lamotrigine 250 mg tablets. The three consecutive batches were labeled as (Batch X, Batch Y, and Batch Z). The three batches of 10,00,000 tablets batch size to be manufactured described in the batch manufacturing record. Current version of standard operating procedures was followed. Further, the observations at compression stage in the data sheets were noted.

List of equipment and stages indicate list of equipment’s which were used in manufacturing process of Lamotrigine tablets and give the involvement of equipment in which manufacturing stage with their make which are mentioned in table 1 and table 2.

Table 1: Equipments/instruments used during manufacturing of validation batch

| Processing stage                  | Processing equipments/instruments                                  |
|-----------------------------------|-------------------------------------------------------------------|
| Weight verification               | Weighing balance                                                  |
| Sitting                            | Mechanical sifter equipped with # 20 and # 40 sieve               |
| Dry mixing                        | Rapid mixer granulator (100 L)                                    |
| Granulation                       | Rapid mixer granulator (100 L)                                    |
| Drying                            | Fluidized bed dryer (60 kg)                                       |
| Mechanical sifter equipped with # 20 sieve | Multi-mill equipped with 1.5 mm and 1.00 mm screen |
| Pre-lubrication and lubrication   | Conta-blender and bin (150 L)                                     |
| Compression                       | Tablet press (45 station double rotary machine)                   |
| De-duster                         | De-dusting units                                                  |
| Metal detection                   | Metal detectors                                                   |
| Coating suspension preparation    | Mechanical stirrer                                                 |
| Coating                           | Coating pan (24")                                                |
| Imprinting of tablets             | Printing machine- Tamprint 60                                     |
| Inspection of tablets             | Inspection machine                                               |

Details of input material indicates material or ingredients which are used in the manufacturing of Lamotrigine tablets with their category which shows in table 3.

Table 2: Equipments/instruments used during in-process testing of validation batch

| Test                          | Processing instruments                      |
|-------------------------------|---------------------------------------------|
| Weight verification           | Weighing balance / Smart test 50            |
| Thickness                     | Vernier caliper / Smart test 50             |
| Hardness                      | Hardness tester / Smart test 50             |
| Friability testing            | Friability tester                          |
| Dissolution                   | Dissolution test apparatus                  |
| Loss on drying                | Halogen moisture balance                    |

Table 3: Composition of Lamotrigine extended release tablets

| Material                      | Category          | Quantity per tablet |
|-------------------------------|-------------------|---------------------|
| Lamotrigine                   | Active Ingredients| 250 mg              |
| Dibasic Calcium Phosphate     | Diluent           | 20 mg               |
| Aerosil 200(Colloidal Silicon Dioxide) | Gildant          | 30 mg               |
| Light Kaolin                 | Disintegrant      | 13 mg               |
| Magnesium Stearate           | Lubricant         | 10 mg               |
| Purified Talc                | Lubricant         | 15 mg               |
| Hydroxy Propyl Methylcellulose| Coating Material  | 17.6 mg             |
| Ethyl Cellulose              | Coating Material  | 6 mg                |
| Isopropyl Alcohol            | Vehicle           | Q.S.                |
| Dichloro Methane             | Vehicle           | Q.S.                |

Colorants

| Opadry Organic 21s53308 ”Orange” | Colour | 1.4 mg |

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2.2 Evaluation

2.2.1 Weight variation

20 tablets were selected randomly from each batch and individually weighed. The average weight and individual weight variation of 20 tablets were calculated. The batch passes the test for individual weight variation test if the not more than two of the individual tablet weight deviate from the average weight by percentage.

2.2.2 Appearance

The general appearance of tablet, its visual identity of size, shape and colour were observed.

2.2.3 Hardness

10 tablets were selected randomly and hardness were measured by Monsanto hardness tester. Average value was found out and reported in finished product testing for all three batches.

2.2.4 Thickness

Thickness of the all tablet formulations were measured using vernier calipers by placing tablet between two arms of the vernier calipers.

2.2.5 Friability

The friability of the tablets was measured by friability tester. Tablets of a known weight (W0) or a sample of 10 tablets were dedusted in a drum for a fixed time (100 revolutions) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below.

\[
\text{Friability (\%)} = \left( \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \right) \times 100
\]

The weight loss should not be more than 1%

2.2.6 Content uniformity

In this test, 10 tablets were randomly selected and the percent drug content was determined, the tablets contained not less than 90% or more than 110% of the labelled drug content can be considered as the test was passed.

2.2.7 Assay

Weighed and finely powdered not less than 20 tablets were taken and transfer an accurately weighed portion of the powder equivalent to about 200 mg of lamotrigine in to a 100 ml volumetric flask. Add approximately 60 ml of methanol and shake and sonicate for 10 min to complete the extraction and dilute the methanolic solution with water to make up the volume. From this, pipette out a 2 ml aliquot into a 100 ml volumetric flask, dilute with mobile phase up to required volume and mixed well. The obtained solution was filtered through the whatman filter paper and the absorbance of solution was measured at 254 nm using UV-visible spectrophotometer.

2.2.8 Dissolution study

Dissolution study was carried out using 0.1M HCl and phosphate buffer pH 6.8. The speed and temperature was 120 rpm and 37± 0.5 °C, respectively. 25ml sample was collected from each vessels and absorbance was measured at 254 nm using UV visible spectrophotometer.

2.2.9 Compression

Compression involves consistent flow of lubricated granules from hopper to die where it is being compressed to form a tablet. Compression was carried out as per batch manufacturing record. Samples were collected from initial, middle and end stage of compression cycle for testing of physical parameters.

2.2.10 Coating

Coating was carried out as per batch manufacturing record. Be coater 48’ was used for coating. Samples were collected at the end of coating stage and carried out the testing of appearance, average weight, individual weight variation, thickness, hardness, weight rise per tablet, assay and dissolution for all the three batches 5-7.

3 Results and Discussions

The Lamotrigine XR tablets were prepared for the study of process validation. Three manufacturing batches were validated in prospective process validation, and were labeled as Batch X, Batch Y and Batch Z at blend stage, compression stage and coating stage.

3.1 Compression stage

The physical parameters studied were performed for three consecutive batches at minimum speed and maximum speed of samples withdraw from compression machine.

The following physical parameters namely appearance, average weight, individual weight variation, thickness, hardness and uniformity of content were determined. The results are illustrated in table 4. The values of appearance, average weight, individual weight variation, thickness, hardness and uniformity of content were under limits of acceptance criteria. The physical parameter of Lamotrigine tablet at minimum speed (08 rpm) and maximum speed (34 rpm) of compression for three validation batches X, Y, Z were found in the range within the acceptance criteria and specification.

It has been reported that the assay, dissolution and content uniformity of extended tablets should be 95% - 105%, NLT 70.0% of the labeled amount is dissolved in 30 minutes and 90 – 110%, respectively. Table 5 demonstrated the value of assay, dissolution and content uniformity of three batches X, Y and Z of Lamotrigine XR tablets were in the range described in official pharmacopoeia.
3.2 Coated tablets

The analysis of pre-heated coated tablet were studied for appearance, average weight, individual weight variation, thickness and hardness of Lamotrigine XR tablets, and results were found to be within acceptable limit (Table 6). Similarly, the findings of appearance, average weight, individual weight variation, thickness, hardness, weight rise per tablet, assay of coating Lamotrigine XR tablets were under acceptable limits (Table 7).

Table 4: Data of compression process of batch X, Y and Z

| Parameter                                           | Analysis | Batch X | Batch Y | Acceptance criteria                                      |
|-----------------------------------------------------|----------|---------|---------|----------------------------------------------------------|
|                                                    | LHS      | RHS     | LHS     | RHS                                                      |
| Low Speed (08 RPM)                                  |          |         |         |                                                          |
| High Speed (34 RPM)                                 |          |         |         |                                                          |
| Appearance (10 tablets)                            | Complies | Complies| Complies| Complies White capsule shaped uncoated tablets plain on both surface |
| Average weight (mg)                                 | 831.40   | 839.27  | 829.45  | 838.28 835.3 – 851.7                                     |
| Individual weight variation (mg) (20 tablets)       | Min.: 817.34 | Min.: 814.18 | Min.: 821.32 | Max.: 818.31 5% of the average weight |
|                                                    | Max.: 847.13 | Max.: 843.17 | 851.45  | Max.: 845.14 |
| Thickness (mm) (10 tablets)                         | Min.: 5.61 | Min.: 5.60 | Min.: 5.67 | Min.: 5.64 5.6 – 5.8                                    |
|                                                    | Max.: 5.74 | Max.: 5.65 | Max.: 5.69 | Max.: 5.69 |
| Hardness (kg/cm²) (10 tablets)                      | Min.: 5.8 | Min.: 5.3 | Min.: 6.0 | Min.: 6.8 4.0 – 8.0                                     |
|                                                    | Max.: 6.6 | Max.: 6.4 | Max.: 6.9 | Max.: 7.2 |
| Friability (% w/w) (10 tablets)                     | 0.12     | 0.19    | 0.17    | 0.20 NMT: 0.8                                          |
| Content Uniformity (%) (10 tablets) (05 tablets from each side) | 98.09 | 95.07 | 90 – 110 |

3.3 Yield at different stages

The yield of three batches X, Y and Z of lubricated blend, compressed tablets and coated tablets of Lamotrigine were evaluated. The outcomes of weight of lubricated blend, compressed tablets and coated tablets for limit, %yield of tablets, actual yield in weight (kg) and no of tablets exhibited under limit value mentioned in official pharmacopoeia (Table 8).
### Thickness (mm) (10 tablets)

| Test     | Initial | Middle | End   |
|----------|---------|--------|-------|
| Min.     | 5.62   | 5.63   | 5.62  |
| Max.     | 5.75   | 5.65   | 5.68  |

### Hardness (kg/cm²) (10 tablets)

| Test     | Initial | Middle | End   |
|----------|---------|--------|-------|
| Min.     | 5.8     | 5.3    | 6.0   |
| Max.     | 6.6     | 6.4    | 6.9   |

### Friability (% w/w) (10 tablets)

| Test     | Initial | Middle | End   |
|----------|---------|--------|-------|
| 0.14     | 0.18    | 0.16   | 0.21  |

### Content Uniformity (%)

| Test     | Initial | Middle | End   |
|----------|---------|--------|-------|
| 98.02    | 95.06   | 90 – 110|

### Batch Z

#### Appearance (10 tablets)

- Complies
- White capsule shaped uncoated tablets plain on both surface

#### Average weight (mg)

| Test     | Initial | Middle | End   |
|----------|---------|--------|-------|
| 831.41   | 839.15  | 829.42 | 838.26|

#### Individual weight variation (mg) (20 tablets)

| Test     | Initial | Middle | End   |
|----------|---------|--------|-------|
| Min.: 817.31 | Min.: 814.19 | Min.: 821.33 | Min.: 818.21 |
| Max.: 847.10  | Max.: 843.15  | Max.: 851.42  | Max.: 845.16  |

#### Thickness (mm) (10 tablets)

| Test     | Initial | Middle | End   |
|----------|---------|--------|-------|
| Min.: 5.60 | Min.: 5.61 | Min.: 5.66 | Min.: 5.65 |
| Max.: 5.73  | Max.: 5.64  | Max.: 5.68  | Max.: 5.67  |

### Hardness (kg/cm²) (10 tablets)

| Test     | Initial | Middle | End   |
|----------|---------|--------|-------|
| Min.: 5.7  | Min.: 5.4  | Min.: 6.1  | Min.: 6.7  |
| Max.: 6.7  | Max.: 6.5  | Max.: 6.8  | Max.: 7.3  |

### Friability (% w/w) (10 tablets)

| Test     | Initial | Middle | End   |
|----------|---------|--------|-------|
| 0.13     | 0.17    | 0.18   | 0.20  |

### Content Uniformity (%)

| Test     | Initial | Middle | End   |
|----------|---------|--------|-------|
| 98.02    | 95.04   | 90 – 110|

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**Table 5: Chemical parameters of batch X, Y and Z**

| Tests             | Analysis | Acceptance criteria |
|-------------------|----------|---------------------|
|                   | Initial  | Middle  | End    |                     |

#### Batch X

- **Assay**
  - 98%  
  - 99%  
  - 102%

- **Dissolution**
  - 84 %  
  - 89%  
  - 78%

- **Content Uniformity**
  - 101.1%  
  - 100.09%  
  - 98.02%

#### Batch Y

- **Assay**
  - 97%  
  - 98%  
  - 103%

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Table 6: Data of pre-heated tablets before coating

| Parameter                          | Analysis       | Acceptance criteria                                      |
|-----------------------------------|----------------|----------------------------------------------------------|
|                                   | Lot - A        | Lot - B                                                  |
|                                   |                |                                                          |
| **Batch X**                       |                |                                                          |
| Appearance (10 tablets)           | Compiles       | Compiles                                                 |
| Average weight (mg)               | 837.44         | 837.40                                                   |
| Individual weight variation (mg)  | Min.: 835.31   | Min.: 817.34                                             |
|                                   | Max.: 845.56   | Max.: 847.13                                             |
| Thickness (mm) (10 tablets)       | Min.: 5.64     | Min.: 5.71                                               |
|                                   | Max.: 5.69     | Max.: 5.74                                               |
| Hardness (kg/cm²) (10 tablets)    | Min.: 5.5      | Min.: 5.0                                               |
|                                   | Max.: 7.5      | Max.: 6.4                                               |
| **Batch Y**                       |                |                                                          |
| Appearance (10 tablets)           | Compiles       | Compiles                                                 |
| Average weight (mg)               | 836.24         | 836.20 mg                                                |
| Individual weight variation (mg)  | Min.: 836.3    | Min.: 818.54 mg                                          |
|                                   | Max.: 846.55   | Max.: 847.14 mg                                          |
| Thickness (mm) (10 tablets)       | Min.: 5.65     | Min.: 5.70 mm                                            |
|                                   | Max.: 5.62     | Max.: 5.72 mm                                            |
| Hardness (kg/cm²) (10 tablets)    | Min.: 5.6      | Min.: 5.1                                               |
|                                   | Max.: 7.4      | Max.: 6.6                                               |
| **Batch Z**                       |                |                                                          |
| Appearance (10 tablets)           | Compiles       | Compiles                                                 |
|                                   |                |                                                          |
| Dissolution 85%                   | 88%            | 77%                                                      |
| Content Uniformity 102.03%        | 100.05%        | 99.01%                                                   |
| NLT 70.0% of the labeled amount is dissolved in 30 minutes |
| 90 – 110% of average value        |
| Assay 97%                        | 99%            | 103%                                                     |
| NLT 70.0% of the labeled amount is dissolved in 30 minutes |
| 95 % - 105 %                     |
| Dissolution 83%                   | 88%            | 79%                                                      |
| Content Uniformity 103.19%        | 100.12%        | 98.32%                                                   |
| 90 – 110% of average value        |                |                                                          |

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### Average weight (mg)

|                | Lot A | Lot B | Acceptance criteria          |
|----------------|-------|-------|------------------------------|
| Average weight (mg) | 836.02 | 837.32 | 818.3 – 851.7                |

### Individual weight variation (mg) (20 tablets)

|                | Lot A | Lot B | Acceptance criteria          |
|----------------|-------|-------|------------------------------|
| Min.: 835.03   | Min.: 816.89 | ± 5% of the average weight |
| Max.: 845.51   | Max.: 848.11 |               |

### Thickness (mm) (10 tablets)

|                | Lot A | Lot B | Acceptance criteria          |
|----------------|-------|-------|------------------------------|
| Min.: 5.66     | Min.: 5.69 | 5.6 – 5.8 |
| Max.: 5.71     | Max.: 5.72 |               |

### Hardness (kg/cm²) (10 tablets)

|                | Lot A | Lot B | Acceptance criteria          |
|----------------|-------|-------|------------------------------|
| Min.: 5.3      | Min.: 5.1 | 4.0 – 8.0 |
| Max.: 7.2      | Max.: 6.2 |               |

### Table 7: Data of tablets after coating

| Parameter                             | Analysis | Acceptance criteria                        |
|---------------------------------------|----------|--------------------------------------------|
|                                       | Lot A    | Lot B                                      |                                        |
|                                       |          |                                            |                                        |
| **Batch X**                            |          |                                            |                                        |
| Appearance (10 tablets)                | Compiles | Compiles                                   | White capsule shaped coated            |
|                                       |          |                                            | tablets plain on both surface          |
| Average weight (mg)                    | 861.44   | 857.44                                     | 842.8 – 877.2                          |
| Individual weight variation (mg) (20 tablets) | Min.: 849.31 | Min.: 845.31 | ± 2% of the average weight |
|                                       | Max.: 865.56 | Max.: 871.50 |               |
| Thickness (mm) (10 tablets)            | Min.: 5.74 | Min.: 5.72 | 5.6 – 5.8 |
|                                       | Max.: 5.79 | Max.: 5.73 |               |
|                                       | Min.: 6.5 | Min.: 6.8 | 5.0 – 10.0 |
| Hardness (kg/cm²) (10 tablets)         | Max.: 8.4 | Max.: 8.5 |               |
| Weight rise per tablet (mg)            | 23       | 24                                           | 25                                      |
| Assay (%)                              | 101.78   | 95 - 105                                    |
| Dissolution (%) (06 tablets)           | 89       | NLT 70.0% of the labeled amount dissolved in 12 hours |
|                                       |          |                                            |                                        |
| **Batch Y**                            |          |                                            |                                        |
| Appearance (10 tablets)                | Compiles | Compiles                                   | White capsule shaped coated            |
|                                       |          |                                            | tablets plain on both surface          |
| Average weight (mg)                    | 862.45   | 858.45                                     | 842.8 – 877.2                          |
| Individual weight variation (mg) (20 tablets) | Min.: 848.30 | Min.: 846.21 | ± 2% of the average weight |
|                                       | Max.: 864.55 | Max.: 870.52 |               |
| Thickness (mm) (10 tablets)            | Min.: 5.73 | Min.: 5.71 | 5.6 – 5.8 |
|                                       | Max.: 5.72 | Max.: 5.73 |               |
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Max.: 5.78  Min.: 5.72

Hardness (kg/cm²) (10 tablets)
Min.: 6.4  Min.: 6.9
Max.: 8.6  Max.: 8.6
5.0 – 10.0
22 mg  24 mg

Weight rise per tablet (mg)

Assay (%) 101.12 % 95 - 105

Dissolution (%) (06 tablets) 87 % NLT 70.0% of the labeled amount dissolved in 12 hours

Batch Z

Appearance (10 tablets) Compiles Compiles White capsule shaped coated tablets plain on both surface

Average weight (mg) 862.42 856.43 842.8 – 877.2

Individual weight variation (mg) (20 tablets)
Min.: 846.11  Min.: 849.31 ± 2% of the average weight
Max.: 863.56  Max.: 872.50

Thickness (mm) (10 tablets)
Min.: 5.74  Min.: 5.72 5.6 – 5.8
Max.: 5.79  Max.: 5.73

Hardness (kg/cm²) (10 tablets)
Min.: 6.4  Min.: 6.6 5.0 – 10.0
Max.: 8.3  Max.: 8.3

Weight rise per tablet (mg) 23.8 22.5 25

Assay (%) 102.03 95 - 105

Dissolution (%) (06 tablets) 86 NLT 70.0% of the labeled amount dissolved in 12 hours

Table 8: Data of yield at different stages

| Stage               | Limit      | Actual Yield in %Yield of tablets |
|---------------------|------------|-----------------------------------|
|                     | Weight (Kg) | No of Tablets                      |

**Batch X**

| Stage                        | Limit     | Weight (Kg) | No of Tablets | %Yield of tablets |
|------------------------------|-----------|-------------|---------------|-------------------|
| Wt. of Lubricated blend      | NLT 98.0%| 828         | 991617        | 99.16             |
| Wt. of Compressed Tablets    | NLT 97.5%| 819         | 980838        | 98.08             |
| Wt. of Coated Tablets        | NLT 97.0%| 840         | 976744        | 97.67             |

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| Batch Y                |              |              |              |
|------------------------|--------------|--------------|--------------|
| Wt. of Lubricated blend| NLT 98.0%    | 827.3 kg     | 990778       |
| Wt. of Compressed Tablets| NLT 97.5%   | 822 kg       | 984431       |
| Wt. of Coated Tablets  | NLT 97.0%    | 844 kg       | 981395       |

| Batch Z                |              |              |              |
|------------------------|--------------|--------------|--------------|
| Wt. of Lubricated blend| NLT 98.0%    | 823 kg       | 985625       |
| Wt. of Compressed Tablets| NLT 97.5%   | 816 kg       | 977245       |
| Wt. of Coated Tablets  | NLT 97.0%    | 839 kg       | 975581       |

4 Conclusion

The process validation of Lamotrigine XR tablet were executed for three batches X, Y and Z, and all the parameters and results were found within the acceptance limit, reported in official pharmacopoeia. The findings exhibited that the validation data of three batches will produce stable product meeting its predetermined specifications and quality attributes, when use in manufacturing of formulation of Lamotrigine XR tablet. The present study suggested that the process used in the formulation of the Lamotrigine XR tablet is pondered to be validated. Hence this validated method will assist the pharmaceutical industry to deliver safe and stable Lamotrigine XR tablet to market.

5 Conflict of interest

Nil

6 Author’s contributions

KJ and MB designed study, carried out data collection and drafted the manuscript. Both the authors read and approved the final copy of the manuscript.

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