4. SUMMARY AND CONCLUSION

4.1 Preparation of Non-Infringement opinion

A capsule formulation comprising Tianeptine was designed. Based on the proposed formulation a search strategy including search terms was decided. Searches were conducted as per the pre determined search strategy with each of the key terms on the available electronic databases. Relevant patents were identified and infringement analysis was done for each of the relevant patents existing in US, UK and CIS countries.

Suggested Formulation:

Formula of the Proposed Formulation

B. Size: 10,000 Capsules

Table 2.1 Batch formula of BRUTINE (Tianeptine sodium Capsules 12.5 mg) for 10000 Capsules.

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Spec</th>
<th>Standard Quantity (Kg)</th>
<th>Quantity required (Kg)</th>
<th>Quantity per Capsules (mg)</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: Granules Preparation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tianeptine sodium BP</td>
<td>BP</td>
<td>* 0.1313</td>
<td>* 0.1313</td>
<td>12.5</td>
<td>Active</td>
</tr>
<tr>
<td>Microcrystalline cellulose (PH 102)</td>
<td>BP</td>
<td>0.5167</td>
<td>0.5167</td>
<td>51.0</td>
<td>Diluent</td>
</tr>
<tr>
<td>Microcrystalline cellulose Plain</td>
<td>BP</td>
<td>0.1000</td>
<td>0.1000</td>
<td>10.0</td>
<td>Diluent</td>
</tr>
<tr>
<td>Maize Starch</td>
<td>BP</td>
<td>0.1000</td>
<td>0.1000</td>
<td>10.0</td>
<td>Diluent</td>
</tr>
<tr>
<td>Magnesium stearate BP</td>
<td>BP</td>
<td>0.0100</td>
<td>0.0100</td>
<td>1.0</td>
<td>Lubricant</td>
</tr>
<tr>
<td>Colloidal anhydrous silica</td>
<td>BP</td>
<td>0.0070</td>
<td>0.0070</td>
<td>0.7</td>
<td>Glidant</td>
</tr>
<tr>
<td>Purified Talc</td>
<td>BP</td>
<td>0.0100</td>
<td>0.0100</td>
<td>1.0</td>
<td>Glidant</td>
</tr>
<tr>
<td>Croscarmellose sodium</td>
<td>BP</td>
<td>0.0150</td>
<td>0.0150</td>
<td>1.5</td>
<td>Disintegrant</td>
</tr>
<tr>
<td>Sodium starch glycolate</td>
<td>BP</td>
<td>0.0150</td>
<td>0.0150</td>
<td>1.5</td>
<td>Disintegrant</td>
</tr>
<tr>
<td>Crospovidone</td>
<td>BP</td>
<td>0.0150</td>
<td>0.0150</td>
<td>1.5</td>
<td>Disintegrant</td>
</tr>
<tr>
<td>B: Capsules shell:</td>
<td>IHS</td>
<td>10200nos</td>
<td>10200nos</td>
<td>1 no</td>
<td>Protective</td>
</tr>
<tr>
<td>Empty Hard gelatin capsule shells Light</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>shell</td>
</tr>
<tr>
<td>green-Light green; Size 5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Overages = 5%

Average weight of a Capsule is 120.5 mg
Conclusion:
On the basis of infringement analysis of the identified patents, it seems that more likely the proposed product and processes were infringing to not any patents. We, therefore suggest our client to launch the suggested formulation as soon as possible in US.

Based on the infringement analysis for UK, we presume that more likely the proposed product was not infringing any of the existing patents. We, therefore suggest our client to file a dossier and to launch the suggested formulation as soon as possible.

Based on the searches, we presume similar strategy for Russia.

But, searches on electronic databases have limitations and chances of missing some relevant patents are always there. We therefore, suggest our client to take services of a patent attorney for advanced level of searches.

4.2 DRUG SUBSTANCE
Refer to “DMF (Open Part) in Annexure 2

4.3 DRUG PRODUCT
4.3.1 Pharmaceutical Development
4.3.1.1 Batch Analyses:
Final summary: Process validation was performed and the result during manufacturing process and analytical result were satisfactory and under predetermined specified limits.

Conclusion: Based on the batch process observations and analytical review it was concluded that the manufacturing process of the BRUTINE (Tianeptine sodium Capsules 12.5 mg) showed consistent results.

All the batch documents were updated as per validated procedure

4.3.1.2 Comparitive Dissolution Profile of BRUTINE and STABLON
The conclusions drawn from the present investigation were given below:-

- Suitable analytical method based on UV-Visible spectrophotometer was developed for Tianeptine sodium Capsules 12.5 mg
• In vitro release profiles of optimized formulations of Tianeptine sodium Capsules were found to be similar to that of theoretical drug release profile. The f1 and f2 values for the comparison of release of drugs from the formulation with the theoretical drug release profile were found to be 6 and 71.0 respectively, for capsules.

Also the manufacturing procedure was standardized and found to be reproducible.

• After 3 month of accelerated stability studies developed formulation was found to be stable. The f1 and f2 values in the comparison of release before and after 3-month storage (at accelerated conditions) were found to be in acceptable limit in the formulation

• The capsules were evaluated for weight uniformity, Identification and In vitro drug release from the product. Capsules of the formulation were passed the weight uniformity, Identification & In vitro drug release testing. In comparison of tablet and capsule formulation, capsule was found to be successful formulation as compared to tablet dosage form.

The result of the study indicates that Capsules of Tianeptine sodium were prepared successfully.

4.3.2 Manufacture

Process Validation:

Summary: The manufacturing process of “Tianeptine Sodium Capsule 12.5 mg” was validated as per the Batch Manufacturing Record to establish documentary evidence that the process had consistently produce the product, meeting its predetermined in-process and finished product specifications by examined the three consecutive production batches.

Retrospective validation was carried out for 3 consecutive production batches for “Tianeptine Sodium Capsule 12.5 mg”; critical steps were monitored and validated. The objective of this process validation report for “Tianeptine Sodium Capsule 12.5 mg” was to establish the documentary evidence & support that the process is capable of producing a product continuously with the predetermined specifications and quality parameters.
Conclusion: Process validation had been performed and the result during manufacturing process and analytical result were satisfactory and under predetermined specified limits.

Based on the batch process observations and analytical review it was concluded that the manufacturing process of the BRUTINE (Tianeptine sodium Capsules 12.5 mg) showed consistency in production.

All the batch documents were updated as per validated procedure

4.3.3 Control of Excipients

Analytical procedures of Excipients as Microcrystalline Cellulose BP, Purified Talc BP, Magnesium Stearate BP, Maize Starch BP, Sodium Starch Glycolate BP, Colloidal Anhydrous Silica BP, Croscarmellose Sodium BP, Crospovidone BP and Purified Water BP are compendial & followed official specifications.

As all the Excipients are present in the official monograph i.e. B.P. and EP, so there was no requirement for the analytical method validation.

Also there was no requirement for the Justification of Specifications for these Excipients.

No Noval Excipient(s) were used in the formulation.

Gelatin used in the manufacture of Capsule shell was BSE free and conferred by a BSE risk free certificate from the Capsule shell manufacturer. Find attachment in “COA’S” in Annexure 1.

4.3.4 Control of Drug Product

4.3.4.1 Analytical Procedures

The testing Procedure was justified from data of analytical method validation and the other methods like dissolution and other In-process results are justified from process validation and Stability study upto the shelf life of Product.
4.3.4.2 Validation of Analytical Procedures

By: UV-visible double beam spectrophotometer
Refer to Annexure 2 “Chromatograms & Testing Procedure”

By HPLC:
i) Specificity
Acceptance Criteria:
No any interference observed at maximum 214nm from the diluents and placebo maxima.

Conclusion:
No any interference observed at maximum at 214 nm from the blank and placebo solution.

Hence, method is specific.

ii) System Suitability
Acceptance Criteria:
- The tailing factor for Tianeptine Sodium peak should NMT 2.0.
- Column efficiency calculated from the Tianeptine Sodium peak should NLT 2500 theoretical plates.
- The % RSD for three replicates absorbance of test solution should NMT 2%.

Conclusion: % RSD of the replicate absorbance of the test solution observed well within the acceptance criteria. Hence, method was suitable for the assay determination of Tianeptine in Tianeptine sodium Capsules.

iii) Method precision
Acceptance Criteria:
% RSD of the assay content from the six sample preparation should be not more than 2.0%

Remark: % Assay of the six sample preparation at target concentration found between 99.1% and 100.9%; and % RSD of the six samples preparation was 0.605%.

Conclusion: % Assay of the six sample preparation found well within the acceptance criteria. Hence, method is precise.

iv) Accuracy
Acceptance Criteria:
% Recovery should be between 95% and 105 % and % RSD of the 9 determination of the samples should be not more than 2.0%

Conclusion: % Recovery of the Tianeptine found well within the acceptance criteria between 95% and 105 % and % RSD of the 9 determination of the samples should be not more than 2.0%.

Hence method is accurate.

v) Limit of detection & Limit of quantitation:
LOD (Limit of detection):
Average response (X)
Standard deviation (SD) was calculated.
LOD = X + (3 x SD).

LOQ (Limit of quantitation)
LOQ = X + (10 x SD).

vi) Conclusion
The determination of assay content of Tianeptine in Tianeptine sodium capsules was verified by using the HPLC. On basis of analytical data and results it was concluded that method was specific, precise, Accurate and system suitability parameters observed well within the pre-defined acceptance criteria.

Hence it was concluded that method for the determination of assay of Tianeptine in Tianeptine sodium capsules was suitable for our intended purpose.

4.3.4.3 Batch Analyses
Batch Analyses for the three consecutive batches of Production scale was completed. The manufacturing process of “Tianeptine Sodium Capsule 12.5 mg” was validated as per the Batch Manufacturing Record to establish documentary evidence that the process would consistently produce the product, meeting its predetermined in-process and finished product specifications by examined the three consecutive production batches.
4.3.5 Container Closure System

Packaging components were compatible with Tianeptine Sodium was not interacted with drug & not produce unacceptable changes in the quality of Capsule. No interactions between a packaging material and capsules were detected during qualification studies. Therefore, no change was noted during stability with reference to the interaction between the capsules and a packaging material.

On the basis of Stability studies report this drug was found stable and does interacted with drug component. The container and closure as said above was during the storage, shipping / transportation and use, was suitable and compatible for the Tianeptine Sodium Capsules 12.5 mg.

4.3.6 Stability

Stability Summary and Conclusion

Product : BRUTINE (Tianeptine sodium Capsules 12.5 mg)
Shelf-life : BRUTINE (Tianeptine sodium Capsules 12.5 mg), packed in a Blister of 10x10 Capsules are stable at least 2 Years from the date of manufacture.
Proposed expiry : 2 Years
Storage : Store below 25°C. Protect from light and moisture.
Stability studies : Accelerated stability study at 40°C and Long term stability study at 25°C were carried out and stability data were attached.

Method of Study

Conditions for stability study:

For accelerated study & Long term study, the products were kept in humidity chamber at following stability conditions:

For accelerated stability study:
At 40°C ±2°C and RH 75% ±5%

For long term stability study:
At 25°C ±2°C and RH 60% ±5%

Testing Intervals for stability study:
For accelerated stability study:
The stored samples were withdrawn at predetermined intervals the intervals are as follows:
0 month, 3 months and 6 months.

**For long term stability study:**
The stored samples were withdrawn at predetermined intervals the intervals are as follows:
0 month, 3 month, 6 months, 9 months, 12 months, 18 months and 24 months

**Conclusion:**
The stability data demonstrates that all lots of the product BRUTINE (Tianeptine sodium Capsules 12.5 mg) were remained within specifications at all times during the study, under natural (long term) temperature and relative humidity conditions indicated above.

Storage under Long term stability study testing condition caused no or less change of assay result of BRUTINE (Tianeptine sodium Capsules 12.5 mg). Significant changes in physical and chemical stabilities were not observed. Since the long-term data and accelerated data showed a little or no change over time and little variability, a statistical analysis was considered unnecessary.

Based on the stability study data, we concluded that the product BRUTINE (Tianeptine sodium Capsules 12.5 mg) was stable for the period of 2 Years.

The method used to conduct the stability studies was taken as ICH guidance document Q1A-(R2).

The study was performed at Brawn Laboratories Limited under the supervision of our analyst manager.
Disclaimer and Limitation:

Although due diligence has been taken while preparing this opinion, but searches on electronic databases have limitations and chances of missing some relevant patents are always there. Even though the opinion may conclude that the proposed product and processes do not infringe the already existing patents found during searching process, there is no such condition that patentee will go for infringement claims in a court of law or that, if found any, such infringement claims would not be successful. The result of such proceeding is unpredictable due to the reason of complexity of the subject matter and the adversarial nature of patent litigation. Thus, this Patent opinion should not be taken as a litigation risk analysis but apart from this, it should be reflecting our best judgment as to the client’s legal rights in view of the patents identified in search.

After drafting the dossier, it was concluded that dossier includes all the necessary information regarding drug substance like synthesis of drug substances, control of drug substance, packaging and Stability study of Tianeptine sodium and Capsules theirof, CMC section But, Bioavailability and other Clinical studies are subjected to territory where, the product is supposed to be commercialized. The registration of product depends on the applicant interest whether they want to share the clinical, SmPC data & other information from innovator & profit that they expect from that country at that time.

The formulas, process descriptions, and safety data described in a dossier are part of company’s Assets & Business. For this reason, the information contained in a dossier is highly proprietary and confidential.