INTRODUCTION

1.1 Non-Infringement Opinion for Patent: (Nagori & Mathur, 2009)

Patent is the right to exclude others from making, using, offering for sale, selling or importing the patented invention for the limited period of time. Infringement of Patent means violation of any monopoly rights conferred to the patentee. Patent opinions like FTO & Non-infringement opinions are legal advice rendered by a patent attorney to his clients of activities that would avoid infringement of unexpired, valid & enforceable patent.

A non-infringement opinion is typically directed to specific patent(s) of which the client has become aware. In contrast Freedom-to-operate (FTO) is broader in scope & addresses the potential for infringement by any patent, whether known or unknown to the client. A competent Non-infringement opinion provides a reasonable basis for determining whether a proposed product, process or technology will infringe third party’s patent or not.

1.2 M4: Common Technical Document (CTD) (July 2003) - The 'Common Technical Document' or 'CTD' is a set of specification for application dossier for the registration of Medicines and designed to be used across Europe, Japan and the United States. The CTD is maintained by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The CTD consists of 5 modules and the structure is given as follows:
  Module 1: Regional administrative information & it is not a part of CTD
  Module 2: Quality overall summary – This consists of Quality summary, Non-clinical overview & summary, Clinical overview & summary.
  Module 3: Quality
  Module 4: Non-clinical study reports
  Module 5: Clinical study reports

Registration of Pharmaceuticals for Human Use (ICH) (Cartwright & Anthony 2006): Common technical document (CTD) format has now become the obligatory format for the EU, Japan, Canada, Switzerland & Australia, & the recommended format in the US. Derivatives of the CTD are becoming widely adopted in other regions, including the ASEAN countries. An electronic CTD (eCTD) was developed in parallel with the CTD & the three ICH regions now accept eCTD filings.
1.3 Medicines and Healthcare products Regulatory Agency (MHRA)

The Medicines and Healthcare products Regulatory Agency (MHRA) is the UK government agency which is responsible for ensuring that medicines and medical devices work properly and are acceptably safe.

- **Abridged products**
  
The approval to market a medicinal product is based on the evaluation of scientific data provided by the company to support its quality, safety and efficacy. However, most of the 'new' products which come onto the market contain drugs which have been previously well tested and approved in other forms or for other companies. In these circumstances the European Directives (in particular Directive 2001/83EC) allow for what are known as 'abridged' applications so that companies do not have to unnecessarily repeat the tests and trials on animals and humans (MHRA 2011 Dec;02).

- **Generic products**
  
  If the new product can be shown to be 'essentially similar' to a product already on the UK market and which has been authorised for ten years or more in the EEC, then the new product can be authorised without its own clinical and pre-clinical testing data. [Directive 2001/83/EC Article 10.1(a)(iii)].

- **European dossier**
  
The MHRA operates a system of licensing before the marketing of medicines. Medicines, which meet the standards of safety, quality and efficacy, are granted a marketing authorisation (previously a product licence), which is normally necessary before they can be prescribed or sold. This authorisation covers all the main activities associated with the marketing of a medicinal product.

  All applications submitted for MHRA approval must follow the common technical dossier format which has been a requirement since 2003. (MHRA 2011 Dec:02).

1.4 General importance of the research:

CTD has revolutionised the regulatory review processes, led to harmonised electronic submission that, in turn, enabled implementation of good review practices. For industries, it has eliminated the need to reformat the information for submission to the different ICH regulatory authorities.
It also significantly reduces the time & resources needed to compile applications for registration of human pharmaceuticals, eases the preparation in electronic submission & simplifies the exchange of regulatory information between regulatory authorities. (The Value and Benefits of ICH to Drug Regulatory Authorities 2010)

Patent opinions are of particular importance in case of developing generic medicines. Non-infringement opinions are important business strategic tools by companies since these opinion assist greatly in critical decision areas like launching of new products, mergers & acquisitions, contract manufacturing & designing of R& D strategies. (Nagori.et.al 2009, January).

1.5 STABLON – Detailed Prescribing Information: (MIMS Singapore 2011)

Pharmaceutical Classification: Antidepressant

<table>
<thead>
<tr>
<th>Active substances</th>
<th>Tianeptine Sodium</th>
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<tbody>
<tr>
<td>Dosage form</td>
<td>Tablets existing in market</td>
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</table>

**Mechanism of action**

In contrast to SSRIs and tricyclic antidepressants, Tianeptine modestly enhances the mesolimbic release of dopamine, but it is also unclear how this occurs because Tianeptine itself has no effect on dopamine transporters, nor does it affect D1, D2, D3, D4 and D5 receptors.

**Pharmacokinetics**

When given orally, tianeptine was absorbed rapidly (tmax = 0.94 ± 0.47 h). The mean systemic availability was estimated to be 99 ±29%. Tianeptine was eliminated from plasma with a half-life of 2.5± 1.1 h, mainly via extrarenal route since its renal clearance averaged 0.38±0.47 ml·min⁻¹. Plasma levels of metabolite MC₅ were lower than those of the parent drug but decreased with a longer half-life (7.2 ±5.7 h).

**Indications and usage**

Treatment of major depressive states of mild, moderate or severe intensity. Angiodepressive states with somatic complaints such as digestive problems Angiodepressive states observed in the alcoholic undergoing detoxification

**Dosage**

Recommended dosage: 1 tablet 3 times daily at the beginning of main meals. In chronic alcoholics, whether cirrhotic or not, no alteration of dosage is necessary. Elderly> 70years & patient with renal Insufficiency: Maximum dose : 2 tablets/day

**Administration**

Should be taken on an empty stomach. (Take before main meals.)

**Special Precautions**

General anaesthesia; tasks requiring mental alertness. Avoid abrupt withdrawal, dosage to be decreased gradually over 7-14 days.
Drug Interactions | Potentially Fatal: Avoid concurrent admin with MAOI, start Tianeptine 2 wk after discontinuation from MAOI.
---|---
Adverse Drug Reactions | Abdominal pain, fatigue, nausea, constipation, lack of appetite, insomnia, drowsiness, palpitations, muscular or joint pain, headache, vertigo, tremor, dry mouth, hepatitis (rare)
Contraindications | With MAO inhibitors (as a rule, there should be an interval of 15 days between a MAOI and Tianeptine treatments)
ATC Classification | N06AX14 - Tianeptine; Belongs to the class of other antidepressants.

### Table: 2 Drug information (Active ingredient Tianeptine Sodium)

<table>
<thead>
<tr>
<th>Physicochemical properties</th>
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<tr>
<td>Chemical structure</td>
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| ![Chemical structure of Tianeptine Sodium](image)
| Chemical name |
| 7-[(3-Chloro-6,11-dihydro-6-methyldibenzo[c,f][1,2]thiazepin-11-yl)-amino]heptanoic acid S,S-dioxide |
| Molecular formula |
| C_{21}H_{24}ClN_{2}NaO_{4}S |
| Molecular weight |
| 458.9 |
| Appearance |
| White or yellowish powder, very hygroscopic. |
| Solubility |
| Freely soluble in water, in methanol and in methylene chloride |

### Pharmacological properties

**Mechanism of action**
Tianeptine is an antidepressant. Tianeptine has the following properties in animals:
- Tianeptine increases the spontaneous activity of pyramidal cells in the hippocampus and accelerates their recovery after functional inhibition;
- Tianeptine increases the rate of serotonin re-uptake by neurons in the cortex and hippocampus.

In man, Tianeptine is characterized by an action on mood disturbances giving it an intermediate position in the bipolar classification between sedative antidepressants and stimulant antidepressants; marked action on somatic complaints, especially gastrointestinal complaints related to anxiety and mood disturbances; an action on the disturbances in the character and behaviour of alcoholics during the withdrawal period.
Moreover, Tianeptine has no effect on sleep and alertness the
cardiovascular system the cholinergic system (no anticholinergic symptoms) drug addiction

**Toxicology:**
Acute, subchronic and chronic toxicity studies: examinations of biological, hepatic function, anatomicopathological and histological show no modification.
Reproduction and teratology studies: no effect on initial parent reproductive functions and on fetuses and progeny.
Mutagenesis studies: devoid of mutagenic effect.