were randomized in 24 centers in Europe. In this trial, all patients were receiving concomitant levodopa
therapy (Part IV), and disease staging (Parts V and VI); an Investigator's Global Assessment of Change
Fluctuating Patients:

Drug Interactions:

SGOT/AST values greater than the upper limit of normal (see
Hepatic Impairment:

Tolcapone is a low-

These data are consistent with previous reports indicating that the plasma levels of tolcapone are more sustained than after administration of levodopa and an aromatic
The precise mechanism of action of tolcapone is unknown, but it is believed to be related to its ability to

Mechanism of Action:

The inhibition is closely related to plasma tolcapone concentrations. With a 200-mg single dose of
distribute widely into tissues due to its high plasma protein binding. The plasma protein binding of

Absorption:

no significant accumulation. With tid dosing of 100 mg or 200 mg, C

the brain and periphery.

COMT catalyzes the transfer of the methyl group of S-adenosyl-Lmethionine to the phenolic group of

physiological substrates of COMT include dopa,

the brain and periphery.

substrates that contain a catechol structure. Physiological substrates of COMT include dopa,

Table 1: N-Acetylation

Table 2: N-Acetylation

Table 3: N-Acetylation
neuroleptic malignant syndrome (characterized by elevated temperature, muscular rigidity, and altered use of direct dopamine agonists. While cases of Hyperpyrexia and Confusion have been reported in the use of drugs that increase dopaminergic activity, although they are most often associated with the Tolcapone tablets has not always been explained (for example, by urinary tract infection or warfarin have two SGPT/ALT or SGOT/AST values greater than the upper limit of normal (see Hepatic Impairment:

PHARMACOLOGY

be a result of the syndrome described in alteration of consciousness and muscular rigidity. It is possible, therefore, that the rhabdomyolysis may determine what role, if any, tolcapone tablets played in their pathogenesis. Severe prolonged motor urges while taking tolcapone tablets physicians should consider dose reduction or stopping the medication if a patient develops such discontinuation. Because patients may not recognize these behaviors as abnormal, it is important for
dopaminergic tone and that are used to treat patients with Parkinson's disease. In some cases, although tablets in conjunction with carbidopa/levodopa, as well as other medications that increase central

42% and 51% of patients treated with tolcapone tablets 100 mg or 200 mg three times daily,

Dyskinesia:

tablets.

Post-marketing reports indicate that patients may experience new or worsening mental status and

dose reduction of 175 mg to 200 mg (20% to 25%) after the onset of the hallucinations. Hallucinations

withdrawal from clinical trials in 0.3% of patients treated with placebo, compared to 1.4% and 1.0% of
documented at least once in 8%, 14% and 13% of the patients treated with placebo, 100 mg and 200 mg

Hypotension/Syncope

etc.). If treatment with tolcapone tablets continues, patients should be advised not to drive and to avoid

Before initiating treatment with tolcapone tablets, advise patients about the potential to develop

about drowsiness or sleepiness during specific activities. Patients who have already experienced

Falling Asleep During Activities of Daily Living and Somnolence

metabolism of catecholamines. It is theoretically possible, therefore, that the combination of tolcapone

diabetes declined within 2 to 3 weeks but in some cases took as long as 1 to 2 months to return to normal.

Elevations usually occurred within 6 weeks to 6 months of starting treatment. In about half the cases

patients continued tolcapone tablets treatment. When treatment was discontinued, enzymes generally

No dosage adjustment is needed in patients with mild to moderate renal impairment,

Effects on "Off" time and levodopa dose did not differ by age or sex.

In clinical trials, diarrhea developed in approximately 8%, 16% and 18% of patients treated

patients vs. 1% on placebo).

- Increased sweating
- Anorexia
- Sleep disorder
- Vomiting
- Urine discoloration
- Somnolence
- Hallucination
- Dystonia

Adverse Reactions in Patients

Table 4. Summary of Patients With Adverse Reactions After Start of Trial Drug

<table>
<thead>
<tr>
<th>Reactions</th>
<th>Tolcapone</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous System</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Visual</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Cardiac</td>
<td>13</td>
<td>17</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>22</td>
<td>298</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>Skin</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>General</td>
<td>22</td>
<td>298</td>
</tr>
</tbody>
</table>

In animal studies, tolcapone was excreted into maternal rat milk. Therefore, tolcapone tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

- Patients receiving tolcapone tablets should be advised about the possibility of developing or worsening of existing dyskinesia and/or dystonia and to exercise caution.

When tolcapone is administered with other drugs, the potential for clinically relevant interactions involving cytochrome P450 2C9 appear unlikely.

- The effect of tolcapone on the pharmacokinetics of the COMT substrate carbidopa was not studied in vivo.

- Carbidopa may influence the pharmacokinetics of tolcapone.

- Tolcapone pharmacokinetics have not been studied in vivo.

- Tolcapone pharmacokinetics have not been adequately studied in women of childbearing potential.

- Tolcapone pharmacokinetics have not been adequately studied in geriatric patients.

- Tolcapone pharmacokinetics have not been adequately studied in patients with hepatic impairment.

Fibrotic Complications:

- Melanoma:
  - Tolcapone exposure greater than 1 mg/day for at least 6 months among 103 patients has been associated with a risk (2- to approximately 6-fold higher) of developing melanoma than the general population.
  - Whether tolcapone exposure alone is responsible or if other factors are involved remains to be determined.

- Neuroleptic Malignant Syndrome:
  - The combination of tolcapone and other dopaminergic drugs, have been reported in association with the abrupt withdrawal or lowering of other drugs.

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  - The combination of tolcapone and other dopaminergic drugs, have been reported in association with the abrupt withdrawal or lowering of other drugs.

- parkinsonian syndrome:
  - parkinsonian syndrome:

- interaction:
  - interaction:

- tolcapone:
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Tolcapone tablets can be combined with both the immediate and sustained release formulations of levodopa/carbidopa. In clinical trials, the average reduction in daily levodopa dose was about 30% in those patients requiring a dose reduction. (Greater than 70% of patients with levodopa doses above 600 mg daily had an initial reduction of at least 70% of the dose, which was usually followed by a slower, sustained levodopa dose reduction.)

The highest dose of tolcapone administered to humans was 800 mg tid, with and without coffee. The peak plasma concentrations of tolcapone at this dose were on average 30 mcg/mL (compared to 3 and 6 mcg/mL with 100 mg and 200 mg tolcapone, respectively). Nausea, vomiting and dizziness were observed, particularly in combination with levodopa/carbidopa.

Respiratory difficulties were observed in rats at high oral (gavage) and intravenous doses and in dogs at high intravenous doses. A transient rise in pulmonary pressure was observed in dogs. No evidence of organ toxicity was observed in any species at doses up to the maximum tolerated dose.

Blood levels of tolcapone in humans were significantly increased in patients with impaired renal function. Based on these considerations, the dose of tolcapone tablets should be reduced in patients with creatinine clearance less than 30 mL/min.

Tolcapone tablets is also 100 mg tid. In clinical trials, elevations in ALT occurred more frequently at the dose of tolcapone tablets is always 100 mg three times per day. The recommended daily dose of tolcapone tablets is 100 mg tid.

Tolcapone tablets can be administered with or without a meal.

Management of Overdose:

In overdose, the possibility of concomitant ingestion of levodopa/carbidopa should be considered. If a patient ingests an overdose of tolcapone tablets, the patient should be observed for at least 12 hours, and if indicated, supportive measures should be administered. No specific antidote is available. Hemodialysis is unlikely to be of benefit.

In rodents, the LD₅₀ of orally administered tolcapone is greater than 5000 mg/kg. In dogs, the LD₅₀ of orally administered tolcapone is 2500 mg/kg.

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**Marketing Information**

- **Marketing Category**: ANDA
- **Application Number or Monograph Citation**: ANDA208937
- **Marketing Start Date**: 08/21/2018
- **Marketing End Date**: 

**Labeler** - Ingenus Pharmaceuticals, LLC (833250017)

**Registrant** - Ingenus Pharmaceuticals, LLC (833250017)

**Establishment**

- **Name**: RA CHEM PHARMA LIMITED
- **Address**: 677637710
- **ID/FEI**: manufacture(50742-193)

**Revised**: 11/2018