CHAPTER - 2

PROJECT DESCRIPTION AND INFRASTRUCTURAL FACILITIES

2.1 BACKGROUND

M/s. Alembic Pharmaceuticals Limited (Unit-I) proposes expansion of APIs in existing unit at Survey No. 119, 120 & 121, At & Post: Panelav, Tehsil: Halol, Dist. Panchmahal, Gujarat.

2.2 MANUFACTURING ACTIVITIES

Manufacturing activities in the project include various processes. The activities shall also include operation of various utilities. The manufacturing process is described in details in following sections. The list of products and their capacity is given in Table 1.1.

PROCESS DESCRIPTION

1. CLARITHROMYCIN

Manufacturing Process

Erythromycin Thiocyanate reacts with liquor ammonia in presence of Methylene dichloride to give erythromycin base. Methylene dichloride layer is separated and washed with water followed by distillation of Methylene dichloride. The residue of erythromycin base reacts with hydroxylamine hydrochloride in presence of Triethyl amine and methanol to give erythromycin Oxime hydrochloride which further reacts with liquor ammonia in Isopropanol to give erythromycin oxime base. Erythromycin oxime base react with 2-methoxy propane in presence of pyridine hydrobromide followed by reaction with hexamethyl disilazane in methylene dichloride.

Reaction mixture is washed with water followed by layer separation of aqueous layer. Methylene dichloride is distilled from reaction mass. The residue further reacts with methyl iodide and potassium hydroxide in presence of toluene and dimethyl sulfoxide. After reaction completion reaction mixture is washed with water. The aqueous layer is separated from reaction mixture; toluene is distilled out from reaction mixture. Residue further reacts with sodium bisulphate in presence of formic acid and ethanol followed by addition of caustic lye to give crude Clarithromycin of 6-o methyl erythromycin crude. Clarithromycin is recrystallized in ethanol to give Clarithromycin or 6-o methyl erythromycin.
Stage 2

Clarithromycin crude (1.65kg) → Reactor RE-023

Alcohol (35.25kg) → Activated charcoal (0.06kg) → Hyflo (0.04 kg) → Reactor RE-023

Filtration → Charcoal + hyflo (0.11kg) → Alcohol recovery (25.78kg) → Alcohol lost (1.33kg)

Water (1.75kg) → Centrifugation → Solvent (8.73kg) → Aqueous effluent (1.57kg)

Drying → Moisture loss (0.25kg)

Milling → Clarithromycin (1 KG)
2. AZITHROMYCIN

Manufacturing Process
Erythromycin thiocyanate reacts with liq-ammonia in presence of Methylene chloride to give erythromycin base. Methylene chloride is separated and distilled off. Residual erythromycin base react with hydroxyl amine hydrochloride and Triethyl amine in presence of methanol to give erythromycin oxime hydrochloride. Methanol is distilled out and erythromycin oxime hydrochloride reacts with liq-ammonia in presence of isopropanol to give erythromycin oxime base.

Erythromycin oxime base reacts with sodium bicarbonate and para toluene sulfonyl chloride in presence of methylene chloride to give erythromycin imino ether. Erythromycin imino ether undergoes catalytic reduction in presence of platinum to give aza erythromycin. Aza erythromycin is further methylated with a mixture of formic acid and formaldehyde in acetone to give Azithromycin.

Chemical Reaction
Material Balance

Stage 1

- Process water (6.63 Kg)
- Erythromycin Oxime base (1.13 Kg)
- Methylene chloride (1.33 Kg)
- Pfa chloride (0.30 Kg)
- Sodium Bicarbonate (0.17 Kg)
- Acetic acid (0.10 Kg)
- Process water (1.53 Kg)

Layer Separation

- Methylene chloride layer (0.89 Kg)

Precipitation

- Caustic soda (0.27 Kg)
- Process water (0.88 Kg)

Centrifugation

- Aqueous Effluent (10.75 Kg)

Drying

- Moisture loss in drying (0.55 Kg)

Packaging 1 Kg

Stage 1 product 1 Kg

Stage 2

- Process water (5.61 Kg)
- Sodium Bicarbonate (0.15 Kg)
- Perchloric acid (0.01 Kg)

NF-006 NUTCH

- Aq water (5.65 Kg)

Reactor-RE-061

- Spent charcoal (0.022 Kg)

Filtration

- Platinum charcoal for regeneration (0.20 Kg)

Process water (1.23 Kg)

- Methanol & Water Distillation

- Methanol recovery (8.37 Kg)
- Methanol loss (2.81 Kg)
- Distill water (1.25 Kg)

Precipitation

Process water (3.83 Kg)

- Caustic soda (0.17 Kg)

Centrifugation

- Aqueous Effluent (7.52 Kg)

Drying

- Moisture loss in drying (0.51 Kg)

Packaging 1 Kg

Stage 2 product 1 Kg
Stage-3

AZ-II (1.19 Kg)
Acetone (3.83 Kg)
Formic acid (0.24 Kg)
Formaldehyde (0.23 Kg)
Act. Charcoal (0.03 Kg)
Caustic soda (0.15 Kg)
Process water (0.30 Kg)
Hyflo (0.01 Kg)

Reactor RE-033/RE-034

Layer Separation → Aqueous Effluent (0.30 Kg)
Filtration → Charcoal (0.05 Kg)
Precipitation

Process water (3.25 Kg)
Process water (0.95 Kg)

Centrifugation → Aqueous Effluent (9.43 Kg)
Drying → Moisture loss in drying (0.42 Kg)
Sieving
Blending
Packing 1 Kgs
3. ROXYTHROMYCIN

Manufacturing Process

Erythromycin thiocyanate reacts with liq. Ammonia in presence of methylene chloride to give Erythromycin base. Methylene chloride is separated and distilled off. Residual Erythromycin base reacts with Hydroxyl Amine Hydrochloride and Triethyl Amine in presence of Methanol to give Erythromycin Oxime Hydrochloride. Methanol is distilled out and Erythromycin Oxime Hydrochloride reacts with Liq. Ammonia in presence of Isopropanol to give Erythromycin Oxime Base.

Erythromycin Oxime Base reacts with sodium Methoxide and Methoxy ethoxy methylene chloride in presence of acetone to give Roxythromycin Crude. Roxythromycin crude is purified in methanol to give Roxythromycin pure.

Chemical Reaction

![Chemical Reaction Diagram]

ERITHROMYCIN-OXIME BASE

ERITHROMYCIN-[O-[2-METHOXY ETHOXY] METHYL] OXIME (ROXYTHROMYCIN)
Material Balance

- Reactor - RE-009
  - Acetone (5.22 kg)
  - Oxime base (1.08 kg)
  - Sodium methoxide (0.09 kg)
  - MEM chloride (0.20 kg)
  - Water (6.96 kg)

- Centrifugation
  - Acetone (0.22 kg)
  - Water (1.96 kg)
  - Aqueous layer (12.64 kg)
  - Water wash (1.91 kg)

- Drying
  - Moisture loss (0.17 kg)

- Drying
  - Roxithromycin (1 KG)
4. VENLAFAXIN HYDROCHLORIDE

Manufacturing Process
Anisole reacts with Aluminium chloride and acetyl chloride in methylene chloride to give 4-methoxy acetophene and 4-methoxy acetophenone reacts with dimethyl formamide, sodium acetate and sulfur to give thioacetamide reacts with Cyclohexanone in presence in presence of grignard reagent to give N,N Dimethyl-2-(1-hydroxy cycloride hexahydrate, in methanol to give N,N Dimethyl-2-(1-hydroxy cyclohexyl)-2-(4-methoxyphenyl)ethyl amine which reacts with Borohydrde and nickel chloride hexahydrate, in methanol to give N,N Dimethyl-2-(1-hydroxy cyclohexyl)-2-(4-methoxyphenyl)ethylamine or (+/-) 1-(2-Dimethylamino)-1-(4-methoxyphenyl)ethyl) cyclohexanol, which further crystallized in hydrochloride formation in isopropanol HCL and ethyl acetate as solvent to give final product Venlafaxine hydrochloride.

Chemical Reaction
Material Balance

**Stage-1**

- **Process Water for Cleaning** (1.19 Kg)
- 4-Methoxy Benzoyl Cyanide (0.71 Kg)
- Methanol (2.57 Kg)
- Sodium Methoxide (0.67 Kg)
- Cyclohexanone (0.65 Kg)

**Reactor**

- (1.19 Kg) Process water

**Crystallization**

- (10.68 Kg) CF-ML

**Centrifugation**

- (14.29 Kg) CF-ML

**Reactor Purification**

- (2.65 Kg) Toluene

**Centrifugation**

- (3.54 Kg) Toluene CF-ML

**Drying**

- (0.07 Kg) Drying Loss

**Stage-1 product 1 KG**

**Stage-2**

- Acetic Acid (8.15 Kg)
- Stage-1 (1.36 Kg)
- Catalyst (0.05 Kg)

**Reactor**

- Process water (7.52 Kg)
- Caustic soda (4.77 Kg)
- Formic acid (1.94 Kg)
- Formaldehyde (1.12 Kg)
- Hydrochloric acid (2.51 Kg)
- Ethyl acetate (0.22 Kg)
- Sodium chloride (0.04 Kg)
- Sodium sulphate (0.02 Kg)
- Hyflo (0.02 Kg)

**Reactor Recovery Filtration Extraction**

- Catalyst (0.05 Kg)
- Acetic acid Recovery (7.73 Kg)
- Acetic acid Recovery loss (0.42 Kg)
- Aqueous layer (Water) (18.57 Kg)
- Sodium Sulphate (0.27 Kg)
- Hyflo (0.02 Kg)

**IP A (12.74 Kg)**

- IPA (1.09 Kg)
- Activated Charcoal (0.01 Kg)
- Hyflo (0.02 Kg)

**Ethyl Acetate Recovery (21.39 Kg)**

- Ethyl Acetate loss (1.14 Kg)
- Activated Charcoal (0.01 Kg)
- Hyflo (0.02 Kg)

**Recovery & Crystallization**

- CF-ML (IPL) (15.50 Kg)

**Centrifugation**

- IPA Drying loss (0.18 Kg)

**Drying**

- Vesafloxine Hydrochloride (1 KG)
5. FENOFIBRATE

Manufacturing Process

4-Chloro-4’hydroxy benzophenone is dissolved in acetone and then sodium hydroxide is added. The corresponding sodium phenoxide precipitates and reflux is affected followed by addition of mixture of acetone and chloroform. After reaction completion solvent is distilled from reaction mixture, water is added and acidified. The mother liquor removed from residue by filtration. The residue is dissolved in sodium bicarbonate solution and extracted from ethyl acetate. The aqueous phase is charcolised and filtered. The filtrate is acidified, filtered and dried to get crude fenofibric acid. The crude fenofibric acid is recrystalised in isopropanol and filtered followed by isopropanol washing to get pure fenofibric acid.

The fenofibric acid is esterified with isopropanol using sulfuric acid as catalyst. After product formation reaction mixture is concentrated by isopropanol distillation up 50 % volume. Reaction mixture filtered and washed with chilled isopropanol. The wet cake material is taken in methylene dichloride, washed with aqueous sodium bicarbonate solution followed by water wash. The organic layer is charcolised, filtered and methylene dichloride distilled to get residue. The residue recrystalised in isopropanol, filters and dried to get fenofibrate.

Chemical Reaction
Material Balance

Acetone (7.66kg)
4-CHBP (1kg)
Caustic soda (1.28kg)
Chloroform (1.26kg) → Reactor
Acetone recov. (7.11kg)
Acetone loss (0.55kg)

Process water (7.33kg)
H2SO4 (0.50kg) → Precipitation

Process water (2.40kg) → Centrifugation
Aqueous layer (10.89kg)

Process water (5.27kg)
Sodium bicarbonate (1.20kg)
Ethyl acetate (11.22kg) → Washing
Ethyl acetate layer (11.22kg)

Process water (1.07kg)
H2SO4 (0.96kg) → Precipitation
CO2 evaporation loss (0.19kg)

Process water (0.89kg) → Centrifugation
Aqueous layer (10.96kg)

Drying
Moisture loss in drying (0.18kg)

Isopropyl alcohol (3kg) → Purification

Centrifugation
CF ML (2.78kg)

Drying
Evaporation loss (0.22kg)

1 kg stage -1 product
6. IRBESARTAN

Manufacturing Process
Cyclopentanone is treated with sodium cyanide in the presence of ammonium chloride and ammonia solution to form 1-aminocyclopentanitrile which is hydrolyzed with hydrochloric acid to get 1-aminocyclopentanecarboxylic acid hydrochloride which on treatment with Valeryl chloride in the presence of pyridine forms 1-valeramido cyclopentanecarboxylic acid.

4'-bromomethyl-2-cyano biphenyl is reacted with phthalimide in the presence of potassium carbonate to form 4'-phthalimidomethyl -2- cyanobiphenyl which gives 4'-aminomethyl-2-cyanobiphenyl by treatment with hydrazine hydrate. Valeramido cyclopentanecarboxylic acid and 4'-aminomethyl-2-cyanobiphenyl are condensed and cyclized in the presence of methane sulfonic acid in refluxing toluene to give 2-(n-butyl)-3-(2'-cyanobiphenyl-4-ylmethyl)-4-oxo-1,3-diazaspiro[4.4] non-1ene which on treatment with tributyltin chloride and sodium azide in refluxing xylene to form Irbesartan which is isolated and purified in alcohol.

Chemical Reaction
Material Balance

Reactor

- Sodium Cyanide (1.34 kg)
- Ammonium Chloride (1.59 kg)
- Ammonia Solution (2.18 kg)
- Cyclopentanol (2.05 kg)
- Methanol (2.05 kg)
- MDC (22.04 kg)

10% Sodium Hypochlorite Solution (2.96 kg)
Water (0.66 kg)

32% Hydrochloric Acid (12.07 kg)
Water (0.92 kg)
Charcoal (0.04 kg)
Hyflo (0.05 kg)

Aq. ML (13 kg)

Stage-1

- Pyridine (8.00 kg)
- Valeryl Chloride (1.69 kg)
32% HCL (12.00 kg)
Water (0.60 kg)

Aq. ML (6.83 kg)

Stage-1

- Dimethyl Formamide
- 4-Bromoethyl Hydrazide
- 2-cyanoethyl (1.63 kg)
- Phthalimide (0.92 kg)
- Potassium Carbonate (1.24 kg)
- DM Water (2.55 kg)

Aq. ML (13.89 kg)
Carbon Dioxide (0.013 kg)

Stage-3

- 80% Hydrazine Hydrazide (0.44 kg)
- Methanol (9.02 kg)
- NaOH (1.05 kg)
- Toluen (16.37 kg)
- Water (0.37 kg)
- NaCL (1.9 kg)

Aq. ML (6.65 kg)
Toluene Recovery (13.09 kg)
Toluene Loss (8.28 kg)

Stage-4

- Toluene (18 kg)
- Methanol Sulfonic Acid (0.60 kg)
- NaOH (1.05 kg)
- Methyl T. Butyl ether (3.18 kg)
- Stage-11 (1.54 kg)
- NaCL (0.6 kg)
- Water (0.7 kg)
- Charcoal (0.05 kg)
- Hyflo (0.05 kg)

Aq. ML (21.36 kg)
Organic ML (5.78 kg)
Recovered Toluene (14.44 kg)
Toluene loss (3.56 kg)
Solid waste (0.1 kg)

Stage-5

- Oxyline (15.22 kg)
- Tributylamine (2.39 kg)
- Sodiomamide (0.72 kg)
- NWOL (0.7 kg)
- HCl (0.78 kg)
- Methyl T. Butyl ether (2.77 kg)
- 5% ethanol (11.13 kg)
- charcoal (0.05 kg)
- Hyflo (0.05 kg)
- NaCL (0.3 kg)
- Water (4.05 kg)

Aq. ML (5.32 kg)
Aq. ML (4.15 kg)
Oxyline recovery (12.13 kg)
Oxyline loss (4.04 kg)
Methyl T. Butyl loss (0.97 kg)
Methyl T. Butyl recovery (1.8 kg)
Ethanol loss (0.98 kg)
Solid waste (0.1 kg)
Residue (1.62 kg)

1 kg Methylene
7. VALSARTAN

Manufacturing Process
There are following steps involved in the synthesis of Valsartan.

Step - 1: Preparation of L- METHYL VALINATE
L- Valine is treated with methanol in presence of Thionyl chloride to get L- Valine methyl ester which was then neutralized with alkali solution to get L-methyl valinate.

Step - 2: Preparation of VALSARTAN OXALATE
L- Methyl valinate is condensed with 4- bromo methyl -2 - cyano biphenyl in presence of potassium carbonate which was then treated with oxalic acid to isolate the Valsartan oxalate.

Step - 3-A: Preparation of VALEROYL VALSARTAN
The Valsartan oxalate is condensed with Valeroyl chloride in presence of potassium, Carbonate in o- xylene to get Valeroyl Valsartan.

Step - 3-B and 3-C: Preparation of CRUDE VALSARTAN
The cyano group of Valeroyl Valsartan is cyclized in presence of tri butyl tin chloride and sodium azide in o-xylene at reflux to get methyl Valsartan. The methyl Valsartan is then hydrolyzed with sodium hydroxide and isolated with dichloromethane and cyclohexane to get crude Valsartan.

Step - 4: Preparation of VALSARTAN CALCIUM
The crude Valsartan is treated with calcium hydroxide in acetone and D I water and filtered to obtained calcium salt of Valsartan.

Step - 5: Preparation of VALSARTAN
Valsartan calcium salt is treated with hydrochloric acid in ethyl acetate and water. The ethyl acetate layer is treated with diisopropyl ether to obtain the pure Valsartan.
Chemical Reaction

**STEP 1**

\[
\text{H}_3\text{N}^+ - \text{COOH} \quad \xrightarrow{\text{SOCl}_2, \text{MeCN}} \quad \text{H}_2\text{N}^+ - \text{COOCH}_3
\]

- L-Valine
- L-Valine Valerate

**STEP 2**

\[
\text{CN} \quad \xrightarrow{\text{K}_2\text{CO}_3, \text{MeCN}} \quad \text{CN} \quad \xrightarrow{\text{K}_2\text{CO}_3, \text{O}_{\text{xylen}}, \text{D.M. Waler}} \quad \text{CN}
\]

- 4-Bromomethyl - 2-Cyano phenyl
- Valassar Oxalate

**STEP 3-A**

\[
\text{CN} \quad \xrightarrow{\text{K}_2\text{CO}_3, \text{O}_{\text{xylen}}, \text{D.M. Waler}} \quad \text{CN}
\]

- Valassar Oxalate

**STEP 3-B**

\[
\text{CN} \quad \xrightarrow{\text{Ti Buyl Ti. Chloride}} \quad \text{CN}
\]

- Valeroyl Valassar
- Methyl Valassar

**STEP 3-C**

\[
\text{CN} \quad \xrightarrow{\text{MDC, NAOH}} \quad \text{CN}
\]

- Methyl Valassar
- Crude Valassar

**STEP 4**

\[
\text{CN} \quad \xrightarrow{\text{D}(\text{O})\text{SO}} \quad \text{CN}
\]

- Crude Valansar
- Calcium Valassar

**STEP 5**

\[
\text{CN} \quad \xrightarrow{\text{HCl, Ethyl Alcohol, DFE}} \quad \text{CN}
\]

- Calcium Valassar
- Valansar
Material Balance

[Diagram showing material balance for different processes and reactions, including substances like L-Valine, Valencyl chloride, Methanol, and various gases and solutions.Each box represents a step in the process, with arrows indicating the flow of materials and products.]
8. TELMISARTAN

Manufacturing Process

2-n-Propyl-4-methyl -6-(1-methyl benzimidazole-2-yl) benzimidazole is treated with methyl-4’-(bromomethyl)-biphenyl-2-carboxylate in acetone in the presence of sodium hydroxide to form 4-[4’-methyl-6-(1-methyl-1H-benzimidazole-2-yl-2-propyl-1H-benzimidazole-1-ylmethyl] biphenyl-2-carboxylic acid methyl ester which is hydrolyzed with sodium hydroxide in aqueous methanol to give telmisartan which is purified in dichloromethane and methanol.

Chemical Reaction
Material Balance

Acetone (5.22kg) → Reactor → Acetone ML (5.77kg)
Sodium Hydroxide (0.17kg) → Reactor → Acetone ML (16.91kg)
RM-II (1.21kg) → Reactor → Acetone ML (30.67kg)
Water (18.50kg) → Reactor → Methanol (15.67kg)

Acetone (30.43kg) → Filtration → Acetone ML (30.67kg)
Charcoal (0.02kg) → Filtration → solid waste (0.07kg)
Hyflo (0.05kg) → Filtration

Methanol (9.40kg) → Reactor → recovered methanol (10.05kg)
Sodium Hydroxide (0.25kg) → Reactor → ML (9.21kg)
Hydrochloric acid (0.72kg) → Reactor → unrecovered product (0.19kg)
Water (5.28kg) → Reactor → solid waste (0.062kg)

Filtration

Methanol (10.35) → Filtration → ML (9.21kg)
MDC (10.02kg) → Filtration → unrecovered product (0.19kg)
Charcoal (0.012kg) → Filtration → solid waste (0.062kg)
Hyflo (0.02kg) → Filtration

Drying

1 kg Telmisartan
9. CLONIDINE HYDROCHLORIDE

Manufacturing Process

2,6 Dichloro aniline reacts with Acetic anhydride and formic acid to give N-(2,6-dichlorophenyl) formamide, which on reaction with Sulfuryl chloride and Thionyl Chloride gives (2,6-dichlorophenyl) carbonimidic dichloride, which on insitu reaction with Ethylene Diamine followed by treatment with IPA HCL gives crude Clonidine Hydrochloride. Clonidine Hydrochloride crude on purification with methanol and Isopropanol gives Clonidine hydrochloride API.

Chemical Reaction
Material Balance

Stage I
- 2,6-Dichloroaniline (1.0 Kg)
  - Acetic Acid (1.75L)
  - Formic Acid (0.52L)
- DMF Water (6.0 L)
- DMF Water (8.0 L)
  - Quenching
  - Filtration
  - Asparagus ML (15.7L)
  - Drying
  - Moisture Loss (0.57L)
- Stage II
  - Thiouyl Chloride (2.36L)
  - Clorodane Stage-I (1.108 Kg)
  - Dimethyl Formamide (0.001 L)
  - Stilbaryl Chloride (0.60L)
- DMF Water (11.8 L)
  - Dichloromethane (0.44L)
  - Reaction
  - Quenching and layer separation
  - HCL+SO2 Scrubber
  - Asparagus Effluent (14.86L)
- Sodium Chloride solution (3.5L)
- Organic layer (0.44L)
- Polyethylene Oxide (0.5L)
- Dichloromethane (1.1L)
  - Reaction
  - Filtration
  - Salt Watr cake (0.63Kg)
  - Organic Filtrate (10.8L)
- Organic Filtrate (10.82L)
- DMF Water (2.26L)
  - IPA HCL (0.94L)
- Dichloromethane (2.16L)
  - Work up
  - Asparagus effluent (2.34L)
  - ML (12.4L)
  - Drying
  - Solvent loss (0.50L)

Stage III
- Methanol (8.8L)
  - Chloroform HCL Crude (1.25Kg)
  - Activated Charcoal (0.13 Kg)
- Methanol (1.23L)
- Hyflo (0.59 Kg)
  - Charcoalization
  - Filtration
  - Hyflo Charcoal = 0.68kg
  - Methanol spent (0.1 L)
  - Residue (0.22L)
  - Methanol Vent loss (0.8L)
- Isopropanol (2.5L)
  - Distillation
  - IPA + Methanol (2.5L)
  - Residue (0.23L)
- Isopropanol (2.5L)
- Isopropanol (2.5L)
  - Crystallization
  - IPA ML (3.5L)
  - Drying
  - IPA vent loss (0.25L)
- Clothar HCL API 1.0 Kg
10. MODAFINIL

Manufacturing Process

Thio Urea and Benzhydrol are reacted in presence of Hydrobromic acid. Then the mass is treated with Ammonia gas and Sulfuric acid. Finally the treatment is done with Acetic Acid and Hydrogen Peroxide to give Modafinil.

Chemical Reaction

SYNTHETIC PATHWAY:

\[
\begin{align*}
\text{BENZHYDROL} & \xrightarrow{\text{Thiourea}} \text{DIPHENYL METHYL THIOACETIC ACID (Stage-I)} \\
& \xrightarrow{\text{Ammonia}} \text{DIPHENYL METHYL THIOACETAMIDE (Stage-II)} \\
& \xrightarrow{\text{Glacial acetic acid, Hydrogen peroxide}} \text{MODAFINIL}
\end{align*}
\]
Material Balance

Stage-1
- 4215 kg Process water
- 40 kg Thio Urea
- 80 kg Benzyl Alcohol
- 340 kg Hydrobromic acid
- 70 kg Caustic Soda
- 47 kg Chloro acetic acid
- 200 kg HCL
- 1064 kg Ethyl Acetate
- 16 kg Sodium Sulphate
- 205.2 kg Hexane
- 78 kg Sodium Bicarbonate

Stage-2
- 99 kg stage-1
- 353.2 kg Methanol
- 30 kg Sulfuric Acid
- 150 kg Ammonia gas
- 2400 kg Process water

Stage-3
- 99 kg Step-II
- 240 kg Acetic Acid
- 17.1 kg Hydrogen
- 1250 kg Process water

Stage-4
- 99 kg Step-III
- 68.7 kg Methanol
- 383.1 kg DM Water

MODAFINIL
110 kgs

Stage-IV 100 kgs

- 1345 kg Aq. layer
- 730 kg Aq.
- 390.8 kg Ethyl acetate rec
- 20.6 kg Ethyl acetate loss
- 16 kg Sodium Sulphate
- 205.2 kg Hexane ML
- 2798 kg Aq. layer
- 87 kg water drying loss
- 673 Ethyl acetate layer

- 2900 kg Aq. effluent
- 33.2 kg water drying loss

- 1502.1 kg Aq. effluent
- 15 kg water drying loss

- 440 kg CF ML
- 9.9 kg Methanol drying loss
11. LEFLUNOMIDE

Manufacturing Process
Triethyl Orthoformate & Acetic anhydride are reacted with Ethyl acetate. Then the mass is reacted with Hydroxyl amine hydrochloride. Next it is reacted with Glacial Acetic acid, followed by chlorination with Thionyl Chloride. Finally, the product is purified in acetone & given carbon treatment.

Chemical Reaction

![Chemical Reaction Diagram]

STAGE I: CONVERSION OF ETHYL ACETOACETATE TO STAGE I

2-ETHOXYMETHYLENE-3-OXO-BUTANONIC ACID ETHYL ESTER
STAGE II: CONVERSION OF STAGE I TO STAGE II

2-ETHOXYMETHYLENE-3-OXO-BUTANONIC ACID ETHYL ESTER

\[ \text{HYDROXYL AMINE HCl} \quad \text{HYDROCHLORIC ACID} \]
\[ \text{METHANOL} \quad \text{SODIUM CHLORIDE} \]
\[ \text{CAUSTIC FLAKES} \quad \text{METHYLENE CHLORIDE} \]
\[ \text{DM WATER} \]

\[ \text{NH}_2\text{OH} \]

STAGE II

ETHYL 5-METHYLSOXAZOLE-4-CARBOXYLATE

\[ \text{HYDROLYSIS} \]

GLACIAL ACETIC ACID
CONC. HYDROCHLORIC ACID
ISOPROPYL ALCOHOL

STAGE III

5-METHYLSOXAZOLE-4-CARBOXYLIC ACID
STAGE IV: CONVERSION OF STAGE III TO STAGE IV

\[
\begin{align*}
 &\text{5-METHYLISOXAZOLE - 4-CARBOXYLIC ACID} \\
\end{align*}
\]

\[
\begin{align*}
 &\text{THIONYL CHLORIDE} \\
 &\text{4-(TRIFLUOROMETHYL) ANILINE} \\
 &\text{CHLOROFORM} \\
 &\text{TOULUENE} \\
 &\text{TRIETHYL AMINE} \\
 &\text{METHYLENE CHLORIDE} \\
 &\text{DI WATER} \\
\end{align*}
\]

\[
\begin{align*}
 &\text{STAGE - IV} \\
 &\text{1-ETHYLXONIDE (CRUDE)} \\
\end{align*}
\]
Material Balance

Stage-1
- 150 kg Ethyl acetic acid
- 266.5 kg Triethyl ortho Formate
- 334.6 kg Acetic Anhydride
- 350 kg Acetic acid rec
- 22 kg loss
- 230.1 kg Spent fraction
- 179 kg Stage-1 product

Stage-2
- 179 kg Stage-1
- 631 kg Process water
- 73.6 kg HCL
- 42.2 kg caustic soda
- 140.52 kg Methanol
- 6 kg HCl
- 72.2 kg NaCl
- 695.6 kg MDC
- 753.37 kg Aq. layer
- 130 kg Methanol rec
- 16.52 kg Methanol rec loss
- 660.85 kg MDC rec
- 34.78 kg MDC rec loss
- 132.3 KG Spent fraction
- 118 kg stage-2 product

Stage-3
- 118 kg Stage-2
- 95.6 kg Glacial Acetic acid
- 95.6 kg HCL
- 23.7 kg IPA
- 257.2 kg Aq. effluent
- 21 kg IPA CF ML
- 2.7 kg IPA CF ML
- 52 kg stage3 product

Stage-4
- 52 kg Stage-3
- 96.8 kg Thiocetyl Chloride
- 384.8 kg Chloroform
- 689 kg MDC
- 45 kg TFA
- 136 kg Process water
- 317.66 kg Toluene
- 68.2 kg Acetone
- 3 kg Carbon
- 2 kg Hyflo
- 3.8 kg Thionyl Chloride rec
- 346.32 kg Chloroform rec
- 38.48 kg loss
- 620.1 kg MDC rec
- 69.6 kg MDC rec loss
- 236 kg water
- 166.83 kg toluene loss
- 8.76 kg Toluene loss
- 3 kg Carbon
- 2 kg Hyflo
- 56.88 kg Acetone rec
- 6.32 kg Acetone rec
- 94.64 kg CF ML
- Drying loss
- 8.16 kg toluene drying loss
- 75 kg Stage-4 product

Stage-5
- 75 kg Stage-4
- 262.98 kg Acetone
- 3.8 kg carbon
- 3.8 kg carbon
- 2 kg Hyflo
- 10.41 kg Acetone loss
- Sold waste (10.5 kg)
- 79.44 kg toluene ML
- 232.36 kg Acetone rec
- 3.38 kg Toluene drying loss

LEFLUNOMIDE
65 KGs
12. ALENDRONATE SODIUM
Manufacturing Process
Alendronate sodium is a single step process. This process involves addition of 4 amino butyric Acid Phosphorus Acid, Phosphorous Trichloride in reactor and heating it up to 65 °C and maintaining it for 7 Hours. The completion of the reaction is monitored by HPLC and on completion the reaction is terminated by addition of Toluene and DMW to extract the product in the aqueous layer. After separating and washing the aqueous layer it is given charcoal treatment and filtered and charged back in reactor. The reaction mass is then heated to distill out the excess DMW and then refluxed for 15 hours. After reflux the mass is cooled and the pH of the reaction mass is then adjusted using caustic solution and again treated with charcoal filtered and charged in the reactor and cooled to 25°C and maintained for 4 hours and centrifuged. The solids so obtained are Alendronate Sodium which is dried in a vacuum dryer.

Chemical Reaction

![Chemical Reaction Diagram](image-url)
### Material Balance

<table>
<thead>
<tr>
<th>Total input kg.</th>
<th>Starting Material</th>
<th>Product output Kg.</th>
<th>Quantity Kg.</th>
<th>Output details</th>
</tr>
</thead>
<tbody>
<tr>
<td>100.00</td>
<td>Diphenyl Oxide</td>
<td>38.00</td>
<td>200.00</td>
<td>Solvent</td>
</tr>
<tr>
<td>20.00</td>
<td>4-Amino butyric acid</td>
<td></td>
<td>151.80</td>
<td>Toluene &amp; Diphenyl Oxide</td>
</tr>
<tr>
<td>48.00</td>
<td>Phosphorous acid</td>
<td></td>
<td>640.00</td>
<td>Aq. Effluent</td>
</tr>
<tr>
<td>79.80</td>
<td>Phosphorous Trichloride</td>
<td></td>
<td></td>
<td>Unreacted product &amp; Salt</td>
</tr>
<tr>
<td>60.00</td>
<td>Toluene</td>
<td></td>
<td></td>
<td>Water</td>
</tr>
<tr>
<td>120.00</td>
<td>DM Water</td>
<td></td>
<td></td>
<td>Solid Waste</td>
</tr>
<tr>
<td>3.00</td>
<td>Activated charcoal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40.00</td>
<td>DM Water</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40.00</td>
<td>Toluene</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40.00</td>
<td>DM Water</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>80.00</td>
<td>DM Water</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>80.00</td>
<td>Caustic soda</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>120.00</td>
<td>DM Water</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.00</td>
<td>Hyflo</td>
<td></td>
<td>4.00</td>
<td>Carbon</td>
</tr>
<tr>
<td>40.00</td>
<td>DM Water</td>
<td></td>
<td>6.00</td>
<td>Hyflo</td>
</tr>
<tr>
<td>2.00</td>
<td>Hyflo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100.00</td>
<td>DM Water</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100.00</td>
<td>Methanol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>1076.80</strong></td>
<td><strong>1076.80</strong></td>
<td><strong>Total</strong></td>
</tr>
</tbody>
</table>
13. O-DESMETHYLE VENLAFAXINE

Manufacturing Process

Sodium Hydride, Ethane Thiol are reacted in presence Dimethyl Formamide. The product is finally purified in methanol.

Chemical Reaction

![Chemical Reaction Diagram]

Material Balance

![Material Balance Diagram]
14. MEPROBAMATE

Manufacturing Process
Meprobamate is a single stage process. It involves charging of Liquor ammonia in reactor which is then cooled and to be charged 2-methyl-2-propyl-1, 3-propanediol dichlorocarbamate in a period of 120 mins then it is stirred for 30 mins and chilled to 5 °C and maintained for 1 hour. The reaction mass is then filtered in a centrifuge and washed with DMW and unloaded. The wet cake thus obtained is charged in Methanol in reactor heated to 65°C and treated with Charcoal and filtered to reactor. The reaction mass is then chilled up to 10°C and maintained for 60 mins. After maintaining the reaction mass is filtered and wet cake is washed with DMW and unloaded. Methanol purification done another 3-times.after the wet cake dry the material.

Chemical Reaction

![Chemical Reaction Diagram]

Material Balance

<table>
<thead>
<tr>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>3324.42</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Starting Material</th>
<th>Product output</th>
<th>Quantity</th>
<th>Output details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ammonia solution</td>
<td>72.00 Kg</td>
<td>3211.50</td>
<td>Aq. Effluent Water (CF ML)</td>
</tr>
<tr>
<td>2-Methyl-2-Propyl-1,3-Propanediol dichlorocarbamate</td>
<td></td>
<td>0.92</td>
<td>Carbon</td>
</tr>
<tr>
<td>3-Propanediol</td>
<td></td>
<td>2.00</td>
<td>Hyflo</td>
</tr>
<tr>
<td>Process water</td>
<td></td>
<td>38.00</td>
<td>Water in drying loss</td>
</tr>
<tr>
<td>Methanol</td>
<td></td>
<td>72.00</td>
<td>Meprobamate</td>
</tr>
<tr>
<td>DM Water</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Activated Charcoal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyflo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM Water</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methanol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM Water</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>3324.42</td>
<td>Total</td>
<td></td>
</tr>
</tbody>
</table>
15. VILDAGLIPTIN

Manufacturing Process

Stage-I

Reaction of (2S)-1-(chloroacetyl)-2-cyanopyrrolidine (KSM-II) with 3-Amino-1-hydroxy adamantane (KSM-I) in presence of Potassium Carbonate and Dimethyl Formamide (DMF) as a solvent gives Vildagliptin crude.

Stage-II

Vildagliptin crude is purified by treatment of Aq. Potassium Hydrogen Sulphate and Aq. Potassium Carbonate in presence of Dichloromethane, followed by Acetone crystallization to give Vildagliptin API.

Chemical Reaction

Route of Synthesis:

Vildagliptin Stage-I: Preparation of Vildagliptin Crude

Vildagliptin Stage-II: Preparation of Vildagliptin API
Material Balance

Stage I
- DMF (4.32L)
- KSM-II (0.72 Kg)
- KSM-I (0.77 Kg)
- Potassium carbonate (0.72 Kg)

  Reaction

  DMF (1.08L)

  Isopropyl Acetate (0.36L)

  Isopropyl Acetate (4.32L)

  Isopropyl Acetate (0.36L)

  K₂CO₃ Cake (1.2 Kg)

  DMF (4.88L)

  Isopropyl Acetate + DMF (1L)

  Vent Loss (0.1L)

  Crystallization

  Centrifugation

  Drying

  Vent Loss (0.37L)

Vildagliptin Stage-I (1.0 Kg)

Stage II
- Dichloromethane (7.5L)
- Vildagliptin Stage-I (1.23 Kg)
- Process Water (5 L)
- Potassium Hydrogen sulfate solution (3.75L)

  Layer separation

  Organic Layer- for recovery (7.5L)

  Aqueous Layer

  Potassium Carbonate solution (1.36L)
  Sodium Chloride (0.63 Kg)
  Dichloromethane (6.22L)

  Layer Separation

  Organic (MDC)Layer-I (6.25L)

  Aqueous Layer

  Dichloromethane (6.22L)
  Potassium Carbonate solution (0.5L)

  Layer Separation

  Organic (MDC)Layer-II (6.25L)

  Organic Layer I-II (12.5L)
  Charcoal (0.05Kg)

  Charcoalization

  Hyflon Charcoal (1.6Kg)

  Dichloromethane (1.25L)

  Distillation and crystallization

  Dichloromethane (13.44L)
  Acetone (10L)

  Acetone (12.5L)

  Centrifugation

  ML (2.6L)

  Drying

  Vent loss (0.6L)

Vildagliptin API (1.0 Kg)
16. RIVASTIGMINE TARTRATE

Manufacturing Process

Stage-I (Rivastigmine Tartrate Crude)
Carbamoylation of (S)-3-(1-dimethyl amino ethyl) phenol carried out with N-ethyl-N-methyl Carbamoyl chloride in Toluene using Triethylamine as base and 4-dimethyl amino pyridine as catalyst at 60-65°C. After completion of reaction cool reaction mass to 25-35°C, filter the reaction mass, wash the solid salt with Toluene. Charge water in to the filtrate, stir and separate layers. Wash the organic layer with Sodium bicarbonate solution, Hydrochloric acid solution and then water and than charcoalized with activated charcoal. Distill out toluene from filtrate to obtain Rivastigmine Base. Charge Denature spirit and L (+) tartaric acid in Rivastigmine Base, and heat to 55-60°C to get clear solution and than charge Ethyl acetate, Cool to 40°C and seed the reaction mass with Rivastigmine Tartrate, cool to 0-5°C and stir for 4-5 hours, filter, Wash with Ethyl acetate and dry the crude Rivastigmine Tartrate at 40-50°C in vacuum oven.

Stage-II (Rivastigmine Tartrate)
Dissolve Rivastigmine Tartrate in Ethyl Alcohol, heat to 55-60°C to get clear solution, charcoialized and distill out Ethyl Alcohol. Charge Ethyl Alcohol, heat to 55-60°C and than charge Ethyl acetate, Cool to 40°C and seed the reaction mass with Rivastigmine Tartrate, cool to 0-5°C and stir for 4-5 hours, filter, Wash with Ethyl acetate and dry the Rivastigmine Tartrate at 40-50°C in vacuum oven till constant weight.

Chemical Reaction
17. TOPIRAMATE

Manufacturing Process
D-Fructose is reacted with Sulphuric Acid in presence of Acetone. The isolation / purification are done in Cyclohexane / IPA. Then the mass is reacted with Sulfuryl Chloride in presence of MDC and then with Pyridine in presence of Citric Acid. Next the mass is reacted with ammonia gas in MDC and acetic Acid. Final purification of the product is done in methanol.

Chemical Reaction
Material Balance

Stage - 1

<table>
<thead>
<tr>
<th>Raw Material</th>
<th>In Put Quantity Kgs</th>
<th>Product Out Put</th>
<th>Quantity Kgs</th>
<th>Out Put Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDC</td>
<td>1525.0</td>
<td>92.5</td>
<td>3105.2</td>
<td>Aqueous spent</td>
</tr>
<tr>
<td>Fructopyranose</td>
<td>100.0</td>
<td></td>
<td>1507.8</td>
<td>Spent MDC</td>
</tr>
<tr>
<td>Pyridine</td>
<td>36.5</td>
<td></td>
<td>801.6</td>
<td>Distilled THF</td>
</tr>
<tr>
<td>Sulfuryl chloride</td>
<td>54.5</td>
<td></td>
<td>69.8</td>
<td>Loss during drying</td>
</tr>
<tr>
<td>Process water</td>
<td>2900.0</td>
<td></td>
<td>92.5</td>
<td>Output</td>
</tr>
<tr>
<td>Citric acid</td>
<td>40.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>20.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>80.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>THF</td>
<td>755.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ammonia gas</td>
<td>25.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium Hydroxide</td>
<td>14.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetic acid</td>
<td>26.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>5576.9</strong></td>
<td></td>
<td><strong>5576.9</strong></td>
<td></td>
</tr>
</tbody>
</table>

Stage – 2

<table>
<thead>
<tr>
<th>Raw Material</th>
<th>In Put Quantity Kgs</th>
<th>Product Out Put</th>
<th>Quantity Kgs</th>
<th>Out Put Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methanol</td>
<td>411.3</td>
<td>69.6</td>
<td>92.5</td>
<td>Spent carbon+ Hyflo</td>
</tr>
<tr>
<td>Topiramate (Stage-I)</td>
<td>80.0</td>
<td></td>
<td>1371.3</td>
<td>Spent Methanol</td>
</tr>
<tr>
<td>Activated carbon</td>
<td>1.6</td>
<td></td>
<td>10.4</td>
<td>Loss during drying</td>
</tr>
<tr>
<td>Hyflo</td>
<td>2.0</td>
<td></td>
<td>69.6</td>
<td>Output</td>
</tr>
<tr>
<td>DM water</td>
<td>960.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1454.9</strong></td>
<td></td>
<td><strong>1454.9</strong></td>
<td></td>
</tr>
</tbody>
</table>
18. LACOSAMIDE

Manufacturing Process
Stage-I: Preparation of (2R)-2-[(tert-butoxycarbonyl)amino]-3-hydroxypropanoic acid from (2R)-2-amino-3-hydroxypropanoic acid (D-Serine)
(2R)-2-amino-3-hydroxypropanoic acid (D-Serine) is react with di-tertiary-butyl-di-carbonate in presence of base using process water as a solvent gives (2R)-2-[(tert-butoxycarbonyl)amino]-3-hydroxypropanoic acid.

Stage-II: Preparation of tert-butyl[(2R)-1-(benzylamino)-3-hydroxy-1-oxopropan-2-yl]carbamate from (2R)-2-[(tert-butoxycarbonyl)amino]-3-hydroxypropanoic acid (Stage-I)
(2R)-2-[(tert-butoxycarbonyl)amino]-3-hydroxypropanoic acid (Stage-I) is react with methyl chloroformate in presence of N-methyl morpholine followed by reaction with benzyl amine using MDC as solvent to give tert-butyl[(2R)-1-(benzylamino)-3-hydroxy-1-oxopropan-2-yl]carbamate.

Stage-III: Preparation of tert-butyl[(2R)-1-(benzylamino)-3-methoxy-1-oxopropan-2-yl]carbamate from tert-butyl[(2R)-1-(benzylamino)-3-hydroxy-1-oxopropan-2-yl]carbamate (Stage-II)
tert-butyl[(2R)-1-(benzylamino)-3-hydroxy-1-oxopropan-2-yl]carbamate (Stage-II) is react with dimethyl sulfate in presence of tetrabutyl ammonium bromide and sodium hydroxide as a base in Toluene solvent and process water as a solvent to give tert-butyl[(2R)-1-(benzylamino)-3-methoxy-1-oxopropan-2-yl]carbamate.

Stage-III: Preparation of (2R)-2-(acetylamino)-N-benzyl-3-methoxypropanamide from tert-butyl[(2R)-1-(benzylamino)-3-methoxy-1-oxopropan-2-yl]carbamate (Stage-III)
tert-butyl[(2R)-1-(benzylamino)-3-methoxy-1-oxopropan-2-yl]carbamate (Stage-III) is react with concentrated Hydrochloric acid in MDC as a solvent to give (2R)-2-amino-N-benzyl-3-methoxypropanamide which is further reacts with acetic anhydride then isolation with isopropyl alcohol and n-Heptane to yield (2R)-2-(acetylamino)-N-benzyl-3-methoxypropanamide.
Chemical Reaction

Manufacturing of tert-Butyl [(2R)-1-(benzylamino)-3-methoxy-1-oxopropan-2-yl] carbamate:

\[
\text{M.W.: } C_9H_{15}N_2O_3 \\
\text{CAS No.: 88546889-3}
\]

Manufacturing of Lacosamide:

\[
\text{M.F.: } C_{10}H_{18}N_2O_3 \\
\text{M.W.: 250.30} \\
\text{CAS No.: 17564836-8}
\]
### Material Balance

#### Stage - 1

<table>
<thead>
<tr>
<th>RAW MATERIAL</th>
<th>INPUT QUANTITY</th>
<th>OUTPUT QUANTITY</th>
<th>OUTPUT DETAILS</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM Water</td>
<td>2475.00</td>
<td>200.00</td>
<td>Liberation of CO2 gas</td>
</tr>
<tr>
<td>Sodium Hydroxide</td>
<td>169.60</td>
<td>225.00</td>
<td>Salt</td>
</tr>
<tr>
<td>D-Serine</td>
<td>165.00</td>
<td>3232.00</td>
<td>Aqueous layer</td>
</tr>
<tr>
<td>Di-tert. Butyl dicarbonate</td>
<td>548.22</td>
<td>1266.50</td>
<td>Distilled Ethyl Acetate</td>
</tr>
<tr>
<td>Ethyl Acetate</td>
<td>1336.50</td>
<td>70.00</td>
<td>Evaporation loss</td>
</tr>
<tr>
<td>Potassium Hydrogen Sulphate</td>
<td>660.00</td>
<td>142.73</td>
<td>Distilled Toluene</td>
</tr>
<tr>
<td>Toluene</td>
<td>1427.25</td>
<td>1350.00</td>
<td>Toluene ML</td>
</tr>
<tr>
<td>Stage-I seeding</td>
<td>1.65</td>
<td>50.00</td>
<td>Toluene condensate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>247.00</td>
<td>Dry output</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>6783.22</strong></td>
<td><strong>6783.22</strong></td>
<td></td>
</tr>
</tbody>
</table>

#### Stage - 2

<table>
<thead>
<tr>
<th>RAW MATERIAL</th>
<th>INPUT QUANTITY</th>
<th>OUTPUT QUANTITY</th>
<th>OUTPUT DETAILS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzylamine</td>
<td>130.0</td>
<td>1007.50</td>
<td>Aqueous layer</td>
</tr>
<tr>
<td>MDC</td>
<td>2650.0</td>
<td>850.00</td>
<td>Aqueous layer</td>
</tr>
<tr>
<td>Stage-1</td>
<td>250.0</td>
<td>3250.00</td>
<td>Aqueous layer</td>
</tr>
<tr>
<td>N-Methyl Morpholine</td>
<td>135.0</td>
<td>2520.00</td>
<td>Distilled MDC</td>
</tr>
<tr>
<td>Methylchloroformate</td>
<td>127.5</td>
<td>145.00</td>
<td>Evaporation loss</td>
</tr>
<tr>
<td>DM Water</td>
<td>4750.0</td>
<td>210.00</td>
<td>Distilled Ethyl Acetate</td>
</tr>
<tr>
<td>Potassium Hydrogen sulphide</td>
<td>75.0</td>
<td>1618.00</td>
<td>Cyclohexane ML</td>
</tr>
<tr>
<td>Ethyl Acetate</td>
<td>225.0</td>
<td>50.00</td>
<td>Cyclohexane condensate</td>
</tr>
<tr>
<td>Cyclohexane</td>
<td>1558.0</td>
<td>250.00</td>
<td>Dry output</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>9900.50</strong></td>
<td><strong>9900.50</strong></td>
<td></td>
</tr>
</tbody>
</table>

#### Stage - 3

<table>
<thead>
<tr>
<th>RAW MATERIAL</th>
<th>INPUT QUANTITY</th>
<th>OUTPUT QUANTITY</th>
<th>OUTPUT DETAILS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toluene</td>
<td>870.00</td>
<td>1300.35</td>
<td>Aqueous layer</td>
</tr>
<tr>
<td>Stage-2</td>
<td>150.00</td>
<td>820.41</td>
<td>Distill Toluene</td>
</tr>
<tr>
<td>Cyclohexane</td>
<td>600.00</td>
<td>116.69</td>
<td>Evaporation loss</td>
</tr>
<tr>
<td>Sodium hydroxide solution</td>
<td>355.95</td>
<td>144.90</td>
<td>Distill Cyclohexane</td>
</tr>
<tr>
<td>Sodium bicarbonate solution</td>
<td>787.50</td>
<td>405.00</td>
<td>Cyclohexane ML</td>
</tr>
<tr>
<td>Tetra butyl ammonium</td>
<td>27.90</td>
<td>133.00</td>
<td>Dry output</td>
</tr>
<tr>
<td>Di methyl sulfate</td>
<td>129.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>2920.35</strong></td>
<td><strong>2920.35</strong></td>
<td></td>
</tr>
</tbody>
</table>
## Stage - 4

<table>
<thead>
<tr>
<th>RAW MATERIAL</th>
<th>INPUT QUANTITY-KG</th>
<th>OUTPUT QUANTITY</th>
<th>OUTPUT DETAILS</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDC</td>
<td>2819.60</td>
<td>891.13</td>
<td>Organic Layer</td>
</tr>
<tr>
<td>Stage-3</td>
<td>133.00</td>
<td>2550.25</td>
<td>Aqueous Layer</td>
</tr>
<tr>
<td>Hydrochloric Acid</td>
<td>226.10</td>
<td>13.65</td>
<td>Spent activated charcoal</td>
</tr>
<tr>
<td>DM water</td>
<td>2128.00</td>
<td>1788.48</td>
<td>Distilled MDC</td>
</tr>
<tr>
<td>Sodium Hydroxide</td>
<td>79.80</td>
<td>225.00</td>
<td>Evaporation Loss</td>
</tr>
<tr>
<td>Sodium Chloride</td>
<td>59.85</td>
<td>288.22</td>
<td>Distilled IPA</td>
</tr>
<tr>
<td>Acetic Anhydride</td>
<td>53.20</td>
<td>1005.47</td>
<td>N-Heptane ML</td>
</tr>
<tr>
<td>Sodium Bicarbonate</td>
<td>13.30</td>
<td>82.00</td>
<td>Dry output</td>
</tr>
<tr>
<td>Activated Charcoal</td>
<td>6.65</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPA</td>
<td>313.22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N-Heptane</td>
<td>1009.47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyflow</td>
<td>2.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>6844.19</strong></td>
<td><strong>6844.19</strong></td>
<td></td>
</tr>
</tbody>
</table>
19. PRAMIPEXOLE DIHYDROCHLORIDE MONOHYDRATE

Manufacturing Process

Stage-I

6(S)-4, 5, 6, 7-tetrahydro-1, 3-benzothiazole-2, 6-dimine react with Propionaldehyde and sodium Borohydride in presence of methanol. Then Methanol distilled out completely and product is extracted in Ethyl Acetate. Ethyl Acetate is completely distilled out and then crude Pramipexole Dihydrochloride Monohydrate stage-I purified with Acetonitrile.

Stage-II

Pramipexole Stage-I is dissolved in ethanol and charcoalized with Activated Charcoal. Reaction mass then filtered through hyflo bed. pH of the reaction mass adjusted with Ethanolic HCL and maintained for crystallization. Reaction mass is then filtered to get wet cake and this wet cake is dried to get Pramipexole Dihydrochloride Monohydrate Stage-II.

Stage-III

Pramipexole Dihydrochloride Monohydrate Stage-II is purified in ethanol to get Pramipexole Dihydrochloride Monohydrate API.

Chemical Reaction
Material Balance

Stage I
- Methanol (45L)
- Propionaldehyde (2.04L)
- Sodium Bicarbonate (0.54 kg)
- Sulphuric Acid (0.013Kg)
- Sodium Chloride (0.90 kg)
- DM Water (4.5L)

Reaction

Distillation
- Methanol → Water ~45L
- Methanol vent loss (3L)

Work-up
- Aqueous Effluent (8.3L)
- Org Layer (50L)

Distillation
- Ethyl Acetate (30L)
- Ethyl Acetate loss (2.75L)

Distillation
- Acetonitrile open - 1.75L
- Acetonitrile vent loss - 0.1L

Purification and filtration
- ML for Recovery - 7.5L

Drying
- Solvent loss - 0.75L

Stage II
- Ethanol (7.2L)
- Pramipexole Stage I (0.60Kg)
- Activated Charcoal (0.02 kg)
- Hyfil (1.50 Kg)

Charcoalisation

Filtration
- Hyfil + Charcoal = 1.55 Kg

Crystallisation

Filtration
- Ethanol ML (9L)

Drying
- Vent loss (0.20L)

Stage III
- Ethanol (4.8L)
- Pramipexole Stage II (1.20 Kg)

Purification

Filtration
- Ethanol ML (4.8L)

Drying
- Vent loss (0.40L)

Pramipexole API - 1.0Kg
20. OLMESARTAN MEDOXOMIL

Manufacturing Process
Trityl Olmesartan Medoxomil dissolved in Dichloromethane and Methanol and reacted with Methanolic HCL. Washed the organic layer with Sodium Bicarbonate solution and DM Water. Dichloromethane distilled out completely and crystallized in Ethyl Acetate gives Olmesartan Medoxomil Stage-III.

Charcoal treatment given to Olmesartan Medoxomil Stage-III after dissolving in Acetone. Reaction mass filtered through hyflo bed and washed with Acetone. Then Acetone is distilled out partially and remaining reaction mass filtered. Wet cake washed with Acetone and the wet cake dried to get Olmesartan Medoxomil API.

Chemical Reaction
Purification of Olmesartan Medoxomil Crude:

\[ \text{Olmesartan Medoxomil Crude} \]
Molecular Formula: \( C_{23}H_{26}N_4O_5 \)
Molecular Weight: 518.59
CAS NO: 144689-63-4

\[ \text{Olmesartan Medoxomil} \]
Molecular Formula: \( C_{23}H_{26}N_4O_5 \)
Molecular Weight: 518.59
CAS NO: 144689-63-4

CAS – Chemical Abstracts Service

Olmesartan Medoxomil - (5-Methyl-2-oxo-1,3-dioxolen-4-yl) methyl -4- (1-hydroxy-1- methyl ethyl)-2-propyl-1-[4-(2-[tetrazol-5-yl]phenyl]phenyl] methyl imidazole-5-carboxylate.
Material Balance

Stage III
- Dichloromethane (17.3 L)
- Methanol (8.66 L)
- Triethyl Olemsaran Medoxomil (1.73 Kg)
- HCL (0.37 L)
- DMWater (16.44 L)
- Sodium Bicarbonate (0.865 Kg)

DMWater (15.57 L) → Layer Separation → Aqu. Effluent (4.9 L)

Ethyl Acetate (3.46 L) → Distillation
- Dichloromethane Spent (13 L)
- MDC Vent Loss (4 L)
- Ethyl Acetate spent (2.8 L)
- Ethyl Acetate Vent loss (0.5 L)

Ethyl Acetate (8.65 L) → Crystallization

Ethyl Acetate (1.73 L) → Centrifugation → ML (10 L) → Drying → Solvent loss (0.36 L)

Olesansar Medoxomil Stage-III (1.0 Kg)

Stage IV
- Acetone (15.68 L)
- Olesansar Medoxomil Stage-III (1.12 Kg)
- Activated Charcoal (0.03 Kg)

Hyflo (1.50 Kg)
- Acetone (1.12 L)

Charcoalization
- Hyflo+ Charcoal (1.68 Kg)

Filtration

Hydroxy Acetone Spent (13 L)
- Vent Loss (0.4 L)

Distillation

Centrifugation → ML (4 L)

Drying → Solvent loss (0.49 L)

Olesansar Medoxomil API (1.0 Kg)
21. LINEZOLID

Manufacturing Process

Stage I - preparation of stage I: KSM react with sodium azide in DMF at 60-65°C after water add the stage I. Preparation of stage II - The reaction of stage I with hydrogen gas over 10% Pd/c in acetate at 15-20°C affords the stage II insitu which is acetylated in acetone with acetic anhydride triethyl amine at 0-5°C gives crude stage II which is then heated in toluene gives pure Linezolid.

Chemical Reaction
## Material Balance

### Stage - 1

<table>
<thead>
<tr>
<th>RAW MATERIAL</th>
<th>INPUT QUANTITY</th>
<th>OUTPUT QUANTITY</th>
<th>OUTPUT DETAILS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dimethyl Formamide (R)-[N-3-(3-fluoro-4- morpholinophenyl)-2-oxo-5- oxazolidinyl] methyl methane</td>
<td>198.00</td>
<td>666.80</td>
<td>Centrifuge ML</td>
</tr>
<tr>
<td>Sulfonate</td>
<td>65.00</td>
<td>15.00</td>
<td>Drying Loss</td>
</tr>
<tr>
<td>Sodium Azide</td>
<td>15.80</td>
<td>52.00</td>
<td>Linezolid Stage 1</td>
</tr>
<tr>
<td>Process Water</td>
<td>455.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>733.80</strong></td>
<td><strong>733.80</strong></td>
<td></td>
</tr>
</tbody>
</table>

### Stage - 2

<table>
<thead>
<tr>
<th>RAW MATERIAL</th>
<th>INPUT QUANTITY</th>
<th>OUTPUT QUANTITY</th>
<th>OUTPUT DETAILS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Process water</td>
<td>2200.00</td>
<td>2300.00</td>
<td>Water</td>
</tr>
<tr>
<td>Palladium on carbon</td>
<td>3.00</td>
<td>200.00</td>
<td>Spent Methanol</td>
</tr>
<tr>
<td>Methanol</td>
<td>200.00</td>
<td>36.00</td>
<td>Hydrogen gas vent</td>
</tr>
<tr>
<td>Ethyl Acetate</td>
<td>1665.00</td>
<td>28.00</td>
<td>Nitrogen gas vent</td>
</tr>
<tr>
<td>Stage-1</td>
<td>45.00</td>
<td>1640.00</td>
<td>Distill Ethyl acetate</td>
</tr>
<tr>
<td>Hydrogen gas</td>
<td>36.00</td>
<td>200.00</td>
<td>Acetone</td>
</tr>
<tr>
<td>Nitrogen gas</td>
<td>28.00</td>
<td>2.00</td>
<td>Hyflo</td>
</tr>
<tr>
<td>Acetic anhydride</td>
<td>14.90</td>
<td>0.90</td>
<td>Activated charcoal</td>
</tr>
<tr>
<td>Triethyl amine</td>
<td>19.85</td>
<td>225.00</td>
<td>Distill Acetone</td>
</tr>
<tr>
<td>Activated charcoal</td>
<td>0.90</td>
<td>599.75</td>
<td>Centrifuge ML (Acetone)</td>
</tr>
<tr>
<td>Acetone</td>
<td>965.00</td>
<td>90.00</td>
<td>Centrifuge ML (Water)</td>
</tr>
<tr>
<td>Hyflo</td>
<td>2.00</td>
<td>290.00</td>
<td>Centrifuge ML (Toluene)</td>
</tr>
<tr>
<td>DM water</td>
<td>190.00</td>
<td>15.00</td>
<td>Drying loss</td>
</tr>
<tr>
<td>Toluene</td>
<td>290.00</td>
<td>3.00</td>
<td>Palladium on carbon</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30.00</td>
<td>Linezolid</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>5659.65</strong></td>
<td><strong>5659.65</strong></td>
<td></td>
</tr>
</tbody>
</table>
22. LERCANIDIPINE HYDROCHLORIDE

Manufacturing Process

Stage-I
1,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridine dicarboxylic acid (L-Acid) condensation with 1-[(3,3-diphenylpropyl)(methyl)amino]-2-methylpropan-2-ol (L-Alcohol) using DCC, DMAP, toluene, Reaction completed then add water and mass is centrifuged wash with Toluene, Filtrate ML taken for layer separation then distilled out Toluene and mass dissolve in Ethyl Acetate and given 1N HCl wash. Ethyl Acetate to be distilled out and the precipitated mass is centrifuged, washed with Ethyl Acetate & dried to get Lercanidipine Hydrochloride Crude.

Stage-II
Crude Lercanidipine Hydrochloride dissolved in Ethanol and charcoalized the reaction mass then cooled and precipitated. The precipitated mass is centrifuged, washed with Ethanol & dried to get 1st pure Lercanidipine Hydrochloride.

Stage-III
1st pure Lercanidipine Hydrochloride dissolved in Ethyl Acetate and wash with Sodium Carbonate solution, wash with 1N HCl solution, Ethyl Acetate distilled and precipitated mass is centrifuged, washed with Ethyl Acetate & dried to get Lercanidipine Hydrochloride API.

Chemical Reaction

![Chemical Reaction Diagram]

A. L-Acid (2,6-Dimethyl-5-methoxycarbonyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid)
B. L-Alcohol (2, N-Dimethyl-N-(3,3-diphenylpropyl)-1-amino-2-propanol)
C. Lercanidipine Hydrochloride Stage-I
Stage-II
Lercanidipine Hydrochloride Stage-I

\[
\text{Ethanol}
\]

Lercanidipine Hydrochloride Stage-II

Stage-III
Lercanidipine Hydrochloride Stage-II

\[
\text{NaCl} + \text{HCO}_3^-
\]

Lercanidipine Hydrochloride API
Material Balance

Stage I
- Toluene (3.85 L)
- L-salt (0.770 Kg)
- DMF (0.029 Kg)
- Alcohol (0.816 Kg)
- DCC (0.574 Kg)
- DMWater (0.77 L)

- Toluene (0.77 L) → Filtration and layer separation → Salt wet cake (0.77 Kg) → Aq Effluent (0.77 L)
- Ethyl Acetate (11.53 L)
  - HCl Solution (27.72 L)
  - DMWater (2.31 L)

- Ethyl Acetate (2.31 L) → Distillation → Spent Ethyl Acetate (12.8 L) → Vent Loss (0.7 L)

- Ethyl Acetate (13.4 L) → Crystallization
- Ethyl Acetate (1.54 L) → Centrifugation

- Lercanidipine Hydrochloride Stage I (1 Kg)

Stage II
- Ethanol (4 L)
- Lercanidipine HCL Stage I (1.3 Kg)
- Charcoal (0.03 Kg)

- Hyflo (1.50 Kg)
- Ethanol (0.65 L)
- Ethanol (0.65 L) → Filtration → Hyflo + charcoal (1.7 Kg)

- Hyflo (1.50 Kg)
  - Ethanol (0.65 L)
  - Ethanol (0.65 L) → Centrifugation → ML (4.8 L) → Drying → Vent loss (0.63 L)

- Lercanidipine Hydrochloride Stage II (1 Kg)

Stage III
- Ethyl Acetate (6 L)
- Lercanidipine HCL Stage II (1.2 Kg)
- Sodium Bicarbonate (0.12 Kg)
- HCl Solution (14.4 L)

- Ethyl Acetate (7.2 L) → Distillation → Spent Ethyl Acetate (12.8 L) → Vent loss (0.7 L)

- Ethyl Acetate (26.4 L)

- Ethyl Acetate (2.1 L) → Crystallization
  - Ethyl Acetate (2.1 L) → Centrifugation → Aqueous ML (26.65)

- Lercanidipine Hydrochloride API (1 Kg)
23. FLUXETINE HYDROCHLORIDE

Manufacturing Process

Stage-I
3-Chloro-1-phenyl propanol reacts with aqueous Monomethylamine to give 3-(Methylamine)-1-phenylpropan-1-ol.

Stage-II (Fluoxetine Hydrochloride Crude)
3-(Methylamine)-1-phenylpropan-1-ol reacts with 4-Chlorobenzotrifluoride gives Fluoxetine base which is converted into its salts by using Ethyl Acetate Hydrochloride solution gives Fluoxetine Hydrochloride Crude.

Stage-III (Fluoxetine Hydrochloride API)
Purification of crude Fluoxetine Hydrochloride in Toluene and DM Water furnished the pure Fluoxetine Hydrochloride.
Chemical Reaction

Stage I

\[
\begin{align*}
&\text{3-Chloro-1-phenyl Propanol} \\
&\text{3-(Methylamino)-1-phenylpropan-1-ol}
\end{align*}
\]

Stage II

\[
\begin{align*}
&\text{3-(Methylamino)-1-phenylpropan-1-ol} \\
&\text{4-Chlorobenzotrifluoride} \\
&\text{Fluoxetine Hydrochloride Crude}
\end{align*}
\]

Stage III

\[
\begin{align*}
&\text{Fluoxetine Hydrochloride Crude} \\
&\text{Fluoxetine Hydrochloride API}
\end{align*}
\]

Material Balance

<table>
<thead>
<tr>
<th>Stage I</th>
<th>Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methanol (3.9L)</td>
<td>3-Chloro-1-Phenyl Propanol (3-CPA) (1.30 kg)</td>
</tr>
<tr>
<td>Aq. Methyl Amine solution (10.4L)</td>
<td>Sodium Iodide (0.05Kg)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Distillation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methanol+ Water (12L)</td>
</tr>
<tr>
<td>Ventr loss (0.50L)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Layer Separation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Process Water (2.6L)</td>
</tr>
<tr>
<td>Toluene (3.23L)</td>
</tr>
<tr>
<td>Toluene (1.9 L)</td>
</tr>
<tr>
<td>Toluene (1.3 L)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Aq. Layer (3.38L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium Hydroxide solution (1.23L)</td>
</tr>
<tr>
<td>Toluene (6.5L)</td>
</tr>
<tr>
<td>Toluene (5.9L)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Distillation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toluene Spent (10L)</td>
</tr>
<tr>
<td>Ventr Loss (0.44L)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Toluene Layer (10.44L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine Hydrochloride Stage 1 (1.0 Kg)</td>
</tr>
</tbody>
</table>
24. DEFERASIROX

Manufacturing Process
Salicylic acid is converted into Salicyloyl Chloride and salicyloyl chloride is converted to Sta presence of salicylamide & O-Xylene. After completion of reaction, reaction mass content vacuum to gives crude stage I which on purification with methanol followed by filtration give stage I on reacting with 4-Hydrazino benzoic acid in presence of ethanol & potassium hy gives crude which on purification with DMF & 30% Hydrogen peroxide yield crude Defera Crude Deferasirox dissolve in mixture of ethyl acetate & methanol. Water is added to it soli concentration of reaction mass.

Chemical Reaction
Stage-II: Manufacturing of 4-[3,5-Bis(2-hydroxyphenyl)-1,2,4-triazol-1-yl]benzoic acid (Deferasirox Crude)

\[ \text{2-(2-hydroxyphenyl)-4H-3,5-benzoxazin-4-one (Stage-I)} \]
Molecular Formula: C\(_8\)H\(_8\)N\(_2\)O\(_3\)
Molecular Weight: 239.2
CAS No: 6210-69-5

\[ \text{4-Hydroxy benzoic acid (KSM-2)} \]
Molecular Formula: C\(_6\)H\(_6\)NO\(_2\)
Molecular Weight: 132.1
CAS No: 67067-05

\[ \text{KHSO\(_4\), Aq Ethanol, 70-75°C} \]

\[ \text{Deferasirox Crude} \]
Molecular Formula: C\(_{29}\)H\(_{22}\)N\(_2\)O\(_8\)
Molecular Weight: 574.4
CAS No: 201350-41-8

Twice Purification with 33% H\(_2\)O\(_2\) & DME
Then Water wash

Deferasirox Crude
Molecular Formula: C\(_{29}\)H\(_{22}\)N\(_2\)O\(_8\)
Molecular Weight: 574.4
CAS No: 201350-41-8

Stage-III: Purification of 4-[3,5-Bis(2-hydroxyphenyl)-1,2,4-triazol-1-yl]benzoic acid (Deferasirox)

\[ \text{Deferasirox Crude} \]
Molecular Formula: C\(_{29}\)H\(_{22}\)N\(_2\)O\(_8\)
Molecular Weight: 574.4
CAS No: 201350-41-8

Purification using methanol, ethyl acetate & Water

Deferasirox
Molecular Formula: C\(_{29}\)H\(_{22}\)N\(_2\)O\(_8\)
Molecular Weight: 574.4
CAS No: 201350-41-8

CAS No: Chemical Abstracts Service Registry Number
## Material Balance

<table>
<thead>
<tr>
<th>Total Input</th>
<th>Material</th>
<th>Product Output</th>
<th>Total Output</th>
<th>Material</th>
</tr>
</thead>
<tbody>
<tr>
<td>340.00</td>
<td>O-Xylene</td>
<td>Deferasirox</td>
<td>26.90</td>
<td>Liberation of ( SO_2 ) gas</td>
</tr>
<tr>
<td>1.70</td>
<td>N,N-Dimethyl Formamide</td>
<td>Stage-1</td>
<td>170.00</td>
<td>Distill o-Xylene</td>
</tr>
<tr>
<td>85.00</td>
<td>Salicylic acid</td>
<td>80.00 kg</td>
<td>587.61</td>
<td>Centrifuge ML(Methanol)</td>
</tr>
<tr>
<td>66.90</td>
<td>Thionyl chloride</td>
<td></td>
<td>15.00</td>
<td>Drying loss</td>
</tr>
<tr>
<td>75.91</td>
<td>Salicylamide</td>
<td></td>
<td>80.00</td>
<td>Deferasirox Stage-1</td>
</tr>
<tr>
<td>310.00</td>
<td>Methanol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>879.51</strong></td>
<td><strong>Total</strong></td>
<td><strong>879.51 Total</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Material</th>
<th>Product Output</th>
<th>Total Output</th>
<th>Material</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.00</td>
<td>Ethanol</td>
<td>Deferasirox</td>
<td>11.85 Centrifuge ML(Ethanol)</td>
</tr>
<tr>
<td>46.00</td>
<td>Process water</td>
<td>Stage-2</td>
<td>34.40 Centrifuge ML(Water)</td>
</tr>
<tr>
<td>1.00</td>
<td>Stage-1</td>
<td></td>
<td>21.00 (N,N-Dimethyl formamide)</td>
</tr>
<tr>
<td>0.70</td>
<td>4-Hydradino benzoic acid</td>
<td></td>
<td>1.50 Drying loss</td>
</tr>
<tr>
<td>0.15</td>
<td>Potassium hydrogen sulphate</td>
<td></td>
<td>1.10 Deferasirox Stage-2</td>
</tr>
<tr>
<td>10.00</td>
<td>N,N-Dimethyl Formamide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.00</td>
<td>Hydrogen peroxide</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>69.85</strong></td>
<td><strong>Total</strong></td>
<td><strong>69.85 Total</strong></td>
<td></td>
</tr>
<tr>
<td>Total Input</td>
<td>Material</td>
<td>Product Output</td>
<td>Total Output</td>
</tr>
<tr>
<td>-------------</td>
<td>----------------</td>
<td>----------------</td>
<td>--------------</td>
</tr>
<tr>
<td>530.00</td>
<td>Methanol</td>
<td></td>
<td>200.00</td>
</tr>
<tr>
<td>330.00</td>
<td>Ethyl acetate</td>
<td>Deferasirox</td>
<td>2.00</td>
</tr>
<tr>
<td>30.00</td>
<td>Stage-2</td>
<td></td>
<td>470.00</td>
</tr>
<tr>
<td>2.00</td>
<td>Hyflo</td>
<td></td>
<td>15.00</td>
</tr>
<tr>
<td>360.00</td>
<td>DM water</td>
<td></td>
<td>27.00</td>
</tr>
<tr>
<td><strong>1252.00</strong></td>
<td><strong>Total</strong></td>
<td><strong>Defera</strong></td>
<td><strong>1252.00</strong></td>
</tr>
</tbody>
</table>
25. ROPINIROLE HYDROCHLORIDE

Manufacturing Process

2-Methyl-3-nitrophenyl ethyl -N,N-di-n-propyl ammonium oxalate undergoes reaction with in presence of potassium ethoide and form Ethyl 2-nitro-6-(N,N-di-n-propylaminoethyl) Phenylpyruvate. Ester hydrolysis and decarboxylation of Ethyl 2-nitro-6-(N,N-di-n-propylaminoethyl)phenyl acetic acid hydrochloride. Reduction and in situ cyclization of 2-Nitro-6-(2-(N-propylamino)ethyl)phenyl acetic acid HCL in presence of 10%palladium on caron using D solvent gives Ropinirole HCL tech. Acid Base purification of ropinirole HCL tech using ethylacetate/sodiumbicarbonate/ethanolic HCL gives Ropinirole Hydrochloride.

Chemical Reaction
Ropinirole Hydrochloride Stage-II: Preparation of Ropinirole hydrochloride

\[
\begin{align*}
\text{H}_2\text{C} & \quad \text{N} \quad \text{CH}_3 \\
\text{H} & \quad \text{C} \quad \text{O} \\
\text{N}_2 & \quad \text{HCl} \\
\end{align*}
\]

[2-Nitro-5-(2-(N,N-di-n-propylamine)-ethylphenyl)propionic acid hydrochloride]
Molecular Formula: \( \text{C}_{16}\text{H}_{22}\text{N}_2\text{O}_3\text{HCl} \)
Molecular Weight: 344.84

Ropinirole hydrochloride
Molecular Formula: \( \text{C}_{16}\text{H}_{24}\text{N}_2\text{O}_3\text{HCl} \)
Molecular Weight: 344.84

Ropinirole Hydrochloride Stage-III: Purification of Ropinirole hydrochloride

\[
\begin{align*}
\text{H}_2\text{C} & \quad \text{N} \quad \text{CH}_3 \\
\text{H} & \quad \text{C} \quad \text{O} \\
\text{N}_2 & \quad \text{HCl} \\
\end{align*}
\]

Purification

Mixture of Ethyl Acetate & Ethanol
Ethanol HCl, Ethyl acetate

Ropinirole hydrochloride
Molecular Formula: \( \text{C}_{16}\text{H}_{24}\text{N}_2\text{O}_3\text{HCl} \)
Molecular Weight: 344.84

Ethanol* = Ethanol distilled with Acetone
## Material Balance

### Stage - 1

<table>
<thead>
<tr>
<th>Raw Material</th>
<th>In Put Quantity Kgs</th>
<th>Product Out Put</th>
<th>Quantity Kgs</th>
<th>Out Put Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Process water</td>
<td>2070.00</td>
<td>34.00 kg</td>
<td>1341.92</td>
<td>Aqueous layer</td>
</tr>
<tr>
<td>Sodium Hydroxide</td>
<td>60.12</td>
<td></td>
<td>15.00</td>
<td>Salt Centrifuge ML</td>
</tr>
<tr>
<td>Methyl-3- Nitrophenylethyl-N,N-di-n-Propyl Ammonium oxalate</td>
<td>60.00</td>
<td></td>
<td>86.00</td>
<td>(Ethyl acetate)</td>
</tr>
<tr>
<td>Ethyl Acetate</td>
<td>1110.00</td>
<td></td>
<td>750.00</td>
<td>Distill Ethyl acetate</td>
</tr>
<tr>
<td>Sodium Sulphate</td>
<td>15.00</td>
<td></td>
<td>265.00</td>
<td>Distill THF</td>
</tr>
<tr>
<td>Tetrahydrofuran</td>
<td>320.00</td>
<td></td>
<td>55.00</td>
<td>Evaporation loss</td>
</tr>
<tr>
<td>Potassium Ethoxide</td>
<td>15.68</td>
<td></td>
<td>180.00</td>
<td>Organic Layer</td>
</tr>
<tr>
<td>Diethyl oxalate</td>
<td>29.72</td>
<td></td>
<td>1239.60</td>
<td>Centrifuge ML(Water)</td>
</tr>
<tr>
<td>Hydrochloric acid</td>
<td>132.00</td>
<td></td>
<td>50.00</td>
<td>Water</td>
</tr>
<tr>
<td>Hydrogen peroxide</td>
<td>24.00</td>
<td></td>
<td>720.00</td>
<td>Distill Ethanol</td>
</tr>
<tr>
<td>Sodium Chloride</td>
<td>180.00</td>
<td></td>
<td>316.00</td>
<td>Centrifuge ML</td>
</tr>
<tr>
<td>Ethanol</td>
<td>1040.00</td>
<td></td>
<td>10.00</td>
<td>Drying loss</td>
</tr>
<tr>
<td>Acetonitrile</td>
<td>6.00</td>
<td></td>
<td>34.00</td>
<td>Ropinorole Hydrochloride Stage-1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>5062.52</strong></td>
<td><strong>5062.52</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Stage – 2

<table>
<thead>
<tr>
<th>Raw Material</th>
<th>In Put Quantity Kgs</th>
<th>Product Out Put</th>
<th>Quantity Kgs</th>
<th>Out Put Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Process Water</td>
<td>1808.00</td>
<td>Ropinorole hydrochloride Stage-2</td>
<td>36.00</td>
<td>Hydrogen gas vent</td>
</tr>
<tr>
<td>Stage-1</td>
<td>30.00</td>
<td></td>
<td>22.50</td>
<td>Nitrogen gas vent</td>
</tr>
<tr>
<td>Palladium on Charcoal (50% wet)</td>
<td>12.00</td>
<td></td>
<td>12.00</td>
<td>Spent Palladium on Charcoal</td>
</tr>
<tr>
<td>Hydrogen gas</td>
<td>36.00</td>
<td></td>
<td>200.00</td>
<td>Water</td>
</tr>
<tr>
<td>Nitrogen gas</td>
<td>22.50</td>
<td></td>
<td>1.50</td>
<td>Activated Charcoal</td>
</tr>
<tr>
<td>Activated Charcoal</td>
<td>1.50</td>
<td></td>
<td>1.50</td>
<td>Hyflo</td>
</tr>
<tr>
<td>Sodium dithionite</td>
<td>1.50</td>
<td></td>
<td>1662.90</td>
<td>Aqueous layer</td>
</tr>
<tr>
<td>Hyflo</td>
<td>1.50</td>
<td></td>
<td>570.00</td>
<td>Distill Ethyl acetate</td>
</tr>
<tr>
<td>Sodium carbonate</td>
<td>11.40</td>
<td></td>
<td>280.00</td>
<td>Centrifuge ML</td>
</tr>
<tr>
<td>Ethyl Acetate</td>
<td>600.00</td>
<td></td>
<td>10.00</td>
<td>Drying loss</td>
</tr>
<tr>
<td>Ethanol</td>
<td>270.00</td>
<td></td>
<td>19.00</td>
<td>Ropinorole hydrochloride Stage-2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>2815.40</strong></td>
<td><strong>2815.40</strong></td>
<td></td>
<td><strong>Total</strong></td>
</tr>
<tr>
<td>Raw Material</td>
<td>In Put Quantity Kgs</td>
<td>Product Out Put</td>
<td>Quantity Kgs</td>
<td>Out Put Details</td>
</tr>
<tr>
<td>-------------------</td>
<td>---------------------</td>
<td>-----------------</td>
<td>--------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>DM Water</td>
<td>644.00</td>
<td>Ropinorole hydrochloride</td>
<td>200.00</td>
<td>DM Water</td>
</tr>
<tr>
<td>Stage-2</td>
<td>21.00</td>
<td></td>
<td>4.00</td>
<td>Hyflo</td>
</tr>
<tr>
<td>Activated Charcoal</td>
<td>1.50</td>
<td></td>
<td>1.05</td>
<td>Activated Charcoal</td>
</tr>
<tr>
<td>Sodium dithionite</td>
<td>1.50</td>
<td></td>
<td>457.40</td>
<td>Aqueous layer</td>
</tr>
<tr>
<td>Hyflo</td>
<td>4.00</td>
<td></td>
<td>200.00</td>
<td>Ethyl acetate</td>
</tr>
<tr>
<td>Ethyl Acetate</td>
<td>908.00</td>
<td></td>
<td>456.00</td>
<td>Distill Ethyl acetate</td>
</tr>
<tr>
<td>Sodium carbonate</td>
<td>7.35</td>
<td></td>
<td>312.00</td>
<td>Centrifuge ML</td>
</tr>
<tr>
<td>Ethanol</td>
<td>42.00</td>
<td></td>
<td>5.00</td>
<td>Drying loss</td>
</tr>
<tr>
<td>Ethanolic HCL</td>
<td>23.10</td>
<td></td>
<td>17.00</td>
<td>Ropinorole hydrochloride</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1652.45</strong></td>
<td><strong>Ropinorole hydrochloride 17.00 Kg</strong></td>
<td><strong>1652.45</strong></td>
<td><strong>Total</strong></td>
</tr>
</tbody>
</table>
26. HYDROCHLOROTHIAZIDE
Manufacturing Process
Stage-I: Preparation of Hydrochlorothiazide Crude
4-Amino-6-chloro-1,3-benzenedisulfonamide (CBD) is heated with Para formaldehyde at 95-100°C in water for 2-4 hours to give crude Hydrochlorothiazide.

Stage-I: Purification of Hydrochlorothiazide Crude
Purification of Hydrochlorothiazide crude is carried out in a mixture of diluted Ammonia and caustic lye solution followed by pH adjustment to give pure Hydrochlorothiazide.

Chemical Reaction
### Material Balance

#### Stage - 1

<table>
<thead>
<tr>
<th>Raw Material</th>
<th>In Put Quantity</th>
<th>Product Out Put</th>
<th>Quantity</th>
<th>Out Put Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>D M water</td>
<td>3420.0</td>
<td></td>
<td>189</td>
<td>3431.6</td>
</tr>
<tr>
<td>CBD</td>
<td>180.0</td>
<td></td>
<td>189</td>
<td>Aqueous Effluent Output</td>
</tr>
<tr>
<td>Para formaldehyde</td>
<td>20.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>3621</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Stage – 2

<table>
<thead>
<tr>
<th>Raw Material</th>
<th>In Put Quantity</th>
<th>Product Out Put</th>
<th>Quantity</th>
<th>Out Put Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium Hydroxide</td>
<td>15.0</td>
<td>135</td>
<td>5.0</td>
<td>Spent carbon</td>
</tr>
<tr>
<td>Hydrochlorothiazide Stage-I</td>
<td>150.0</td>
<td></td>
<td>2189.4</td>
<td>Aqueous Effluent</td>
</tr>
<tr>
<td>DM Water</td>
<td>1490.0</td>
<td></td>
<td>99.4</td>
<td>loss during drying</td>
</tr>
<tr>
<td>Ammonia solution</td>
<td>333.8</td>
<td></td>
<td>135.0</td>
<td>Output</td>
</tr>
<tr>
<td>Activated Charcoal</td>
<td>3.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyflo</td>
<td>2.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrochloric Acid</td>
<td>435.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>2428.8</td>
<td></td>
<td>2428.8</td>
<td></td>
</tr>
</tbody>
</table>
27. LAMOTRIGINE

Manufacturing Process
Amino Guanidine bicarbonate is reacted 2,3 DBN & then purified in n-Propanol.

Chemical Reaction
### Material Balance

#### Stage - 1

<table>
<thead>
<tr>
<th>Raw Material</th>
<th>In Put Quantity Kgs</th>
<th>Product Out Put</th>
<th>Quantity Kgs</th>
<th>Out Put Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Process water</td>
<td>4113.0</td>
<td></td>
<td></td>
<td>15359.8</td>
</tr>
<tr>
<td>Process water for cake</td>
<td>9326.0</td>
<td></td>
<td></td>
<td>Aqueous Effluent</td>
</tr>
<tr>
<td>wash Sulphuric Acid</td>
<td>2512.5</td>
<td></td>
<td></td>
<td>752.0</td>
</tr>
<tr>
<td>Dichloro Benzoyl Nitrile</td>
<td>250.0</td>
<td></td>
<td></td>
<td>Aqueous Wash</td>
</tr>
<tr>
<td>Acetonitrile</td>
<td>4.0</td>
<td></td>
<td></td>
<td>water loss in drying</td>
</tr>
<tr>
<td>Total</td>
<td>16461.8</td>
<td>16461.8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Stage - 2

<table>
<thead>
<tr>
<th>Raw Material</th>
<th>In Put Quantity Kgs</th>
<th>Product Out Put</th>
<th>Quantity Kgs</th>
<th>Out Put Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>n-Propanol</td>
<td>1026.2</td>
<td>53.94</td>
<td>6.1</td>
<td>Spent carbon + Hyflow</td>
</tr>
<tr>
<td>Activated carbon</td>
<td>3.1</td>
<td></td>
<td>1026.2</td>
<td>Dilute n-Propanol</td>
</tr>
<tr>
<td>Lamotrigine (Stage-I)</td>
<td>62.0</td>
<td></td>
<td>8.06</td>
<td>vapor loss on Drying</td>
</tr>
<tr>
<td>Hyflo</td>
<td>3.0</td>
<td></td>
<td>53.94</td>
<td>Output</td>
</tr>
<tr>
<td>Total</td>
<td>1094.3</td>
<td>1094.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Stage - 3

<table>
<thead>
<tr>
<th>Raw Material</th>
<th>In Put Quantity Kgs</th>
<th>Product Out Put</th>
<th>Quantity Kgs</th>
<th>Out Put Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>n-Propanol</td>
<td>5192.1</td>
<td>21.8</td>
<td></td>
<td>Spent carbon + Hyflow</td>
</tr>
<tr>
<td>Activated carbon</td>
<td>18.8</td>
<td></td>
<td>5192.1</td>
<td>Dilute n-Propanol</td>
</tr>
<tr>
<td>Lamotrigine (Stage-I)</td>
<td>375.0</td>
<td></td>
<td>48.75</td>
<td>vapor loss on Drying</td>
</tr>
<tr>
<td>Hyflo</td>
<td>3.0</td>
<td></td>
<td>326.25</td>
<td>Output</td>
</tr>
<tr>
<td>Total</td>
<td>5588.8</td>
<td>5588.8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
28. **METOPROLOL TARTRATE**

**Manufacturing Process**

NaOH is added to a hot solution of 4-(2-methoxyethyl) phenol and Epichlorohydrine and stirred for 2.5 hour to give epoxy compound which on reacting with Mono isopropyl amine in water to give Metoprolol Base. After addition of L-(+)-Tartaric acid to a solution of Metoprolol Base in Acetone gives Metoprolol Tartrate.

**Chemical Reaction**

![Chemical Reaction Diagram]

- **Metoprolol Tartrate Stage – 1**: Preparation of 1-(Isopropylamino)-3-[4-(2-methoxyethyl) phenoxylpropan-2-ol (ar) Metoprolol
Material Balance
Stage - 1

<table>
<thead>
<tr>
<th>Raw Material</th>
<th>In Put Quantity Kgs</th>
<th>Product Out Put Quantity Kgs</th>
<th>Out Put Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methanol</td>
<td>1676.8</td>
<td>405.6</td>
<td>methanol loss</td>
</tr>
<tr>
<td>Hy. HCl</td>
<td>355.9</td>
<td></td>
<td>Spent Methanol</td>
</tr>
<tr>
<td>Sodium Carbonate</td>
<td>115.4</td>
<td></td>
<td>Aqueous Effluent</td>
</tr>
<tr>
<td>Erythromycin 'A'</td>
<td>600.0</td>
<td></td>
<td>Aqueous Wash</td>
</tr>
<tr>
<td>Process water</td>
<td>2878.8</td>
<td></td>
<td>water loss in drying</td>
</tr>
<tr>
<td>Process water for cake</td>
<td>871.2</td>
<td></td>
<td>405.6 Out Put</td>
</tr>
<tr>
<td>Process water for cake</td>
<td>340.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>6838.9</td>
<td>6838.9</td>
<td></td>
</tr>
</tbody>
</table>

Stage - 2

<table>
<thead>
<tr>
<th>Raw Material</th>
<th>In Put Quantity Kgs</th>
<th>Product Out Put</th>
<th>Quantity Kgs</th>
<th>Out Put Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetone</td>
<td>2991.6</td>
<td>81.75</td>
<td>2931</td>
<td>Spent Acetone</td>
</tr>
<tr>
<td>MTT (Stage-I)</td>
<td>75.0</td>
<td></td>
<td>4.65</td>
<td>ML</td>
</tr>
<tr>
<td>Activated carbon</td>
<td>3.8</td>
<td></td>
<td>75</td>
<td>Solid Waste</td>
</tr>
<tr>
<td>Tartaric acid</td>
<td>20.0</td>
<td></td>
<td>81.75</td>
<td>Out Put</td>
</tr>
<tr>
<td>Hyflo</td>
<td>2.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>3092.4</td>
<td>3092.4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
29. METOPROLOL SUCCINATE

Manufacturing Process
Sodium Hydroxide is added to a hot solution of 4-(2-methoxyethyl) phenol and Epichlorohydrine and stirred for 2.5 hour to give Epoxy compound which on reacting with Mono isopropyl amine in water to give Metoprolol Base. After addition of Succinic acid to a solution of Metoprolol Base in Acetone give Metoprolol Succinate.

Chemical Reaction

![Chemical Reaction Diagram]
Material Balance
Stage - 1

<table>
<thead>
<tr>
<th>Raw Material</th>
<th>In Put Quantity</th>
<th>Product Out Put</th>
<th>Quantity Kgs</th>
<th>Out Put Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetone</td>
<td>4918.3</td>
<td>185</td>
<td>11.3</td>
<td>Spent carbon + Hyflo</td>
</tr>
<tr>
<td>Metoprolol Tartrate Stage-I</td>
<td>185.0</td>
<td></td>
<td>4918.3</td>
<td>Acetone CF ML</td>
</tr>
<tr>
<td>Activated carbon</td>
<td>9.3</td>
<td></td>
<td>38.9</td>
<td>Loss during drying</td>
</tr>
<tr>
<td>Succinic Acid</td>
<td>38.8</td>
<td></td>
<td>185.0</td>
<td>Output</td>
</tr>
<tr>
<td>Hyflo</td>
<td>2.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>5153</td>
<td>5153</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
30. QUETIAPINE FUMARATE

Manufacturing Process

Stage-I: Formation of Quetiapine Fumarate Crude
Dibenzo[b,f][1,4]Tiazepine-11(10H)-one (DBT) is reacted with Phosphorous Oxychloride in presence of N,N-Dimethyl Aniline (DMA) as a base in Toluene at 110-115°C to give residue of 11-Chlorodibenzo[b,f][1,4]Thiazepine (Stage-Ia).

11-Chlorodibenzo[b,f][1,4]Thiazepine (Stage-Ia) is reacted with 1-[2-(2-hydroxyethoxy)ethyl] Piperazine [HEEP] in a mixture of Toluene/ water at 95-105°C temperature to give viscous oil of Quetiapine Fumarate (Stage-Ib).

Quetiapine Fumarate Crude (Stage-I) is formed by reacting with Fumaric acid in Methanol.

Stage-II: Formation of Quetiapine Fumarate
Quetiapine Fumarate Crude (Stage-I) is Purified from Methanol/ Water at 60-65°C.
Chemical Reaction

Quetiapine Fumarate Stage-I: Preparation of Quetiapine Fumarate Crude

Quetiapine Fumarate Stage-II: Purification of Quetiapine Fumarate
Material Balance

### Qutapine Fumarate

#### STEP 1(a): Preparation of CD8T

**Input**

<table>
<thead>
<tr>
<th>Name</th>
<th>Material (g)</th>
<th>Description</th>
<th>HEP (g)</th>
<th>Water (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD8T Glutathione - Glutathione - Glutathione</td>
<td>227.25</td>
<td>CD8T Glutathione - Glutathione - Glutathione</td>
<td>153.3</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>412</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Output**

<table>
<thead>
<tr>
<th>Name</th>
<th>Material (g)</th>
<th>Description</th>
<th>HEP (g)</th>
<th>Water (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD8T Glutathione - Glutathione - Glutathione</td>
<td>246.73</td>
<td>CD8T Glutathione - Glutathione - Glutathione</td>
<td>39.5</td>
<td>25.00</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>412</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### STEP 1(b): Preparation of Qutapine Base

**Input**

<table>
<thead>
<tr>
<th>Name</th>
<th>Material (g)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD8T Glutathione - Glutathione - Glutathione</td>
<td>246.73</td>
<td>CD8T Glutathione - Glutathione - Glutathione</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>420</td>
</tr>
</tbody>
</table>

**Output**

<table>
<thead>
<tr>
<th>Name</th>
<th>Material (g)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD8T Glutathione - Glutathione - Glutathione</td>
<td>235.35</td>
<td>CD8T Glutathione - Glutathione - Glutathione</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>420</td>
</tr>
</tbody>
</table>

#### STEP 1: Preparation of Qutapine Fumarate Crude

**Input**

<table>
<thead>
<tr>
<th>Name</th>
<th>Material (g)</th>
<th>Fumaric Acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qutapine Base</td>
<td>383.51</td>
<td>116.07</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>503.1</td>
</tr>
</tbody>
</table>

**Output**

<table>
<thead>
<tr>
<th>Name</th>
<th>Material (g)</th>
<th>Fumaric Acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qutapine Fumarate Crude</td>
<td>883.07</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>883.1</td>
</tr>
</tbody>
</table>
31. PENTOSAN POLYSULPHATE SODIUM

Manufacturing Process

Stage I: Preparation of sodium salt of sulfuric acid ester of Xylan- Xylan is esterified with chlorosulfonic acid pyridine to give sulfuric acid ester of Xylan, which is isolated as sodium salt of sulfuric acid of Xylan by trihydroxide in methanol.

Stage II: Prep Pentosan Polysulfate Sodium:- Sodium salt of sulfuric acid ester of Xylan is subjected to oxidative depolymerization of hydrogen peroxide and sulfuric acid gives crude Pentosan Polysulfate Sodium. Pentosan Polysulfate sodium (crude) is purified by reverse osmosis to yield pure pentosan Polysulfate sod by crystallization from methanol.

Chemical Reaction

Pentosan Polysulfate Sodium Stage – I : Sodium salt of sulfuric acid ester of Xylan

Pentosan Polysulfate Sodium Stage – II : Pentosan Polysulfate sodium
Route of Synthesis depicting the presence of 4-O-methyl glucuronate side chain:

4-O-methyl glucuronate will be linked to 2-position of any (Pentose) Xylose ring between 4\textsuperscript{th} and 10\textsuperscript{th} unit.

**Pentosan Polysulfate Sodium Stage – I:** Sodium salt of sulfuric acid ester of Xylan

![Chemical Structure of Xylan](Image)

- **Xylan**
  - \(\text{MF: } [C_9H_8O_4]_n\)
  - \(\text{MW: } 3000-25000\ D\)
  - \(\text{CAS No. } [9014-63-1]\)

- **H$_2$SO$_4$**
  - **Chromosulfonic acid**
  - \(\text{MW: } 116.52\)
  - \(\text{CAS No. } [7796-94-5]\)

- **Examination**
  - **Pyridine Methanol**

- **In-situ intermediate**
  - (Sulfuric acid ester of Xylan)
  - \(\text{MF: } [C_9H_8O_4S_3]_n\)

- **Salt formation**
  - **NaOH CH$_3$COOH**

**Pentosan Polysulfate Sodium Stage – II:** Pentosan Polysulfate sodium

- **Pentosan Polysulfate Sodium Stage – I**
  - (Sodium salt of sulfuric acid ester of Xylan)
  - \(\text{MF: } [C_9H_8Na_3O_4S_3]_n\)

- **Oxidative depolymerization**
  - \(\text{H}_2\text{O}_2/\text{dilute }\text{H}_2\text{SO}_4\)
  - **NaOH CH$_3$COOH Methanol**

**Pentosan Polysulfate Sodium**

- \(\text{MF: } [K_2C_9H_8Na_2O_4S_3]_n\)
- \(\text{MW: } 4000-5000\ \text{Dalton}\)
- \(\text{CAS No. } [17319-17-8]\)
### Material Balance

#### Stage-1

<table>
<thead>
<tr>
<th>Input Details</th>
<th>Reaction &amp; Equipment</th>
<th>Output Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality Type</td>
<td>Reaction Type</td>
<td>Output Type</td>
</tr>
<tr>
<td>Solution A</td>
<td>Reactor RE-046</td>
<td>Cartridge CF-014</td>
</tr>
<tr>
<td>Solution B</td>
<td>Reactor RE-047</td>
<td>Cartridge ML (Methanol)</td>
</tr>
<tr>
<td>Solution C</td>
<td>Reactor RE-048</td>
<td>Cartridge CF-014</td>
</tr>
<tr>
<td>Solution D</td>
<td>Reactor RE-049</td>
<td>Drying 40-400</td>
</tr>
</tbody>
</table>

#### Total Inputs:

<table>
<thead>
<tr>
<th>No.</th>
<th>Starting Material</th>
<th>Product Output</th>
<th>Quantity (Kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.31</td>
<td>Water</td>
<td>Product A</td>
<td>1000 Kg</td>
</tr>
<tr>
<td>2.30</td>
<td>Water</td>
<td>Product B</td>
<td>500 Kg</td>
</tr>
<tr>
<td>4.20</td>
<td>Water</td>
<td>Product C</td>
<td>450 Kg</td>
</tr>
<tr>
<td>17.20</td>
<td>Water</td>
<td>Product D</td>
<td>500 Kg</td>
</tr>
<tr>
<td>17.70</td>
<td>Water</td>
<td>Product E</td>
<td>500 Kg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No.</th>
<th>Water</th>
<th>Cartridge CF-014</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.31</td>
<td>Water</td>
<td>5000 Kg</td>
</tr>
<tr>
<td>2.30</td>
<td>Water</td>
<td>1000 Kg</td>
</tr>
<tr>
<td>4.20</td>
<td>Water</td>
<td>450 Kg</td>
</tr>
<tr>
<td>17.20</td>
<td>Water</td>
<td>500 Kg</td>
</tr>
<tr>
<td>17.70</td>
<td>Water</td>
<td>500 Kg</td>
</tr>
</tbody>
</table>

#### Output Details:

- 1000 Kg Cartridge CF-014
- 5000 Kg Cartridge ML (Methanol)
- Drying 40-400 Kg
### Stage II

<table>
<thead>
<tr>
<th>Input Details</th>
<th>Raw Material</th>
<th>Position &amp; Equipment</th>
<th>Output Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quantity (kg.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4268.40</td>
<td>DI water</td>
<td>Reservoir</td>
<td>300.50</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DI water</td>
</tr>
<tr>
<td>1.50</td>
<td>Polyethylene</td>
<td></td>
<td>1.2</td>
</tr>
<tr>
<td>1.00</td>
<td>Methanol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>72.00</td>
<td>Methanol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.00</td>
<td>Methanol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>323.20</td>
<td>Centrifuge</td>
<td></td>
<td>16.00</td>
</tr>
<tr>
<td>1.00</td>
<td>Methanol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18.00</td>
<td>Drying loss</td>
<td></td>
<td></td>
</tr>
<tr>
<td>526.97</td>
<td>Total</td>
<td></td>
<td>4168.40</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total Input</th>
<th>Raw Material</th>
<th>Product Output</th>
<th>Quantity (kg.)</th>
<th>Output Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>4268.40</td>
<td>DI water</td>
<td>Drying loss</td>
<td>16.00</td>
<td></td>
</tr>
<tr>
<td>1.50</td>
<td>Polyethylene</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>72.00</td>
<td>Methanol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>323.20</td>
<td>Centrifuge</td>
<td></td>
<td>16.00</td>
<td></td>
</tr>
<tr>
<td>526.97</td>
<td>Total</td>
<td></td>
<td>4168.40</td>
<td></td>
</tr>
</tbody>
</table>

**Note:** The table and diagram provide a detailed breakdown of the stages involved, including the materials used, their quantities, and the equipment used. The output details include the quantities of each component and the final output.