

Study of pharmacovigilance related drug cetirizine

Author:-omkar vishwanath khole

Co-outher:-

1)Gore Shankar datta

2)Khade Abhijit Mhatarba

3)Arbat Achal Manohar

Student, Pharmacy, Matoshri Miratai Aher College Of Pharmacy, Tal-Parner, Dist.-Ahmednagar, Maharashtra, India.

Assistant Professor, Matoshri Miratai Aher Collage Of Pharmacy, Tal-Parner, Dist.-Ahmednagar, Maharashtra, India.

Abstract

Cetirizine, the active metabolite of the piperazine H1-receptor antagonist hydroxyzine, minimizes or eliminates the symptoms of chronic idiopathic urticaria, perennial allergic rhinitis, allergic asthma, and atopic dermatitis. It has anti-inflammatory properties that may play a role in asthma management. Food had no effect on cetirizine exposure; however, T_{max} was delayed by 1.7 hours, and C_{max} was decreased by 23% in the fed state. Between 70 and 85% of an orally administered dose can be found in the urine and 10 to 13% in the feces.

Keyword: Antihistamine, Clinical practice, Histamine, H1 receptors.

Introduction

- Cetirizine and its enantiomer levocetirizine are second generation antihistamines that are used for the treatment of allergic rhinitis, angioedema and chronic urticaria. Cetirizine and levocetirizine have been linked to rare, isolated instances of clinically apparent acute liver injury.
- Cetirizine is an effective and well tolerated agent for the treatment of symptoms of seasonal allergic rhinitis (SAR), perennial allergic rhinitis (PAR) and chronic idiopathic urticaria (CIU) in adult, adolescent and pediatric patients.

Drug name : Cetirizine

Generic Name: Cetirizine

Cetirizine: Cetirizine is the selective histamine 1-antagonist drug used in allergic urticaria.

DEVELOPMENT AND DISCOVERY OF CETRIZINE :

Cetirizine is a second-generation antihistamine and was launched in the Italian market in 1989, which is about 30 years ago.

In these years, cetirizine was the most relevant compound in its class and is still very popular.

It was patented in 1981 and came into medical use in 1987.

It is on the World Health Organization's list of medicines.

It is available as a generic medication.

In 2019, it was the 67th most commonly prescribed medication in the United States, with more than 11 million prescriptions.

Preclinical trials:

Inhibitions of histamine release from the mast cells.

Mitogen-induced lymphocyte proliferation.

Inhibition of T-cell proliferation.

PFC (plaque-forming colony) test in vivo.

Inhibitions of dihydroorotate dehydrogenase.

Clinical trials:

- Phase 1:

It is the first time a drug will be tested in people and often involves a small group of volunteers with no health conditions.

- Phase 2:

Phase 2 is sometimes broken down further into phases L and L.

- During phase I of the clinical trial, focus on dosage requirements, investigate dosage, and determine the optimal frequency of dosage.

- Phase 2-3:

Protect patients and address their needs.

meet regulatory standards.

Ensure data integrity.

reduce the burden on sites.

- Phase 3b-4:

Global presence with local market presence to customize solutions.

-Focused site management and world-wide remote monitoring capacity to manage costs.

MECHANISM OF ACTION:

- Cetirizine, a metabolite of hydroxyzine, is an antihistamine drug. Its main effects are achieved through selective inhibition of peripheral H1 receptors.
- The antihistamine activity of cetirizine has been shown in a variety of animal and human models. In vivo and ex vivo animal models have shown insignificant anticholinergic and antiserotonergic effects. In clinical studies, however, dry mouth was found to be more frequent with cetirizine than with a placebo. In vitro receptor binding studies have demonstrated no detectable affinity of cetirizine for histamine receptors other than the H1 receptors.

ALLERGY SYMPTOMS:

- Watery eyes
- Runny nose
- Itching eyes/nose
- Sneezing

Common side effects include:

- Headache
- Dry mouth
- Feeling sick
- Dizziness

- Tummy pain
- Diarrhoea

PHARMACOLOGY:

- Seasonal Allergic Rhinitis:

indicated for the relief of symptoms associated with the seasonal allergic rhinitis caused by allergens such as ragweed grass and three pollens in adults and children 2 years of age and older.

- Perennial allergic rhinitis:

This drug is indicated for the relief of symptoms associated with perennial allergic rhinitis due to allergens including dust mites, animal dander, and moulds in adults and children 6 months of age and older.

- Chronic urticaria:

Cetirizine is indicated for the treatment of the uncomplicated skin of chronic idiopathic urticaria in adults and children 6 months of age and older.

PHARMACOKINETIC:

- General effects and respiratory effects:

Cetirizine, the active metabolite of the piperazine H₁-receptor antagonist hydroxyzine, minimises or eliminates the symptoms of chronic idiopathic urticaria, perennial allergic rhinitis, seasonal allergic rhinitis, allergic asthma, physical urticaria, and atopic dermatitis. The clinical efficacy of cetirizine for allergic respiratory diseases has been well established in numerous trials.

- Effects on urticaria/anti-inflammatory effects:

It has anti-inflammatory properties that may play a role in asthma management. There is evidence that cetirizine improves the symptoms of urticaria. Marked clinical inhibition of a wheal and flare response occurs in infants, children, and adults within 20 minutes of one oral dose and lasts for 24 h. Concomitant use of cetirizine reduces the duration and dose of topical anti-inflammatory formulas used for the treatment of atopic dermatitis.

ABSORPTION:

- Cetirizine was rapidly absorbed, with a time to maximum concentration (T_{max}) of about 1 hour after oral administration of tablets or syrup formulations in adult volunteers. The bioavailability was found to be similar between the tablet and syrup dosage forms.

EFFECT OF FOOD ON ABSORPTION:

- Food had no effect on cetirizine exposure; however, T_{max} was delayed by 1.7 hours, and C_{max} was decreased by 23% in the fed state.

Volume of distribution:

- Apparent volume of distribution: 0.44 +/- 0.19 L/kg.

PROTEIN BINDING:

- The mean plasma protein binding of cetirizine is 93%.

Route of Elimination:

- Mainly eliminated in the urine,

Between 70 and 85% of an orally administered dose can be found in the urine and 10 to 13% in the feces.

HALF LIFE:

- Plasma elimination half-life is 8.3 hours.

CLEARANCE:

- Apparent total body clearance: approximately 53 ml/min.

ADR:**Toxicity:**

- Oral LD50 (rat): 365 mg/kg; intraperitoneal LDLO (mouse): 138 mg/kg; oral TDLO (rat): 50 mg/kg; oral TDLO (mouse): 0.1 mg/kg.

DRUG INTERACTION:

- Avoid the use of alcohol.

Sedatives and tranquillizers like cetirizine can increase the risk of drowsiness.

- Citirizine may cause central nervous system depression.
- Avoid activities requiring mental acuity until you become accustomed to the medication.

FOOD INTERACTION:

Avoid alcohol:-

- Take with or without food.
- The absorption is unaffected by food.

BRAND NAME:-

- Cetirizine.
- M- Cetirizine.
- Zyrtec.

Clinical Efficacies of Cetirizine:

- Chronic urticaria is a problem for both physicians and patients.
- In an effort to avoid the risk associated with treatment.

REPRODUCTIVE TOXICITY:

- Impatient with fertility:

In a fertility and reproduction study in mice, cetirizine did not negatively impact fertility at an oral dose of 64 mg/kg (approximately 25 times the maximum recommended daily oral dose in adults).

- Pregnancy category:

In mice, rats, and rabbits, cetirizine was not teratogenic at oral doses up to 96, 225, and 135 mg/kg, respectively (approximately 40, 180, and 220 times the maximum recommended daily oral dose in adults). There are no adequate and well-controlled studies in pregnant women. Because animal studies are not always predictive of the human response, cetirizine should be used in pregnancy only if clearly needed.

- Use in breast-feeding or nursing:

Cetirizine has been reported to be excreted in human breast milk. The use of cetirizine by nursing mothers is not recommended.

Post Marketing and Monitoring:

Patients taking Cetirizine require monitoring for the relief of symptoms.

Members of the health care team should also monitor patients for adverse effects such as fatigue and somnolence in adults and headache in children.

The kidney primarily excretes cetirizine, and as a result, the risk of toxicity is typically higher in patients with impaired renal function.

Patients with renal impairment should take a lower dosage of medication for their age bracket.

Genotoxicity:

- Information about the genotoxic effects of anti-inflammatory drugs and antipyretics was retrieved for only 62 of the 120 marketed drugs considered
- This finding is in contrast to the relative non genotoxicity of this compound.
- Rapid detection of chromosomal damage with high sensitivity throughout the micronucleus assay
- Identify genotoxic high-levels through ames and micronuclei assays.

Selection of a drug class:

- Selling of drugs:

Cetirizine hydrochloride (trade names: Zirtec, Xyrtec, Reactine) is a second-generation antihistamine used in the treatment of fever, allergies, angioedema, and urticaria.

**Market Analysis and Insights:**

- Due to the COVID-19 pandemic, the global Cetirizine Hydrochloride market size is estimated to be worth US\$ 854.7 million in 2022 and is forecast to reach a readjusted size of US\$ 945.6 million by 2028, with a CAGR of 1.7% during the review period.
- Fully considering the economic change caused by this health crisis, tablets, which accounted for % of the cetirizine hydrochloride global market in 2021, are projected to be worth US\$ million by 2028, growing at a revised % CAGR in the post-COVID-19 period. While the Hospital segment is altered to a % CAGR throughout this forecast period,
- The major players in the industry are J & J, UCB Pharma, GSK, etc. The proportion of revenue in 2019 is 29.00%, 25.87%, and 11.39%. North America has the highest market share by region, accounting for more than 33.8 percent of revenue.
- Global Cetirizine Hydrochloride Scope and Segment

The cetirizine hydrochloride market is segmented by type and by application. Players, stakeholders, and other participants in the global cetirizine hydrochloride market will be able to gain the upper hand as they use the report as a powerful resource. The segmental analysis focuses on sales, revenue, and forecasts by type and by application for the period 2017–2028.

Segment by Type

- Tablet.
- Capsule.
- Solution.

Segment by Application

- Hospital.
- Drug Store.
- By company.

Commercial Availability:

Cetirizine dihydrochloride 10 mg film-coated tablets.

- Brand:- Cipla EU Ltd.

Active ingredient:-

- Cetirizine dihydrochloride

ATC Code: RO6AE07

Each film:-

The coated tablets contain 10 mg of cetirizine.

Excipients with known effects:

Each film-coated tablet contains 100.2 mg of lactose monohydrate.

Film-coated tablet:

The diameter of each tablet is 8 mm.

white-colored, circular, biconvex film coated

tablets, marked with an "A" on one side and a break-line score on the other.

IDENTIFICATION OF MOST WIDELY PRESCRIBED FROM A CLASS(CONSUMPTION REPORT) APPROACHING PHARMACY STORES,COMPANY REPRESENTING AND PHARMA COMPANIES WEB PORTALS:

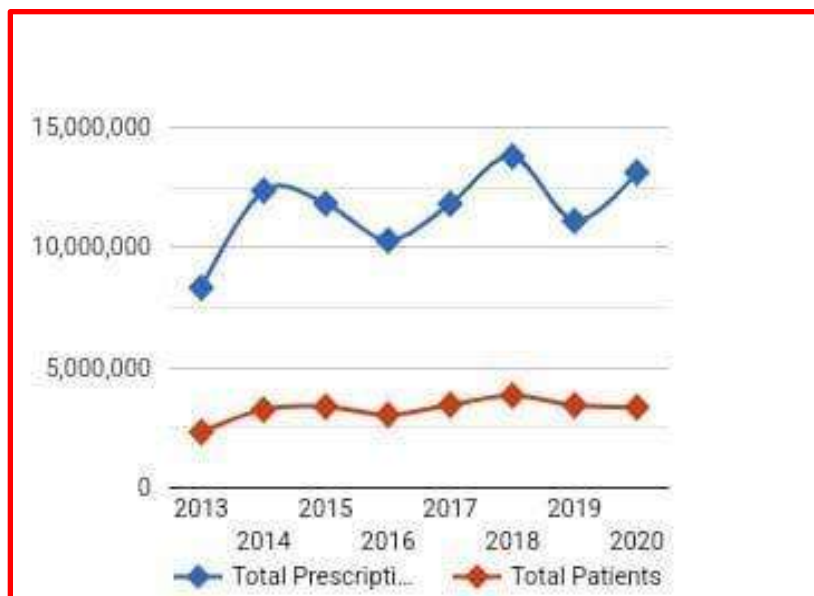
- Cetirizine Summary for 2020:-

Top drug Rank	#52(↑□15)
Estimated number of prescriptions in the United States (2020)	13,125,543
Estimated number of patients in the United States (2020)	3,357,330

Average out-of -pocket cost (USD)

Per Prescription	\$4.50
Per day of therapy	\$0.06/day

- Total prescriptions and patient per year (2013-2020):-



- Rank of top drugs overtime:-

Year	Rank	Change
2013	87	↑ □ 12
2014	69	↑ □ 18
2015	72	↓ □ 3
2016	74	↓ □ 2
2017	66	↑ □ 8
2018	55	↑ □ 11
2019	67	↓ □ 12
2020	52	↑ □ 15

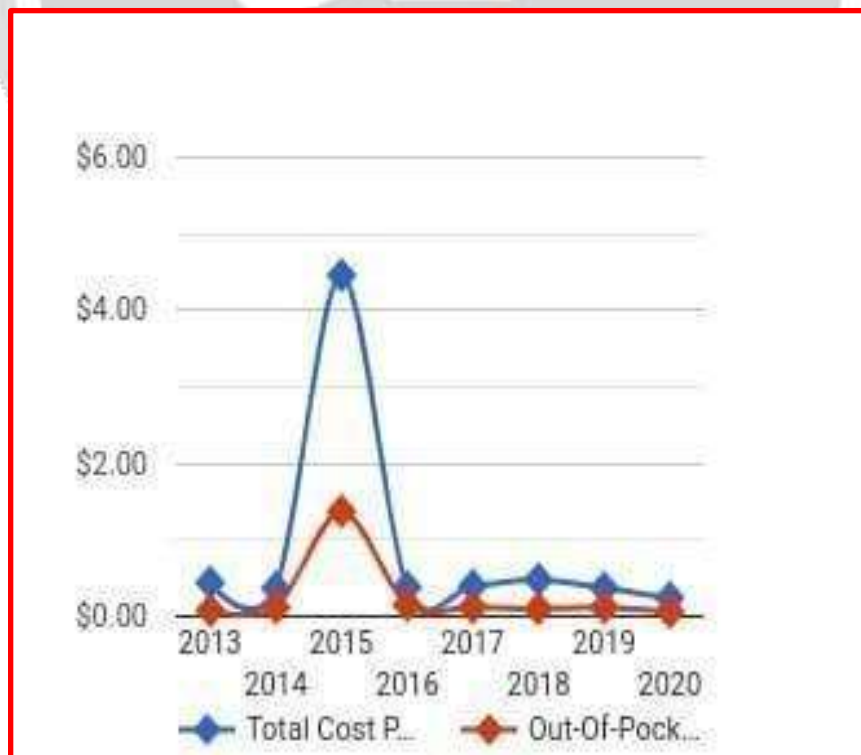
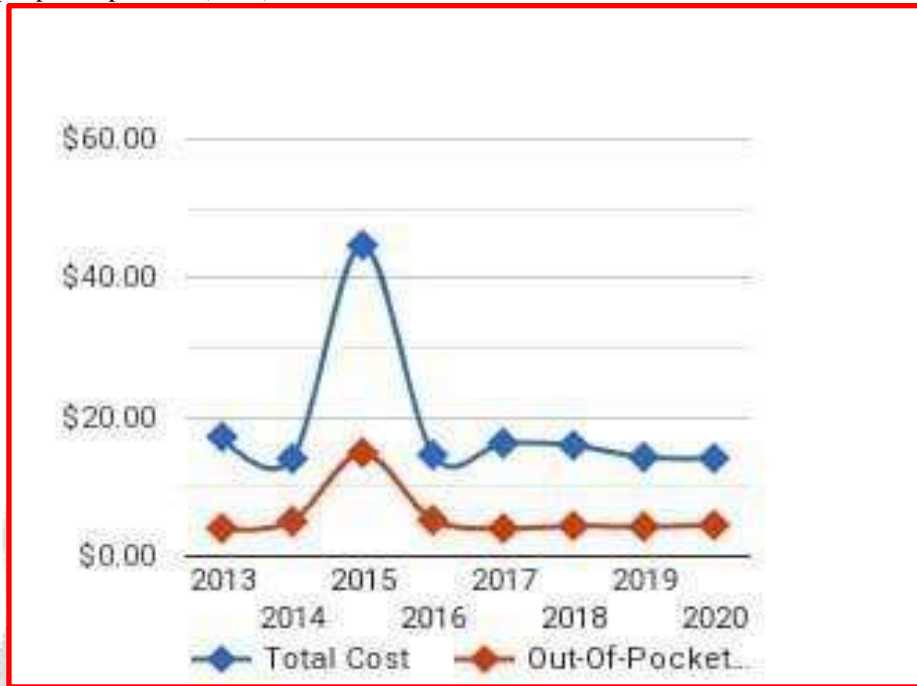
Drug cost over time (2013-2020):

- Cost Per Prescription Fill: Average cost per filled prescription, regardless of how many days of therapy the prescription is filled for (e.g., 10 days, 30 days, 90 days, etc.)
- Cost per Day of Therapy: The average cost per prescription fill divided by the days of therapy For example, a 10-day antibiotic course costing \$30 would be \$3 per day. Similarly, a 30-day supply of an oral antihypertensive costing \$30 would be \$1 per day.
- Total cost: The average total cost of the medication, including the out-of-pocket cost (see below) plus the amount paid by other parties (Medicare, Medicaid, private insurance, the Veterans Administration, TRICARE, other state and federal sources, worker's compensation, and other miscellaneous sources).

Out-of-pocket cost:

The average payment made by the patient, which may include deductibles, coinsurance, copayments, or the cash price paid without insurance coverage.

- Cost per prescription fill(USD):-



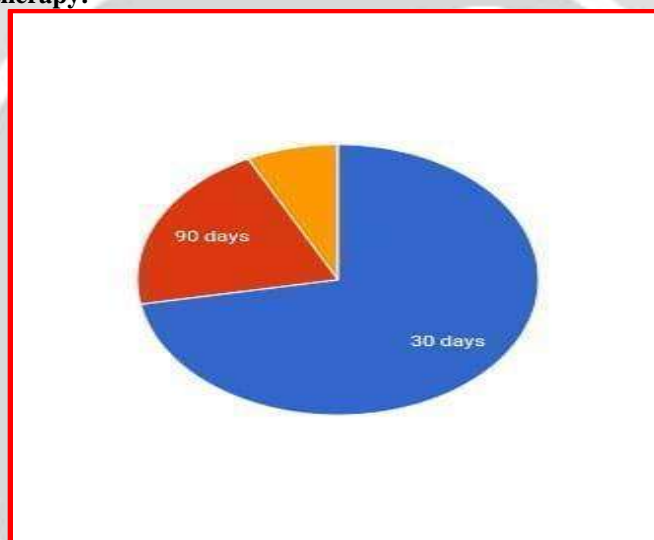
- Distribution of dispensed dosage forms(2020):-

Dosage Form	Strength	% of dispensed products
Tablet/Capsule	10mg	80.7%
Solution	1mg/ml	14.7%
Other,unspecified or misc	-	4.6%

- Distribution of day supplied(2020):-

Days supply" is defined as the number of days that a prescription should last. For example, a prescription of 60 tablets that is taken twice daily has a day supply of 30 days.

- Cost per day of therapy:



- FDA approval information:-

Established pharmacologic class(EPC)	Histamine-1 receptor Antagonists
initial FDA approval date	27/9/1996
First FDA applicant	Disch
First dosage form	Syrup(oral)

Market Analysis and Size:

- In recent years, the antihistamine drugs market has been anticipated to grow rapidly during the forecast period. Histamine is a critical mediator of localized hypersensitivity reactions, assisting in vasodilation, smooth muscle contraction, increased vascular permeability, inflammation, and edema.
- Antihistamines are a type of medication that works by blocking histamine type 1 (H1) receptors. As per the World Health Organization's "White Book on Allergy 2011–2012," allergic rhinitis impacted 10%–30% of the global population, whereas urticarial prevalence was higher than 20% worldwide.



IDENTIFICATION OF ADVERSE EFFECTS OF SELECTED DRUG:

Adverse effects of cetirizine:

- Somnolence
- Headache
- Fatigue
- Dry mouth
- Dizziness
- Diarrhea
- Malaise
- Vomiting
- Epistaxis
- Stomach pain
- Drowsiness
- Angioedema
- Fussiness
- Hallucinations
- Hypotension
- Tremor
- Tongue discoloration

Adverse Effects of Cetirizine:

What happens if I miss a dose?

- If it is almost time for your next dose, take the missed dose as soon as you remember.

Common side effects:

- Pounding or uneven heartbeat
- Weakness, tremors, or sleep problems
- Severe restless feeling
- Confusion
- Problems with vision
- Urinating less often or not at all.

Side effects of Cetirizine:

- Sleepiness
- Headache
- Fatigue
- Dry mouth
- Diarrhea
- Malaise

- Difficulty in breathing
- Vomiting
- Nose bleed
- Stomach pain
- Drowsiness
- Rapid swelling
- Hallucinations
- Low blood pressure
- Tremor
- Tongue

ADVERSE DRUG REACTION MONITORING FORM:

	Indian pharmacopeia commission	For AMC/NCC use only
	report type clinical follow up	AMC report no-
A	patient information	world wide uniq no -12
1	patient initial	relevant test/laboratory data with date
2	age at time event	-
3	M. F. Other.	13 relevant medical history e.g pregnancy allergy
a	weight. Kg/s	-
B	Suspected adverse reaction.	14 seriousness reactions
5	date of started	<ul style="list-style-type: none"> ● death ● Congited ano
6	Date of recovery	<ul style="list-style-type: none"> ● life threatening
7	Describes reaction problems	<ul style="list-style-type: none"> ● Disability
		15 outcomes
		<ul style="list-style-type: none"> ● Recovery ● Rp covered

2: Concentration comitant medical products including self medication and herbal remedies with therapy date (excluding those and treatments) :

<ul style="list-style-type: none"> ● Additional information 	<p>D. Reporter details</p> <p>16- Name and professional adr</p> <p>Pin- Email-</p> <p>Tel.no- (With std code)</p> <p>Occupation- Sign-</p> <p>17- date this report</p>
--	---

Hospital Visits:

Talk to your doctor or pharmacist if these side effects bother you or do not go away:

- headaches
- dry mouth
- feeling sick (nausea)
- feeling dizzy
- diarrhea
- sore throat
- sneezing or a blocked and runny nose.

Serious side effects:

It's rare to have a serious side effect with cetirizine.

Call your doctor right away if you have bruising or bleeding that's more than normal.

Serious allergic reaction:

In rare cases, it's possible to have a serious allergic reaction (anaphylaxis) to cetirizine.

Dosage:

Adult and paediatric dosages

Tablet:

- 5 mg
- 10 mg

Tablet, oral-disintegrating:

- 10 mg

Tablet, chewable:

- 5 mg
- 10 mg

Syrup:

- 5 mg/5 ml

Routes of administration:

- Oral route

Conclusion:

- Cetirizine is well established in the treatment of symptoms of SAR, PAR, or CIU. It demonstrated a corticosteroid-sparing effect and reduced the relative risk of developing asthma in sensitized infants with atopic dermatitis.
- Cetirizine was effective in the treatment of allergic cough and mosquito bites; however, its precise role in these indications has yet to be clearly established. On the basis of its favorable efficacy and tolerability profiles and rapid onset of action, cetirizine provides an important option for the treatment of a wide range of allergic disorders.

Reference:-

- www.wikipedia.com
- www.parexel.com
- <https://go.drugbank.com/drugs/DB00341>
- <https://www.sciencedirect.com/topics/medicine-and-dentistry/cetirizine>
- <https://www.ncbi.nlm.nih.gov/books/NBK549776/>
- <https://www.360researchreports.com/amp/global-cetirizine-hydrochloride-industry-18252343>
- <https://www.medicines.org.uk/emc/product/3474/smpc#gref>
- <https://clinical.com/DrugStats/Drugs/Cetirizine>
- [https://www.rxlist.com/consumer_cetirizine_zyrtec/drugs-condition.htm#:~:text=Cetirizine%20is%20a%20prescription%20approved,not%20caused%20by%20an%20allergy\).](https://www.rxlist.com/consumer_cetirizine_zyrtec/drugs-condition.htm#:~:text=Cetirizine%20is%20a%20prescription%20approved,not%20caused%20by%20an%20allergy).)
- <https://reference.medscape.com/drug/quzyttir-zyrtec-cetirizine-34338>
- <https://go.drugbank.com/salts/DBSALT001214#>
- https://cdsco.gov.in/openems/export/sites/CDSCO_WEB/Pdf-documents/Consumer_Section_PDFs/ADRRF_2.pdf

