



Study of Tramadol drug related with pharmacovigilance

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Abstract

Pharmacovigilance (PV) plays a key role in the healthcare system through assessment, monitoring and discovery of interactions amongst drugs and their effects in humans. Pharmaceutical and biotechnological medicines are designed to cure, prevent or treat diseases; however, there are also risks particularly adverse drug reactions (ADRs) can cause serious harm to patients. Thus, for safety medication ADRs monitoring is required for each medicine throughout its life cycle, during development of drugs such as pre-marketing including early stages of drug design, clinical trials, and post-marketing surveillance. PV is concerned with the detection, assessment, understanding and prevention of ADRs. Pharmacogenetics and pharmacogenomics are an indispensable part of clinical research. Variation in the human genome is a cause of variable response to drugs and susceptibility to diseases are determined, which is important for early drug discovery to PV. Moreover, PV has traditionally been involved in mining spontaneous reports submitted to national surveillance systems. The research focus is shifting toward the use of data generated from platforms outside the conventional framework such as electronic medical records, biomedical literature, and patient-reported data in health forums. The emerging trend in PV is to link premarketing data with human safety information observed in the post-marketing phase. The PV system team obtains valuable additional information, building up the scientific data contained in the original report and making it more informative. This necessitates an utmost requirement for effective regulations of the drug approval process and conscious pre and post approval vigilance of the undesired effects, especially in India.

Clinical Research.....

Clinical trials are prospective biomedical or behavioural research studies on human participants designed to answer specific questions about biomedical or behavioural interventions, including new treatments and known interventions that warrant further study and comparison.

Preclinical trials

Introduction

Details of non-clinical/per-clinical studies are discussed under ICH m3 guidance.

The Non-clinical study recommendations for the marketing approval of a pharmaceutical product include: safety pharmacology studies repeated dose toxicity Studies toxicokinetics and non-clinical pharmacokinetic studies reproduction toxicity studies and genotoxicity studies.

A Typically both In vitro and In Vivo tests will be performed Studies of drug toxicity includes which organs are targeted by that drug, as well if there are any long term Carcinogenic effects or toxic effects causing illness.

Phases of preclinical trials

Safety pharmacology :-

The core safety Pharmacology study includes the assessment of affect cardiovascular, central nervous, respiratory the consideration is given to an any in vivo valuation as addition to general toxicity. Care should be taken to reduce number of animal used

Toxicokinetic & Pharmacokinetic studies:-

In vitro metabolic data for animals and humans & expose data in animals to prior initiating human clinical trials. Further absorption, distribution, metabolism and excretion in animals should be available for treading long duration.

Acute toxicity studies:-

This information has been obtained From single dose toxicity studies in two mammation species using both the clinical and parenteral route of administration.

This available to phase III clinical trials for higher risks overdose eg. Depression, pain, dementia.

Respected Dose toxicity:

In principle the duration of animal toxicity studies conducted in two mammals species.

Local Tolerance studies:-

To evaluate local tolerance by the intended therapeutic bouts as a part of the general toxicity studied. To support limited human adm by non-therapeutic rough eg. (single IV).

Genotoxicity studies:-

An assay for gene mutation is generally considered sufficient to support all single dose clinical development trials.

Carcinogenicity studies:-

- It should be conducted for the marketing application.
- For pharmaceutical development treat certain serious diseases for adults paediatrics patients carcinogenicity testing.

Reproductive toxicity:-

It is Should be conducted as appropriate as the population that is to be exposed. There are four categories: women not of child bearing, women of child bearing in pregnant women.

Other toxicity:-

Non-clinical study eg. identify potential biomarkers

Clinical trials

Introduction

The clinical trials are the Research studies performed in the people that are aimed at evaluating medical, surgical or behavioural intervention that is called clinical trials.

The evolution of the modern clinical trial dates back at least to the eighteenth century. Lind, in his classical study on board the Salisbury, evaluated six treatments for scurvy in 12 patients. One of the two who was given oranges and lemons recovered quickly and was fit for duty after 6 days. The second was the best recovered of the others and was assigned the role of nurse to the remaining ten patients. Several other comparative studies were also conducted in the eighteenth and nineteenth centuries. The comparison groups comprised literature controls, other historical controls, and concurrent controls.

Phases of clinical trials

Phase 0:-

The Phase-0 trials are the exploratory trials that also exist as small clinical trials that involve dosing at a sub-therapeutic level.

Therapy area-any indication

Dosage -sub therapeutic dosing

Trial length -usually Less than one week

It involves 10 to 15 patients

Phase 1:-

Phase 1 trials are the first studies of an investigational new drug in humans.

Phase 1 trials may be conducted in individuals who have the disease the drug is intended to treat.

The Phase-1 has a duration of 1 month to 12 months.

Phase 1 generally involves between 20 to 30 participants.

Phase 2:-

Phase 2 clinical trials test to determine more about how safe the treatment is and how well it will work. Doctors also test whether a new treatment works for a specific cancer.

It is approximately 33% of drugs.

The duration is 12 to 24 months.

It involved no more than several 100 participants.

Phase 3:-

The main objective of phase 3 is to verify the therapeutic action of a new substance in a large number of patients to determine the risk/benefit reaction.

The duration is 1 to 4 years.

It has 300 to 3000 volunteers involved.

Phase 4:-

A type of clinical trials that studies the side effects caused over time by a new treatment after it has been approved and is a market. This tracks 100k side effects that were not seen in earlier trials that may study how well a new treatment works over a long period.

Its duration is a minimum of two years.

It involves several thousand volunteers who have the disease.

Function of Drug Controller General of India (DCGI)

DCGI lays down the standard and quality of manufacturing, selling, import and distribution of drugs in India.

Preparation and maintenance of national reference standards.

To bring about uniformity in the enforcement of the Drugs and Cosmetics Act.

Training of Drug Analysts deputed by State Drug Control Laboratories and other Institutions

Analysis of Cosmetics received as survey samples from CDSCO (central drug standard control organisation)

With the notification of Medical Device Rules 2017 by the Government of India, DCGI will also act as Central Licensing Authority (CLA) for the medical devices which fall under the purview of these rules. Out of four Classes of medical devices from Class A to Class D, DCGI will be the direct licensing authority for Class C and Class D devices, whereas it will coordinate licensing for Class A and B devices through State drug controllers, who will act as State Licensing Authority or SLA.

Function of Central Drug Standard Control Organization (CDSCO)

Under the Drug and Cosmetics Act, the regulation of manufacture, sale and distribution of Drugs is primarily the concern of the State authorities while the Central Authorities are responsible for approval of New Drugs, Clinical Trials in the country, laying down the standards for Drugs, control over the quality of imported Drugs, coordination of the activities of State Drug Control Organisations and providing expert advice with a view of bring about the uniformity in the enforcement of the Drugs and Cosmetics Act.

Types of regulatory application:

Investigational New Drug (IND)

A drug that has not been approved for general use by the food and drug administration but is under investigation in clinical trials regarding its safety and effectiveness first by clinical investigators and then by practising physicians using patients who have given informed consent to participate.

Duration

30 days an IND application may 90 into effect 30 days after FDA receives the application unless FDA notifies the sponsor that the investigations described in the application are subjected to a clinical hold or on career notification by FDA that the clinical investigations in the IND may begin.

New Drug Application (NDA)

The identify and contact information of the sponsor and the phase of the trials. A commitment that an IRB will be responsible for initial and continuing review of The trials. The name of the drug is a list of its active ingredient and its dosage and route of Administration. The objective and planned duration of the proposed clinical trials. Identities and qualifications of all investigators

Duration

Submission of an NDA is the form step asking the FDA to consider a drug for marketing approval. The FDA has 60 days to decide whether to file it so it can be reviewed.

Abbreviated New Drug Application (ANDA)

An abbreviated new drug application ANDA contains data which is submitted to FDA for the review and potentially approval of a generic drug product. Once approved an applicant may manufacture and market the generic drug product to provide a safe, effective, lower cost alternative to the brand name drug it references.

Duration. This act also premises brand name companies to apply for exclusive patient right to cover their new drug for up to 5 years.

Good clinical practice.

● Objective :-

- To provide an overview of the history of a good clinical practice (ICH).
- To emphasize the importance of ICH GCP compliance when conducting clinical trials.
- To recognise implications of non-compliance.
- To review positive and negative cause studies.
- Avoid trial duplication (saving the memory resources).
- The trial requirements for medicinal products containing new.

Scope of GCP:-

- Good clinical laboratory should be used by all laboratories, where tests are done on biological specimen diagnosis, patients' cure, disease cannot.
- Microbiology and serology.
- Hematology and blood banking.
- Molecular biology and molecular pathology.
- Clinical pathology.
- Histopathology.
- Studies physiological biochemical and pathological process of the response to a specific intervention whether physical and chemical.

New drug and clinical trials rules 2019.

In new rules 2019 such research has been defined to include studies that have basic applied and operational research or clinical research designed primarily to increase scientific knowledge about disease and its condition or their detection and cause evolving strategy for health promotion prevention or amelioration of disease and rehabilitation but does not include C.T the study types include ;

- In vitro diagnostic performance testing for research.
- New surgical intervention
- Assisted reproductive technology
- Public health.
- Epidemiology health survey.
- Observational and non-interventional study of old drugs.

Rules applicable to biomedical and health research would be applicable from 15 sep 2019.

Academic clinical trials:-

New rule 2019 described Academic clinical trials as per the drug already approved for a certain claim initiated by any investigator academic research institution for a new indication of new administration or new dose or new dosage form. Where the results of such trials are used for the academic clinical trials.

Some important points for academic clinical trials.

- Only for approved drugs .
- CT initiated by investigator academic or research institute can be conducted for the new indication are new route, new dosage form result only for academic .
- Data cannot be used for seeking approval in any country.

Ethics committee (ECS).

- As delineated in 2019 CT rule and additional resources india has a decentralised process for the ethical review of clinical trials application and ethical committee approval for each trial use.
- In accordance with the 2019 CT rule and additional resources, all ethics committees that review drug clinical trials are required to register with the new drug controller general of India (DCGI).
- In addition, the 2019 CT rule established a separate registration and monitoring system for ECS that overase bio -medical and health research studies.
- Ec composition .
 - Pursuant to the 2019 CT rule and ICMR guidelines,institutional / independent EC should be multidisciplinary,multisectorial,representing mixed gender age composition.
 - As per 2019 CT rule ICMR guidelines composition should below.
 - Chairperson from outside the institute.
 - One to two basic medical sciences preferable one pharmacologist.
 - One to two clinicals from various institutions.
 - Legal experts or retired judges.
 - one philosopher /ethicist.
 - One member independent institutions is non- scientific.
- Phase iv and post marketing studies.
 - New rule 2019 phase iv study.
 - Drug drug interactions.
 - Dose response or safety studies.
 - Trial designed to support use under approved indication.
 - Post marketing surveillance studies.
 - Such studies are conducted with new drug approved condition of its use with scientist objective by CLA.
- Orphan drug registration.
 - New rule 2019 defines orphan drug as a drug intended to treat a condition which affects more than five lakh (500,000) people in india.
 - Provision for fast - track approval process special status orphan drug include complete fee waiver CT filling.
 - Provision expedited review process in situations where evidence for clinical safety efficiency have been established.

Post trial access .

- New rule 2019 defines post trial access as making new drug investigational new drug available to trial subjects after completion of clinical trials through which said drug has been found beneficial to a trial subject during clinical trials.
- There are still some gap in understanding questions raised about issue needed to address (CDSCO)
- How long post trial access medicine should provide to patients this is of special importance there is chronic disease with long treatment.
- How is safety signal monitored for this period would sponsor /investigator/ ethics committee.
- Should sponsors continue to provide drugs under post - trial access marketing Authorization approval and drug availability in the market.
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- Other significant updates.
 - New clinical trials approval timelines also have been included for the clinical trials of drugs developed outside of India , there is a go working day limit of the CLA response.

Concept of pharmacovigilance.

1. Definition , objective , type and components of pharmacovigilance.

Definition :-

Pharmacovigilance is the science and activities relating to the detection , assessment, understanding, and prevention of adverse effects or any other medicine / vaccine rated problem for patients safety.

- Objective:-
- Improvement of patients care and safety in relation to the use of medicine and paramedical intervention remains to be an important parameter.
- The main objective of pharmacovigilance involves exhibiting the efficacy of drugs by monitoring their adverse effects profile for many years from the lab to the pharmacy ; tracking and drastic effect of drug improving public health and safety in relation to the use of medicine.
- Promoting understanding education and clinical training in pharmacovigilance and effective communication to the general public.
- In addition, providing information to consumer practitioners and regulators on the effective use drug .

Types.

- There are four types of pharmacovigilance.
- Passive surveillance.
- Active surveillance.
- Cohort event monitoring.
- Targeted clinical investigation.

Passive surveillance :-

Passive surveillance methods involve the usage of spontaneous adverse event reports voluntarily sent by healthcare professionals or patients to the marketing authorization holder or regulatory authority. Here, data related to the adverse reactions are collected in a central or regional database. The identity of the reporter remains anonymous, but patient-related details like country, age, gender, and pre-existing comorbidities can be recovered from the reporting forms.

Examples of spontaneous reporting systems include the -

FAERS (FDA Adverse Event Reporting System) database run by FDA

VigiBase™, the WHO Global Individual Case Safety Report (ICSR) database

For Europe: EudraVigilance maintained by the European Medicines Agency.

2.Active surveillance:-

This method aims to monitor certain specific drug-related adverse events and seeks to ascertain the number of adverse drug reactions entirely through a pre-planned process. It is commonly known as toxicity monitoring or safety monitoring.

3.cohort event monitoring :-

This method, the surveillance study is planned prior to beginning the treatment with the medication. A group of people are exposed to a drug for a defined period and actively followed up during treatment.

Adverse events of the target drug or the events associated with one or more medicines taken with that drug are monitored.

4.Targeted clinical investigation:-

These kinds of investigations are performed to identify and characterize the adverse reactions related to a drug among special populations like people with some genetic disorders, pregnant women, and older people.

Components :-

- Adverse Event Case Management Including Expedited Report
- pharmacovigilance laws mean that ALL spontaneous reports regarding serious adverse reactions must be expedited within 15 days. In addition, as of 22nd November 2017 all non-serious adverse reactions, with an origin within the EU, require expediting EMA within 90 days.
 - Fact:
- These laws will mean that ALL suspected reactions provoked by a medicinal product must be expedited – regardless of seriousness.
 - Expedited reports
- Remaining compliant throughout all the changes to EU legislation can be a challenging endeavor for any company. This is particularly the case with Expedited Reporting – one of the pillars of all EU pharmacovigilance work.
 - Fact:

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 - Fact:
- These laws will mean that ALL suspected reactions provoked by a medicinal product must be expedited – regardless of seriousness.
 - Fact:
- One of the most common causes of critical findings in Drug Safety Inspections is non-compliance with the expedited reporting of spontaneous adverse drug reactions.
- Non-compliance can result in time-consuming and costly remedial work and/or penalties imposed by regulators. These can include inspections, CAPAs, and suspensions of Marketing Authorisations.
 - What Is Expedited Reporting?
- In the EU post-marketing environment, an Individual Case Safety Report (ICSR) may involve a serious or non-serious adverse reaction – regardless of expectedness. Such cases must be submitted to the regulatory authorities within 15 days or 90 days respectively. As a Marketing Authorisation Holder, you need to be fully versed in each change to the drug safety laws in concerned territories around expedited reporting as and when it happens. With regards to these updates, you as the Marketing Authorisation Holder need to implement them to remain fully compliant. With the right support, you can rapidly respond to the challenges in line with your Standard Operating Procedures.
- Post-Marketing Phases
- Any clinical trials including post-authorization studies during the post-marketing phase of a product will need to be correctly processed and expedited according to regulatory requirements.

Aggregate Reporting

- Aggregate reporting is the process that reviews the cumulative safety information from a wide range of sources, on a periodic basis and submits the findings to regulators worldwide.
- The aggregate safety reports are presented to regulators as soon as the medicine is marketed anywhere in the world and enables understanding of the risk and benefit profile of the product over a period of time.
- These reports focus not so much on individual cases, but rather on overview, assessment of the safety profile and benefit-risk-evaluation of Adverse Drug Reaction (ADR) and the Serious Adverse Event (SAE) and pregnancy reports.
- Why is aggregate reporting important?
- Though the Individual case safety reports were submitted on expedited basis to regulatory authorities, detailed analysis and evaluation of the benefit/risk ratio of a drug is not possible at this level. Therefore periodically reviewing safety reports received cumulatively worldwide, becomes highly significant to analyze the benefit/risk balance of the product.
- These reports need special diligence and attention to detail on the one hand, overview and a sense of what is essential on the other hand.
 - Types of aggregate reports:
 - Pre-marketing report:
- IND annual reports • Clinical study reports (CSR)
- Development Safety Update Report (DSUR)
- Annual safety reports (ASRS) in Europe

- Post-marketing report:
 - Periodic Benefit Risk Evaluation Report (PBRER)/Periodic Safety Update Report (PSUR)
 - Periodic Adverse Drug Experience Report (PADER).
 - NDA and ANDA annual reports
 - Addendum to clinical overviews (ACO).

Signal Detection and management in Pharmacovigilance.

Pharmacovigilance involves the collection of data on Adverse Reactions which must then be analysed and evaluated to create meaningful safety information.

Signal detection in Pharmacovigilance involves looking at the adverse reaction data for patterns that suggest new safety information. This page provides a brief introduction to the definition and purpose of signals and some of the key methodologies employed to generate them.

- What Is A Signal?
 - The term is most commonly associated with drugs during the post-marketing phase, although it may also be used during pre-marketing clinical trials. The definition of a signal as provided by the CIOMS Working Group 8 is:
 - information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify vericatory action".
 - This could be a problem which has never previously been suspected to be associated with the product; or a known event which is now occurring within a patient group for whom it has not been documented before or perhaps occurring with greater frequency than anticipated. The signal may be generated from qualitative analysis of spontaneous reports or quantitative analysis through data mining and statistical activities.

What Is Signal Management in Pharmacovigilance?

- The process of signal management in pharmacovigilance is a set of activities which aim to determine:
 - whether there are new risks associated with a particular drug, or
 - whether risks associated with a particular drug have changed
- Sources for the detection of signals can come from:
 - spontaneous reporting
 - active monitoring systems
 - interventional studies (clinical trials)
 - non-interventional studies (pharmacoepidemiology studies)
 - non-clinical studies (e.g. animal toxicology studies)
 - systematic reviews (i.e. thorough review of the published literature)
 - meta-analyses (i.e. mathematical pooling of all the clinical trial data)
 - other relevant sources.
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Risk Management

Risk management in pharmacovigilance is undertaken to promote safe use of medicines and safeguard health of patients. It is a set of activities performed for identification of risk, risk assessment, and risk minimization and prevention. Risk management has the following stages: identification and characterization of the safety profile of the medicinal product; planning of pharmacovigilance activities to characterize risks and identify new risks; planning and implementation of risk minimization and mitigation and assessment of the effectiveness of these activities; and document postapproval obligations that have been imposed as a condition of the marketing authorization.

All these activities together constitute the risk management plan, which is required to be submitted during the authorization of the drug. The overall aim of risk management is to ensure that the benefits of the medicinal product outweigh the risks by a wide margin for the treatment of a particular indication both at individual level and for the target population as a whole.²⁾ Constitutional objective of pharmacovigilance of india :-

The purpose of the Pharmacovigilance Program of India is to collect, collate and analyze data to arrive at an inference to recommend regulatory interventions, besides communicating risks to healthcare professionals and the public.

Pharmacovigilance Programme of India (PvPI):-

The Central Drugs Standard Control Organization (CDSCO), Directorate General of Health Services under the aegis of Ministry of Health & Family Welfare, Government of India in collaboration with Department of Pharmacology, All India Institute of Medical Sciences (AIIMS), New Delhi has launched the nation-wide Pharmacovigilance programme for protecting the health of the patients by ensuring drug safety. The programme is coordinated by the Department of Pharmacology at AIIMS as a National Coordinating Centre (NCC).

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Objective:-

- To monitor Adverse Drug Reactions (ADRs) in Indian population
- To create awareness amongst health care professionals about the importance of ADR reporting in India .
- To monitor benefit-risk profile of medicines
- Generate independent, evidence based recommendations on the safety of medicines.

- Function of AMC
- To monitor the ADR.
- TO Optimize safe and effective use of medicines in over set up.
- To create awareness amongst health care professionals about the importance of ADR Reporting.
- To monitor benefits risk profile of medicines.
- Generate independent, evidence based recommendations on the safety of medicines.
- Support the CDSCO for formulating safety related regulatory decisions for medicines.
- Communicate finding with all key stakeholders.
- Create a national centre of excellence as per with global drug safety monitoring standards.

SAFETY MONITORING DURING CLINICAL TRIAL

Keywords: Contraindications, Indications, Pain management, Tramadol

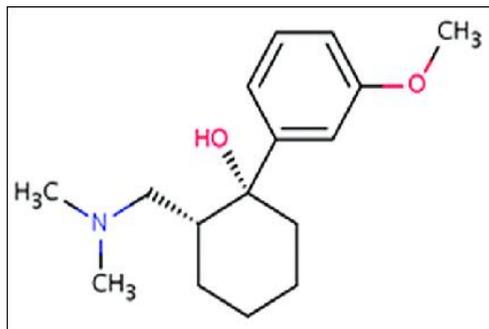
Introduction:

Tramadol is an opioid drug that, unlike classic opioids, also modulates the monoaminergic system by inhibiting noradrenergic and serotonergic reuptake. For this reason, tramadol is considered an atypical opioid. These special pharmacological characteristics have made tramadol one of the most commonly prescribed analgesic drugs to treat moderate to severe pain.

Areas covered: The aim of this review is to provide a historical description of the biochemistry, pharmacokinetics and particularly, the mechanisms of action of tramadol. In addition, a summary is offered of the analgesic effects of tramadol in a variety of animal models of acute and chronic pain. Finally, clinical studies that demonstrate the efficacy and safety of tramadol in the treatment of pain are also assessed.

Expert opinion: The discovery that tramadol combines opioid and monoaminergic effects represented a milestone in the evolution of pain treatment. Given its mild effect on opioid receptors, tramadol induces fewer side effects than classic opioids. Tramadol produces satisfactory analgesia against various types of pain and it is currently approved for the treatment of moderate to severe pain. Thus, the combination of monoamine .

Structure of tramadol drug



TRAMADOL MOLECULAR FORMULA:C16H25NO2

DRUG CLASS:Narcotic Analgesics

Generic Name:Tramadol.

Patent history

The U.S. Food and Drug Administration (FDA) approved tramadol in March 1995, and an extended-release (ER) formulation in September 2005. ER Tramadol was protected by US patents nos. 6,254,887 and 7,074,430.[104][105] The FDA listed the patents' expiration as 10 May 2014.[104] However, in August 2009, US District Court for the District of Delaware ruled the patents invalid, a decision upheld the following year by the Court of Appeals for the Federal Circuit. Manufacture and distribution of generic equivalents of Ultram ER in the United States was therefore permitted prior to the expiration of the patents.

Development-

Effective 18 August 2014, tramadol has been placed into Schedule IV of the federal Controlled Substances Act in the United States.[107][108] Before that, some US states had already classified tramadol as a Schedule IV controlled substance under their respective state laws.[109][110][111]

Tramadol is classified in Schedule 4 (prescription only) in Australia, rather than as a Schedule 8 Controlled Drug (Possession without authority illegal) like most other opioids.

Effective May 2008, Sweden classified tramadol as a controlled substance in the same category as codeine and dextropropoxyphene, but allows a normal prescription to be used.

Pharmacodynamics :

Effect of tramadol on the opioid system Since the first preclinical studies, it was thought that tramadol-induced antinociception was mediated exclusively via the opioid system . However, it was soon noted that tramadol does not produce the classic side effects associated with opioids, such as constipation, respiratory depression, or sedation , suggesting that it might not act exclusively on the opioid system. In vitro studies performed on rat pontine slices demonstrated that tramadol has a low affinity for opioid receptors. Specifically, tramadol has a modest affinity for μ -opioid receptors ($K_i = 2.1 \mu\text{M}$), as well as a weak affinity for δ - and κ - opioid receptors ($K_i = 57.6 \mu\text{M}$ and $42.7 \mu\text{M}$, respectively), representing a 10-fold and 6000-fold weaker affinity than codeine and morphine, respectively .Interestingly, the affinity for μ -opioid receptors differs between the

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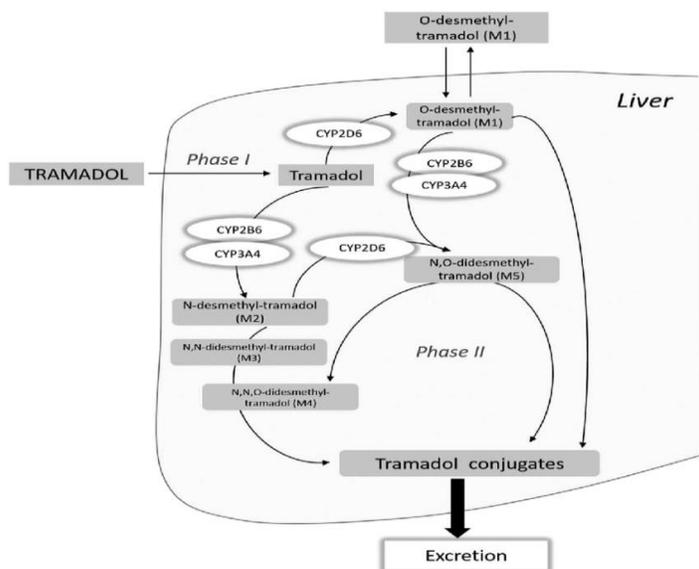


Figure 2. Schematic representation of human tramadol metabolism pathway.

enantiomers of tramadol, with (tramadol binding more strongly to the μ -opioid receptor ($K_i = 1.3\mu\text{M}$) than (–)-tramadol ($K_i = 24.8\mu\text{M}$) [1]. Given the modest affinity of tramadol and its enantiomers for μ -opioid receptors, the affinity of the racemic mix, the enantiomers, and its main metabolite (M1) was studied by ectopically expressing cloned human μ -, δ -, and κ -opioid receptors in neuroblastoma cells. Accordingly, M1 shows greater affinity for μ -opioid receptors than the parental compound ($K_i = 0.0054\mu\text{M}$). In confirmatory studies, M5 displayed high affinity for μ -opioid receptors ($K_i = 0.1\mu\text{M}$), albeit less than M1, while the M2, M3, and M4 metabolites displayed little or no affinity for these cloned human opioid receptors. Moreover, as the analgesic effect of tramadol is only partially blocked by naloxone in different antinociceptive tests, it would appear that tramadol also acts through pathways that do not involve opioid receptors.

Preclinical studies on tramadol:

Acute pain models Initial studies on models of acute pain indicated that intrathecal administration of tramadol to rats suppresses the pain tail-flick response. This effect is reversed by opioid antagonists. Thus, tramadol-induced antinociception appears to be exclusively mediated by spinal opioid mechanisms. However, local tramadol administration in the periaqueductal grey (PAG) prolongs the tail-flick latency, and it reduces evoked A δ and C fiber activity. As the PAG activates descending pain inhibition, tramadol may produce antinociception via spinal and supraspinal pathways. Later studies confirmed this concept, as tramadol administered by different routes (subcutaneously, orally, and intraperitoneally) resulted in antinociception in the abdominal constriction,

hot plate, and tail-flick tests. Moreover, this was the first preclinical data demonstrating that unlike morphine or codeine, tramadol antinociception is only partially antagonized by naloxone, suggesting 1284 L. BRAVO ET AL. Downloaded by [Universidad De Cadiz] at 01:25 10 November 2017 the involvement of opioid and non-opioid mechanisms in its analgesic activity. Such findings were consistent with clinical studies demonstrating that yohimbine (an alpha2-adrenoceptor antagonist) reduced the analgesic effects of tramadol in healthy volunteers [30], suggesting that its mechanism of action in part involves non-opioid-driven effects. Subsequently, the analgesic effect of tramadol in the hot plate (mice) and plantar test (rats) was shown to be enhanced by co-administration of pindolol, a 5HT1A blocker. Moreover, in the hot plate and the tail-flick test the analgesic effect of tramadol in μ -opioid receptor knockout (KO) mice was mainly mediated by μ -opioid and alpha2-adrenoceptor activation [58]. Alternatively, K⁺ channel blockade and the inhibition of nitric oxide synthase also reduce the antinociceptive effect of tramadol in mice in the hot plate test suggesting other possible sites of action for tramadol.

Chronic pain models.
Inflammatory pain The efficacy of tramadol in animal models of chronic pain was initially reported in mono arthritic rats). In this model of inflammatory pain, acute tramadol administration produces a dose-dependent analgesic effect. In turn, chronic administration of tramadol is effective for 8–10 days after treatment in this model, an effect correlated with an increase in 5HT2A receptor-positive cells in the nucleus of raphe magnus, ventrolateral periaqueductal gray, and spinal dorsal horn. In addition, intraperitoneal and intraarticular administration of tramadol also seems to provide analgesic relief from peripheral edema, an effect associated with a decrease in prostaglandin (PGE₂) in peripheral exudates. Elsewhere, intraplantar administration of a selective A1 receptor antagonist blocks the effect of tramadol in the formalin test, indicating a possible role for adenosine receptors in the local analgesia induced by tramadol]. Hence, tramadol seems to be effective in relieving the central and peripheral consequences of inflammatory pain. In addition, tramadol dampens pain-related behavior in the second phase of the formalin test, without affecting the first phase. This effect was reversed by the 5HT2 receptor antagonist ketanserin but not by naloxone, and as fluoxetine enhances the analgesic effect of low doses of tramadol in the formalin test, the serotonergic system seems to be implicated in this phenomenon.

Neuropathic pain Tramadol appears to be effective in several models of neuropathic pain that mimic clinical scenarios (Table 3). Acute and chronic administration of tramadol relieves thermal hypersensitivity in a rat model involving chronic constriction injury (CCI) of the sciatic nerve (6 days post-surgery). A similar effect was also reported after acute administration of tramadol, evident as a decrease in paw lifts in the cold plate test 7 days after CCI surgery. Since this analgesic effect is enhanced by blocking 5HT1A receptors, the combination of tramadol and 5HT1A antagonists could be suitable to alleviate neuropathic pain. Dose-dependent effects of acute treatments have been reported in long-term neuropathic Table 2. rats when sensorial hypersensitivity is most severe (15 and opioid mechanisms open new avenues for the design of innovative analgesics. 21 days post-surgery). Moreover, tramadol has also shown better efficacy compared to opioids (morphine) in neuropathic pain models. Interestingly, acute tramadol treatment also relieves mechanical hypersensitivity in a rat model of diabetic neuropathy, in conjunction with NA release in the LC. This effect is similar to that of clomipramine, a tricyclic antidepressant that is a first-line drug used in patients suffering neuropathic pain. In addition, acute administration of tramadol is effective in a rat model of myalgia and chronic tramadol treatment suppresses the anxiety-like behavior associated with chronic pain in CCI rats 25 days after surgery. These findings demonstrate that tramadol has beneficial effects in the treatment of chronic neuropathic pain. Finally, robust synergistic

anti_hypersensitivity is evident in neuropathic rats after combin_ing tramadol with paracetamol , a combination commonly used in clinical practice.

Visceral pain In chronic visceral pain models, such as in a rat model of ureteral calculus, semi-chronic tramadol therapy is effective in relieving visceral pain). Moreover, it protects against the phenomenon of viscerovisceral hyperalgesia in a rat model of ureteral calculus plus endometriosis . Hence, tramadol might be an interesting option for the relief of chronic visceral pain

5. From preclinical studies to the clinical use of tramadol:

The evaluation of the analgesic effect of tramadol in humans has benefited from preclinical data. Clinical trials first reported that tramadol's efficacy is similar to that of the analgesics available on the market at that time (acetylsalicylic acid, phe_nacetin, codeine and phenobarbital). A particularly rele_vant study was an open multicenter trial with a total of 840 patients suffering acute pain of diverse origin..This study reported efficacy in more than 80% of the patients after intramuscular, intravenous, and rectal administration, with no serious adverse effects. In the 1990s, the efficacy of tramadol was compared to that of morphine ,pentazocine, and ketorolac], mainly relieving acute pain in post-operative situations. After a range of clinical studies reporting that tramadol is well tolerated in acute pain patients, this compound was included in controlled clinical trials to study its efficacy in relieving different conditions of chronic pain. Thus, there are reports of the effectiveness of tramadol in cancer , and chronic non-cancer pain like osteoarthritis ,low back pain , diabetic neuropathy, and polyneuropathy .These studies have led to tramadol being commonly prescribed to relieve acute and cancer pain today. More recently, its effec_tiveness is being potentiated by combining it with paraceta_mol and dexketoprofen,and it is thought to be a good candidate to reduce intra- and post-anesthetic shivering

Pharmacokinetics:

Tramadol is readily absorbed

following oral administration and the bioavailability is 75%

but is subject to first pass metabolism. The rate or extent of

Tramadol absorption is not significantly affected by food.

It is metabolized by N-and O- methylation and

glucuronidation and sulfation in the liver and produce active

metabolite O-desmethylTramadol which is

pharmacologically active. Production of active metabolite

is dependent on the cytochrome P450 isoenzyme CYP2D6,

which exhibits genetic polymorphism. Approximately 30%

of the dose is excreted in the urine as unchanged drug,

whereas 60% of the dose is excreted as metabolites.

Tramadol is widely distributed, crosses the placenta and present in small amounts in breast milk.

Mechanism of action:

Tramadol possesses a weak affinity

for the mu-opioid receptor and even less for the kappa and

delta receptors. Its affinity is about 1/6000 times that of morphine and one tenth that of codeine. The (+) enantiomer

of Tramadol and its major metabolite bind more strongly to

the mu-opioid receptor than the respective (-) enantiomers.

The opioid and 5-hydroxytryptamine (serotonin) reuptake

inhibitory effect is about 4 times more potent in the (+)

enantiomer, whereas the noradrenaline reuptake inhibitory

effect is in the (-) enantiomer. The uptake inhibition in both

the non-opioid and opioid systems takes place in the same

concentration range (0.5 to 50 micromolar). 6

Dosage and administration:

Tramadol can be given orally,

intravenously or rectally as a suppository. The

an intramuscular route has also been used. It may also be given

by infusion. Usual oral dose is 50 to 100 mg every 4-6 hours.

It may also be given orally as a modified release preparation

once or twice daily. The total daily dosage by mouth should

not exceed 400 mg. A dose of 50 to 100 mg may be given

every 4-6 hours by IV injection over 2 to 3 minutes; or by IV

infusion. Rectal dose by suppository is 100 mg up to 4

times daily.

Fixed dose combination of Tramadol:

combination (FDC) of Tramadol/paracetamol is available as tablets containing 37.5/ 325 milligrams (mg). For relief of acute pain, the manufacturer recommends a dose of two tablets every 4 to 6 hours. Duration of treatment of 5 days or less, and a maximum daily dose of 8 tablets is suggested. 8

In a randomized, double-blind, placebo- and active controlled, single-dose study in patients with, at least moderate pain following dental extraction, 2 Tramadol/Acetaminophen tablets were as effective as 1 hydrocodone/Acetaminophen tablet in relieving pain. 9

In another

placebo-controlled study of the FDC, a single dose of two tablets was superior to placebo in treating pain following oral surgical procedures; the combination was at least as effective as Tramadol and Acetaminophen given alone in the same doses.

Adverse effects:

1, 3 Tramadol can produce common as well as serious adverse effects. Some of the common side effects include pruritus, constipation, diarrhea, nausea, vomiting, dizziness, headache, somnolence, vertigo. The serious side effects are postural hypotension (rare), syncope (rare), tachyarrhythmia (rare) anaphylactoid reaction, impaired cognition, seizure (at therapeutic dose range), hallucinations and dyspnea (rare).

It is also known to cause difficulty in concentration, paresthesia, suicidal tendencies, symptoms of serotonin syndrome (e.g. hyperreflexia, fever, shivering, agitation,

diaphoresis etc). These adverse effects are reported in less than 1% of patients receiving the drugs.

Availability:

In Nepal, Tramadol is available as 50 mg capsule costing NRs 10.00 (Approx) and controlled release tab 100 mg costing NRs 28.00 (approx). It is also available as 50 mg Inj costing NRs 22.00 (approx) and 100 mg costing NRs 40.00 (approx).

Precautions for tramadol use.

Tramadol Injection 2 ml will be administered by a healthcare professional; do not self-administer.

Moderate to severe pain

See also This medication is used to help relieve severe ongoing pain. Tramadol belongs to a class of drugs known as opioid analgesics. It works in the brain to change how your body feels and responds to pain.

MISSED DOSE:

If you miss a dose, take it as soon as you remember. If it is near the time of the next dose, skip the missed dose. Take your next dose at the regular time. Do not double the dose to catch up.

- Side Effects of Tramadol drug
- Nausea
- Dizziness
- Headache
- Vomiting
- Dry mouth
- Drowsiness
- Constipation
- Sweating

PRECAUTIONS:

ALCOHOL

CONSULT YOUR DOCTOR

Avoid consumption of alcohol with Tramadol Injection 2 ml as it may cause drowsiness or increase the risk of side effects.

PREGNANCY

Tramadol Injection 2 ml is usually not recommended during pregnancy as chronic use of Tramadol Injection 2 ml during pregnancy may lead to withdrawal symptoms in newborns. However, please inform your doctor if you are pregnant before taking Tramadol Injection 2 ml.

BREAST FEEDING

Tramadol Injection 2 ml may be excreted into breastmilk. Please consult your doctor. Your doctor will decide if Tramadol Injection 2 ml can be given to breastfeeding mothers or not.

DRIVING

CONSULT YOUR DOCTOR

Tramadol Injection 2 ml may cause dizziness, blurred vision or drowsiness in some people. Therefore, avoid driving if you feel drowsy, dizzy or experience any vision problems after taking Tramadol Injection 2 ml.

LIVER

Take Tramadol Injection 2 ml with caution, especially if you have a history of Liver diseases/conditions. The dose may be adjusted by your doctor as required.

KIDNEY

Take Tramadol Injection 2 ml with caution, especially if you have a history of Kidney diseases/conditions. The dose may be adjusted by your doctor as required.

CHILDREN

Tramadol Injection 2 ml should be used in doses recommended by a doctor for children above 1 year. It is not recommended for children with breathing problems as it may worsen tramadol toxicity symptoms.

Habit Forming

Diet & Lifestyle Advice

- Do regular exercises such as swimming or walking.
- Drink plenty of water while taking Tramadol Injection 2 ml to avoid dry mouth.
- Maintain a fibre-rich diet and eat plenty of fresh fruits and vegetables to avoid constipation while taking Tramadol Injection 2 ml.
- Avoid consumption of alcohol and quit smoking.
- Patients with severe liver or kidney insufficiency should avoid taking Tramadol Injection 2 ml.
- Drug Interactions

Drug-Drug Interactions: TRAMADOL+ACETAMINOPHEN may interact with anticonvulsants (carbamazepine, pregabalin), opioid painkillers (pentazocine, buprenorphine, nalbuphine, morphine), cough medication (codeine), muscle relaxant (baclofen), blood thinners (warfarin, phenprocoumon), antiemetic drugs (ondansetron,

metoclopramide, domperidone), high cholesterol lowering medicine (cholestyramine), sedative-hypnotics (zolpidem), pain relievers (celecoxib), antidepressants (duloxetine, escitalopram), and anti-anxiety drugs (alprazolam).

Drug- Food Interactions: Avoid foods rich in carbohydrates, pectin including jellies, cabbage, Brussels sprouts and broccoli as TRAMADOL+ACETAMINOPHEN may interact with these foods. TRAMADOL+ACETAMINOPHEN may interact with grapefruit juice. Therefore, avoid intake of grapefruit juice with TRAMADOL+ACETAMINOPHEN as it may increase TRAMADOL+ACETAMINOPHEN levels in the body. Also, avoid alcohol consumption while taking TRAMADOL+ACETAMINOPHEN as it may increase drowsiness.

Drug-Disease Interactions: If you have fits, asthma, severe lung problems, severe headaches associated with vomiting, drug dependence, liver or kidney problems or if you have recently suffered from shock or head injury, inform your doctor before taking TRAMADOL+ACETAMINOPHEN.

Drug-Drug Interactions Checker List:

- · CARBAMAZEPINE
- · ONDANSETRON
- · FLUOXETINE
- · DOXEPIN
- · DROPERIDOL
- · MORPHINE
- · CODEINE
- · WARFARIN

Toxic Mechanism:

Tramadol is a weak partial agonist at mu opioid receptors. It also inhibits serotonin and noradrenaline reuptake in the CNS, hence the serotonin toxicity, tachycardia and risk of seizures.

Toxicokinetics:

- Rapid absorption
- Peak levels at 1-3 hours but can range from 2-12 hours for modified release (even longer in overdose)
- Volume of distribution 2-3L/kg
- Hepatic metabolism and renal excretion.

EFFICACY

Efficacy evaluations included: Western Ontario and McMaster University Osteoarthritis Index (WOMAC) scores (pain, stiffness, physical function and global), daily efficacy ratings (post-dose: tramadol OAD 24 hours; tramadol BID 12 hours), pain ratings over 24 hours, and patient and investigator overall ratings. Non-inferiority was demonstrated for the primary endpoint, mean percentage change in WOMAC pain score from baseline to week 12 (tramadol OAD 58%; tramadol BID 59%) [95% CI -7.67, 3.82]. The median optimum dose received was 200mg (both treatments). In 73% of patients, pain was mild to absent at the end of the dosing interval for both treatments (tramadol OAD 24 hours; tramadol BID 12 hours). Pain ratings over 24 hours were similar between groups, indicating 24-hour sustained efficacy for tramadol OAD. More tramadol BID patients reported dizziness/vertigo (37% vs 26%), vomiting (14% vs

8%) and headache (18% vs 13%) while tramadol OAD patients reported more somnolence (30% vs 21%).

OVERDOSE:

If someone has overdosed and has serious symptoms such as passing out or trouble breathing, give them naloxone if available, then call 911. If the person is awake and has no symptoms, call a poison control center right away. US residents can call their local poison control center at 1-800-222-1222. Canada residents can call a provincial poison control center. Symptoms of overdose may include: slow breathing, slow/irregular heartbeat, coma, seizure.

NOTES:

Do not share this medication with others. Sharing it is against the law. This medication has been prescribed for your current condition only. Do not use it later for another condition unless told to do so by your doctor. A different medication may be necessary in that case.

Drug Warnings

If you are allergic to Tramadol or any other medicines, please tell your doctor. Tramadol Injection 2 ml is not recommended for children suffering from breathing problems as it may worsen the symptoms of tramadol toxicity. If you are pregnant or breastfeeding or have a history of fits, please inform your doctor before taking Tramadol Injection 2 ml. Do not consume alcohol with Tramadol Injection 2 ml as it may increase the risk of side effects. Tramadol Injection 2 ml may cause withdrawal symptoms if stopped abruptly. Avoid frequent or high doses as it may lead to addiction.

Conclusions: The efficacy of tramadol for the management of moderate to severe postoperative pain has been demonstrated in both inpatients and day surgery patients. Most importantly, unlike other opioids, tramadol has no clinically relevant effects on respiratory or cardiovascular parameters. Tramadol may prove particularly useful in patients with poor cardiopulmonary function, including the elderly, the obese and smokers, in patients with impaired hepatic or renal function, and in patients in whom nonsteroidal anti-inflammatory drugs are not recommended or need to be used with caution. Parenteral or oral tramadol has proved to be an effective and well tolerated analgesic agent in the perioperative setting.

*selection of a drug class for pharmacovigilance study using different criteria(e.g commercial availability)

#Availability.

Tramadol is available in various dosage forms

- Tablets
- Capsules
- Sprays
- IV,IM

Tramadol is used to treat moderate to severe pain

It is available in combination with paracetamol

Tramadol was patented in 1963 & launched under the name “tramal” in 1977 by the west german pharmaceutical company grunenthal.in the mid-1990s.it was approved in the united kingdom and the united states.

It is available as a generic medication and marketed under many brand names worldwide.

#various types of brands available in the market like.

-selling of drug :

Tramadol is a dangerous opioid painkiller that is not given without physician advice.

China is the number one supplier of fentanyl to the US and also supply in Canada and mexico.

Tramadol is a less powerful opioid though more potent if taken with chemical makeup and it's not regulated by international conventions in many countries.

Tramadol is prescribed as a pain medication.

Indian tramadol networks have even been linked to ISIS and BOKO HARAM ,raising security concerns.

Cost of Tramadol

Profiling of selection drug class

(Eg-MOA,pharmacological effect ,ADR,drug interactions,contraindications)

*(Above the point information are already mentioned in module no:4)

Tramadol

Drug Usage Statistics, United States, 2013 — 2020.

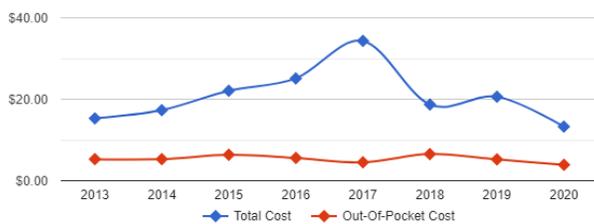
Tramadol Summary for 2020

Top drug rank	#35 (0)
Estimated number of prescriptions in the United States (2020)	17,475,419
Estimated number of patients in the United States (2020)	4,878,951
Average total drug cost (USD)	
Per prescription	\$13.27
Per day of therapy	\$0.95/day
Average out-of-pocket cost (USD)	

Per prescription	\$3.89
Per day of therapy	\$0.27/day

Total Prescriptions and Patients Per Year (2013 - 2020)

[Save Image](#)



Rank of Top Drugs Over Time

"Rank" refers to the frequency that a given medication is prescribed within a calendar year compared to all other medications. A rank of "4" would indicate that the medication was the fourth most commonly prescribed medication.

Year	Rank	Change
2013	29	1
2014	24	5
2015	27	3
2016	38	11
Year	Rank	Change
2017	31	7
2018	25	6

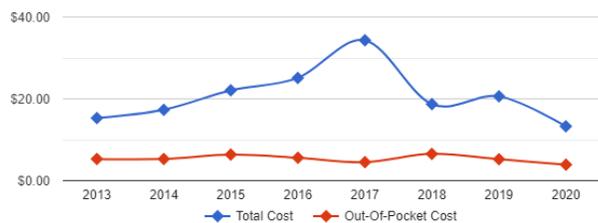
Year	Rank	Change
2019	35	10
2020	35	0

Drug Cost Over Time (2013 - 2020)

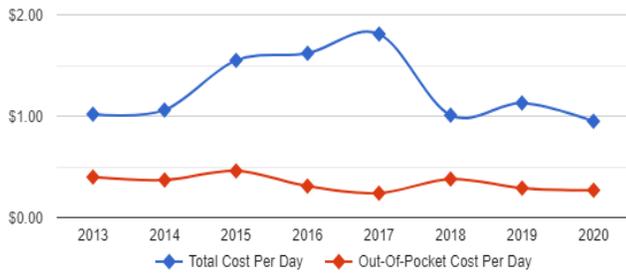
- **Cost Per Prescription Fill:** Average cost per filled prescription regardless of how many days of therapy the prescription is filled for (e.g. 10 days, 30 days, 90 days, etc.)
- **Cost per Day of Therapy:** The average cost per prescription fill divided by the days of therapy. For example, a 10-day 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, Veterans Administration, TRICARE, other state/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)



Cost Per Day of Therapy (USD/day)



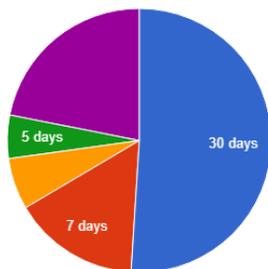
[Save Image](#)

Distribution of Dispensed Dosage Forms (2020)

Dosage Form	Strength	% of Dispensed Products
Tablet/capsule	50 mg	96.9%
Other, unspecified, or misc.		3.1%

Distribution of Days 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.



Related Drugs

Drug Name	Total Prescriptions (2020)
<u>Acetaminophen; Hydrocodone</u>	30,100,356
<u>Tramadol (this drug)</u>	17,475,420
<u>Oxycodone</u>	12,289,519
<u>Acetaminophen; Oxycodone</u>	10,086,467
<u>Morphine</u>	4,384,337
<u>Acetaminophen; Codeine</u>	2,791,618
<u>Hydromorphone</u>	1,747,152
<u>Loperamide</u>	799,680
<u>Codeine; Guaifenesin</u>	415,672
<u>Homatropine; Hydrocodone</u>	49,346
<u>Chlorpheniramine; Hydrocodone</u>	13,840

- Therapeutic Classes
- Central Nervous System Agents
- Analgesics
- Narcotic Analgesics
- Drug Synonyms

Drug synonyms are used during the sanitation and standardization process of "cleaning" the original data source (MEPS). Occasionally, brand names may be listed below that are no longer on the market or are very infrequently used.

Brand Name Synonyms

- Conzip
- Qdoba
- Rybix Odt
- Ryzolt

- Ultram
- Ultram ER

Generic Drug Synonyms and Salts

- Tramadol Hydrochloride
- Tramadol

FDA Approval Information

Established Pharmacologic Class (EPC):	<u>Opioid Agonist</u>
Initial FDA approval date:	3/3/1995
First FDA applicant:	Rx
First dosage form:	Tablet (oral)

Before taking this medicine :-

- Tramadol may be taken with or without food.
- The long-acting formulation must be swallowed whole; do not crush or chew as you may receive a dangerous or fatal dose. ...
- May make you sleepy and affect your ability to drive or operate machinery. ...

Avoid alcohol. ...

- Ask a doctor before using this medicine if you are pregnant or breastfeeding:-

Pregnancy.

- TRAMADOL+ACETAMINOPHEN is not recommended for pregnant women as it may cause withdrawal symptoms in the newborn baby. However, please consult your doctor if you are pregnant.

Breast Feeding.

- TRAMADOL+ACETAMINOPHEN may be excreted in breast milk and cause adverse effects in the baby. However, please consult a doctor if you are breastfeeding.

Side effect of tramadol

- Drowsiness
- Nausea
- Dizziness

- Headache
- Vomiting
- Dry mouth
- Constipation
- Excessive sweating
- Shaking
- Confusion
- Mood changes
-

OVERDOSE:

- If someone has overdosed and has serious symptoms such as passing out or trouble breathing, give them naloxone if available, then call 911. If the person is awake and has no symptoms, call a poison control center right away. Symptoms of overdose may include: slow breathing, slow/irreg

What to avoid :-

- Take TRAMADOL+ACETAMINOPHEN with caution, especially if you have a history of Kidney diseases/conditions. The dose may be adjusted by your doctor as required. Avoid taking TRAMADOL+ACETAMINOPHEN if you have severe kidney insufficiency ular heartbeat, coma, seizure.

Adverse Drug Reaction (ADR) Monitoring Form :-

Preparation of ADR monitoring form as per guidelines given by AMCs (e.g. Indian Pharmacopoeia Commission)

Adverse drug reactions monitoring form:-

Sr .no	Indian pharmacopoeia commission	For AMC/NCC Use only
	Report type clinical follow up -	AMC report no -

		World wide unique no -
A	Patient information	12-Relevant test/laboratory date with date

1	Patient initial	13-Relevant medical history e.g- pregnancy allergy
2	Age at time event	
3	M-. F-. Other -	
a	Weigh. <u>Kg/s</u>	
B	Suspect adverse reactions	14- serious relations
5-	Date of started	Death. Congited
6-	Date of recovery	Life threatening
7-	D described reaction problem	Disability
		15- outcome Recover Rp covering

Suspected medication:-

Sr .n	Name Brand generic	Manufacturers	Batch no	Exp date	Dose used	Freque ncy	Route used	Indicati on casualt
-------	--------------------	---------------	----------	----------	-----------	------------	------------	---------------------

Disease:- pain caused by headaches, fevers, and other illnesses.

Drug :Tramadol

Drug ADR:-

- Nausea.
- Vomiting.
- Weakness.
- Sleepiness.

Dosage :- Ultracet

Paracetamol 325 mg.

Tramadol(37.5mg)

Routes of administration:-

Oral route of administration.

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