Summary of Background Research for Vasopressin in Renal Failure

**Conducted on February 2024**

# Table of Contents

**1. Title**

**2. Objective**

**3. A summary of findings from nonclinical in vitro or in vivo studies that have potential clinical significance**

*3.1 Summary*

*3.2 Background*

*3.3 Structure*

*3.4 Weight*

*3.5 Chemical Formula*

*3.6 Indications and usage*

*3.7 Associated Conditions*

*3.8 Associated Therapies*

*3.9 Mechanism of action*

*3.10 Metabolism*

*3.11 Route of elimination*

*3.12 Half life*

*3.13 Toxicity*

*3.14 Dosage and administration*

*3.15 Contraindications of the drug*

*3.16 Warnings and precautions*

*3.17 Clinical Pharmacology- Pharmacodynamics, Pharmacokinetics*

*3.18 Non-clinical toxicology*

*3.19 Clinical Studies*

*3.20 Storage and handling*

**4. A summary of relevant clinical research and any history of human use or exposure to the study intervention, including use in other countries, and clinical pharmacology studies**

*4.1 Results Overview from previous clinical trials*

*4.2 Trial Description: Brief Summary of study type/design*

*4.3 Drug trial snapshots*

*4.4 Participant Flow*

*4.5 Record History*

*4.6 Study record dates*

*4.7 Intervention and Treatment*

*4.8 Outcome Measures of previous clinical trials*

**5. Discussion of important literature and data that are relevant to the trial and that provide background for the trial**

*5.1 Summary of related research articles*

*5.2 Main outcomes and measures- of research articles*

*5.3 Demographic profile*

*5.4 Study Design for background*

**6. Applicable clinical, epidemiological, or public health background or context of the clinical trial**

*6.1 Importance of the research*

*6.2 Objective of the research*

*6.3 Use of the drug in specific populations*

**7. Importance of the clinical trial and any relevant treatment issues or controversies**

*7.1 Adverse events*

*7.2 Possible side effects*

*7.3 Drug interactions*

*7.4 Over dosage*

**2. Objective**

The objective of this document is to generate concise and informative summaries of previous clinical trials sourced from various data repositories. The automated summary will extract key information from diverse clinical trial datasets, condensing the findings into digestible formats for easy consumption by researchers, healthcare professionals, and decision-makers

**3. Findings from nonclinical in vitro or in vivo studies that have potential clinical significance**

**3.1 Summary**

Vasopressin, a peptide hormone, is employed to elevate blood pressure in individuals experiencing vasodilatory shock, especially those who do not respond adequately to conventional fluid and catecholamine treatments.

**3.2 Background**

Vasopressin, also known as arginine-vasopressin or antidiuretic hormone, is a nonapeptide primarily synthesized in the hypothalamus, with diverse physiological functions encompassing diuresis, hemodynamic regulation, and behavioral modulation. It closely resembles oxytocin but differs in the third and eighth amino acids. Despite its multifaceted roles, exogenous vasopressin is predominantly utilized to manage blood pressure in systemic shock by inducing vasoconstriction and enhancing renal fluid reabsorption through activation of V1 and V2 cellular receptors.

The vasopressive properties of extracts from the posterior pituitary gland were first observed in 1895, but vasopressin itself was not isolated and purified until 1951. Over the past five decades, it has been employed for various medical conditions, including variceal bleeding, diabetes insipidus, and more recently, vasodilatory shock. Currently, it is commercially available under the trademark VASOSTRICT® by PAR Pharmaceuticals.

**3.3 Structure**

**3.4 Weight**

Average: 2140.46

Monoisotopic: 2138.869561874

**3.5 Chemical Formula**

C92H130N28O24S4

**3.6 Indications and Usage**

Vasopressin injection is prescribed for adults experiencing vasodilatory shock, characterized by persistent hypotension even after administration of fluids and catecholamines, aiming to elevate blood pressure.

**3.7 Associated conditions**

Used in treatment of Vasodilatory shock

**3.8 Associated therapies**

Dental Local anesthesia

**3.9 Mechanism of Action**

Vasopressin, known chemically as Cyclo (1-6) L-Cysteinyl-L-Tyrosyl-L-PhenylalanylL-Glutaminyl-L-Asparaginyl-L-Cysteinyl-L-Prolyl-L-Arginyl-L-Glycinamide, is a cyclic nonapeptide hormone primarily synthesized by the supraoptic and periventricular nuclei within the hypothalamus. The release of vasopressin is triggered by sensory pathways, responding to either a 2% rise in plasma osmolarity or a 10% drop in blood pressure. Upon release, vasopressin exerts diverse physiological effects, both centrally and systemically, predominantly through its binding to G-protein-coupled receptors named V1 (V1A), V2, and V3 (formerly V1B).

V1 receptors are prominently expressed in the brain, where vasopressin binding can elevate blood pressure via autonomic pathways. In peripheral tissues, V1 is found in blood vessels, platelets, adrenal glands, kidneys, and liver. Activation of V1 receptors triggers intracellular signaling cascades leading to vasoconstriction, mediated by increased intracellular calcium levels and muscle contraction. Interestingly, vasopressin can also induce vasodilation by binding to oxytocin receptors and stimulating endothelial nitric oxide synthesis, which antagonizes muscle contraction. Additionally, vasopressin, acting through V1 and oxytocin receptors, may prompt the cardiac release of atrial natriuretic peptide, impacting heart rate and cardiac output.

V2 receptors are predominantly found in the distal convoluted tubules and collecting ducts of the kidneys. Vasopressin binding to V2 receptors activates protein kinase A through cyclic adenosine monophosphate (cAMP) signaling, leading to phosphorylation of aquaporin-2 channels and subsequent water reabsorption, resulting in antidiuretic effects.

V3 receptors, primarily located in the anterior pituitary and brain, mediate the release of adrenocorticotropic hormone during acute stress and modulate various effects within the brain, including recognition, memory, aggression, anxiety, and depression.

In cases of vasodilatory shock, where there is an excessive vasodilation, vasopressin levels increase significantly, but normal serum levels may be insufficient to counteract the pathological vasodilation. Vasopressin administration helps restore vascular smooth muscle sensitivity to catecholamines, inhibits excessive nitric oxide production, and decreases the dose requirement for norepinephrine, often administered alongside it to restore normal blood pressure in shock states.

**3.10 Metabolism**

Animal studies suggest that vasopressin is metabolized by serine proteases, carboxypeptidases, and disulphide oxidoreductases, primarily in the liver and kidneys. These cleavage events occur at sites important for vasopressin's activity, and hence the metabolites are expected to be inactive

**3.11 Route of elimination**

Vasopressin is primarily eliminated in the urine, where only 6% of the dose is excreted unchanged

**3.12 Half life**

Vasopressin administered at 0.01-0.1 U/min has an apparent t1/2 of ≤10 minutes, although half-lives of up to 44 minutes have been reported in the literature.

**3.13 Toxicity**

An overdose of vasopressin is anticipated to manifest with adverse effects stemming from excessive vasoconstriction in peripheral, mesenteric, and coronary vascular beds, along with potential complications such as hyponatremia, ventricular tachyarrhythmias, rhabdomyolysis, and gastrointestinal symptoms. However, due to vasopressin's rapid metabolism and clearance from the body, discontinuation of vasopressin administration typically leads to the resolution of symptoms.

**3.14 Dosage and Administration**

To prepare for intravenous administration, dilute the contents of the 20 units/mL single-dose vial with either normal saline (0.9% sodium chloride) or 5% dextrose in water (D5W) to achieve concentrations of either 0.1 units/mL or 1 unit/mL. Any unused diluted solution should be discarded after 18 hours at room temperature or within 24 hours if refrigerated.

For the management of post-cardiotomy shock, administer vasopressin at a rate ranging from 0.03 to 0.1 units per minute.

In cases of septic shock, the recommended infusion rate is between 0.01 to 0.07 units per minute.

**3.15 Contradictions**

The 10 mL multiple dose vial of Vasopressin injection should not be used in patients who have a known allergy or hypersensitivity to either 8-L-arginine vasopressin or chlorobutanol. Conversely, the 1 mL single-dose vial, which lacks chlorobutanol, is contraindicated only in individuals with a confirmed allergy or hypersensitivity to 8-L-arginine vasopressin.

**3.16 Warnings and precautions**

May exacerbate cardiac function

Transient diabetes insipidus

**3.17 Clinical Pharmacology**

**Pharmacodynamics**

At therapeutic levels, exogenous vasopressin induces vasoconstriction in various vascular beds, including the splanchnic, renal, and cutaneous circulations. Furthermore, at pressor doses, vasopressin prompts smooth muscle contractions in the gastrointestinal tract via muscular V1 receptors, and stimulates the release of prolactin and ACTH through V3 receptors. At lower concentrations typical for its antidiuretic function, vasopressin inhibits water diuresis via renal V2 receptors. Moreover, vasopressin has been shown to induce vasodilation in numerous vascular beds, mediated by V2, V3, oxytocin, and purinergic P2 receptors.

In individuals experiencing vasodilatory shock, therapeutic doses of vasopressin augment systemic vascular resistance and mean arterial blood pressure, while reducing the need for norepinephrine. Vasopressin typically decreases heart rate and cardiac output. The pressor effect is directly proportional to the infusion rate of exogenous vasopressin, reaching its peak within 15 minutes and dissipating within 20 minutes after infusion cessation. Notably, there is no evidence of tachyphylaxis or tolerance to vasopressin's pressor effect in patients.

**Pharmacokinetics**

Plasma concentrations of vasopressin rise in a linear fashion with escalating infusion rates ranging from 10 to 200 μU/kg/min. Steady-state plasma concentrations are attained approximately 30 minutes after the initiation of continuous intravenous infusion.

**3.18 Non-clinical toxicology**

**Carcinogenesis, Mutagenesis, Impairment of Fertility:**

Formal studies examining the carcinogenic potential or effects on fertility of vasopressin in animals have not been conducted. In vitro tests, including the bacterial mutagenicity (Ames) test and the Chinese hamster ovary (CHO) cell chromosome aberration test, yielded negative results for vasopressin. However, in mice, vasopressin has been reported to impact the function and fertilizing ability of spermatozoa.

**Animal Toxicology and/or Pharmacology:**

No specific toxicology studies regarding the effects of vasopressin in animals have been performed.

**3.19 Clinical Studies**

Increases in both systolic and mean blood pressure have been documented following the administration of vasopressin in seven studies involving septic shock and eight studies involving post-cardiotomy vasodilatory shock

**3.20 Storage and handling**

| **Condition** | **Temperature Range** | **Storage Duration** |
| --- | --- | --- |
| Unopened Refrigerated | 2°C to 8°C (36°F to 46°F) | Until manufacturer expiration date |
| Unopened Room Temperature | 20°C to 25°C (68°F to 77°F) | 12 months or until manufacturer expiration date, whichever is earlier |

**4 Summary of relevant clinical research and any history of human use or exposure to the study intervention, including use in other countries, and clinical pharmacology studies**

**4.1 Results Overview**

Conditions: Hypertension, End Stage Renal Disease

**4.2 Trial Description**

Allocation: Randomized

Interventional model: Parallel Assignment

Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)

Primary Purpose: Treatment

**4.3 Drug trial snapshot of related drugs**

TERLIVAZ is a vasopressin receptor agonist indicated for improving kidney function in adults diagnosed with hepatorenal syndrome (HRS) and experiencing rapid reduction in kidney function.

TERLIVAZ is administered via injection every six hours, with treatment duration extending up to 14 days.

The FDA approval of TERLIVAZ relied on findings from the CONFIRM clinical trial, which enrolled 199 patients diagnosed with HRS and experiencing rapid decline in kidney function. The trial was conducted across 60 sites spanning two countries: United States (55 sites) and Canada (5 sites). Both efficacy and safety assessments were conducted within the same trial.

The effectiveness of TERLIVAZ was evaluated through a double-blind study design. Participants diagnosed with HRS and encountering rapid kidney function decline were randomly assigned to receive either TERLIVAZ (199 participants) or a placebo (101 participants). The treatment regimen involved intravenous administration of either 0.85 mg of TERLIVAZ or a placebo every six hours for a maximum duration of 14 days. Dosing adjustments were made based on changes in kidney function.

**4.4 Participant flow**

|  |  |  |  |
| --- | --- | --- | --- |
| **Arm/Group Title** | **Very low dose** | **Low dose** | **Placebo** |
| Arm/Group Description | Very Low Dose: Active Comparator 0.15 mU per kg per minute | Low Dose: Active Comparator 0.30 mU per kg per minute | No Dose - Placebo Comparator |
| Overall Study | | | |
| Started | 4 | 4 | 4 |
| Completed | 3 | 3 | 4 |
| Not Completed | 1 | 1 | 0 |
| Reason not completed | | | |
| Physician Decision | 1 | 0 | 0 |
| Withdrawal by Subject | 0 | 1 | 0 |

**4.5 Record History**



**4.6 Study record dates**

First Submitted

2010-11-22

First Posted

2010-11-24

Results First Submitted

2011-04-04

Results First Posted

2011-04-28

Last Update Posted

2019-11-18

Last Verified

2019-10

**4.7 Intervention and Treatment**

Drug: Vasopressin - Very Low Dose

Drug: Vasopressin - Low Dose

Drug: Placebo Comparator

**4.8 Outcome and Measures**

**Primary (Current):** Change in Mean Interdialytic 44-hour Ambulatory Systolic Blood Pressure Over a 2 Week Follow-up Period [Time Frame: Baseline and Two Weeks]: This is designed to measure if the administration of intradialytic AVP will result in change in systolic blood pressure.

**Primary (Original):** Change in mean interdialytic 44-hour ambulatory blood pressure [Time Frame: (a) At baseline, before study visit 1, and (b) Two weeks later after visit 6 (the last pilot study treatment visit).]

**5.1 Summary of related research articles**

Acute renal failure (ARF) often occurs in critically ill patients, often with multisystem organ failure syndrome. While the mortality rate of ARF remains elevated, animal studies suggest that proactive measures and prompt intervention could potentially reduce both morbidity and mortality. This review outlines ARF criteria using indicators such as urine volume, laboratory metrics, and clinical symptoms.

Currently, norepinephrine is the recommended first-line vasopressor for treating septic shock. Nevertheless, some suggest considering early vasopressin administration as an alternative approach.

The influence of dietary protein intake on the progression of CHRONIC RENAL FAILURE may also involve VASOPRESSIN and the operation of the concentrating process. VASOPRESSIN receptors have been identified in glomeruli, and VASOPRESSIN can constrict mesangial cells as does angiotensin II. Acute VASOPRESSIN infusion increases the glomerular transcapillary hydraulic pressure difference, and chronic VASOPRESSIN infusion increases GFR.

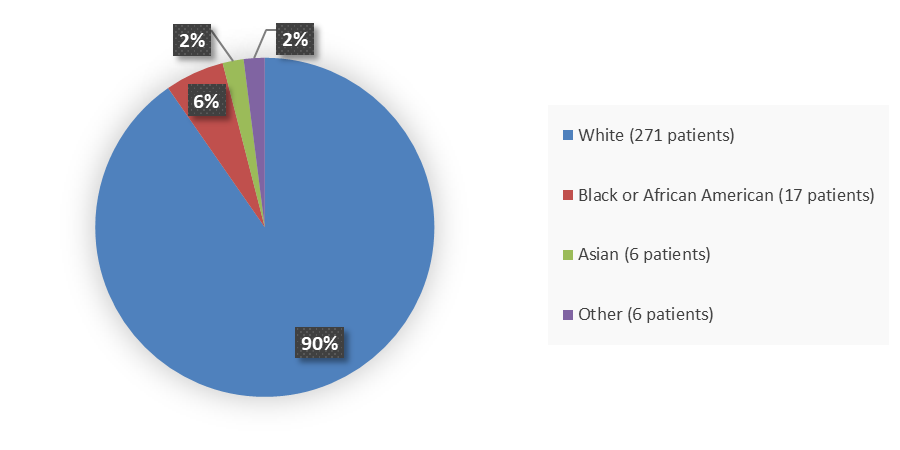
**5.2 Main outcomes and measures of related research articles**

In adults experiencing septic shock, administering vasopressin early on instead of norepinephrine did not result in a significant improvement in the number of kidney failure-free days. While these results do not advocate for replacing norepinephrine with vasopressin as the initial treatment in such cases, it's worth noting that the confidence interval allowed for the possibility of a clinically significant benefit with vasopressin. Consequently, larger trials may be necessary to delve deeper into this potential benefit. The recent acknowledgment of acute kidney injury (AKI) as a potential precursor to chronic kidney disease and end-stage renal disease, along with the associated rise in mortality rates, has sparked interest in both the clinical epidemiology and mechanistic understanding of renal recovery following AKI episodes. Currently, there is no standardized definition for what constitutes recovery after AKI, and various factors need to be considered when formulating such a definition. The extent of renal recovery following an AKI incident can influence clinical decisions regarding the initiation of renal replacement therapy and holds significant implications for assessing biomarkers and identifying mechanistic targets for potential future clinical trials.

**5.3 Demographic profile**

The demographic of people involved in this study were:

* All 18 years and above
* In end Stage Renal Disease on Hemodialysis greater than 3 months
* Had hypertension (Predialysis systolic blood pressure (SBP) greater than 140 mmHg, averaged over preceding 6 dialysis treatments)
* Had a stable dry weight over preceding 6 dialysis treatments



**5.4 Study Design for background**

The main objective is to assess how impaired renal function affects the pharmacokinetics (PK) of the drug and to ascertain whether the observed changes warrant a dosage adjustment. This objective can be achieved through various methods, tailored to the drug's properties and the target patient population.

To comprehensively understand how impaired renal function influences the pharmacokinetics (PK) of a drug, it's essential to include participants with a spectrum of renal function, ranging from normal to severely impaired. The renal function classification provided in Table 1 serves as a useful tool for enrolling participants in dedicated renal impairment studies. Additionally, it can aid in formulating dosing recommendations based on the observed PK outcomes.

**Sec 6** **Applicable clinical, epidemiological, or public health background or context of the clinical trial**

**6.1 Importance of the research**

Chronic kidney disease (CKD) is rare in horses with an overall prevalence reported to be 0.12%. There is often a continuum from Acute Kidney Injury (AKI) to CKD, and patients with CKD may be predisposed to episodes of AKI. The most common clinical signs are non-specific with weight loss, polyuria/polydipsia and ventral edema. Less common clinical signs are poor appetite and performance, dull hair coat, oral ulcerations, gastro-intestinal ulceration, gingivitis, dental tartar and diarrhea.

Norepinephrine is currently recommended as the first-line vasopressor in septic shock; however, early vasopressin use has been proposed as an alternative. Hence, the effectiveness of Vasopressin is important to be established.

**6.2 Objective of the research**

To measure the effectiveness of early vasopressin in comparison on kidney failure in patients with septic shock.

**6.3 Use of the drug in specific populations**

Pregnancy Risk Summary:

There is a lack of available data on the use of vasopressin in pregnant women, making it difficult to assess the risk of major birth defects, miscarriage, or adverse outcomes for both the mother and fetus.

Clinical Considerations: Dose adjustments during pregnancy and the postpartum period: Due to increased clearance of vasopressin in the second and third trimesters, it may be necessary to adjust the dosage of vasopressin accordingly. Maternal adverse reactions: Vasopressin could lead to uterine contractions that may risk continuing pregnancy.

Lactation: There is no available data regarding the presence of vasopressin injection in human or animal milk, its effects on breast-fed infants, or its impact on milk production.

Pediatric Use: The safety and efficacy of vasopressin in pediatric patients with vasodilatory shock have not been established.

Geriatric Use: Clinical trials involving vasopressin did not involve enough subjects aged 65 and older to determine if they respond differently compared to younger subjects. However, reported clinical experience has not indicated any notable differences in responses between elderly and younger patients. Generally, caution should be exercised in selecting doses for elderly patients, typically starting at the lower end of the dosage range, due to the higher likelihood of decreased hepatic, renal, or cardiac function, as well as the presence of concurrent diseases or other medications.

**Sec 7** **Importance of the clinical trial and any relevant treatment issues or controversies**

**7.1 Adverse events**

Method of systematic assessment used was Physician assessment.

The time frame would be for 3 weeks.

**7.2 Possible side effects**

TERLIVAZ increases the risk of serious or fatal respiratory (breathing) failure. Patients with low oxygen in their blood should not start the medication. During treatment, patients should be monitored for breathing problems with a pulse oximeter, a tool that measures oxygen levels in the blood. Side effects of TERLIVAZ may prevent patients from receiving a liver transplant. TERLIVAZ can cause ischemic events (that occur when blood does not reach certain parts of the body) that may require pausing or stopping treatment; the medication may also cause fetal harm when used during pregnancy.

**7.3 Drug interactions**

|  |  |
| --- | --- |
| A[mitriptyline](https://go.drugbank.com/drugs/DB00321) | Amitriptyline may increase the fluid retaining and vasopressor activities of Vasopressin. |
| [Amitriptylinoxide](https://go.drugbank.com/drugs/DB13114) | Amitriptylinoxide may increase the fluid retaining and vasopressor activities of Vasopressin. |
| [Amoxapine](https://go.drugbank.com/drugs/DB00543) | Amoxapine may increase the fluid retaining and vasopressor activities of Vasopressin. |
| [Ardeparin](https://go.drugbank.com/drugs/DB00407) | The therapeutic efficacy of Vasopressin can be decreased when used in combination with Ardeparin. |
| [Bemiparin](https://go.drugbank.com/drugs/DB09258) | The therapeutic efficacy of Vasopressin can be decreased when used in combination with Bemiparin. |

**7.4 Over dosage**

Overdosage with vasopressin can be expected to manifest as consequences of vasoconstriction of various vascular beds (peripheral, mesenteric, and coronary) and as hyponatremia. In addition, overdosage may lead less commonly to ventricular tachyarrhythmias (including Torsade de Pointes), rhabdomyolysis, and non-specific gastrointestinal symptoms. Direct effects will resolve within minutes of withdrawal of treatment.

**Explanation:**

**Section 3:** *This section displays a summary of different factors related to drug-related information from sources like DailyMed, DrugBank like Summary, Background, Structure, Weight, Chemical Formula, Indications and usage, Associated Conditions, Associated Therapies, Mechanism of action, Metabolism, Route of elimination, Half-life, Toxicity, Dosage and administration, Contraindications, Warnings and precautions, Clinical Pharmacology- Pharmacodynamics, Pharmacokinetics, Non-clinical toxicology, Clinical Studies and Storage and handling information of the drug*

**Section 4:** *This section displays a summary of different aspects to relevant clinical research from sources like Clinicaltrials.gov and* [*FDA website*](https://www.fda.gov/drugs/drug-approvals-and-databases/drug-trials-snapshots-terlivaz)

*4.1 Results Overview from previous clinical trials: This displays a summary of what has happened in the previous clinical trials and what conditions the drug is associated with*

*4.2 Trial Description: This displays a brief summary of study type or the design of the trial*

*4.3 Drug trial snapshots: This shows a quick overview of related drugs to the one in the study*

*4.4 Participant Flow: This section shows progression of participants through various stages of a clinical trial, from enrollment to completion. This includes the number of participants who started, completed, and dropped out of the study, also highlighting the reasons why the trial was discontinued*

*4.5 Record History: This table shows all the versions of this study record arranged in order by submitted date*

*4.6 Study record dates: These dates track the progress of study record and summary results submissions to ClinicalTrials.gov*

*4.7 Intervention and Treatment: this section shows processes or actions that is the focus of a clinical study. Interventions include drugs, medical devices, procedures, vaccines, and other products that are either investigational or already available.*

*4.8 Outcome Measures of previous clinical trials: This section highlights the specific parameters, variables, or endpoints used to evaluate the effects of an intervention or treatment being studied*

**Section 5:**

*5.1 Summary of related research articles – This part contains information summarized from the relevant research articles*

*5.2 Main outcomes and measures of research articles- This includes the results found in various research papers pertaining to our topic.*

*5.3 Demographic profile-* *This talks about the various demographic profiles of the selected candidates for the trial.*

*5.4 Study Design for background- This part talks about how we are going to design the trial or the study of the patients. We will need understanding of the trial objectives and data about study design to design the study in a way that gives optimum results. This data can be gathered from FDA site.*

**Section 6:** This section talks about the importance or the context to why this particular clinical trial is being conducted. It will contain the major objectives and importance of the trial with giving some background on the patient population.

*6.1 Importance of the research*

*6.2 Objective of the research*

*6.3 Use of the drug in specific populations- This refers to the various complications or issues that can arise in certain populations on consuming this drug. This information can be found in portals like DailyMed which give all round information about the drug.*

**Section 7:** This sectionre-instates the importance of the clinical trial and gives information on any relevant treatment issues or controversies occurred in the past trials or any research.

*7.1 Adverse events - Refers to any unforeseen complications occurring in any past records.*

*7.2 Possible side effects*

*7.3 Drug interactions*

*7.4 Over dosage*