

**DOCTOR AS ARTIST**

# Painting through emotional pain

*Art helped Dr. David Haughton deal with the unfairness of disease he has witnessed. Now he is inspired by more peaceful things*

by Michelle Cinelli

DR. DAVID HAUGHTON has a distant memory of being five years old and in an after-school art program as the time when he decided he was an artist above all else.

"I remember wanting to make something beautiful and knowing that what was going on the paper was just awful, and being very angry about it," he says. "So I wanted to be an artist literally as long as I can remember."

Today, Dr. Haughton works in the pediatric emergency department at BC Children's Hospital in Vancouver, and has created hundreds of pieces of art spanning more than 35 years.

Dr. Haughton's work ranges from beautiful landscapes inspired by his surroundings to dark and symbolic expressions of emotional upheaval. And there are two categories for the incubation of his ideas.

"First is an immediate visual stimulus; I'll just be walking along and—wham!—something will hit me, an emotional and intellectual response. I think, 'Oh, I want to try to make something that gives the same kind of wham!' Then I try to figure out what it is. As an artist you can really emphasize the parts that had the emotional energy, and bring those out."

For darker, figurative pieces, such as Dr. Haughton's Kindertotentanz series that combines many themes and symbols, the process is different.

"There's some emotional question, dilemma, or something that I struggle with. Those tend to be painful, and it can take decades for me to chew over before I can come up with an idea on how to paint it."

Excited in high school by the drawings of the famous Japanese artist Katsushika Hokusai, Dr. Haughton began etching and doing pen and ink drawings, all the while finding his own style, following a theory borrowed from Hokusai that art gets better with time.

During his pediatric residency at Cornell University in New York between 1984 and 1987, Dr. Haughton began the

Kindertotentanz series, a dark emotional response to what he was living every day.

"Kindertotentanz" literally means "children's dance of death," and the series of paintings depicts children and embryos as they suffer through debilitating and often life-threatening diseases. The works borrow imagery from New



Photos courtesy of David Haughton

adjustments of TRIDURAL dose, acetaminophen or ibuprofen may be given. If immediate-release tramadol is used for breakthrough pain, the total daily dose of tramadol should not exceed 300 mg. Selection of breakthrough medication should be based on individual patient conditions. **Missed Dose:** If a patient forgets to take one or more doses, they should take their next dose at the normal time and in the normal amount. **Discontinuation:** Clinical experience suggests that signs and symptoms of withdrawal may be avoided by tapering medication when discontinuing tramadol therapy.

## Study References

TRIDURAL Product Monograph, Labopharm Inc., 2008.

## Supplemental Product Information

### ADVERSE REACTIONS

#### Clinical Trial Adverse Drug Reactions

Table 1. Percentage of Patients with Incidence of Adverse Events  $\geq 1\%$  from Three 12-week Placebo-Controlled Studies (MDT3-002, MDT3-003 and MDT3-005).

| Adverse Events  | Tridural          |                   |                   |                    | Placebo<br>N = 668 |
|---|-------------------|-------------------|-------------------|--------------------|--------------------|
|   | 100 mg<br>N = 216 | 200 mg<br>N = 311 | 300 mg<br>N = 530 | Total*<br>N = 1095 |                    |
| <b>Any TEAE</b>   | 125 (57.9%)       | 184 (59.2%)       | 302 (57.0%)       | 690 (63.0%)        | 338 (50.6%)        |
| <b>Ear and labyrinth disorders</b>                          |                   |                   |                   |                    |                    |
| Vertigo   | 3 (1.4%)          | 3 (1.0%)          | 8 (1.5%)          | 27 (2.5%)          | 3 (0.4%)           |
| <b>Gastrointestinal disorders</b>                           |                   |                   |                   |                    |                    |
| Abdominal pain NOS  | 2 (0.9%)          | 5 (1.6%)          | 8 (1.5%)          | 17 (1.6%)          | 7 (1.0%)           |
| Abdominal pain upper  | 3 (1.4%)          | 4 (1.3%)          | 9 (1.7%)          | 18 (1.6%)          | 4 (0.6%)           |
| Constipation  | 21 (9.7%)         | 38 (12.2%)        | 53 (10.0%)        | 143 (13.1%)        | 27 (4.0%)          |
| Diarrhea  | 6 (2.8%)          | 1 (0.3%)          | 10 (1.9%)         | 21 (1.9%)          | 20 (3.0%)          |
| Dry mouth   | 7 (3.2%)          | 17 (5.5%)         | 7 (1.3%)          | 38 (3.5%)          | 8 (1.2%)           |
| Dyspepsia   | 3 (1.4%)          | 6 (1.9%)          | 4 (0.8%)          | 13 (1.2%)          | 7 (1.0%)           |
| Nausea  | 29 (13.4%)        | 50 (16.1%)        | 88 (16.6%)        | 202 (18.4%)        | 39 (5.8%)          |
| Vomiting  | 8 (3.7%)          | 19 (6.1%)         | 36 (6.8%)         | 71 (6.5%)          | 6 (0.9%)           |
| <b>General disorders and administration site conditions</b> |                   |                   |                   |                    |                    |
| Fatigue   | 6 (2.8%)          | 10 (3.2%)         | 9 (1.7%)          | 29 (2.6%)          | 6 (0.9%)           |
| Pain exacerbated  | 6 (2.8%)          | 3 (1.0%)          | 6 (1.1%)          | 18 (1.6%)          | 16 (2.4%)          |
| Weakness  | 3 (1.4%)          | 5 (1.6%)          | 4 (0.8%)          | 12 (1.1%)          | 1 (0.1%)           |
| <b>Infections and infestations</b>                          |                   |                   |                   |                    |                    |
| Influenza   | 2 (0.9%)          | 1 (0.3%)          | 8 (1.5%)          | 11 (1.0%)          | 3 (0.4%)           |
| Nasopharyngitis   | 4 (1.9%)          | 7 (2.3%)          | 7 (1.3%)          | 20 (1.8%)          | 18 (2.7%)          |
| Upper respiratory tract infection NOS                       | 3 (1.4%)          | 5 (1.6%)          | 6 (1.1%)          | 16 (1.5%)          | 17 (2.5%)          |
| Urinary tract infection NOS                                 | 2 (0.9%)          | 3 (1.0%)          | 6 (1.1%)          | 12 (1.1%)          | 10 (1.5%)          |
| <b>Investigations</b>                                       |                   |                   |                   |                    |                    |
| Weight decreased  | 1 (0.5%)          | 5 (1.6%)          | 11 (2.1%)         | 20 (1.8%)          | 1 (0.1%)           |
| <b>Metabolism and nutrition disorders</b>                   |                   |                   |                   |                    |                    |
| Anorexia  | 5 (2.3%)          | 4 (1.3%)          | 11 (2.1%)         | 27 (2.5%)          | 2 (0.3%)           |
| <b>Musculoskeletal and connective tissue disorders</b>      |                   |                   |                   |                    |                    |
| Arthralgia  | 2 (0.9%)          | 3 (1.0%)          | 8 (1.5%)          | 15 (1.4%)          | 14 (2.1%)          |
| <b>Nervous system disorders</b>                             |                   |                   |                   |                    |                    |
| Dizziness   | 18 (8.3%)         | 31 (10.0%)        | 59 (11.1%)        | 119 (10.9%)        | 21 (3.1%)          |
| Headache NOS  | 13 (6.0%)         | 18 (5.8%)         | 26 (4.9%)         | 64 (5.8%)          | 43 (6.4%)          |
| Somnolence  | 12 (5.6%)         | 23 (7.4%)         | 26 (4.9%)         | 82 (7.5%)          | 13 (1.9%)          |
| Tremor  | 1 (0.5%)          | 3 (1.0%)          | 6 (1.1%)          | 11 (1.0%)          | 1 (0.1%)           |
| <b>Psychiatric disorders</b>                                |                   |                   |                   |                    |                    |
| Anxiety NEC   | 1 (0.5%)          | 6 (1.9%)          | 4 (0.8%)          | 11 (1.0%)          | 1 (0.1%)           |
| Insomnia  | 3 (1.4%)          | 9 (2.9%)          | 11 (2.1%)         | 25 (2.3%)          | 8 (1.2%)           |
| <b>Skin and subcutaneous tissue disorders</b>               |                   |                   |                   |                    |                    |
| Pruritus NOS  | 11 (5.1%)         | 16 (5.1%)         | 23 (4.3%)         | 60 (5.5%)          | 7 (1.0%)           |
| Sweating increased  | 1 (0.5%)          | 10 (3.2%)         | 16 (3.0%)         | 38 (3.5%)          | 6 (0.9%)           |
| <b>Vascular disorders</b>                                   |                   |                   |                   |                    |                    |
| Hot flushes NOS   | 1 (0.5%)          | 3 (1.0%)          | 7 (1.3%)          | 12 (1.1%)          | 1 (0.1%)           |

\* Due to the difference in study design of MDT3-005, only the results of the double-blind phase of the study are presented and the dose specific results include maintenance period data only.

**Adverse events with an incidence of <1.0% (whether considered by the clinical investigator to be related to the study drug or not):**

**Blood and lymphatic system disorders:** anaemia, lymphadenopathy, thrombocytopenia.  
**Cardiac disorders:** acute myocardial infarction, angina pectoris, angina unstable, atrial fibrillation, bradycardia, cardiovascular disorder, palpitations, sinus tachycardia, tachycardia.  
**Ear and labyrinth disorders:** cerumen impaction, ear congestion, ear discomfort, ear pain, labyrinthitis, tinnitus.  
**Endocrine disorders:** hypothyroidism.  
**Eye disorders:** cataract, dry eyes, eye pain, eyelid disorder, lacrimation increased, photopsia, scleral haemorrhage, blurred vision, visual disturbance.  
**Gastrointestinal disorders:** abdominal discomfort, abdominal distension, lower abdominal pain, abdominal tenderness, change in bowel habit, constipation aggravated, diverticulitis, dyspepsia aggravated, dysphagia, faecal impaction, feces discoloured, flatulence, food poisoning, gastric irritation, gastritis, gastrointestinal haemorrhage, gastrointestinal irritation, gastro-oesophageal reflux disease, hiccups, lip blister, loose stools, pancreatitis aggravated, rectal haemorrhage, rectal prolapse, retching, small intestinal obstruction, toothache.  
**General disorders and administration site conditions:** asthenia, chest pain, chest tightness, fall, feeling abnormal, feeling cold, inflammation localised, inflammation, influenza like illness, lethargy, malaise, mass, oedema peripheral, pain, rigors, thirst.  
**Hepatobiliary disorders:** biliary tract disorder, cholelithiasis.  
**Immune system disorders:** hypersensitivity, seasonal allergy.  
**Infections and infestations:** abscess limb, bladder infection, bronchitis, ear infection, erysipelas, foot infection fungal, fungal infection, gastroenteritis, gastroenteritis viral, gastrointestinal infection, helicobacter infection,

herpes simplex, herpes zoster, laryngitis acute, nail fungal infection, otitis externa, otitis media, otitis media serous, pharyngitis, respiratory tract infection viral, sinusitis, sty, tooth abscess, tooth infection, tracheitis, vaginosis fungal, viral infection, wound infection.

**Injury, poisoning and procedural complications:** abrasion, arthropod bite, back injury, blister, concussion, eye injury, face injury, hand fracture, head injury, joint sprain, laceration, ligament injury, limb injury, muscle injury, muscle strain, neck injury, postoperative wound complication, soft tissue injury, tendon injury, wrist fracture.

**Investigations:** alanine aminotransferase decreased, alanine aminotransferase increased, aspartate aminotransferase decreased, aspartate aminotransferase increased, blood amylase increased, blood calcium increased, blood cholesterol increased, blood creatinine increased, blood glucose abnormal, blood glucose increased, blood in stool, blood potassium abnormal, blood pressure increased, blood urea increased, body temperature increased, cardiac murmur, c-reactive protein increased, gamma-glutamyltransferase increased, haematocrit decreased, haematocrit increased, haemoglobin decreased, haemoglobin increased, low density lipoprotein increased, lymphocyte count increased, mammogram abnormal, mean platelet volume decreased, neutrophil count decreased, protein total decreased, red blood cell count decreased, red blood cell count increased, red blood cell sedimentation rate increased, red cell distribution width increased, white blood cell count increased.

**Metabolism and nutrition disorders:** decreased appetite, dehydration, diabetes mellitus, gout, hypercholesterolemia, hyperglycaemia, hyperlipidemia, hypertriglyceridaemia, hyperuricaemia, hypocalcaemia, hypokalaemia.

**Musculoskeletal and connective tissue disorders:** back disorder, back pain, bone pain, bone spur, bursitis, ganglion, groin pain, joint crepitation, joint disorder, joint stiffness, joint swelling, muscle cramps, muscle spasms, musculoskeletal discomfort, musculoskeletal stiffness, myalgia, neck pain, neck stiffness, osteoarthritis aggravated, osteopenia, osteoporosis, pain in limb, plantar fasciitis, polyarthralgia, rheumatoid arthritis, temporomandibular joint arthralgia, tendonitis.

**Neoplasms benign, malignant and unspecified (including cysts and polyps):** benign breast neoplasm, breast cancer invasive, breast cancer, thyroid neoplasm, uterine fibroids.

**Nervous system disorders:** ataxia, burning sensation, disturbance in attention, dysarthria, dysgeusia, gait abnormal, headache aggravated, hypoesthesia, mental impairment, migraine, neuralgia, paraesthesia, sedation, sinus headache, sleep apnoea syndrome, syncope.

**Psychiatric disorders:** abnormal behaviour, agitation, bipolar disorder, confusion, depression, emotional disturbance, euphoric mood, indifference, irritability, libido decreased, nervousness, sleep disorder.

**Renal and urinary disorders:** calculus renal, difficulty in micturition, dysuria, haematuria, micturition urgency, nocturia, renal impairment, renal pain, urinary frequency, urinary hesitation, urinary incontinence, urinary retention.

**Reproductive system and breast disorders:** dysmenorrhoea, erectile dysfunction, genital pruritus female, menometrorrhagia, prostatitis, sexual dysfunction, vaginal cyst, vaginal discharge.

**Respiratory, thoracic and mediastinal disorders:** asthma aggravated, asthma, chest wall pain, cough, crackles lung, dry throat, dyspnoea, epistaxis, nasal congestion, nasal oedema, pharyngolaryngeal pain, productive cough, rhinitis allergic, rhinitis, rhinorrhoea, rhonchi, sinus congestion, sinus pain, throat irritation.

**Skin and subcutaneous tissue disorders:** acne, cold sweat, contusion, dermatitis allergic, dermatitis contact, dermatitis, dermatitis aggravated, dermatosis, dry skin, eczema exacerbated, eczema, erythema, hyperkeratosis, ingrowing nail, night sweat, pallor, piloerection, prurigo, pruritus generalised, rash, rash pruritic, rosacea, skin ulcer, urticaria.

**Surgical and medical procedures:** cardiac pacemaker replacement, colon polypectomy, endodontic procedure, foot operation, hernia repair, lesion excision, tumour excision.

**Vascular disorders:** aortic aneurysm, deep venous thrombosis, flushing, haematoma, hot flushes aggravated, hypertension aggravated, hypertension, hypotension, orthostatic hypotension, poor peripheral circulation, vascular insufficiency, wound haemorrhage.

### Abnormal Hematologic and Clinical Chemistry Findings

In clinical trials where clinical abnormalities were recorded (N = 106), the following abnormalities were reported: Sedimentation rate increased (0.7%), glucose abnormalities (0.5%), GGT increased (0.4%).

The following abnormalities occurred in 0.2% of patients: cholesterol abnormalities, LDH increased, uric acid increased, hemoglobin decreased, red cell count decreased.

The following abnormalities occurred in <0.1% of patients: hemocrit decreased, alanine aminotransferase increased, aspartate aminotransferase increased, urea increased, liver function tests abnormal.

The following abnormalities were single occurrences: alanine aminotransferase decreased, aspartate aminotransferase decreased, amylase increased, bilirubin increased, calcium increased, creatinine increased, potassium abnormal, C-Reactive Protein increased, haematocrit increased, haemoglobin increased, low density lipoprotein increased, lymphocyte count decreased, mean platelet volume decreased, neutrophil count decreased, platelet count decreased, protein total decreased, red cell count increased, red cell distribution width increased, white cell count increased.

### Other Adverse Experiences Previously Reported in Clinical Trials or Post-Marketing Reports with Tramadol Hydrochloride

Adverse events which have been reported with the use of tramadol products include: allergic reactions (including anaphylaxis, angioneurotic edema and urticaria), bradycardia, convulsions, drug dependence, drug withdrawal (including agitation, anxiety, gastrointestinal symptoms, hyperkinesia, insomnia, nervousness, tremors), hyperactivity, hypoactivity, hypotension and respiratory depression. Other adverse events which have been reported with the use of tramadol products and for which a causal association has not been determined include: difficulty concentrating, hepatitis liver failure, pulmonary edema, Stevens-Johnson syndrome and suicidal tendency.

Serotonin syndrome (whose symptoms may include mental status change, hyperreflexia, fever, shivering, tremor, agitation, diaphoresis, seizures and coma) has been reported with tramadol when used concomitantly with other serotonergic agents such as SSRIs and MAOIs.

### DRUG ABUSE, ADDICTION AND DEPENDENCE

#### Withdrawal Symptoms

Withdrawal symptoms have been studied in 325 patients, 3 and 7 days after discontinuation of treatment with TRIDURAL. The majority of symptoms were mild to moderate in nature. Onset of the post-treatment adverse events occurred more frequently within the first 3 days after treatment was stopped. Less than 1% of patients taking TRIDURAL met the DSM-IV criteria for a diagnosis of opioid withdrawal.

#### DRUG INTERACTIONS

##### Overview

*In vitro* studies indicate that tramadol is unlikely to inhibit the CYP3A4-mediated metabolism of other drugs when it is administered concomitantly at therapeutic doses. Tramadol does not appear to induce its own metabolism in humans, since observed maximal plasma concentrations after multiple oral doses are higher than expected based on single dose data. Tramadol is a mild inducer of selected drug metabolism pathways measured in animals. Administration of CYP3A4 inhibitors, such as ketoconazole and erythromycin, or inducers, such as rifampin and St. John's Wort, with TRIDURAL may affect the metabolism of tramadol leading to altered tramadol exposure.

##### Drug-Drug Interactions

###### MAO Inhibitors

Tramadol is contraindicated in patients receiving MAO inhibitors or who have used them within the previous 14 days.

###### Drugs that Lower Seizure Threshold

Tramadol can increase the potential for selective serotonin reuptake inhibitors (SSRIs), tricyclic anti-depressants (TCAs), anti-psychotics and other seizure threshold lowering drugs to cause convulsions.

###### CNS Depressants

Concurrent administration of tramadol with other centrally acting drugs, including alcohol, centrally acting analgesics, opioids and psychotropic drugs may potentiate CNS depressant effects.

###### Use with Carbamazepine

Patients taking carbamazepine, a CYP3A4 inducer, may have a significantly reduced analgesic effect. Because carbamazepine increases tramadol metabolism and because of the seizure risk associated with tramadol,

Dr. David Haughton's painting, *Ship of Woe*, from the Kindertotentanz series (left) was inspired by the suffering he saw during his pediatric residency. His more recent work has focused on landscapes, including scenes near his home in Vancouver: *Foggy Morning/Second Narrows V* (above, right) and *Nocturne - Nitinaht Lake* (below, right) are two examples.

Zealand's Maori people.

"I came across an exhibition in New York of the Maori people, and there were images there of nastiness and energy and scary life-force and death-force that I was seeing on a daily basis," Dr. Haughton recalls. "I went home and started to draw, and I knew immediately this was the vocabulary I could borrow, like Picasso used African masks."

Some of the pieces are etchings, which Dr. Haughton does with nitric acid on a zinc plate and prints with oil-based ink on soaked rag paper. Others are

paintings, earlier ones a hybrid of pen and water colour, and others acrylic.

Dr. Haughton says these paintings are an expression of his feelings, but the process is completely unique compared with his other art.

"There's the emotional, intellectual, medical, ethical and religious wave-length, and all of that is fed into a massive hard drive that I record and keep deep in my brain, and play back like a DVD." In order to paint, Dr. Haughton has to be in that emotional state, and that comes from being the



bearer of bad news, or the witness to someone's life going off a cliff.

"Billy now has leukemia, and you're there making the diagnosis. And it hits you. And when I see it, it won't make me cry or make me upset then because I just say, 'I have to deal with this later,' and I grab the whole thing, throw it over my emotional right shoulder into a box, and it's all jumbled in no particular order."

When painting, he goes back to that place in his brain, and deals with all the images and ethical dilemmas his medical work brings about.

"I go back and forth thinking, 'That's not fair, why the hell did that happen? Is there a god, and if there is why did he or she allow that to happen?' And then I take the emotional turbulence and the Maori images and try to provide something deep in texture that's emotional, intellectual and hopefully esthetic," he says.

### Struggles and symbolism

The Maori symbols that Dr. Haughton uses seem to perfectly depict the emotions running through the art, evoking a sense of sadness, but curiosity as well.

"The beaky birds that bite everything are the malevolence of disease, the nastiness of what life can give you. And they look malicious, just like a nasty cancer."

He explains that while he was not trying to be historically or ethically accurate, the symbolism was reflective of some of his personal struggles.

"The lizard is a symbol of both life and death and the humanoid objects are sort of wrestling with it because if it jumps in their mouth, the child will die. But in my case the children are sick and in pain, so the question is: Are they wrestling to live, or to die quicker? It blurs the answers to the questions I'm asking."

Dr. Haughton still works in pediatric emergency, but he says he's pretty much left the series alone at this point after years of starting and stopping again.

"I want them to be genuine, so I have to come from a genuine place. A lot of my



Dr. David Haughton and his wife, emergency physician Dr. Lyne Filiatraut, enjoy the beach in Tofino, B.C., on a painting trip.

landscapes are pretty, and I'm looking to make something beautiful. But these, they aren't contrived just to paint pretty pictures; it's because I had an emotional response to something I've seen, and they're done to give others that same emotional response."

The emotional nudge needed to do this series was present at certain times in his life, but Dr. Haughton says his life is happy right now, and to go there again would be artificial.

The passion and dedication to art Dr. Haughton possesses is reflected in his office, which is 90% full of art, books and supplies, and 10% full of medical trappings. Another reflection is the time he spends painting, which he estimates as close to two full months a year, sometimes working on 20 or 30 paintings at a time, with hundreds more started and unfinished.

Dr. Haughton's most recent works are done in acrylic, and are beautiful landscape series titled "Island Paintings," "Paintings of the Wind" and "Paintings of the Sun," most of which are views from Vancou-

ver Island, as well as paintings of Spain or Greece. The newest series he is developing is a short history of Greece that will play with ideas about evil and how to define it. Dr. Haughton says he has spent the last decade preparing for this series by cutting out pictures he sees in magazines, as he does for most of landscapes, always keeping an eye out for inspiration.

"It's my vocation. I take the medicine very seriously, I sometimes facetiously call it my hobby. I think I do a very good job, but it's not my calling. It's something I'm good at and I care about passionately, but it's not so much me as the art is. Whole months go by where I can't paint, but I consider myself an artist first. Heck, I was an artist first."



In addition to the Doctor Art gallery at Medicalpost.com, more information on Dr. Haughton's creations can be found on his website, [www.haughton-art.ca](http://www.haughton-art.ca). He is also featured in shows at Gallery 110 in Seattle ([www.gallery110.com](http://www.gallery110.com)) in June and October.

concomitant administration of TRIDURAL and carbamazepine is not recommended.

#### Use with Quinidine

Tramadol is metabolized to M1 by CYP2D6. Quinidine is a selective inhibitor of that isoenzyme, so that concomitant administration of quinidine and tramadol products results in increased concentrations of tramadol and reduced concentrations of M1. The clinical consequences of these findings are unknown. *In vitro* drug interaction studies in human liver microsomes indicate that tramadol has no effect on quinidine metabolism.

#### Use with Inhibitors of CYP2D6

*In vitro* drug interaction studies in human liver microsomes indicate that concomitant administration with inhibitors of CYP2D6 such as fluoxetine, paroxetine, and amitriptyline could result in some inhibition of the metabolism of tramadol.

#### Inhibitors or Inducers of CYP3A4

Administration of CYP3A4 inhibitors, such as ketoconazole and erythromycin, or inducers, such as rifampin and St. John's Wort may affect the metabolism of tramadol, leading to altered tramadol exposure.

#### Use with Cimetidine

Concomitant administration of tramadol immediate-release tablets with cimetidine does not result in clinically significant changes in tramadol pharmacokinetics. No alteration of the TRIDURAL dosage regimen with cimetidine is recommended.

#### Protease Inhibitors, e.g., ritonavir

Co-administered ritonavir may increase the serum concentration of tramadol, resulting in tramadol toxicity.

#### Use with Digoxin

Post-marketing surveillance of tramadol has revealed rare reports of digoxin toxicity.

#### Use with Warfarin-Like Compounds

Post-marketing surveillance of tramadol has revealed rare reports of alteration of warfarin effect, including elevation of prothrombin times. While such changes have been generally of limited clinical significance for tramadol, periodic evaluation of prothrombin time should be performed when TRIDURAL tablets and warfarin-like compounds are administered concurrently.

#### Drug-Food Interactions

Co-administration with food did not significantly change the overall exposure to tramadol; however, peak plasma concentrations increased. In the presence of food, the availability and controlled-release properties of TRIDURAL tablets were maintained with no evidence of dose dumping. TRIDURAL was administered either with breakfast or before breakfast in all clinical trials.

#### OVERDOSAGE

Deaths due to overdose have been reported with abuse and misuse of tramadol, by ingesting, inhaling, or injecting the crushed tablets. Review of case reports has indicated that the risk of fatal overdose is further increased when tramadol is abused concurrently with alcohol or other CNS depressants, including other opioids.

#### Symptoms of Overdose:

Acute overdosage with tramadol can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, bradycardia, hypotension, and death.

#### Treatment of Overdose

A single or multiple overdose with TRIDURAL may be a potentially lethal drug overdose, and consultation with a regional poison control centre is recommended.

In treating an overdose, primary attention should be given to maintaining adequate ventilation along with general supportive treatment. Supportive measures (including oxygen and vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

While naloxone will reverse some, but not all, symptoms caused by overdosage with tramadol, the risk of seizures is also increased with naloxone administration. In animals, convulsions following the administration of toxic doses of tramadol could be suppressed with barbiturates or benzodiazepines but were increased with naloxone. Naloxone administration did not change the lethality of an overdose in mice.

Hemodialysis is not expected to be helpful in an overdose because it removes less than 7% of the administered dose in a 4-hour dialysis period.

Emptying of the gastric contents may be useful to remove any unabsorbed drug.

Complete Product Monograph is available upon request.



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