ALOSETRON Hydrochloride
Tablets

10006481/01

HIGHLIGHTS OF PRESCR BING NFORMATION
These highlights do not include all he informat on needed to use ALOSETRON Hydrochloride Tablets safely and effectively See full prescrib ng nformation for ALOSETRON Hydrochloride Ta blets

ALOSETRON Hydrochloride Tablets
In tial U S Approval 2000

WARNING SER OUS GASTROINTESTINAL ADVERSE REACT ONS
See full prescribing information for complete boxed warning

Infrequent but ser ous gastrointest nal adverse reactions have been reported wi h the use of Alosetron Hydrochlor de Tablets These even s includ ng ischemic colit s and serious compl cat ons of cons t pation have resulted n hospitalizat on and rarely blood transfusi on surgery and death

- Only prescribe s who have en olled n he Aloset on REMS Pro gram should prescribe Aloset on Hydrochlor de Tablets (5 3)
- Alosetron Hyd ochlor de Tablets are indicated only for women with severe diarrhea predom nant irr table bowel syndrome (IBS) who have not responded adequately to conventional herapy (1)
- Discontinue Aloset on Hydrochloride Table s mmed ately n pa tients who develop const pat on or symptoms of ischem c col tis Do not esume Aloset on Hydrochloride Table s n patien s who develop ischem c col t s (2 1 5 1 5 2)

RECENT MAJOR CHANGES

Contraind cat ons Lack of Understand ng of Pat ent Acknowledgement Form (4 3)	09/2010
Warn ngs and Precautions Alosetron REMS Program (5 3)	09/2010
Patient Counsel ng Informat on (17)	09/2010

INDICAT ONS AND USAGE

Aloset on Hydrochloride Table s are a select ve seroton n 5 HT_3 an tagon st indicated only for women wi h severe d arrhea predom nant irr table bowel syndrome (IBS) who have

- chron c IBS symptoms (generally lasting 6 months or longe)
- had anatomic or biochem cal abnormalities of the gastrointestinal tract excluded and
- not esponded adequately to conventional therapy (1)

Severe IBS includes diarrhea and 1 or more of the follow ng

- frequent and severe abdominal pain/discomfort
- frequent bowel urgency or fecal ncont nence
- disab lity or restr ction of daily activities due to IBS (1)

DOSAGE AND ADMIN STRAT ON

- Start ng dose is 0 5 mg twice a day (2 1)
- May inc ease dose to 1 mg twice a day after 4 weeks if starting dosage s well tolerated but does not adequately control BS sym ptoms (2 1)
- Discontinue Alosetron Hydrochlor de Tablets n patients who have not had adequate control of IBS symptoms a ter 4 weeks of treat ment w th 1 mg twice a day (2 1)

DOSAGE FORMS AND STRENGTHS

Table s 0 5 and 1 mg (3)

CONTRAINDICATIONS

- Do not init ate n patien s with constipation (4 1)
- H story of ch onic or severe const pation or sequelae from const pa t on ntest nal obstruction stricture tox c megacolon gastrointesti nal perforation and/or adhes ons ischem c col tis impaired intesti nal c rculat on thrombophleb tis or hype coagulable state Crohn's disease or ulce at ve colitis diverticulitis severe hepat c impa rment (4 2)
- Inability to understand or comply with he Pat ent Acknowledgement Form (4 3)
- Concom tant use of fluvoxam ne (4 4)

WARNINGS AND PRECAUT ONS

- Serious Complications of Const pation May occur n some pat ents w thout wa ning Include obst uction ileus impaction tox c mega colon and secondary bowel ischem a and n are cases perforat on and dea h have been reported Risk is increased in pat ents who are elderly debil tated or tak ng medications that decrease bowel motility (5 1)
- D scont nue Alosetron Hydrochlo ide Tablets immediately if consti pat on occurs (5 1)
- Ischemic colit s May occur n some patien s without warning P omp ly evaluate patien s with signs of schemic colitis (e g rectal bleeding bloody diarrhea new or wo sen ng abdom nal pa n) (5 2)
- D scont nue Alosetron Hydrochloride Tablets immediately if signs of schemic colit s occur such as rectal bleed ng bloody diarrhea or new or worsen ng abdominal pa n (5 2)
- To prescribe Alosetron Hydrochloride Tablets prescr bers must be enrolled in the Alosetron REMS P ogram and adhere to all compo nents of the Program (5 3)

ADVERSE REACT ONS

Most common adverse reactions (inc dence >2% and >placebo) in cl nical studies were constipation abdom nal d scomfort and pain nausea and gastrointest nal discomfort and pain (6 1)

To report SUSPECTED ADVERSE REACTIONS contact Roxane Laboratories Inc at 1 800 962 8364 or FDA at 1 800 FDA 1088 or www fda gov/medwatch

DRUG INTERACTIONS

- CYP1A2 inh b tors Avo d concom tant uses because of ncreased exposure and ha f life of alosetron Use w th fluvoxam ne is contra ndicated (4 3 7 1)
- CYP3A4 nhibitors Use with caut on n comb nation due to ncreased exposure of alosetron (7 2)

USE IN SPEC FIC POPULAT ONS

- Hepat c mpairment Contraind cated n severe hepat c mpairment Use with caution n patients w th m ld or moderate hepatic impa r ment (4 2 8 6)
- Geriatric use Elderly patients may be at greater r sk for complica t ons of constipat on (8 5)

See 17 for PAT ENT COUNSELING INFORMATION and Med cation Gu de

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FULL PRESCR BING NFORMATION

WARN NG SERIOUS GASTRO NTESTINAL ADVERSE REACTIONS

Infrequent but serious gastrointestinal adverse reactions have been reported w th the use of Alosetron Hyd ochloride Tablets These events including ischemic colit s and serious complications of const pation have resulted in hosp talizat on and rarely blood transfusion surgery and death

- **The Alosetron REMS Program was mplemented to help reduce risks of serious gas tro ntest nal adverse reactions Only prescribers who have enrolled in he Aloset ron REMS Program based on their understanding of the benefits and risks should prescribe Alosetron Hydrochlor de Tablets *[see Warn ngs And Precautions (5 3)]***
- **Alosetron Hydrochloride Tablets are indicated only for women w th severe diarrhea predominant rritable bowel syndrome (IBS) who have not responded adequately to conventional therapy *[see Indicat ons and Usage (1)]* Before receiving the in ti al prescr pt on for Alosetron Hydrochlor de Tablets the patient must read and sign the Patient Acknowledgement Form for Alosetron Hydrochlor de Tablets *[see Patient Counsel ng Informat on (17)]***
- **Alosetron Hydrochloride Tablets should be discontinued mmediately in pat ents who develop constipation or symptoms of ischemic colitis Pat en s should mmediately report const pation or symptoms of ischemic colitis to their prescr ber Alosetron Hy drochloride Tablets should not be resumed in patients who develop ischemic colitis Patients who have constipation should immediately contact their prescriber if the constipation does not resolve after Alosetron Hydrochloride Tablets s discontinued Patients with resolved constipation should resume Alosetron Hydrochloride Tablets only on the advice of their treating prescriber *[see Dosage and Administration (2 1) Warn ngs and Precautions (5 1) (5 2)]***

1 IND CAT ONS AND USAGE

Alosetron Hyd ochlor de Tablets are ind cated only for women wi h severe d ar hea predom nant irr table bowel syndrome (IBS) who have

- chronic IBS symptoms (generally last ng 6 months or longer)
- had anatomic or b ochemical abno mal ties of the gastro ntestinal tract excluded and
- not responded adequately to convent onal the apy

Diarrhea predom nant IBS is severe if it includes diarrhea and one or more of the follow ng

- frequent and severe abdom nal pain/discomfort
- frequent bowel urgency or fecal ncont nence
- disab lity or restr ction of daily activities due to IBS

Because of infrequent but serious gastrointestinal adverse eactions associated with Alosetron Hydrochloride Table s he ind cat on is restr cted to hose pat ents for whom he benefit to risk balance s most favorable Clinical studies have not been pe fo med to adequately confirm he benefi s of Alosetron Hydrochlor de Tablets n men

2 DOSAGE AND ADM NISTRATION

For safety reasons only physic ans who enroll in the Alosetron REMS Program should prescr be Alosetron Hydrochlor de Tablets *[see Warn ngs And Precaut ons (5 3)]*

2 1 Adult Pat ents

To lower the risk of constipation Aloset on Hyd ochlor de Tablets should be started at a dosage of 0 5 mg tw ce a day Patien s who become constipated at this dosage should stop tak ng Alosetron Hydrochloride Tablets unt l he constipat on resolves They may be restarted at 0 5 mg once a day If constipation recurs at the lower dose Alosetron Hyd ochlor de Tablets should be discont nued immediately

Pat ents we l controlled on 0 5 mg once or twice a day may be ma nta ned on h s regimen f after 4 weeks the dosage is well tolerated but does not adequately control BS symptoms then he dosage can be inc eased to up to 1 mg tw ce a day **Alosetron Hydrochloride Tablets should be discont nued in patients who have not had adequate control of IBS symptoms after 4 weeks of treatment with 1 mg twice a day**

Alosetron Hydrochlor de Tablets can be taken w th or w thout food *[see Clinical Pharmacology (12 3)]*

Alosetron Hydrochloride Table s should be discontinued mmediately n pat ents who develop const pat on or signs of schemic col tis Aloset on Hydrochlor de Tablets should not be restarted in patien s who develop schem c col tis

Cl n cal trial and postmarketing experience suggest that deb l tated patients or pat ents tak ng add tional med cat ons that dec ease gastro ntest nal motil ty may be at greater risk of serious complications of constipat on Therefore appropriate caution and fo low up should be exercised f Alosetron Hydrochlor de Tablets are prescr bed for these patients

Postmarketing exper ence suggests that elderly patients may be at greater r sk for complications of const pat on herefore appropr ate caution and fo low up should be exercised f Alosetron Hyd rochloride Table s are prescribed for hese patients *[see Warn ngs And Precaut ons (5 1]*

2 2 Patients With Hepatic Impairment

Alosetron Hyd ochlor de Tablets s extensively metabolized by he l ver and increased exposure to Aloset on Hydrochlor de Tablets s likely to occur in patients w th hepat c impairment Increased drug exposure may inc ease he risk of serious adverse react ons Alosetron Hydrochloride Tablets should be used w th caution n patien s with mild or moderate hepat c impairment and is contrain d cated n pat ents wi h severe hepatic impa rment *[see Contraind cat ons (4)] and Use In Specific Populations (8 6)]*

2 3 Informat on for Pharmacists

Alosetron Hydrochloride Table s may be dispensed only on presentation of a prescr pt on for Alosetron Hydrochlor de Tablets w th a st cker for he Alosetron REMS Prog am attached A Medi cat on Gu de for Alosetron Hydrochloride Tablets must be g ven to the patient each time Alosetron Hydrochloride Tablets a e dispensed as required by law No telephone facs mile or compute ized prescr ptions are perm tted wi h h s prog am Refil s are perm tted to be wr tten on prescr ptions

3 DOSAGE FORMS AND STRENGTHS

0 5 mg and 1 mg tablets

Alosetron Hydrochlo ide Table s 0 5 mg (0 562 mg alosetron HCl equivalent to 0 5 mg alosetron) are white to off wh te round biconvex tablets debossed w th 54 628 on one side and plain on he other side

Alosetron Hydrochlor de Tablets 1 mg (1 124 mg alosetron HCl equivalent to 1 mg alosetron) are white to off wh te
round biconvex tablets debossed w th 54 974 on one side and pla n on the other s de

4 CONTRAINDICAT ONS

4 1 Const pation

Alosetron Hydrochlor de Tablets should not be n tiated n pat ents wi h constipation *[see War n ngs And Precaut ons (5 1)]*

4 2 History of Severe Bowel or Hepatic Disorders

Alosetron Hydrochlor de Tablets are contraind cated n patien s wi h a history of the fo lowing

- chronic or severe const pat on or sequelae from const pat on
- ntest nal obstruct on str cture tox c megacolon gastro ntest nal perforation and/or adhesions
- schem c col tis impaired intest nal c rculat on hrombophleb tis or hypercoagulable state
- Crohn s d sease or ulcerat ve colit s
- diverticulitis
- severe hepat c impa rment

4 3 Lack of Understanding of Pat ent Acknowledgement Form

Alosetron Hydrochlor de Tablets should not be used by pat ents who are unable to understand or comply w th the Pat ent Acknowledgement Form for Alosetron Hydrochloride Tablets *[see Patient Counseling Information 17)]*

4 4 Concomitant Use of Fluvoxamine

Concomitant adm n stration of Alosetron Hydrochlor de Tablets with fluvoxamine are cont a ndica ted Fluvoxamine a known st ong nhibitor of CYP1A2 has been shown to increase mean alose tron plasma concentrations (AUC) approximately 6 fold and prolong the ha f life by approximately 3 fold *[see Drug Interact ons (7 1)]*

5 WARNINGS AND PRECAUT ONS

5 1 Ser ous Complications of Constipation

Some pat ents have experienced serious complications of const pation without warning

Se ious complications of const pat on includ ng obstruct on leus mpact on toxic megacolon and secondary bowel schemia have been reported w th use of Alosetron Hydrochloride Tablets dur ng clinical tr a s Compl cations of constipat on have been reported w th use of 1 mg twice da ly and with lower doses A dose response relat onsh p has not been establ shed for ser ous compl cat ons of constipation **The incidence of serious complications of constipat on was approximately 0 1% (1 per 1 000 pat ents) in women receiv ng e ther Alosetron Hydrochlori de Tablets or placebo** In addit on are cases of perforat on and dea h have been eported from postmarket ng clinical p actice In some cases complications of const pation equ red intestinal surgery nclud ng colectomy Patients who a e elde ly deb litated or taking additional med cat ons hat decrease gastro ntest nal motility may be at greater r sk for complications of constipation

Alosetron Hydrochloride Tablets should be d scontinued immed ately in pat ents who develop constipation *[see Boxed Warning]*

5 2 Ischemic Col tis

Some pat ents have experienced ischemic col tis without warning

Ischem c col tis has been reported in pat ents rece v ng Alosetron Hydrochloride Tablets in cl n cal trials as we l as dur ng marketed use of the drug **In IBS cl nical trials he cumulative incidence of ischemic colitis in women receiving Alosetron Hydrochloride Table s was 0 2% (2 per 1 000 patients 95% confidence interval 1 to 3) through 3 months and was 0 3% (3 per 1 000 pat ents 95% confidence interval 1 to 4) hrough 6 months** Ischem c colit s has been reported w th use of 1 mg twice daily and with lower doses A dose response relat onship has not been es tabl shed Ischem c col tis was reported n one patient receiv ng placebo The patient exper ence n controlled cl n cal trials s insufficient to est mate the incidence of schemic colitis in patients taking Alosetron Hydrochloride Table s for longer than 6 months

Alosetron Hydrochloride Tablets should be discontinued mmed ately n pat ents with signs of schemic colitis such as ectal bleeding bloody d arrhea or new or worsening abdominal pain Be cause schem c col tis can be life threatening patien s with signs or symptoms of ischemic colit s should be evaluated p omp ly and have appropr ate diagnost c test ng performed Treatment w th Alosetron Hydrochloride Table s should not be resumed n patien s who develop schemic colitis

5 3 Alosetron REMS Program

To p escribe Alosetron Hyd ochlor de Tablets the prescr ber must be enro led n the Alosetron REMS Program To enro l prescr bers must understand the benefits and risks of t eatment w th Alosetron Hydrochloride Table s for seve e diarrhea predominant BS including the nformation in he Prescr b ng Informat on Med cat on Gu de and Pat ent Acknowledgement Form for Alosetron Hydrochloride Table s

To enroll n the Alosetron REMS Program ca l 1 844 267 8675 or visit www Aloset onREMS com to complete the Prescriber Enro lment Form

6 ADVERSE REACT ONS

The fo lowing adverse reactions are descr bed in more detail n other sections of he label

- Compl cat ons of constipat on *[see Boxed Warn ng Warn ngs And Precaut ons (5 1)]*
- Ischemic colit s *[See Boxed Warn ng Warn ngs And Precaut ons (5 2)]*

6 1 Clinical Tr als Experience

Because cl n cal trials are conducted under widely vary ng conditions adve se reaction rates observed in the clinical tr a s of a drug cannot be d rec ly compared to ates in the clinical tr a s of another drug and may not reflect the ates observed n practice

Patien s Wi h Irritable Bowel Syndrome Table 1 summarizes adverse react ons from 22 repeat dose studies n patien s w th IBS who were treated w th 1 mg of aloset on hydrochlo ide tablets twice da ly for 8 to 24 weeks The adverse react ons in Table 1 were eported in 1% or more of patients who received alosetron hydrochlor de tablets and occurred mo e frequen ly on alosetron hydrochlor de tablets han on placebo A statistically significant d fference was observed for cons tipat on n patients treated with alosetron hyd ochlor de tablets compared to placebo (p<0 0001)

Table 1 Adverse React ons Reported in ≥1% of Patients With Irritable Bowel Syndrome and More Frequently on Alosetron Hydrochlor de Tablets 1 mg Twice Daily Than Placebo

Body System Adverse Reaction	Placebo (n=2 363)	Alose ron HCl 1 mg twice da ly (n=8 328)
Gastro ntestinal		
Constipat on	6%	29%
Abdom nal d scomfort and pain	4%	7%
Nausea	5%	6%
Gastroin estinal d scomfort and pa n	3%	5%
Abdom nal d s ention	1%	2%
Regurgitation and reflux	2%	2%
Hemorrhoids	1%	2%

Gastrointest nal Const pation is a frequent and dose related side effect of treatment with aloset ron hydrochloride tablets *[see Warnings And Precautions (5 1)]* In cl n cal studies const pat on was reported in approximately 29% of patien s with IBS treated w th alosetron hydrochloride tablets 1 mg tw ce da ly (n 9 316) Th s e fect was stat stica ly sign ficant compared to placebo (p<0 0001) Eleven pe cent (11%) of pat ents treated with alosetron hydrochloride table s 1 mg tw ce daily w thdrew from the stud es due to const pat on A though the number of patien s w th IBS treated w th alosetron hydrochloride tablets 0 5 mg twice daily s elat vely sma l (n 243) only 11% of hose pat ents reported const pat on and 4% withdrew f om clinical studies due to constipation Among the patients treated wi h alosetron hydrochloride tablets 1 mg twice daily who reported constipation 75% reported a single ep sode and most repo ts of const pat on (70%) occurred du r ng he first month of treatment wi h he median t me to first report of constipation onset of 8 days Occurrences of const pat on in cl n cal trials were generally m ld to mode ate n ntens ty transient n nature and resolved either spontaneously with continued treatment or w th an interrupt on of treatment However ser ous complications of const pat on have been reported in clinical studies and in postmarketing experience *[see Boxed Warn ng And Warnings And P ecaut ons (5 1)]* In Studies 1 and 2 9% of pat ents treated w th alosetron hydrochloride tablets reported const pation and 4 consecutive days with no bowel movement *[See Clinical Studies (14 2)]* Fo lowing inter upti on of treatment 78% of the affected patien s resumed bowel movements w thin a 2 day period and were able to re n tiate treatment w th alosetron hydrochloride tablets

Hepatic A similar inc dence in elevat on of ALT (>2 fold) was seen in patients ece v ng alosetron hydrochlor de tablets or placebo (1% vs 1 2%) A s ngle case of hepat tis (elevated ALT AST a kaline phosphatase and b l rubin) w thout jaundice in a pat ent ece v ng alosetron hydrochloride table s was reported in a 12 week study A causal assoc at on w th alosetron hydrochloride tablets has not been establ shed

Long Term Safety Patient exper ence n contro led clinical t ials is nsuffic ent to est mate the inci dence of schem c col tis n pat ents taking aloset on hydrochloride tablets for longer than 6 months

W W th S D h P d t l t bl B l Sy d Table 2 summarizes the gastrointestinal adverse react ons from 1 epeat dose study in female pat ents with seve e d a rhea predominant IBS who were treated for 12 weeks The adverse react ons in Table 2 we e reported in 3% or more of patients who received alosetron hydrochlor de tablets and occurred more frequently with alosetron hydrochlor de tablets than w th placebo Other events reported n 3% or more of patients who received alosetron hydrochloride table s and occurr ng more frequently wi h alosetron hyd ochlor de table s han w th placebo ncluded upper respiratory tract infect on viral gast oenter tis muscle spasms headaches and fatigue

Table 2 Gastrointestinal Adverse React ons Reported in ≥3% of Women With Severe Di arrhea Predominant Irritable Bowel Syndrome and More Frequently on Alosetron Hydrochloride Tablets Than Placebo

Adverse Reaction	P acebo (n=176)	A osetron 0 5 mg once da ly (n=175)	Alosetron 1 mg once da ly (n=172)	Alose ron 1 mg tw ce daily (n=176)
Constipation	5%	9%	16%	19%
Abdominal pa n	3%	5%	6%	7%
D arrhea	2%	3%	2%	2%
Hemorrhoidal hemorrhage	2%	3%	2%	2%
Flatu ence				
Hemorrhoids	2%	2%	1%	3%
Abdominal pa n upper	2%	1%	1%	3%
	1%	3%	1%	1%

Adverse react ons reported n ano her study of 701 women with severe dia rhea predominant BS were s m lar to hose shown in Table 2 Gastrointest nal adverse eactions reported n 3% or mo e of patients who received aloset on hydrochloride tablets and occurr ng more frequen ly w th aloset ron hydrochlor de table s than wi h placebo included constipation (14% and 10% of pat ents taking alosetron hydrochlor de table s 1 mg twice daily or 0 5 mg as needed respect vely compared wi h 2% taking placebo) abdom nal pain nausea vomit ng and flatulence Other events reported n 3% or more of patients who received alosetron hydrochloride table s and occurr ng more frequently wi h alosetron hyd ochlor de table s han w th placebo included nasopharyngit s s nusit s upper respiratory tract infection ur nary tract nfection viral gastroenter tis and cough

Const pat on Const pation was the most frequent adverse react on among women with seve e d a rhea predominant BS epresented in Table 2 There was a dose response in the g oups treated wi h alosetron hydrochlor de table s in the number of patients wi hdrawn due to constipat on (2% on placebo 5% on 0 5 mg once daily 8% on 1 mg once daily and 11% on 1 mg tw ce da ly) Among these patients with severe diarrhea predom nant IBS treated with alosetron hydrochlor de tablets who reported constipation most (75%) reported one ep sode wh ch occurred within the first 15 days of treatment and persisted for 4 to 5 days

O her Events Observed During Cl n cal Evaluation of Alosetron Hydrochloride Tablets During its assessment n clinical tr a s mu tiple and single doses of alosetron hydrochloride tablets were ad ministered esu ting in 11 874 subject exposures n 86 completed clinical stud es The conditions dosages and durat on of exposure to alosetron hydrochloride tablets varied between trials and the studies included healthy male and female volunteers as we l as male and female patients wi h IBS and o her ndications

In the list ng that fo lows repo ted adverse reactions were class fied using a standardized co d ng dict onary Only those events that an invest gator bel eved were poss bly related to alosetron hydrochloride tablets occurred n at least 2 patien s and occurred at a greater frequency during treatment w th aloset on hydrochlo ide table s than during placebo adm n st at on are presented Serious adverse react ons occurr ng in at least 1 pat ent for whom an investigator believed the e was reasonable possibility that he event was related to treatment w th alosetron hydrochloride table s and occurr ng at a greater frequency n patien s treated wi h alosetron hydrochloride tablets than placebo treated patients are a so presented

In he follow ng listing even s are categor zed by body system Wi h n each body system events a e presented n descend ng order of frequency The fo lowing defin t ons are used *infrequent* adverse reactions are those occurr ng on one or more occas on in 1/100 to 1 1 000 patients *ra e* adverse react ons are those occu ring on one or more occasion in fewer than 1/1 000 pat ents

Although he events reported occurred during treatment wi h alosetron hydrochlor de table s they were not necessa ily caused by it

Blood and Lymphatic Rare Quant tative red ce l or hemoglobin defects and hemorrhage

Cardiovascular Inf equent Tachyarrhythm as *Rare* Arrhy hmias ncreased blood pressure and extrasystoles

Drug Inte act on Ove dose and Trauma Rare Contusions and hematomas

Ear Nose and Throat Rare Ear nose and throat nfect ons vi al ear nose and throat infections and laryngit s

Endocrine and Metabolic Rare D sorders of calcium and phosphate metabolism hyperglycemia hypo halamus/pituitary hypofunction hypoglycemia and flu d d sturbances

Eye Rare Light sens t v ty of eyes

Gastro ntest nal Infrequent Hyposalivation dyspept c symptoms gastrointestinal spasms ischemic col t s *[see Warn ngs and Precaut ons (5 2)]* and gastro ntestinal lesions *Rare* Abnor mal tenderness colitis gastrointestinal s gns and symptoms proct tis diverticulitis positive fecal occu t blood hype acidity dec eased gast o ntestinal mot l ty and leus gastrointestinal obstruc t ons o al symptoms gastrointest nal intussusception gastritis gastroduoden tis gastroenteritis and ulcerative colit s

Hepatob l ary Tract and Pancreas Rare Abnormal bilirub n levels and cholecyst tis

Lower Resp ratory Infrequent Breathing disorders

Musculoskeletal Rare Muscle pain muscle st ffness tightness and rigidity and bone and skel etal pa n

Neu ological Infrequent Hypnagogic effec s *Rare* Memory effects t emo s dreams cognit ve funct on d sorders disturbances of sense of taste d sorders of equilib ium confusion sedat on and hypoes hesia

Non Site Spec fic Inf equent Mala se and fatigue cramps pa n tempe ature regulation distur bances *Rare* Burning sensations hot and cold sensations cold sensations and fungal infect ons

Psych atry Infrequent Anxiety *Ra e* Depressive moods

Rep oduct on Rare Sexual function d sorders female eproduct ve tract bleed ng and hemorrha ge reproductive infect ons and fungal reproductive infections

Sk n Infrequent Sweat ng and urticar a *Rare* Hair loss and alopec a acne and fo l cul tis d sor ders of sweat and sebum allergic skin react on eczema sk n infections dermat tis and dermatosis and nail disorde s

U ology Infrequent Ur nary frequency *Rare* Bladder nflammation polyu ia and diuresis and u inary t act hemorrhage

6 2 Postmarketing Experience

In addit on to even s reported n clinical trials he follow ng events have been ident fied during use of alosetron hydrochloride tablets n cl n cal practice Because they were reported volunta ily

MEDICATION GUIDE

ALOSETRON (a-LOW-zeh-tron) Hydrochloride Tablets

Before using alosetron hydrochloride tablets for the first time, you should:

- Understand that alosetron hydrochloride tablets have serious risks for some people
- Read and follow the directions in this Medication Guide
- Sign a Patient Acknowledgement Form

Read this Medication Guide carefully before you sign the Patient Acknowledgement Form You must sign the Patient Acknowledgement Form before you start alo setron hydrochloride tablets Read the Medication Gui de you get w th each refi l for alosetron hydrochloride tablets There may be new information This Medication Guide does not take the place of talking with your doc tor

1. What is the most important information I should know about alosetron hydrochloride tablets?

A. Alosetron hydrochloride tablets are a medi cine only for some women with severe chronic irritable bowel syndrome (IBS) whose:

- main problem is diarrhea and
- IBS symptoms have not been helped enough by other treatments

B. Some patients have developed serious bo wel side effects while taking alosetron hydro chloride tablets. Serious bowel (intestine) side effects can happen suddenly, including the fol lowing.

1. Serious complications of constipation: About 1 out of every 1,000 women who take alosetron hydrochloride tablets may get serious complications of constipation These compli cations **may lead to a hospital stay and, in rare cases, blood transfusions, surgery, and death.** People who are older, who are weak from illness, or who take other constipating medicines may be more ikely to have serious complications of constipation with alosetron hy drochloride tablets

To lower your chances of getting serious complications of constipation, do the fol lowing

- **If you are constipated,** do not start taking alosetron hydrochloride tablets
- **If you get constipated while taking alo setron hydrochloride tablets,** stop taking it right away and call your doctor
- **If your constipation does not get better after stopping alosetron hydrochloride tablets,** call your doctor again
- **If you stopped taking alosetron hydro chloride tablets, do not start taking alo setron hydrochloride tablets again** un less your doctor tells you to do so

2. Ischemic colitis (reduced blood flow to the bowel): About 3 out of every 1,000 women who take alosetron hydrochloride tablets over a 6 month period may get a serious problem where blood flow to parts of the large bowel is reduced This is called ischemic colitis The chance of getting ischemic colitis when you take alosetron hydrochloride tablets for more than 6 months is not known **Ischemic colitis may lead to a hospital stay and, in rare cases, blood transfusions, surgery, and death.**

To lower your chances of getting serious complications of ischemic colitis, stop ta king alosetron hydrochloride tablets and call your doctor right away if you get:

- new or worse pain in your stomach area (abdomen) or
- blood in your bowel movements

C. Are alosetron hydrochloride tablets right for you?

Alosetron hydrochloride tablets may be right for you if all of these things are true about you:

- Your doctor has told you that your symptoms are due to IBS
- Your IBS bowel problem is diarrhea
- Your IBS has lasted for 6 months or longer
- You tried other IBS treatments and they did not give you the re ief you need
- Your IBS is severe

You can tell if your IBS is severe if **at least 1** of the following is true for you

- You have lots of painful stomach cramps or bloating
- You often cannot control the need to have a bo wel movement, or you have "accidents" where your underwear gets dirty from diarrhea or bo wel movements
- You cannot lead a normal home or work ife be cause you need to be near a bathroom

Enough testing has not been done to confirm alosetron hydrochloride tablets works in men or children under age 18

D. There is a special prescribing program for alosetron hydrochloride tablets.

Only doctors who have signed up with the Aloset ron REMS Program should write prescriptions for alosetron hydrochloride tablets As part of signing up, these doctors have said that they understand about IBS and the possible side effects of alosetron hydrochloride tablets They have agreed to use a special sticker on **written** prescriptions for alose tron hydrochloride tablets, so the pharmacist will know that the doctors have signed up w th the Alo setron REMS Program No telephone, facsimile, or computerized prescriptions are permitted with this program Refills may be wr tten on prescriptions

You may be taught about alosetron hydrochloride tablets by your doctor or healthcare provider under a doctor's direction Your doctor will ask you to sign a Patient Acknowledgement Form after you read this Medication Guide for the first time Signing the Patient Acknowledgement Form means that you understand the benefits and risks of alosetron hy drochloride tablets and that you have read and un derstand this Medication Guide

2. What are alosetron hydrochloride tablets?

Alosetron hydrochloride tablets are a medicine only for some women with severe chronic IBS whose

- main problem is diarrhea and
- IBS symptoms have not been helped enough by other treatments

Alosetron hydrochloride tablets does not cure IBS, and it may not help every person who takes it For those who are helped, alosetron hydrochloride tablets redu ces lower stomach area (abdominal) pain and discom fort, the sudden need to have a bowel movement (bo wel urgency), and diarrhea from IBS If you stop taking alosetron hydrochloride tablets, your IBS symptoms may return within 1 or 2 weeks to what they were be fore you started taking alosetron hydrochloride tablets Alosetron hydrochloride tablets are not recommended

for children

3. Who should not take alosetron hydrochloride tablets?

Alosetron hydrochloride tablets are not right for every one **Do not take alosetron hydrochloride tablets if any of the following apply to you:**

- Your main IBS problem is constipation or you are constipated most of the time
- You have had a serious problem from constipa tion **If you are constipated now, do not start taking alosetron hydrochloride tablets.**
- You have had serious bowel blockages
- You have had blood flow problems to your bo wels, such as ischemic colitis
- You have had blood clots
- You have had Crohn's disease, ulcerative coli tis, diverticulitis, or severe liver disease
- You do not understand this Medication Guide or the Patient Acknowledgement Form, or you are not willing to follow them
- You are taking fluvoxamine (LUVOX®)

4. What should I talk about with my doctor before taking alosetron hydrochloride tablets?

Talk with your doctor

- about the possible benefits and risks of aloset ron hydrochloride tablets
- about how much of a problem IBS is in your life and what treatments you have tried
- about any other llnesses you have and medi cines you take or plan to take These include prescription and nonprescription medicines, supplements, and herbal remedies Certain ill nesses and medicines can increase your chan ce of getting serious side effects while taking alosetron hydrochloride tablets Other medici nes may interact with how the body handles alo setron hydrochloride tablets
- about any allergies that you have See the end of the Medication Guide for a complete list of ingredients in alosetron hydrochloride tablets
- if you are pregnant, planning to get pregnant, or breastfeeding

5. How should I take alosetron hydrochloride ta blets?

- Take alosetron hydrochloride tablets exactly as your doctor prescribes it You can take alosetron hydrochloride tablets with or without food
- Begin w th 0 5 mg two times a day for 4 weeks to see how alosetron hydrochloride tablets af fects you You and your doctor may decide that you should keep taking this dose if you are do ing well
- Check with your doctor 4 weeks after starting alosetron hydrochloride tablets
  - If you try 0 5 mg two times a day for 4 weeks, it may not control your symptoms If you do not get constipation or other side effects from alosetron hydrochloride tablets, your doctor may increase your dose up to 1 mg two times a day
  - If 1 mg two times a day does not work after 4 weeks, alosetron hydrochloride tablets is not likely to help you You should stop taking it and call your doctor
- **If you miss a dose of alosetron hydrochlo ride tablets,** just skip that dose Do not take 2 doses the next time Wa t unt l the next time you are supposed to take t and then take your nor mal dose
- **Follow the important instructions in the sec tion "What is the most important information I should know about alosetron hydrochloride tablets?"** about when you must stop taking the medicine and when you should call your doctor
- **If you see other doctors** about your IBS or side effects from alosetron hydrochloride tablets, tell the doctor who prescribed alosetron hydrochlo ride tablets

6. What are the possible side effects of alosetron hydrochloride tablets?

Constipation is the most common side effect among women with IBS who take alosetron hydrochloride tab lets **Some patients have developed serious bowel side effects while taking alosetron hydrochloride tablets.** Read the section **"What is the most impor tant information I should know about alosetron hy drochloride tablets?"** at the beginning of this Medica tion Guide for information about the serious side effects you may get with alosetron hydrochloride tablets

This Medication Guide does not te l you about all the possible side effects of alosetron hydrochloride tablets Your doctor or pharmacist can give you a more com plete list

Call your doctor for medical advice about side effects You may report side effects to FDA at 1 800 FDA 1088

7. How should I store alosetron hydrochloride ta blets?

- Store alosetron hydrochloride tablets at 68°F to 77°F (20°C to 25°C) [See USP Controlled Room Temperature]
- Protect alosetron hydrochloride tablets from light and getting wet (moisture)

Keep alosetron hydrochloride tablets and all medi cines out of the reach of children.

8. General information about the safe and effecti ve use of alosetron hydrochloride tablets

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide If you have any questions or concerns about alosetron hydro chloride tablets, ask your doctor Do not use alosetron hydrochloride tablets for a condition for which it was not prescribed Do not share your medicine with other people It may harm them

Your doctor or pharmacist can give you more informati on about alosetron hydrochloride tablets that was writ ten for hea thcare professionals You can also contact the Alosetron REMS Program (toll free) at 1 844 267 8675 or at www AlosetronREMS com

9. What are the ingredients of alosetron hydro chloride tablets?

Active Ingredient: alosetron hydrochloride

Inactive Ingredients: lactose (anhydrous), magnesi um stearate, microcrystal ine cellulose, and pregelati nized starch

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Roxane Laboratories, Inc
Columbus, Ohio 43216

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Boehringer Ingelheim
Roxane Laboratories

from a populat on of unknown s ze est mates of frequency cannot be made These events have been chosen for nclus on due to a comb nat on of the r se iousness frequency of eporting or potent al causal connect on to alosetron hydrochlor de table s

Gastrointestinal Impact on perforation ulceration small bowel mesenter c ischemia
Neurolog cal Headache
Skin Rash

7 DRUG INTERACTIONS

In vivo data suggest that aloset on is pr marily metabol zed by cytochrome P450 (CYP) 1A2 w th m nor contributions from CYP3A4 and CYP2C9 Therefore nducers or inh b to s of these enzymes may change he clearance of alosetron

7 1 CYP1A2 Inh bitors

Fluvoxamine is a known strong nhibitor of CYP1A2 and also inhibi s CYP3A4 CYP2C9 and CYP2C19 In a pharmacokinet c study 40 hea thy female subjects received fluvoxamine in escalating doses from 50 to 200 mg/day for 16 days with coadm n stration of alosetron 1 mg on the last day Fluvoxamine ncreased mean alo set on plasma concent at ons (AUC) app oximately 6 fold and prolonged the half life by app oximately 3 fold Concom tant adm n stration of alosetron and fluvoxamine s contra ndicated *[see Contraind cations (4 3)]*

Concom tant adm n stration of alosetron and moderate CYP1A2 nhibitors nclud ng quinolone antibiotics and c met d ne has not been evaluated but should be avo ded unless cl n cally necessary because of sim lar potential drug nteractions

7 2 CYP3A4 Inh bitors

Ketoconazole is a known strong inh b tor of CYP3A4 In a pharmacokinetic study 38 healthy female subjects received ketoconazole 200 mg twice da ly for 7 days wi h coadm n stration of alosetron 1 mg on the last day Ketoconazole increased mean aloset on plasma concent at ons (AUC) by 29% Caution should be used when alosetron and ketoconazole are administered concomitan ly Coadm n stration of alosetron and strong CYP3A4 inh b tors such as clari hromycin tel thromycin p otease inh b to s voriconazole and itraconazole has not been evaluated but should be undertaken w th caution because of similar potent al drug inte act ons The effect of induction or inh b tion of other pathways on exposure to alosetron and its metabolites s not known

7 3 Other CYP Enzymes

In vit o human liver m c osome studies and an *n vivo* metabolic probe study demonstrated that alosetron d d not nhibit CYP enzymes 3A4 2C9 or 2C19 *In vitro* at total drug concentrations 27 fold higher han peak plasma concent at ons observed w th the 1 mg dose alosetron nhibited CYP enzymes 1A2 (60%) and 2E1 (50%) In an *in vivo* metabolic probe study alosetron d d not nhibit CYP2E1 but did produce 30% inhibit on of both CYP1A2 and N acetylt ansferase Al hough not studied with alosetron inh b tion of N acety transferase may have clinica ly relevant consequences for drugs such as soniaz d procainam de and hydralaz ne The e fect on CYP1A2 was explored fur her in a clinical interact on study wi h theophylline and no effect on me tabol sm was observed Ano her study showed that alosetron had no cl nically sign ficant effect on plasma concentrations of he oral contraceptive agen s ethinyl estrad ol and levono gestrel (CYP3A4 substrates) A cli n cal interact on study was a so conducted w th alosetron and the CYP3A4 substrate cisapr de No s gnificant e fec s on c sapride metabolism or QT nterval were noted The effects of alosetron on monoam ne ox dases and on intestinal first pass secondary to h gh intraluminal concentrations have not been exam ned Based on the above data from *n vitro* and *n vivo* studies it is unl kely that alosetron w ll inh b t the hepatic metabolic clearance of d ugs metabol zed by he CYP enzymes 2C9 2C19 or 2E1

Alosetron does not appear to nduce the major cytochrome P450 drug metabolizing enzyme 3A Alosetron a so does not appear to nduce CYP enzymes 2E1 or 2C19 It s not known whether aloset on might induce o her enzymes

8 USE IN SPECIFIC POPULATIONS

8 1 Pregnancy

Te atogenic Effects Pregnancy Category B Reproduction stud es have been performed n ra s at doses up to 40 mg/kg/day (about 160 times he recommended human dose based on body surface area) and abb ts at o al doses up to 30 mg/kg/day (about 240 times the recommended daily human dose based on body surface a ea) These studies have evealed no evidence of mpaired fertility or harm to the fetus due to alosetron The re are however no adequate and well contro led stud es n pregnant women Because animal reproduct on studies are not always p edictive of human response alosetron hydrochloride tablets should be used dur ng p egnancy only f clearly needed

8 3 Nursing Mothers

Alosetron and/or metabol tes of alosetron are excreted in the breast milk of lactating rats t is not known whether alosetron s excreted n human mi k Because many drugs are excreted in human m lk caution should be exercised when aloset on hydrochloride tablets are adm n stered to a nursing woman

8 4 Ped atr c Use

Safety and effectiveness in pediatric pat ents have not been establ shed Use of alosetron hydrochlor de table s s not ecommended in the ped atric population based upon the risk of ser ous complications of cons t pation and ischem c col tis n adu ts

8 5 Geriatric Use

In some studies in hea thy men or women plasma concentrations were elevated by approx mately 40% in ind viduals 65 years and older compared to young adu ts *[see Warn ngs And Precaut ons (5 1)]* However this e fect was not consistently observed n men

Postma ket ng exper ence suggests that elderly pat ents may be at greater r sk for compl cat ons of consti pat on therefore app opriate caution and follow up should be exercised if alosetron hydrochloride tablets is p esc ibed for these pat ents *[see Warn ngs And Precaut ons (5 1)]*

8 6 Hepatic Impairment

Due to the extensive hepatic metabolism of alosetron increased exposure to alosetron and/or ts metabolites is l kely to occur in patien s w th hepat c mpairment Alosetron should not be used n patien s w th severe hepat c impai ment and should be used w th caution in pat ents w th m ld or moderate hepatic mpa rment

A single 1 mg oral dose of alosetron was adm n stered to 1 female and 5 male pat ents w th moderate hepatic impa rment (Child Pugh score of 7 to 9) and to 1 female and 2 male pat ents w th severe hepatic impa rment (Child Pugh score of >9) In comparison with historical data from hea thy subjects patients wi h severe hepatic impa rment displayed higher systemic exposure to alosetron The female w th severe hepat c impa rment dis played approximately 14 fold h gher exposure while he female w th moderate hepat c impairment d splayed approximately 1 6 fold higher exposure than healthy females Due to the sma l number of subjects and h gh intersubject variab l ty n he pharmacokinet c find ngs no definitive quantitat ve conclusions can be made However due to the greater exposure to alosetron n he female w th severe hepat c mpairment alosetron should not be used n females with severe hepatic impa rment *[see Dosage And Adm n stration (2 2) Cont raind cations (4)]*

8 7 Renal Impairment

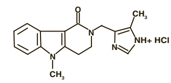
Renal impairment (c eatinine clearance 4 to 56 mL/min) has no effect on the renal elim nation of alosetron due to the m nor cont ibut on of h s pathway to el minat on The effect of renal impa rment on metabol te phar macok netics and the effect of end stage renal d sease have not been assessed

10 OVERDOSAGE

There s no spec fic ant dote for overdose of alosetron hydrochlor de tablets Patien s should be managed wi h approp iate supportive therapy Individual oral doses as la ge as 16 mg have been administered n clinical studies without s gnificant adverse reactions This dose s 8 t mes h gher han he recommended total da ly dose Inh b tion of the metabolic el minat on and reduced fi st pass of other drugs m ght occur w th overdoses of alosetron hydrochlor de table s *[see Drug Interactions (7)]*

11 DESCRIPTION

The active ingred ent in Alosetron Hyd ochlor de Table s is alosetron hyd ochlor de (HCl) a potent and selec t ve antagonist of the serotonin 5 HT_3 receptor type Chemically alosetron is designated as 2 3 4 5 tet ahydro 5 methyl 2 [(5 methyl 1H im dazol 4 yl)methy] 1H pyr do[4 3 b] ndol 1 one monohydrochloride Aloset on is achiral and has the empi ical formula $C_{17}H_{18}N_4O$ HCl representing a molecular weight of 330 8 Alosetron is a wh te to beige sol d that has a solubility of 61 mg/mL in water 42 mg/mL in 0 1M hydrochlor c acid 0 3 mg/mL in pH 6 phosphate bu fer and <0 1 mg/mL in pH 8 phosphate buffer The chem cal structure of alosetron is



Alosetron Hydrochloride Tablets a e supplied for oral administrat on as 0 5 mg (wh te to o f white) and 1 mg (white to off wh te) tablets The 0 5 mg tablet conta ns 0 562 mg alosetron HCl equivalent to 0 5 mg aloset ron and the 1 mg tablet conta ns 1 124 mg alosetron HCl equivalent to 1 mg of alosetron Each tablet also contains he inact ve ingred ents lactose (anhyd ous) magnes um stearate microcrysta l ne cellulose and pregelatinized starch

12 CLIN CAL PHARMACOLOGY

12 1 Mechanism of Action

Alosetron is a potent and select ve 5 HT_3 receptor antagonist 5 HT_3 eceptors a e ligand gated cation chan ne s that are extensively d stributed on enteric neurons in the human gastrointestinal tract as well as other per phe al and central locations Activation of hese channels and the resu ting neuronal depolarization affect he regulation of v sceral pain colonic transit and gastro ntestinal secretions processes that relate to the pa hophys ology of IBS 5 HT_3 receptor antagonists such as alosetron nhibit act vat on of non select ve cation channels which resul s n the modulation of the enter c nervous system

The cause of IBS is unknown IBS is character zed by visce al hypersensit v ty and hyperactivity of the gas tro ntestinal tract which lead to abnormal sensations of pain and motor activ ty Fo lowing distent on of the rectum patien s w th BS exhibit pain and discomfort at lower volumes han heal hy volunteers Fo lowing such distent on aloset on reduced pain and exaggerated motor responses possibly due to blockade of 5 HT_3 receptors

12 2 Pharmacodynam cs

In hea thy volunteers and patien s with IBS alosetron (2 mg ora ly twice daily for 8 days) ncreased colonic trans t time wi hout a fecting orocecal transit t me In healthy volunteers alosetron also increased basal jejunal water and sodium absorpt on a ter a single 4 mg dose In pat ents w th IBS mult ple oral dosages of alosetron (4 mg tw ce da ly for 6 5 days) significantly increased colon c compliance

Single oral doses of alosetron administered to hea thy men produced a dose dependent reduct on in the fla e response seen after intradermal injection of serotonin Ur nary 6 β hydroxycortisol excretion decreased by 52% n elde ly subjects after 27 5 days of alosetron 2 mg adm n stered orally twice da ly This decrease was not statist cally s gnificant In another study ut l z ng alosetron 1 mg adm n stered orally twice daily for 4 days here was a s gnificant decrease in urinary 6 β hyd oxycortisol exc et on However here was no change n he ratio of 6 β hyd oxycort sol to cortisol ind cating a possible decrease in cort sol production The cl n cal sign ficance of these findings is unknown

12 3 Pharmacok netics

The pharmacok netics of alosetron have been studied after single oral doses rang ng f om 0 05 to 16 mg n heal hy men The pharmacokinet cs of aloset on have a so been evaluated n hea thy women and men and n patients w th IBS after repeated o al dosages ranging from 1 mg twice daily to 8 mg tw ce da ly

Absorpt on Alosetron was rap dly absorbed a ter o al administration with a mean absolute b oavailability of approx mately 50% to 60% (approximate range 30% to >90%) After adm n stration of radiolabeled alosetron only 1% of the dose was ecovered in the feces as unchanged drug Follow ng oral adm n stration of a 1 mg alosetron dose to young men a peak plasma concentrat on of app oximately 5 ng/mL occurred at 1 hour In young women the mean peak plasma concentrat on was approximately 9 ng/mL with a similar time to peak

Plasma concentrations were 30% to 50% lower and less var able n men compared to women g ven the same oral dose Populat on pharmacokinetic analys s in IBS pat ents confirmed hat alosetron concent at ons we e nfluenced by gender (27% lower n men)

Food E fects Alosetron abso pt on s dec eased by approx mately 25% by co adm n stration with food wi h a mean delay in time to peak concentration of 15 minutes *[see Dosage and Adm n stration (2 1)]*

Distr bution Alosetron demonstrates a volume of distribution of approx mately 65 to 95 L Plasma prote n bind ng s 82% over a concent at on range of 20 to 4 000 ng/mL

Metabol sm and El minat on Plasma concentrat ons of alosetron ncrease proportionately wi h ncreasing single oral doses up to 8 mg and more han proportionately at a s ngle o al dose of 16 mg Twice daily oral dosing of alosetron does not result in accumulation The term nal elimination ha f l fe of alosetron s approxi mately 1 5 hours (plasma clearance is app oximately 600 mL/min) Populat on pha macokinetic analys s n patients w th IBS confi med that alosetron clearance is m n mally influenced by doses up to 8 mg

Renal elimination of unchanged alosetron accounts for only 13% of the dose Renal clearance s approxi mately 112 mL/m n

A study w th ^{14}C labeled alosetron n Caucasian males (n 3) and females (n 3) and an Asian male (n 1) showed sim lar serum metabol te profiles Unchanged alosetron was he major component in serum wi h other metabol tes be ng p esent at low concentrat ons none amount ng to mo e han 15% of the unmetabo lized alosetron concent at on The c rculat ng metabolites we e dentified as 6 hydroxy glucuron de 6 hydroxy sulphate 7 hyd oxy sulphate hydroxymethyl im dazole and mono and b s oxygenated midazole derivatives of alosetron The metabolites a e unlikely to contr bute to the biolog cal act v ty of alosetron Of he circulating Phase I metabol tes only he hydroxyme hyl imidazole has weak pharmacolog cal activity around 10 fold less potent han alosetron Total ecovery of radioactivity n the excreta was 85 ± 6% The major ty of the radiolabe led dose is excreted n the urine (74 ± 5%) The major urinary metabol tes were the 6 hydroxy glucuron de and he mono and b s oxygenated m dazole der vat ves of alosetron 11 ± 4% of the radiolabeled dose was excreted in the feces w th less han 1% of the dose be ng excreted as the unchanged alosetron

Alosetron is metabolized by human microsomal cytochrome P450 (CYP) shown *in vit o* to nvolve enzymes 2C9 (30%) 3A4 (18%) and 1A2 (10%) Non CYP mediated Phase I metabolic conversion a so contr butes to an extent of about 11% However *n v vo* data suggest hat CYP1A2 plays a more prominent role n alose tron metabolism (62 to 97% of alosetron clearance) based on co relat on of alosetron clearance w th *in v vo* CYP1A2 activity measured by probe substrate ncreased clearance induced by smok ng and inh b tion of clea ance by fluvoxam ne *[see Contraind cations (4) Drug Interactions (7)]*

13 NONCLINICAL TOXICOLOGY

13 1 Carcinogenesis Mutagenesis Impa rment of Fert lity

In 2 year o al studies aloset on was not ca c nogen c n m ce at doses up to 30 mg/kg/day or in ra s at doses up to 40 mg/kg/day These doses are about 60 to 160 times respectively he recommended human dose of alosetron of 2 mg/day (1 mg twice daily) based on body surface area Aloset on was not genotoxic n he Ames tests he mouse lymphoma ce l (L5178Y/TK±) forward gene mutation test the human lymphocyte ch omosome aberration test the ex v vo rat hepatocyte unscheduled DNA synthesis (UDS) test or the *n vivo* rat micronucleus test for mutagenicity Alosetron at o al doses up to 40 mg/kg/day (about 160 t mes the recommended daily human dose based on body surface area) was found to have no effect on fert l ty and rep oduct ve performance of male or female rats

14 CLIN CAL STUD ES

14 1 Dose Ranging Study

Data from a dose ranging study of women (n 85) who received alosetron hydrochloride table s 0 5 mg twice da ly nd cated hat the inc dence of const pat on (14%) was lower than that experienced by women receiving 1 mg twice daily (29%) Therefore to lower the r sk of const pation alosetron hydrochlor de table s should be started at a dosage of 0 5 mg twice a day The efficacy of he 0 5 mg twice daily dosage in treating severe d arrhea predom nant IBS has not been adequately evaluated n clin cal tr a s *[see Dosage And Administration (2 1)]*

14 2 Efficacy Stud es

Alosetron hydrochloride has been studied n women w th BS n five 12 week US mult center randomized double blind placebo controlled clinical stud es

Table 3 E ficacy Studies Conducted in Women With Irritable Bowel Syndrome (IBS)

Study	Patient Population	Placebo (n)	Alosetron HCl Dose (n)
1 and 2	Non const pated women w th IBS	(640)	1 mg twice daily (633)
3 and 4	Women with severe d arrhea predom nant IBS (defi ned as bowel urgency ≥ 50% of days)	(515)	1 mg twice daily (778)
5	Women wi h severe diarrhea predominant IBS (de fined as average pain ≥moderate urgency ≥50% of days and/or restrict on of da ly activit es ≥25% of days)	(176)	0 5 mg once daily (177)
			1 mg once daily (175)
			1 mg twice daily (177)

Studies in Non Const pated Women wi h Irritable Bowel Syndrome Stud es 1 and 2 we e conducted in non const pated women wi h BS meet ng the Rome Criteria[1] for at least 6 months Women w th severe pain or a history of severe const pation were excluded A 2 week run n period established basel ne IBS symptoms

About two h rds of the women had d ar hea predom nant IBS Compared w th placebo 10% to 19% more women w th d arrhea predom nant IBS who rece ved alosetron hydrochloride tablets had adequate rel ef of IBS abdominal pain and discomfort dur ng each month of the study

Studies in Women Wi h Severe Diarrhea Predominant I ritable Bowel Syndrome Aloset on hydrochloride ta blets is ind cated only for women with severe d a rhea predominant IBS [see **INDICAT ONS AND USAGE (1)**] The efficacy of alosetron hydrochlo ide tablets n h s subset of the women stud ed n clinical tr a s is supported by prospect ve and retrospect ve analyses

Prospective Analyses Stud es 3 and 4 were conducted n women with diarrhea predominant BS and bowel urgency on at least 50% of days at entry Women rece v ng alosetron hydrochloride tablets had sign ficant increases over placebo (13% to 16%) n the med an percentage of days w th urgency control

The lower gastro ntestinal funct ons of stool consistency stool frequency and sense of ncomplete evacua tion were also evaluated by pat ents' daily reports Stool cons stency was evaluated on a scale of 1 to 5 (1 very hard 2 hard 3 formed 4 loose and 5 watery) At baseline average stool cons stency was appro x mately 4 (loose) for both treatment groups During he 12 weeks of treatment the ave age stool consistency dec eased to app oximately 3 0 (formed) for patients who received alosetron hydrochlo ide tablets and 3 5 for the patients who received placebo n the 2 studies

At basel ne average stool frequency was approximately 3 2 per day for bo h treatment groups Du ing the 12 weeks of treatment he average daily stool frequency decreased to approx mately 2 1 and 2 2 for patients receiving aloset on hydrochloride tablets and 2 7 and 2 8 for patien s ece v ng placebo n the 2 studies

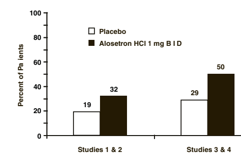
The e was no consistent effect upon the sense of ncomplete evacuation dur ng the 12 weeks of treatment for pat ents rece v ng alosetron hydrochlo ide tablets as compared to patients receiving placebo in ei her study

Study 5 was conducted in women w th severe d ar hea predom nant IBS and 1 or more of the fo lowing frequent and severe abdominal pain or d scomfo t frequent bowel urgency or fecal incontinence d sab l ty or restr ction of daily act v ties due to IBS To evaluate the proport on of pat ents who responded to treatment pa tien s were asked every 4 weeks to compa e heir IBS symptoms during the prev ous month of treatment w th how they usually felt during the 3 mon hs prior to he study us ng an ordered 7 point scale (substantially worse to substantially imp oved) A esponder was defined as a subject who eported moderate or substant al impro vement on this global imp ovement scale (G S) At Week 12 all three groups receiving alosetron hydrochloride tablets had sign ficantly g eater percentages of GIS esponders compared to he placebo group (43% to 51% vs 31%) using a Last Observat on Carried Fo ward (LOCF) analysis t should be noted that app oximately 4% of subjec s n each alosetron hydrochlor de tablets dose group who were classified as responders using th s app oach were observed only th ough week 4 At each of the 4 week ntervals of the treatment phase all th ee dosages of alosetron hydrochlo ide tablets p ovided mprovement n the average adequate el ef rate of IBS pain and d scomfo t stool consistency stool frequency and sense of urgency compared w th placebo

Retrospect ve Analyses In analyses of pat ents from Stud es 1 and 2 who had d ar hea predom nant IBS and indicated heir basel ne run n IBS symptoms were severe at the start of the trial alosetron hydrochloride tablets prov ded greater adequate rel ef of IBS pa n and d scomfort than placebo In further analyses of Studies 1 and 2 57% of patien s had urgency at basel ne on 5 or more days per week In th s subset 32% of patients on alosetron hyd ochlor de tablets had u gency no more than 1 day in the last week of the t ial compared w th 19% of pat ents on placebo

In Studies 3 and 4 66% of pat ents had urgency at baseline on 5 or mo e days per week In th s subset 50% of patien s on alosetron hydrochloride tablets had urgency no more han 1 day in the last week of the trial compared w th 29% of patients on placebo Moreover n the same subset 12% on alosetron hydrochloride tablets had urgency no more than 2 days per week n any of the 12 weeks on treatment compared with 1% of placebo pat ents

Figure 1 Percent of Pat ents Wi h Urgency on >5 Days/Week at Baseline Who Improved to No More Than 1 Day n he Final Week



In Stud es 1 and 2 patient reported subjective outcomes related to IBS were assessed by quest onnaires obtained at basel ne and week 12 Patien s n the mo e severe subset who rece ved alosetron hydrochloride tablets reported less di ficulty sleep ng less t redness fewer eat ng problems and less interference with soc al act v ties and work/main activities due to IBS symptoms or problems compared to those who received placebo Change in the mpact of IBS symptoms and problems on emotional and mental d stress and on physical and sexual activ ty in women who received aloset on hydrochloride tablets were not statist cally d fferent from those reported by women who rece ved placebo

14 3 Long Term Use

In a 48 week mu t national double bl nd placebo cont o led study alosetron hydrochlo ide tablets 1 mg tw ce da ly was evaluated in 714 women with non constipated IBS A retrospect ve analysis of the subset of women w th severe d a rhea predom nant IBS (u gency on at least 10 days dur ng the 2 week baseline period) was performed Of he 417 pat ents wi h severe diarrhea predominant BS 62% completed the trial

Alosetron hyd ochlor de table s (n 198) prov ded a greater average rate of adequate rel ef of IBS pain and discomfort (52% vs 41%) and a g eater average rate of satisfactory control of bowel urgency (60% vs 48%) compared with placebo (n 219) Significant mprovement of these symptoms occu red for most of he 48 week t eatment pe iod w th no evidence of tachyphylaxis

15 REFERENCES

1 Thompson WG Creed F Drossman DA et al Functional bowel d sease and functional abdom nal pain Gast oenterol Int 1992 5 75 91

16 HOW SUPPLIED/STORAGE AND HANDL NG

Alosetron Hydrochloride Tablets 0 5 mg (0 562 mg alosetron HCl equivalent to 0 5 mg alosetron) are white to off white round biconvex tablets debossed w th 54 628 on one s de and pla n on the other s de

Bot les of 30 (NDC 0054 0295 13) wi h child resistant closu es

Alosetron Hydrochloride Table s 1 mg (1 124 mg alosetron HCl equivalent to 1 mg alosetron) are white to off white round biconvex tablets debossed w th 54 974 on one side and pla n on the other s de

Bot les of 30 (NDC 0054 0296 13) wi h child resistant closu es

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature] Protect from l ght and moisture

17 PATIENT COUNSELING INFORMATION

See Medication Guide

Prescriber and Patient Respons bilities

Patients should be fully counseled on and understand the r sks and benefits of alosetron hyd ochlor de table s befo e an n tial prescript on is wri ten The patient may be educated by he enro led prescriber or a healthcare provider under a prescriber's direction

Prescr bers must

- counsel patients for whom alosetron hydrochloride tablets are app opriate about the benefits and r sks of alosetron hydrochloride tablets and discuss the mpact of IBS symptoms on the patient s l fe
- give the pat ent a copy of the Medication Guide wh ch outlines the benefits and isks of alosetron hydrochlor de table s and instruct he pat ent to read it carefu ly Answer all quest ons the patient may have about alosetron hydrochlor de table s The complete text of the Medication Guide is printed at the end of h s document
- eview he Pat ent Acknowledgement Form for alosetron hydrochloride tablets w th the patient answer all questions and give a copy of the signed Patient Acknowledgement Form to the pat ent
- prov de each patient w th appropriate instruct ons for tak ng alosetron hydrochlor de tablets

Copies of the Patient Acknowledgement Form for alosetron hydrochlor de tablets and add t onal cop es of the Medicat on Guide are available by contacting the Alosetron REMS P ogram at 1 844 267 8675 or visit ng www AlosetronREMS com

Patients who are prescribed alosetron hydrochlor de tablets should be instructed to

- ead the Med cat on Gu de before start ng alosetron hyd ochlor de tablets and each time they efill the r prescr pt on
- not start taking aloset on hydrochloride tablets if they are constipated
- mmediately discont nue alosetron hydrochlor de tablets and contact heir prescriber f they become const pated or have symptoms of ischemic colit s such as new or worsen ng abdominal pa n bloody diarrhea or blood n the stool Contact their p escriber aga n f heir const pat on does not resolve after discont nuat on of alosetron hydrochloride tablets Resume alosetron hydrochlor de table s only if the r const pation has resolved and after discuss on w th and the agreement of the r treating prescr ber
- stop tak ng alosetron hydrochlor de tablets and contact the r prescriber if alosetron hydrochloride tab le s does not adequately control IBS symptoms after 4 weeks of tak ng 1 mg twice a day

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