PSUR 2009-2012

Drug Substance Zolmitriptan

Date

Agreed Core Safety Profile –zolmitriptan

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1. SECTIONS 4.3 – 4.9 FROM THE MR SMPC FOR ZOLMITRIPTAN–NASAL SPRAY (DATED 19 AUGUST 2010)

4.3 Contraindications

Hypersensitivity to zolmitriptan or to any of the excipients.

Moderate and severe hypertension, and mild uncontrolled hypertension.

This class of compounds (5HT1B/1D receptor agonists), has been associated with coronary vasospasm, as a result, patients with ischaemic heart disease were excluded from clinical trials. Therefore zolmitriptan Nasal should not be given to patients who have had myocardial infarction or have ischaemic heart disease, coronary vasospasm (Prinzmetal's angina), peripheral vascular disease or patients who have symptoms or signs consistent with ischaemic heart disease.

Concurrent administration of ergotamine or ergotamine derivatives (including methysergide), and other 5HT1B/1D receptor agonists with zolmitriptan is contraindicated (see section 4.5).

Zolmitriptan should not be administered to patients with a history of cerebrovascular accident (CVA) or transient ischaemic attack (TIA).

Zolmitriptan is contraindicated in patients with a creatinine clearance of less than 15 ml/min.

4.4 Special warnings and precautions for use

zolmitriptan Nasal should only be used where a clear diagnosis of migraine or cluster headache has been established. As with other acute headache therapies, before treating patients not previously diagnosed as migraineurs or cluster headache sufferers, and in patients who present with atypical symptoms, care should be taken to exclude other potentially serious neurological conditions. Zolmitriptan is not indicated for use in hemiplegic, basilar or ophthalmophlegic migraine. Stroke and other cerebrovascular events have been reported in patients treated with 5HT1B/1D agonists. It should be noted that patients may be at risk of certain cerebrovascular events.

Zolmitriptan should not be given to patients with symptomatic Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathways.

In very rare cases, as with other 5HT1B/1D agonists, coronary vasospasm, angina pectoris and myocardial infarction have been reported. For patients with risk factors for ischaemic heart disease (e.g. smoking, hypertension, hyperlipidaemia, diabetes mellitus, heredity) a prior cardiovascular evaluation should be made before treatment with zolmitriptan is initiated (see section 4.3). Special consideration should be given to postmenopausal women and males over 40 with these risk factors. These evaluations, however, may not identify every patient who has

cardiac disease, and in very rare cases, serious cardiac events have occurred in patients without underlying cardiovascular disease.

As with other 5HT1B/1D receptor agonists, heaviness, pressure or tightness over the precordium (see section 4.8) have been reported after the administration of zolmitriptan. If chest pain or symptoms consistent with ischaemic heart disease occur, no further doses of zolmitriptan should be taken until after appropriate medical evaluation has been carried out.

As with other 5HT1B/1D agonists transient increases in systemic blood pressure have been reported in patients with and without a history of hypertension. Very rarely these increases in blood pressure have been associated with significant clinical events. The dose recommendation for zolmitriptan should not be exceeded. Undesirable effects may be more common during concomitant use of triptans and herbal preparations containing St John's wort (Hypericum perforatum).

Serotonin Syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) has been reported following concomitant treatment with triptans, and selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs). These reactions can be severe. If concomitant treatment with zolmitriptan and an SSRI or SNRI is clinically warranted, appropriate observation of the patient is advised, particularly during treatment initiation, with dose increases, or with addition of another serotoninergic medication (see section 4.5).

Prolonged use of any type of painkiller for headaches can make them worse. If this situation is experienced or suspected, medical advice should be obtained and treatment should be discontinued. The diagnosis of medication overuse headache should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of headache medications.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Data from healthy subjects suggests there are no clinically significant interactions between zolmitriptan and ergotamine. However, the increased risk of coronary vasospasm is a theoretical possibility, and concomitant administration is contraindicated. It is advised to wait at least 24 hours following the use of ergotamine containing preparations before administering zolmitriptan. Conversely it is advised to wait at least six hours following use of zolmitriptan before administering an ergotamine containing product (see section 4.3).

Pharmacokinetic interactions (effects of zolmitriptan on the pharmacokinetics of other medicinal products)

Following administration of moclobemide, specific MAO-A inhibitor, there was a small increase (26%) in AUC for zolmitriptan and a 3 fold increase in AUC of the active metabolite. Therefore, a maximum intake of 5 mg zolmitriptan in 24 hours is recommended in patients

taking a MAO-A inhibitor. The medicinal products should not be used together if doses of moclobemide higher than 150 mg b.i.d. are administered.

Following the administration of cimetidine, a general P450 inhibitor, the half life of zolmitriptan was increased by 44% and the AUC increased by 48%. In addition, the half life and AUC of the active, N-desmethylated, metabolite (183C91) were doubled.A maximum dose of 5 mg zolmitriptan in 24 hours is recommended in patients taking cimetidine

Treatment with potent CYP1A2 inhibitors may increase the plasma concentrations of zolmitriptan and reduce the concentrations of the active metabolite. The clinical relevance of this is unknown. Dosage reduction is recommended with compounds of this type, such as fluvoxamine and the quinolones (e.g. ciprofloxacin).

Selegiline (a MAO-B inhibitor) and fluoxetine (an SSRI) did not result in any pharmacokinetic interaction with zolmitriptan. However, there have been reports describing patients with symptoms compatible with Serotonin Syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) following the use of selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs) and triptans (see section 4.4).

As with other 5HT1B/1D receptor agonists zolmitriptan could delay the absorption of other medicinal products.

Concomitant administration of other $5HT_{1B/1D}$ agonists within 24 hours of zolmitriptan treatment should be avoided. Similarly, administration of zolmitriptan within 24 hours of the use of other $5HT_{1B/1D}$ agonists should be avoided.

Pharmacokinetic interactions (effects of other medicinal products on the pharmacokinetics of zolmitriptan)

Interaction studies were performed with caffeine, ergotamine, dihydroergotamine, paracetamol, metoclopramide, pizotifen, fluoxetine, rifampicin, and propranolol and no clinically relevant differences in the pharmacokinetics of zolmitriptan or its active metabolite were observed.

The absorption and pharmacokinetics of zolmitriptan is unaltered by prior administration of the sympathomimetic vasoconstrictor, xylometazoline.

Interaction studies discussed above were performed in adults, however there is no indication of a different interaction profile among adolescents.

4.6 Pregnancy and lactation

Pregnancy

The safety of this medical product for use in human pregnancy has not been established. Evaluation of experimental animal studies does not indicate direct teratogenic effects.

However, some findings in embryotoxicity studies suggested impaired embryo viability. Administration of zolmitriptan should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus.

Lactation

Studies have shown that zolmitriptan passes into the milk of lactating animals. No data exist for passage of zolmitriptan into human breast milk. Therefore, caution should be exercised when administering zolmitriptan to women who are breast-feeding. Infant exposure should be minimised by avoiding breast feeding for 24 hours after treatment.

4.7 Effects on ability to drive and use machines

In a small group of healthy individuals there was no significant impairment of performance of psychomotor tests with doses up to 20 mg zolmitriptan. Caution is recommended in patients driving or operating machinery as drowsiness and other symptoms may occur during a migraine attack.

4.8 Undesirable effects

Possible undesirable effects are typically transient, tend to occur within four hours of dosing, are no more frequent following repeated dosing and resolve spontaneously without additional treatment.

The following definitions apply to the incidence of the undesirable effects:

Very common (≥1/10); common (≥1/100 , <1/10); uncommon (≥1/1000, <1/100), rare (≥1/10000, < 1/1000), very rare (<1/10000).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

The following undesirable effects have been reported following administration with zolmitriptan:

System Organ Class	Frequency	Undesirable Effect
Immune system disorders	Rare	Hypersensitivity reactions including urticaria, angioedema and anaphylactic reactions
Nervous system disorders	Very common	Taste disturbances

System Organ Class	Frequency	Undesirable Effect
	Common	Abnormalities or disturbances or sensation; Dizziness; Headache; Hyperaesthesia; Paraesthesia; Somnolence; Warm sensation
Cardiac disorders	Common	Palpitations
	Uncommon	Tachycardia
	Very rare	Myocardial infarction; Angina pectoris; Coronary vasospasm
Vascular disorders	Uncommon	Slight increases in blood pressure; Transient increases in systemic blood pressure
Respiratory, thoracic and mediastinal disorders	Common	Nose bleed; Discomfort of nasal cavity; Non-infectious rhinitis
Gastrointestinal disorders	Common	Abdominal pain; Nausea; Vomiting; Dry mouth Dysphagia
	Very rare	Ischaemia or infarction (e.g. intestinal ischaemia, intestinal infarction, splenic infarction) which may present as bloody diarrhoea or abdominal pain
Musculoskeletal and connective tissue disorders	Common	Muscle weakness; Myalgia
Renal and Urinary disorders	Uncommon	Polyuria; Increased urinary frequency
	Very rare	Urinary urgency
General disorders and administration site disorders	Common	Asthenia; Heaviness, tightness, pain or pressure in throat, neck, limbs or chest.

Pripombe dodal [c1]: Dysphagia

The incidence of local adverse events was dose related.

Certain symptoms, may be part of the migraine attack itself.

Frequency, type and severity of adverse events are similar in adults and adolescents.

4.9 Overdose

Volunteers receiving single oral doses of 50 mg zolmitriptan commonly experienced sedation.

The elimination half-life of zolmitriptan is 2.5 to 3 hours, (see section 5.2) and therefore monitoring of patients after overdose with-zolmitriptanNasal should continue for at least 15 hours or while symptoms or signs persist.

There is no specific antidote to zolmitriptan. In cases of severe intoxication, intensive care procedures are recommended, including establishing and maintaining a patent airway, ensuring adequate oxygenation and ventilation, and monitoring and support of the cardiovascular system.

It is unknown what effect haemodialysis or peritoneal dialysis has on the serum concentrations of zolmitriptan.

2. SECTIONS 4.3 – 4.9 FROM THE MR SMPC FOR ZOLMITRIPTAN LOZENGE (DATED 19 AUGUST 2010)

Pripombe dodal [c2]: Changed to accepted wording

4.3 Contraindications

~~'Zolmitriptan' is contraindicated in patients with known hypersensitivity to zolmitriptan or to any of the excipients.~~

Hypersensitivity to zolmitriptan or to any of the excipients.

Pripombe dodal [c3]: Changed to accepted wording

Moderate or severe hypertension, and mild uncontrolled hypertension.

This class of compounds (5HT1B/1D receptor agonists), has been associated with coronary vasospasm, as a result, patients with ischaemic heart disease were excluded from clinical trials. Therefore 'zolmitriptan should not be given to patients who have had myocardial infarction or have ischaemic heart disease, coronary vasospasm (Prinzmetal's angina), peripheral vascular disease or patients who have symptoms or signs consistent with ischaemic heart disease.

Concurrent administration of ergotamine, ergotamine derivatives (including methysergide), sumatriptan, naratriptan and other 5HT1B/1D receptor agonists with zolmitriptan is contraindicated (see Section 4.5).

Zolmitriptan should not be administered to patients with a history of cerebrovascular accident (CVA) or transient ischaemic attack (TIA).

Zolmitriptan is contraindicated in patients with a creatinine clearance of less than 15 ml/min.

4.4 Special warnings and special precautions for use

Zolmitriptan should only be used where a clear diagnosis of migraine has been established. As with other acute migraine therapies, before treating headaches in patients not previously diagnosed as migraineurs, and in migraineurs who present with atypical symptoms, care should be taken to exclude other potentially serious neurological conditions. Zolmitriptan is not indicated for use in hemiplegic, basilar or ophthalmoplegic migraine. Stroke and other cerebrovascular events have been reported in patients treated with 5HT1B/1D agonists. It should be noted that migraneurs may be at risk of certain cerebrovascular events.

Zolmitriptan should not be given to patients with symptomatic Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathways.

In very rare cases, as with other 5HT1B/1D agonists, coronary vasospasm, angina pectoris and myocardial infarction have been reported. zolmitriptan-should not be given to patients with risk factors for ischaemic heart disease (e.g. smoking, hypertension, hyperlipidaemia, diabetes

mellitus, heredity) without prior cardiovascular evaluation (see Section 4.3). Special consideration should be given to postmenopausal women and males over 40 with these risk factors. These evaluations, however, may not identify every patient who has cardiac disease, and in very rare cases, serious cardiac events have occurred in patients without underlying cardiovascular disease.

As with other 5HT1B/1D receptor agonists, heaviness, pressure or tightness over the precordium (See Section 4.8) have been reported after the administration of zolmitriptan. If chest pain or symptoms consistent with ischaemic heart disease occur, no further doses of zolmitriptan should be taken until after appropriate medical evaluation has been carried out.

As with other 5HT1B/1D agonists transient increases in systemic blood pressure have been reported in patients with and without a history of hypertension. Very rarely these increases in blood pressure have been associated with significant clinical events. The dose recommendation for zolmitriptan should not be exceeded.

Patients with phenylketonuria should be informed that zolmitriptan contains phenylalanine (a component of aspartame). Each 2.5 mg tablet contains 2.81 mg of phenylalanine and each 5 mg tablet contains 5.62 mg of phenylalanine.

Undesirable effects may be more common during concomitant use of triptans and herbal preparations containing St John's wort (Hypericum perforatum).

Serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) has been reported following concomitant treatment with triptans and selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs). These reactions can be severe. If concomitant treatment with zolmitriptan and an SSRI or SNRI is clinically warranted, appropriate observation of the patient is advised, particularly during treatment initiation, with dose increases, or with addition of another serotonergic medication (see section 4.5)

Prolonged use of any type of painkiller for headaches can make them worse. If this situation is experienced or suspected, medical advice should be obtained and treatment should be discontinued. The diagnosis of medication overuse headache should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of headache medications.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies were performed with caffeine, ergotamine, dihydroergotamine, paracetamol, metoclopramide, pizotifen, fluoxetine, rifampicin and propranolol and no clinically relevant differences in the pharmacokinetics of zolmitriptan or its active metabolite were observed.

Data from healthy subjects suggests there are no pharmacokinetic or clinically significant interactions between zolmitriptan and ergotamine. However, the increased risk of coronary

vasospasm is a theoretical possibility, and concomitant administration is contraindicated. It is advised to wait at least 24 hours following the use of ergotamine containing preparations before administering zolmitriptan. Conversely it is advised to wait at least six hours following use of zolmitriptan before administering an ergotamine containing product (see section 4.3).

Following administration of moclobemide, a specific MAO-A inhibitor, there was a small increase (26%) in AUC for zolmitriptan and a 3 fold increase in AUC of the active metabolite. Therefore, a maximum intake of 5 mg zolmitriptan in 24 hours, is recommended in patients taking a MAO-A inhibitor. The drugs should not be used together if doses of moclobemide higher than 150 mg b.i.d. are administered.

Following the administration of cimetidine, a general P450 inhibitor, the half life of zolmitriptan was increased by 44% and the AUC increased by 48%. In addition, the half life and AUC of the active, N-desmethylated, metabolite (183C91) were doubled. A maximum dose of 5 mg zolmitriptan in 24 hours is recommended in patients taking cimetidine. Based on the overall interaction profile, an interaction with specific inhibitors of CYP 1A2 cannot be excluded. Therefore, the same dosage reduction is recommended with compounds of this type, such as fluvoxamine and the quinolones (eg ciprofloxacin).

Selegiline (a MAO-B inhibitor) and fluoxetine (an SSRI) did not result in any pharmacokinetic interaction with zolmitriptan. However, there have been reports describing patients with symptoms compatible with serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) following the use of selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs) and triptans (see section 4.4).

As with other 5HT1B/1D receptor agonists, zolmitriptan could delay the absorption of other medicinal products.

Concomitant administration of other $5HT_{1B/1D}$ agonists within 24 hours of zolmitriptan treatment should be avoided. Similarly, administration of zolmitriptan within 24 hours of the use of other $5HT_{1B/1D}$ agonists should be avoided.

4.6 Pregnancy and lactation

Pregnancy:
The safety of this medical product for use in human pregnancy has not been established. Evaluation of experimental animals studies does not indicate direct teratogenic effects. However, some findings in embryotoxicity studies suggested impaired embryo viability. Administration of zolmitriptan should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus.

Lactation:
Studies have shown that zolmitriptan passes into the milk of lactating animals. No data exist for passage of zolmitriptan into human breast milk. Therefore, caution should be exercised

when administering zolmitriptan to women who are breast-feeding. Infant exposure should be minimised by avoiding breast feeding for 24 hours after treatment

4.7 Effects on ability to drive and use machines

In a small group of healthy individuals there was no significant impairment of performance of psychomotor tests with doses up to 20 mg zolmitriptan. Caution is recommended in patients performing skilled tasks (eg driving or operating machinery) as drowsiness and other symptoms may occur during a migraine attack.

4.8 Undesirable effects

Possible undesirable effects are typically transient, tend to occur within four hours of dosing, are no more frequent following repeated dosing and resolve spontaneously without additional treatment.

The following definitions apply to the incidence of the undesirable effects:

Very common (≥1/10); common (≥ 1/100 , <1/10); uncommon (≥1/1000, <1/100), rare (≥1/10000, <1/1,000), very rare (<1/10000).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

The following undesirable effects have been reported following administration of zolmitriptan:

System Organ Class	Frequency	Undesirable Effect
Immune system disorders	Rare	Hypersensitivity reactions including urticaria, angioedema and anaphylactic reactions
Nervous system disorders	Common	Abnormalities or disturbances or sensation; Dizziness; Headache; Hyperaesthesia; Paraesthesia; Somnolence; Warm sensation
Cardiac disorders	Common	Palpitations
	Uncommon	Tachycardia
	Very rare	Myocardial infarction; Angina pectoris; Coronary vasospasm

System Organ Class	Frequency	Undesirable Effect
Vascular disorders	Uncommon	Slight increases in blood pressure; Transient increases in systemic blood pressure
Gastrointestinal disorders	Common	Abdominal pain; Nausea; Vomiting; Dry mouth Dysphagia
	Very rare	Ischaemia or infarction (e.g. intestinal ischaemia, intestinal infarction, splenic infarction) which may present as bloody diarrhoea or abdominal pain
Musculoskeletal and connective tissue disorders	Common	Muscle weakness; Myalgia
Renal and Urinary disorders	Uncommon	Polyuria; Increased urinary frequency
	Very rare	Urinary urgency
General disorders and administration site disorders	Common	Asthenia; Heaviness, tightness, pain or pressure in throat, neck, limbs or chest.

Certain symptoms, may be part of the migraine attack itself.

4.9 Overdose

Volunteers receiving single oral doses of 50 mg commonly experienced sedation.

The elimination half-life of zolmitriptan tablets is 2.5 to 3 hours, (see Section 5.2) and therefore monitoring of patients after overdose with '~~ZolmitriptanZolmitriptan Rapimelt~~'zolmitriptan orodispersible tablets should continue for at least 15 hours or while symptoms or signs persist.

There is no specific antidote to zolmitriptan . In cases of severe intoxication, intensive care procedures are recommended, including establishing and maintaining a patent airway, ensuring adequate oxygenation and ventilation, and monitoring and support of the cardiovascular system.

It is unknown what effect haemodialysis or peritoneal dialysis has on the serum concentrations of zolmitriptan.

3. SECTIONS 4.3 – 4.9 FROM THE MR SMPC FOR ZOLMITRIPTAN FILM-COATED TABLETS (DATED 19 AUGUST 2010)

4.3 Contraindications

~~'Zolmitriptan' is contraindicated in patients with known hypersensitivity to zolmitriptan or to any of the excipients.~~

Hypersensitivity to zolmitriptan or to any of the excipients.

Moderate or severe hypertension, and mild uncontrolled hypertension.

This class of compounds (5HT1B/1D receptor agonists), has been associated with coronary vasospasm, as a result, patients with ischaemic heart disease were excluded from clinical trials. Therefore zolmitriptan should not be given to patients who have had myocardial infarction or have ischaemic heart disease, coronary vasospasm (Prinzmetal's angina), peripheral vascular disease or patients who have symptoms or signs consistent with ischaemic heart disease.

Concurrent administration of ergotamine, ergotamine derivatives (including methysergide), sumatriptan, naratriptan and other 5HT1B/1D receptor agonists with zolmitriptan is contraindicated (see Section 4.5)

Zolmitriptan should not be administered to patients with a history of cerebrovascular accident (CVA) or transient ischaemic attack (TIA).

Zolmitriptan is contraindicated in patients with a creatinine clearance of less than 15 ml/min.

4.4 Special warnings and special precautions for use

Zolmitriptan should only be used where a clear diagnosis of migraine has been established. As with other acute migraine therapies, before treating headaches in patients no previously diagnosed as migraineurs, and in migraineurs who present with atypical symptoms, care should be taken to exclude other potentially serious neurological conditions. Zolmitriptan is not indicated for use in hemiplegic, basilar or ophthalmophlegic migraine. Stroke and other cerebrovascular events have been reported in patients treated with 5HT1B/1D agonists. It should be noted that migraneurs may be at risk of certain cerebrovascular events.

Zolmitriptan should not be given to patients with symptomatic Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathways.

In very rare cases, as with other 5HT1B/1D agonists, coronary vaspspasm, angina pectoris and myocardial infarction have been reported. zolmitriptan should not be given to patients with risk factors for ischaemic heart disease (e.g. smoking, hypertension, hyperlipidaemia, diabetes mellitus, heredity) without prior cardiovascular evaluation (see Section 4.3). Special consideration should be given to postmenopausal women and males over 40 with these risk factors. These evaluations, however, may not identify every patient who has cardiac disease, and in very rare cases, serious cardiac events have occurred in patients without underlying cardiovascular disease.

As with other 5HT1B/1D receptor agonists, heaviness, pressure or tightness over the precordium (See Section 4.8) have been reported after the administration of zolmitriptan. If chest pain or symptoms consistent with ischaemic heart disease occur, no further doses of zolmitriptan should be taken until after appropriate medical evaluation has been carried out.

As with other 5HT1B/1D agonists transient increases in systemic blood pressure have been reported in patients with and without a history of hypertension. Very rarely these increases in blood pressure have been associated with significant clinical events. The dose recommendation for zolmitriptan should not be exceeded.

Undesirable effects may be more common during concomitant use of triptans and herbal preparations containing St John's wort (Hypericum perforatum).

Serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) has been reported following concomitant treatment with triptans and selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs). These reactions can be severe. If concomitant treatment with zolmitriptan and an SSRI or SNRI is clinically warranted, appropriate observation of the patient is advised, particularly during treatment initiation, with dose increases, or with addition of another serotonergic medication (see section 4.5).

Prolonged use of any type of painkiller for headaches can make them worse. If this situation is experienced or suspected, medical advice should be obtained and treatment should be discontinued. The diagnosis of medication overuse headache should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of headache medications.

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies were performed with caffeine, ergotamine, dihydroergotamine, paracetamol, metoclopramide, pizotifen, fluoxetine, rifampicin and propranolol and no clinically relevant differences in the pharmacokinetics of zolmitriptan or its active metabolite were observed.

Data from healthy subjects suggests there are no pharmacokinetic or clinically significant interactions between zolmitriptan and ergotamine. However, the increased risk of coronary vasospasm is a theoretical possibility, and concomitant administration is contraindicated. It is advised to wait at least 24 hours following the use of ergotamine containing preparations before administering zolmitriptan. Conversely it is advised to wait at least six hours following use of zolmitriptan before administering an ergotamine containing product (see section 4.3).

Following administration of moclobemide, a specific MAO-A inhibitor, there was a small increase (26%) in AUC for zolmitriptan and a 3 fold increase in AUC of the active metabolite. Therefore, a maximum intake of 5 mg zolmitriptan in 24 hours, is recommended in patients taking a MAO-A inhibitor. The medicinal products should not be used together if doses of moclobemide higher than 150 mg b.i.d. are administered.

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As with other 5HT1B/1D receptor agonists, zolmitriptan could delay the absorption of other medicinal products.

Concomitant administration of other $5HT_{1B/1D}$ agonists within 24 hours of zolmitriptan treatment should be avoided. Similarly, administration of zolmitriptan within 24 hours of the use of other $5HT_{1B/1D}$ agonists should be avoided.

4.6 Pregnancy and lactation

Pregnancy The safety of this medical product for use in human pregnancy has not been established. Evaluation of experimental animals studies does not indicate direct teratogenic effects. However, some findings in embryotoxicity studies suggested impaired embryo viability. Administration of zolmitriptan should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus.

Lactation Studies have shown that zolmitriptan passes into the milk of lactating animals. No data exist for passage of zolmitriptan into human breast milk. Therefore, caution should be

exercised when administering zolmitriptan to women who are breast-feeding. Infant exposure should be minimised by avoiding breast feeding for 24 hours after treatment

4.7 Effects on ability to drive and use machines

In a small group of healthy individuals there was no significant impairment of performance of psychomotor tests with doses up to 20 mg zolmitriptan. Caution is recommended in patients performing skilled tasks (eg driving or operating machinery) as drowsiness and other symptoms may occur during a migraine attack.

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Possible undesirable effects are typically transient, tend to occur within four hours of dosing, are no more frequent following repeated dosing and resolve spontaneously without additional treatment.

The following definitions apply to the incidence of the undesirable effects:

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Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

The following undesirable effects have been reported following administration of zolmitriptan:

System Organ Class	Frequency	Undesirable Effect
Immune system disorders	Rare	Hypersensitivity reactions including urticaria, angioedema and anaphylactic reactions
Nervous system disorders	Common	Abnormalities or disturbances or sensation; Dizziness; Headache; Hyperaesthesia; Paraesthesia; Somnolence; Warm sensation
Cardiac disorders	Common	Palpitations
	Uncommon	Tachycardia
	Very rare	Myocardial infarction; Angina pectoris; Coronary vasospasm
Vascular disorders	Uncommon	Slight increases in blood pressure; Transient increases in systemic blood

System Organ Class	Frequency	Undesirable Effect
		pressure
Gastrointestinal disorders	Common	Abdominal pain; Nausea; Vomiting; Dry mouth Dysphagia
	Very rare	Ischaemia or infarction (e.g. intestinal ischaemia, intestinal infarction, splenic infarction) which may present as bloody diarrhoea or abdominal pain
Musculoskeletal and connective tissue disorders	Common	Muscle weakness; Myalgia
Renal and Urinary disorders	Uncommon	Polyuria; Increased urinary frequency
	Very rare	Urinary urgency
General disorders and administration site disorders	Common	Asthenia; Heaviness, tightness, pain or pressure in throat, neck, limbs or chest.

Certain symptoms, may be part of the migraine attack itself.

4.9 Overdose

Volunteers receiving single oral doses of 50 mg commonly experienced sedation.

The elimination half-life of zolmitriptan tablets is 2.5 to 3 hours, (see Section 5.2) and therefore monitoring of patients after overdose with zolmitriptan tablets should continue for at least 15 hours or while symptoms or signs persist.

There is no specific antidote to zolmitriptan. In cases of severe intoxication, intensive care procedures are recommended, including establishing and maintaining a patent airway, ensuring adequate oxygenation and ventilation, and monitoring and support of the cardiovascular system.

It is unknown what effect haemodialysis or peritoneal dialysis has on the serum concentrations of zolmitriptan.