

New Zealand Data Sheet

Versacloz™ (clozapine) can cause agranulocytosis. Its use should be limited to patients:

- with schizophrenia who are non-responsive to or intolerant of classical antipsychotic agents, or with schizophrenia or schizoaffective disorder who are at risk of recurrent suicidal behaviour (*see section 4.1*),
- who have initially normal leukocyte findings (white blood cell count (WBC) $\geq 3500/\text{mm}^3$ ($3.5 \times 10^9/\text{L}$), and absolute neutrophil counts (ANC) $\geq 2000/\text{mm}^3$ ($2.0 \times 10^9/\text{L}$)),
- and in whom regular white blood cell counts and absolute neutrophil counts can be performed as follows: weekly during the first 18 weeks of therapy, and at least every 4 weeks thereafter throughout treatment. Monitoring must continue throughout treatment and for 4 weeks after complete discontinuation of Versacloz (see Section 4.4).

Prescribing physicians should comply fully with the required safety measures. At each consultation, a patient receiving Versacloz should be reminded to contact the treating physician immediately if any kind of infection begins to develop. Particular attention should be paid to flu-like complaints such as fever or a sore throat and to other evidence of infection, which may be indicative of neutropenia (see Section 4.4). Close monitoring of bowel habits is also recommended for any signs of constipation or gastrointestinal hypomotility.

Versacloz must be prescribed and dispensed in accordance with appropriate local guidelines. The following conditions apply to the sale, supply and use of Versacloz in New Zealand under the consent notice from Medsafe. Douglas draws prescribers, nurses and patients' attention to the following criteria:

1. Clozapine may only be initiated and prescribed by:

- Registered medical practitioners as defined in the Health Practitioners Competence Assurance Act 2003 who are certified by the Medical Council of New Zealand as competent in the scope of practice of psychiatry (i.e. psychiatrists).
- Medical practitioners or nurse practitioners, who are under the supervision of the persons referred to above.
- Medical officers who are in the employment of Health New Zealand – Te Whatu Ora, and are under the supervision of persons who are registered medical practitioners as defined in the Health Practitioners Competence Assurance Act 2003 who are certified by the Medical Council of New Zealand as competent in the scope of practice of psychiatry.
- Registered medical practitioners as defined in the Health Practitioners Competence Assurance Act 2003 who are registered with the Medical Council of New Zealand within the vocational scope of practice of general practice. The general practitioner must be continuing the prescribing of clozapine for a specific patient whose illness is well-controlled in collaboration, or following consultation, with the relevant Community Mental Health Team.

2. Persons prescribing the medicine must comply with appropriate local treatment guidelines.

3. The medicine must be dispensed in accordance with appropriate local dispensing guidelines.
4. Sale or marketing of this medicine may only occur if the sponsor has an appropriate blood monitoring and patient record database in place.

Due to the risk of agranulocytosis, all patients prescribed Versacloz in New Zealand must be registered to ClopineCentral™, the Clopine® Monitoring System by a registered medical practitioner or nurse practitioner. Additionally, prescribing physicians and nurse practitioners must also register themselves onto ClopineCentral™ to access patient information. Brand swapping between clozapine products is discouraged and should occur on the advice of a clinician.

Prescribers and dispensers should verify that the patient has not previously developed an adverse reaction to clozapine that contraindicates further use of any clozapine containing product.

Clozapine is associated with an increased risk of myocarditis which has, in rare cases, been fatal. The increased risk of myocarditis is greatest in the first two months of treatment. Fatal cases of cardiomyopathy have also been reported rarely. Myocarditis and cardiomyopathy should be suspected in patients who experience persistent tachycardia at rest especially in the first two months of treatment and/or palpitations, arrhythmias, chest pain and other signs and symptoms of heart failure (e.g. unexplained fatigue, dyspnoea, tachypnoea) or symptoms that mimic myocardial infarction. If myocarditis or cardiomyopathy is suspected, Versacloz treatment should promptly be stopped and the patient immediately referred to a cardiologist.

1. PRODUCT NAME

Versacloz™ 50 mg/mL oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL of Versacloz suspension contains 50 mg of clozapine.

Excipient(s) with known effects

Versacloz suspension contains sorbitol and hydroxybenzoates. For a full list of excipients, *see section 6.1.*

3. PHARMACEUTICAL FORM

Versacloz suspension is a free-flowing yellow suspension.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Treatment-resistant schizophrenia.

Versacloz is indicated in patients with treatment-resistant schizophrenia, i.e., patients with schizophrenia who are non-responsive to or intolerant of classic antipsychotics.

Non-responsiveness is defined as a lack of satisfactory clinical improvement despite the use of adequate doses of at least two marketed antipsychotics prescribed for adequate durations.

Intolerance is defined as the impossibility of achieving adequate clinical benefit with classic antipsychotics because of severe and untreatable neurological adverse reactions (extrapyramidal side effects or tardive dyskinesia).

Versacloz suspension is only indicated in patients aged 16 years and above.

4.2. Dose and method of administration

Brand swapping between clozapine products is discouraged and should only occur on the advice of a clinician.

Dose

The dosage must be adjusted individually. For each patient, the lowest effective dose should be used. Cautious titration and a divided dosage schedule are necessary to minimise the risks of hypotension, seizure, and sedation.

Initiation of clozapine treatment must be restricted to those patients with a white blood cell (WBC) count $\geq 3500/\text{mm}^3$ ($3.5 \times 10^9/\text{L}$) and an absolute neutrophil count (ANC) $\geq 2000/\text{mm}^3$ ($2.0 \times 10^9/\text{L}$) and within standardised normal limits.

Dose adjustment is indicated in patients who are also receiving medicinal products that have pharmacokinetic interactions with clozapine, such as benzodiazepines or selective serotonin reuptake inhibitors (*see section 4.5*).

In patients with a history of seizures or suffering from renal or cardiovascular disorders (note: severe renal or cardiovascular disorders are contraindications) the initial dose should be 12.5 mg given once on the first day, and dosage increase should be slow and in small increments.

Switching from a previous antipsychotic therapy to Versacloz

It is generally recommended that clozapine should not be used in combination with other antipsychotics. When clozapine therapy is to be initiated in a patient undergoing oral antipsychotic therapy, it is recommended that the dosage of other antipsychotics be reduced or discontinued by gradually tapering it downwards. Based on the clinical circumstances, the prescribing physician should judge whether or not to discontinue the other antipsychotic therapy before initiating treatment with Versacloz.

Treatment-resistant schizophrenia

Starting therapy, Versacloz should be started with 12.5 mg once or twice on the first day, followed by 25 mg to 50 mg on the second day. If well tolerated, the daily dose may then be increased slowly in increments of 25 mg to 50 mg in order to achieve a dose level of up to 300 mg/day within 2 to 3 weeks. Thereafter, if required, the daily dose may be further

increased in increments of 50 mg to 100 mg at half-weekly or, preferably, weekly intervals.

Therapeutic dose range

In most patients, antipsychotic efficacy can be expected with 200 to 450 mg/day given in divided doses. Some patients may be treated with lower doses, and some patients may require doses up to 600 mg/day. The total daily dose may be divided unevenly, with the larger portion being taken at bedtime.

Maximum dose

To obtain a full therapeutic benefit, a few patients may require larger doses, in which case judicious increments (not exceeding 100 mg) are permissible up to 900 mg/day. The possibility of increased adverse reactions (in particular seizures) occurring at doses over 450 mg/day must be borne in mind.

Maintenance dose

After achieving maximum therapeutic benefit, patients can be maintained effectively on lower doses. Careful downward titration is recommended to the lowest effective dose for the individual patient. Treatment should be maintained for at least 6 months. If the daily dose does not exceed 200 mg, once-daily administration in the evening may be appropriate.

Ending therapy

In the event of planned termination of Versacloz therapy, a gradual reduction in dose over a 1- to 2-week period is recommended. If abrupt discontinuation is necessary (e.g. because of leucopenia), the patient should be carefully observed for the recurrence of psychotic symptoms and symptoms related to cholinergic rebound (*see section 4.4*).

Re-starting therapy

In patients in whom the interval since the last dose of Versacloz exceeds 2 days, treatment should be reinitiated with 12.5 mg given once or twice on the first day. If this dose is well-tolerated, it may be feasible to titrate the dose to the therapeutic level more quickly than is recommended for initial treatment. However, in any patient who has previously experienced respiratory or cardiac arrest with initial dosing (*see section 4.4*) but was then able to be successfully titrated to a therapeutic dose, re-titration should be done with extreme caution.

Special populations

Cardiovascular disorders

In patients suffering from cardiovascular disorders (note: severe cardiovascular disorders are contraindications, *see section 4.3*) the initial dose should be 12.5 mg given once on the first day, and dosage increase should be slow and in small increments.

Renal impairment

In patients with mild to moderate renal impairment the initial dose should be 12.5 mg given once on the first day, and dosage increase should be slow and in small increments.

Hepatic impairment

Patients with hepatic impairment should receive Versacloz with caution along with regular monitoring of liver function tests (*see section 4.4*).

Patients 60 years of age and older

It is recommended that treatment in patients 60 years and older is initiated at a particularly low dose (12.5 mg given once on the first day) with subsequent dose increments restricted to 25 mg/day.

Versacloz is not approved for the treatment of dementia-related behavioural disturbances (*see section 4.4*).

Paediatric population

No paediatric studies have been performed.

Children and adolescents

The safety and efficacy of clozapine in children and adolescents up to 16-years of age have not been established.

Method of Administration

Versacloz is administered orally.

4.3. Contraindications

- Known hypersensitivity to clozapine or to any of the excipients of Versacloz (*see section 6.1*).
- Patients unable to undergo regular blood tests.
- History of toxic or idiosyncratic granulocytopenia/agranulocytosis (with the exception of granulocytopenia/agranulocytosis from previous chemotherapy).
- Drug-induced agranulocytosis
- Impaired bone marrow function.
- Uncontrolled epilepsy.
- Alcoholic and other toxic psychoses, drug intoxication, comatose conditions.
- Circulatory collapse and/or CNS depression of any cause.
- Severe renal or cardiac disorders (e.g. myocarditis).
- Active liver disease associated with nausea, anorexia or jaundice; progressive liver disease, hepatic failure.
- Paralytic ileus.

4.4. Special warnings and precautions for use

Agranulocytosis

Prescribers and dispensers should verify that the patient has not previously developed an adverse reaction to clozapine that contraindicates further use of any clozapine containing product.

Because of the association of clozapine with **agranulocytosis**, the following precautionary measures are mandatory:

Medicines known to have a substantial potential to depress bone marrow function should not be used concurrently with Versacloz. In addition, the concomitant use of long-acting depot antipsychotics should be avoided because of the impossibility of removing these medications, which may be potentially myelosuppressive, from the body rapidly in situations where this may be required, e.g., granulocytopenia.

Patients with a history of primary bone marrow disorders may be treated only if the benefit outweighs the risk. They should be carefully reviewed by a haematologist prior to starting Versacloz.

Patients who have low white blood cell (WBC) counts because of benign ethnic neutropenia should be given special consideration and may be started on Versacloz after agreement of a haematologist.

Versacloz must be dispensed under strict medical supervision in accordance with official recommendations.

White Blood Cell (WBC) counts and Absolute Neutrophil Count (ANC) monitoring

White blood cell (WBC) and differential blood counts must be performed within 10 days prior to starting Versacloz treatment to ensure that only patients with normal leukocyte and absolute neutrophil counts ($WBC \geq 3500/\text{mm}^3$ ($\geq 3.5 \times 10^9/\text{L}$) and $ANC \geq 2000/\text{mm}^3$ ($\geq 2.0 \times 10^9/\text{L}$)) will receive Versacloz. After the start of Versacloz treatment, regular WBC count and ANC must be performed and monitored weekly for 18 weeks, and thereafter at least every four weeks throughout treatment, and for 4 weeks after complete discontinuation of Versacloz.

Prescribing physicians should comply fully with the required safety measures. At each consultation, the patient should be reminded to contact the treating physician immediately if any kind of infection begins to develop. Particular attention should be paid to flu-like complaints such as fever, or a sore throat and to other evidence of infection, which may be indicative of neutropenia. A differential blood count must be performed immediately if any symptoms or signs of an infection occur.

Low WBC count and/or ANC

If during Versacloz therapy, either the WBC count falls to between $3500/\text{mm}^3$ ($3.5 \times 10^9/\text{L}$) and $3000/\text{mm}^3$ ($3.0 \times 10^9/\text{L}$) or the ANC falls to between $2000/\text{mm}^3$ ($2.0 \times 10^9/\text{L}$) and $1500/\text{mm}^3$ ($1.5 \times 10^9/\text{L}$), haematological evaluations must be performed at least twice weekly until the patients WBC count and ANC stabilise within the range $3000 - 3500/\text{mm}^3$ ($3.0 - 3.5 \times 10^9/\text{L}$) and $1500 - 2000/\text{mm}^3$ ($1.5 - 2.0 \times 10^9/\text{L}$), respectively, or higher.

In addition, if, during Versacloz therapy, the WBC count is found to have dropped by a substantial amount from baseline, a repeat WBC count and a differential blood count should be performed.

A substantial drop is defined as a single drop of 3000 mm³ (3.0 x 10⁹/L) or more in the WBC count or a cumulative drop of 3000 mm³ (3.0 x 10⁹/L) or more within three weeks.

Immediate discontinuation of Versacloz is mandatory if the WBC count is less than 3000/mm³ (3.0 x 10⁹/L) or the ANC is less than 1500/mm³ (1.5 x 10⁹/L). WBC counts and differential blood counts should then be performed daily, and patients should be carefully monitored for flu-like symptoms or other symptoms suggestive of infection. Following discontinuation of Versacloz, haematological evaluation is required until haematological recovery has occurred.

If Versacloz has been withdrawn and WBC count falls further to below 2000/mm³ (2.0 x 10⁹/L) and/or the ANC falls below 1000/mm³ (1.0 x 10⁹/L), the management of this condition must be guided by an experienced haematologist. If possible, the patient should be referred to a specialised haematological unit, where protective isolation and the administration of GM-CSF (granulocyte-macrophage colony-stimulating factor) or G-CSF (granulocyte colony-stimulating factor) may be indicated. It is recommended that the colony-stimulating factor therapy to be discontinued when the neutrophil count has returned to a level above 1000/mm³ (1.0 x 10⁹/L).

Patients in whom Versacloz has been discontinued as a result of white blood cell deficiencies (see above) must not be re-exposed to Versacloz.

It is recommended that the haematological values be confirmed by performing two blood counts on two consecutive days; however, Versacloz should be discontinued after the first blood count.

Table 1: Blood monitoring during the of Versacloz therapy

Blood cell count		Action required
WBC/mm ³ (/L)	ANC/mm ³ (/L)	
≥ 3500 (≥ 3.5 x 10 ⁹)	≥ 2000 (≥ 2.0 x 10 ⁹)	Continue Versacloz treatment.
Between ≥ 3000 and < 3500 (≥ 3.0 and < 3.5 x 10 ⁹)	Between ≥ 1500 and < 2000 (≥ 1.5 x 10 ⁹ and < 2.0 x 10 ⁹)	Continue Versacloz treatment, sample blood twice weekly until counts stabilise or increase.
< 3000 (< 3.0 x 10 ⁹) (<3.0 x 10 ⁹)	< 1500 (< 1.5 x 10 ⁹) (<1.5 x 10 ⁹)	Immediately stop Versacloz treatment, sample blood daily until haematological abnormality is resolved, and monitor for infection. Do not re-expose the patient.

In the event of interruption of therapy for non-haematological reasons

Patients who have been on Versacloz for more than 18 weeks and have had their treatment interrupted for more than 3 days but less than 4 weeks should have their WBC count and ANC monitored weekly for an additional 6 weeks. If no haematological abnormality occurs, monitoring at intervals not exceeding 4 weeks may be resumed. If Versacloz treatment has been interrupted for 4 weeks or longer, weekly monitoring is required for the next 18 weeks of treatment, *see section 4.2*.

Other precautions

Eosinophilia

In the event of eosinophilia, discontinuation of Versacloz is recommended if the eosinophil count rises above $3000/\text{mm}^3$ ($3.0 \times 10^9/\text{L}$). Therapy should be re-started only after the eosinophil count has fallen below $1000/\text{mm}^3$ ($1.0 \times 10^9/\text{L}$).

Thrombocytopenia

In the event of thrombocytopenia, discontinuation of Versacloz is recommended if the platelet count falls below $50,000/\text{mm}^3$ ($50.0 \times 10^9/\text{L}$).

Cardiovascular disorders

In patients suffering from cardiovascular disorders (note: severe cardiovascular disorders are contraindications, *see section 4.3*) the initial dose should be 12.5 mg given once on the first day, and dosage increase should be slow and in small increments (*see section 4.2*).

Orthostatic hypotension

Orthostatic hypotension, with or without syncope, can occur during clozapine treatment. Rarely (about one case per 3,000 clozapine-treated patients), collapse can be profound and may be accompanied by cardiac and/or respiratory arrest. Such events are more likely to occur during initial titration in association with rapid dose escalation; on very rare occasions they occurred even after the first dose. Therefore, patients commencing Versacloz treatment require close medical supervision.

Myocarditis and cardiomyopathy

Tachycardia that persists at rest, accompanied by arrhythmias, shortness of breath or signs and symptoms of heart failure, may rarely occur during the first month of treatment and very rarely thereafter. The occurrence of these signs and symptoms necessitates an urgent diagnostic evaluation for myocarditis, especially during the titration period. Therefore, the possibility of myocarditis should be considered in patients receiving Versacloz who present with unexplained fatigue, dyspnoea, tachypnoea, fever, chest pain, tachycardia, palpitations, other signs and symptoms of heart failure, ECG changes (such as ST-T wave abnormalities) or arrhythmias. It is not known whether eosinophilia is a reliable predictor of myocarditis. The incidence of myocarditis reported globally is rare ($<0.1\%$) during the first month of therapy and very rare ($<0.01\%$) thereafter. Some cases of myocarditis have been reported to be fatal (incidence of approximately 0.2 cases/100,000 patient-years). Most reported cases of myocarditis have occurred in the first month of therapy, therefore there should be a high index of suspicion in the first 6-8 weeks of therapy.

If the diagnosis of myocarditis is confirmed, Versacloz should be discontinued. There have been post-marketing reports of myocarditis including fatal cases. Later in treatment, the same signs and symptoms may very rarely occur and may be linked to cardiomyopathy. Further investigation should be performed and if the diagnosis is confirmed, the treatment should be stopped unless the benefit clearly outweighs the risk to the patient. If patients are diagnosed with cardiomyopathy while on Versacloz treatment, there is potential to develop mitral valve incompetence. Mitral valve incompetence has been reported in cases of cardiomyopathy related to clozapine treatment. These cases of mitral

valve incompetence reported either mild or moderate mitral regurgitation on two-dimensional echocardiography (2DEcho) (see section 4.8).

Monitoring of standing and supine blood pressure is necessary during the first weeks of treatment in patients with Parkinson's disease.

Patients with clozapine-induced myocarditis or cardiomyopathy should not be re-exposed to Versacloz.

Myocardial infarction

In addition, there have been post-marketing reports of myocardial infarction including fatal cases. Causality assessment was difficult in the majority of these cases because of serious pre-existing cardiac disease and plausible alternative causes.

Seizures

Clozapine may lower seizure threshold. In patients with a history of seizures the initial dose should be 12.5 mg given once on the first day, and dosage increase should be slow and in small increments (see section 4.2).

Anticholinergic effects

Clozapine exerts anticholinergic **activity**, which may produce adverse effects throughout the body. Careful supervision is indicated in the presence of **prostatic enlargement** and **narrow-angle glaucoma**.

Gastrointestinal hypomotility and constipation

Probably on account of its anticholinergic properties, Clozapine has been associated with varying degrees of **impairment of intestinal peristalsis**, ranging from **constipation** to **intestinal obstruction, faecal impaction, paralytic ileus, megacolon** and **intestinal infarction/ischaemia** (see section 4.8). On rare occasions, these cases have proved fatal.

Since complications have been associated with delayed diagnosis, patients should be questioned about their bowel habits. Careful monitoring during treatment with clozapine to identify early, the onset of constipation, followed by effective management of constipation are recommended to prevent complications.

Particular care is necessary in patients who are receiving concomitant medications known to cause constipation (especially those with anticholinergic properties such as some antipsychotics, antidepressants and antiparkinsonian treatments), have a history of colonic disease or a history of lower abdominal surgery as these may exacerbate the situation. It is vital that constipation is recognised, and actively treated. The risk for constipation may be greater with higher levels of clozapine. Prophylactic treatment with laxatives may be considered for patients at high risk for constipation or who may not be able to adequately describe symptoms of constipation.

Fever

During Versacloz therapy, patients may experience transient **temperature elevations** above 38°C, with the peak incidence within the first 3 weeks of treatment. This fever is generally benign. Occasionally, it may be associated with an increase or decrease in the WBC count. Patients with fever should be carefully evaluated to rule out the possibility of

an underlying infection or the development of agranulocytosis. In the presence of high fever, the possibility of **neuroleptic malignant syndrome (NMS)** must be considered.

Neuroleptic Malignant Syndrome (NMS)

If the diagnosis of **NMS** is confirmed, Versacloz should be discontinued immediately and appropriate medical measures should be administered.

Falls

Clozapine may cause seizures, somnolence, postural hypotension, motor and sensory instability, which may lead to falls and, consequently, fractures or other injuries. For patients with diseases, conditions, or medications that could exacerbate these effects, complete fall risk assessments when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

Metabolic changes

Atypical antipsychotic drugs, including clozapine, have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes may include hyperglycaemia, dyslipidaemia, and body weight gain. While atypical antipsychotic drugs may produce some metabolic changes, each drug in the class has its own specific risk profile.

Hyperglycaemia and diabetes mellitus

Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients with atypical antipsychotics including clozapine. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycaemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycaemia-related adverse events in patients treated with the atypical antipsychotics studied. Precise risk estimates for hyperglycaemia-related adverse events in patients treated with atypical antipsychotics are not available. The available data are insufficient to provide reliable estimates of differences in hyperglycaemia related adverse event risk among the marketed atypical antipsychotics. Glucose levels returned to normal in most patients after discontinuation of clozapine, and re-challenge produced a recurrence of hyperglycaemia in a few cases.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the baseline and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia, or weakness. Patients who develop symptoms of hyperglycaemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when the atypical antipsychotic was

discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug. In patients with significant treatment-emergent hyperglycaemia, discontinuation of Versacloz should be considered.

There is a risk of altering the metabolic balance resulting in slight impairment of glucose homeostasis and a possibility of unmasking a pre-diabetic condition or aggravating pre-existing diabetes.

Dyslipidaemia

Undesirable alterations in **lipids** have been observed in patients treated with atypical antipsychotics, including clozapine. Clinical monitoring, including baseline and periodic follow up lipid evaluations in patients using clozapine, is recommended.

Weight gain

Weight gain has been observed with atypical antipsychotic use, including clozapine. Clinical monitoring of **weight** is recommended.

Risk of thromboembolism

Since clozapine may cause sedation and weight gain, thereby increasing the risk of **thromboembolism**, immobilisation of patients should be avoided.

Cerebrovascular adverse events

An increased risk of **cerebrovascular adverse events** has been seen in the dementia population with some atypical antipsychotics. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. Versacloz should be used with caution in patients with risk factors for stroke.

Prolongation of QT interval

As with other antipsychotics, caution is advised in patients with known cardiovascular disease or family history of QT prolongation.

As with other antipsychotics, caution should be exercised when Versacloz is prescribed with medicines known to increase the QTc interval.

Parkinson's disease

Physicians should weigh the risks versus the benefits when prescribing clozapine to patients with Parkinson's Disease or dementia with Lewy Bodies (DLB) since both groups may be at increased risk of Neuroleptic Malignant Syndrome as well as having an increased sensitivity to antipsychotics. Manifestation of this increased sensitivity can include confusion, obtundation, postural instability with frequent falls, in addition to extrapyramidal symptoms.

Suicide

The possibility of a **suicide** attempt is inherent in schizophrenia and close supervision of high-risk patients should accompany therapy.

Smoking

Stopping or starting smoking (but not nicotine replacement therapy or vaping) affects the plasma concentration of clozapine (*see section 4.5*).

Special populations

Hepatic impairment

Patients with stable pre-existing liver disorders may receive Versacloz but must undergo regular liver function tests. Such tests should be performed immediately in patients who develop symptoms of possible liver dysfunction such as nausea, vomiting and/or anorexia during Versacloz treatment. If the elevation of the values is clinically relevant or if symptoms of jaundice occur, treatment with Versacloz must be discontinued. It may be resumed (*see section 4.2*) only when the results of liver function tests are normal. In such cases, liver function should be closely monitored after re-introduction of Versacloz.

Renal impairment

In patients suffering from mild to moderate renal impairment, an initial dose of 12.5 mg/day is recommended (*see section 4.2*).

Patients aged 60 years and older

It is recommended that treatment be initiated at a particularly low dose (12.5 mg given once on the first day) and subsequent dose increments be restricted to 25 mg/day (*see section 4.2*).

Clinical studies with clozapine did not include sufficient numbers of subjects aged 60 years and over to determine whether or not they respond differently from younger subjects.

Orthostatic hypotension can occur with clozapine treatment and there have been rare reports of tachycardia, which may be sustained, in patients taking clozapine. Patients aged 60 years and over, particularly those with compromised cardiovascular function, may be more susceptible to these effects.

Patients aged 60 years and over may also be particularly susceptible to the anticholinergic effects of clozapine, such as urinary retention and constipation.

Patients aged 60 years and older with Dementia-related Psychosis

In patients aged 60 years and over with dementia-related psychosis, the efficacy and safety of clozapine have not been studied. Observational studies suggest that patients aged 60 years and over with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. In the published literature, risk factors that may predispose this patient population to increased risk of death when treated with antipsychotics include sedation, the presence of cardiac conditions (e.g., cardiac arrhythmias) or pulmonary conditions (e.g. pneumonia, with or without aspiration). Versacloz is not approved for the treatment of dementia-related behavioural disturbances.

Rebound, withdrawal effects

If abrupt discontinuation of Versacloz is necessary (e.g. because of leucopenia), the patient should be carefully observed for the recurrence of psychotic symptoms and

symptoms related to cholinergic rebound such as profuse sweating, headache, nausea, vomiting and diarrhoea.

4.5. Interaction with other medicines and other forms of interaction

Pharmacodynamic-related interactions

Anticipated pharmacodynamic interactions resulting in concomitant use not being recommended

Medicinal products known to have a substantial potential to depress bone marrow function should not be used concurrently with Versacloz (*see section 4.4*).

As with other antipsychotics, caution should be exercised when Versacloz is prescribed with medicines known to increase the QTc interval or cause electrolyte imbalance.

Observed pharmacodynamic interactions to be considered

Particular caution is recommended when Versacloz therapy is initiated in patients who are receiving (or have recently received) a benzodiazepine or any other psychotropic agent, as these patients may have an increased risk of circulatory collapse, which, on rare occasions, can be profound and may lead to cardiac and/or respiratory arrest.

Concomitant use of lithium or other CNS-active agents may increase the risk of development of neuroleptic malignant syndrome (NMS).

Rare but serious reports of seizures, including onset of seizures in non-epileptic patients, and isolated cases of delirium where clozapine was co-administered with valproic acid have been reported. These effects are possibly due to a pharmacodynamic interaction, the mechanism of which has not been determined.

Anticipated pharmacodynamic interactions to be considered

Clozapine may enhance the central effects of alcohol, MAO inhibitors and CNS depressants such as narcotics, antihistamines, and benzodiazepines.

Because of the possibility of additive effects, caution is essential when substances possessing anticholinergic, hypotensive, or respiratory depressant effects are given concomitantly.

Owing to its anti-alpha-adrenergic properties, clozapine may reduce the blood pressure, increasing the effect of noradrenaline, or other predominantly alpha-adrenergic agents and reverse the pressor effect of adrenaline.

Pharmacokinetic-related interactions

Clozapine is a substrate for many CYP 450 isoenzymes, in particular 1A2 and 3A4. The risk of metabolic interactions caused by an effect on an individual isoform is therefore minimised. Nevertheless, caution is called for in patients receiving concomitant treatment with other substances that are either inhibitors or inducers of these enzymes.

No clinically relevant interactions have been observed thus far with tricyclic antidepressants, phenothiazines or type 1C antiarrhythmics, which are known to bind to cytochrome P450 2D6.

Observed pharmacokinetic interactions to be considered

Concomitant administration of substances known to induce cytochrome P450 enzymes may decrease the plasma levels of clozapine.

- Substances known to induce the activity of 3A4 and with reported interactions with clozapine include, for instance, carbamazepine, phenytoin and rifampicin.

Concomitant administration of substances known to inhibit the activity of cytochrome P450 isozymes may increase the plasma levels of clozapine.

- Substances known to inhibit the activity of the major isozymes involved in the metabolism of clozapine and with reported interactions include, for instance, cimetidine, erythromycin (3A4), fluvoxamine (1A2), perazine (1A2), ciprofloxacin (1A2) and oral contraceptives (1A2, 3A4, 2C19).
- The plasma concentration of clozapine is increased by caffeine (1A2) intake and decreased by nearly 50% following a 5-day caffeine-free period.
- Elevated clozapine plasma concentrations also have been reported in patients receiving the substances in combination with selective serotonin re-uptake inhibitors (SSRIs) such as paroxetine (1A2), sertraline, fluoxetine or citalopram.

Anticipated pharmacokinetic interactions to be considered

Concomitant administration of substances known to induce cytochrome P450 enzymes may decrease the plasma levels of clozapine.

- Known inducers of 1A2 include, for instance, omeprazole and tobacco smoke. In cases of sudden cessation of tobacco smoking, the plasma clozapine concentration may be increased, which may result in an increased risk of adverse drug reactions. Dose reduction is strongly recommended in the first week with therapeutic monitoring and further adjustment over the next four weeks, see local guidelines.

Concomitant administration of substances known to inhibit the activity of cytochrome P450 isozymes may increase the plasma levels of clozapine.

- Potent inhibitors of CYP3A, such as azole antimycotics and protease inhibitors, could potentially also increase clozapine plasma concentrations; no interactions have been reported to date, however.

4.6. Fertility, pregnancy and lactation

Women of childbearing potential and contraceptive measures

Some female patients treated with antipsychotics other than clozapine may become amenorrheic. A return to normal menstruation may occur as a result of switching from other antipsychotics to Versacloz. Adequate contraceptive measures must, therefore, be ensured in women of childbearing potential.

Pregnancy

Reproduction studies in animals have revealed no evidence of impaired fertility or harm to the foetus due to clozapine. However, the safe use of clozapine in pregnant women has not been established. Therefore, Versacloz should be used during pregnancy only if the expected benefit clearly outweighs any potential risk.

Non-teratogenic effects

Neonates exposed to antipsychotic drugs, during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalisation.

Antipsychotic drugs, including clozapine, should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Breast-feeding

Animal studies suggest that clozapine is excreted in breast milk and has an effect in the suckling offspring; therefore, mothers receiving Versacloz should not breast-feed.

Fertility

No data available. For pre-clinical fertility, data refer to section 5.3.

4.7. Effects on ability to drive and use machines

Owing to the ability of clozapine to cause sedation and lower the seizure threshold, activities such as driving or operating machinery should be avoided, especially during the initial weeks of treatment.

4.8. Undesirable effects

The adverse effects of clozapine are most often predictable based on its pharmacological properties with the exception of agranulocytosis (*see section 4.4*).

The most serious adverse reactions experienced with clozapine are agranulocytosis, seizure, cardiovascular effects and fever (*see section 4.4*). The most common side effects are drowsiness/sedation, dizziness, tachycardia, constipation, and hypersalivation.

Data from the clinical trials experience showed that a varying proportion of clozapine-treated patients (from 7.1 to 15.6%) were discontinued treatment due to an adverse event, including only those that could be reasonably attributed to clozapine. The more common events considered to be causes of discontinuation were leukopenia; somnolence; dizziness (excluding vertigo); and psychotic disorder.

Table 2: Treatment-emergent adverse experience frequency estimate from spontaneous and clinical trial reports

Adverse reactions are ranked by MedDRA system organ class under headings of frequency using the following convention: Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$), including isolated reports.

Blood and lymphatic system disorders

Common:	Leukopenia/decreased WBC/neutropenia, eosinophilia, leukocytosis
Uncommon:	Agranulocytosis
Rare:	Anaemia
Very rare:	Thrombocytopenia, thrombocythaemia
Metabolism and nutrition disorders*	
Common:	Weight gain
Rare:	Impaired glucose tolerance, new onset diabetes, diabetes aggravated, obesity
Very rare:	Ketoacidosis, hyperosmolar coma, severe hyperglycaemia, hypercholesterolemia, hypertriglyceridemia
Psychiatric disorders	
Common:	Dysarthria
Uncommon:	Dysphemia
Rare:	Agitation, restlessness
Very rare	Obsessive compulsive symptoms
Nervous system disorders	
Very common:	Drowsiness/sedation, dizziness
Common:	Headache, tremor, rigidity, akathisia, extrapyramidal symptoms, seizures/convulsions/myoclonic jerks,
Uncommon:	Neuroleptic malignant syndrome
Rare:	Confusion, delirium
Very rare:	Tardive dyskinesia
Eye disorders	
Common:	Blurred vision
Cardiac disorders **	
Very common:	Tachycardia
Common:	ECG changes
Rare:	Circulatory collapse, arrhythmias, myocarditis**, pericarditis
Very rare:	Cardiomyopathy
Vascular disorders	
Common:	Hypertension, postural hypotension, syncope

Rare:	Thromboembolism
Respiratory, thoracic and mediastinal disorders	
Rare:	Aspiration of ingested food, sleep apnoea syndrome, pneumonia and lower respiratory tract infection which may be fatal
Very rare:	Respiratory depression/arrest
Gastrointestinal disorders	
Very common:	Constipation, hypersalivation
Common:	Nausea, vomiting, dry mouth
Rare:	Dysphagia
Very rare:	Parotid gland enlargement, intestinal obstruction/ileus/faecal impaction, abdominal discomfort, heartburn
Hepatobiliary disorders	
Common:	Elevated liver enzymes
Rare:	Hepatitis, cholestatic jaundice, pancreatitis
Very rare:	Fulminant hepatic necrosis
Skin and subcutaneous tissue disorders	
Very rare:	Skin reactions
Renal and urinary disorders	
Common:	Urinary incontinence urinary retention
Very rare:	Tubulointerstitial nephritis, nocturnal enuresis
Reproductive system and breast disorders	
Very rare:	Priapism
General disorders and administration site conditions	
Common:	Fatigue, benign hyperthermia, disturbances in sweating/temperature regulation
Very rare:	Sudden unexplained death
Injury, poisoning and procedural complications	
Uncommon:	Falls (associated with clozapine-induced seizures, somnolence, postural hypotension, motor and sensor instability)
Investigations	
Rare:	Increased CPK

* Occasionally patients with pre-existing hyperglycaemia have had an exacerbation

**The prompt discontinuation of Versacloz therapy is warranted upon suspicion of myocarditis (see section 4.4).

Very rare events of ventricular tachycardia and QT prolongation which may be associated with Torsades De Pointes have been observed although there is no conclusive causal relationship to the use of this medicine.

AEs from spontaneous reports and literature (frequency unknown)

The following post-marketing adverse effects were derived from experience with clozapine via spontaneous case reports and literature cases and have been categorised according to MedDRA system organ class (Table 3). Because these have been reported voluntarily from a population of uncertain size and are subject to confounding factors, these post-marketing AEs have been categorised with a frequency of “unknown” since it is not possible to reliably estimate their frequency. Adverse effects are listed according to system organ classes (SOC) in MedDRA.

Within each system organ class, AEs are presented in order of decreasing seriousness.

Table 3: Adverse drug reactions from spontaneous reports and literature (frequency not known)

Infections and infestations
Sepsis
Immune system disorders
Drug rash with eosinophilia and systemic symptoms (DRESS), angioedema, leukocytoclastic vasculitis
Endocrine disorders
Pseudophaeochromocytoma
Nervous system disorders
Cholinergic syndrome, EEG changes, pleurothotonus, restless legs syndrome
Cardiac disorders
Myocardial infarction sometimes fatal, myocarditis sometimes fatal, chest pain/angina pectoris, palpitations, atrial fibrillation, mitral valve incompetence associated with clozapine-related cardiomyopathy
Vascular disorders
Hypotension
Respiratory, thoracic and mediastinal disorders
Pleural effusion, nasal congestion
Gastrointestinal disorders

Megacolon sometimes fatal, intestinal infarction/ischaemia sometimes fatal, intestinal necrosis sometimes fatal, intestinal ulceration sometimes fatal, intestinal perforation sometimes fatal, diarrhoea, abdominal discomfort/heartburn/dyspepsia, colitis
Hepatobiliary disorders
Hepatic steatosis, hepatic necrosis, hepatotoxicity, hepatic fibrosis, hepatic cirrhosis, liver disorders including those hepatic events leading to life-threatening consequences such as liver injury (hepatic, cholestatic and mixed), liver failure which may be fatal and liver transplant
Skin and subcutaneous tissue disorders
Pigmentation disorder
Musculoskeletal & connective tissue disorders
Rhabdomyolysis, muscle weakness, muscle spasms, muscle pain, systemic lupus erythematosus
Renal and urinary disorders
Renal failure, nocturnal enuresis
Reproductive system and breast disorders
Retrograde ejaculation
General disorders and administration site conditions
Polyserositis

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9. Overdose

In cases of acute intentional or accidental clozapine overdose, for which information on the outcome is available, to date, the mortality is about 12%. Most of the fatalities were associated with cardiac failure or pneumonia caused by aspiration and occurred at doses above 2000 mg.

There have been reports of patients recovering from an overdose in excess of 10,000 mg. However, in a few adult individuals, primarily those not previously exposed to clozapine, the ingestion of doses as low as 400 mg led to life-threatening comatose conditions and, in one case, to death. In young children, the intake of 50 mg to 200 mg resulted in strong sedation or coma without being lethal.

Signs and symptoms

Drowsiness, lethargy, areflexia, coma, confusion, hallucinations, agitation, delirium, extrapyramidal symptoms, hyperreflexia, convulsions; hypersalivation, mydriasis, blurred vision, thermolability; hypotension, collapse, tachycardia, cardiac arrhythmias; aspiration pneumonia, dyspnoea, respiratory depression or failure.

Treatment

There are no specific antidotes for clozapine.

The administration of activated charcoal within the first 6 hours after Versacloz ingestion. (Peritoneal dialysis and haemodialysis are unlikely to be effective.) Symptomatic treatment under continuous cardiac monitoring, surveillance of respiration, establishing and maintaining an airway, monitoring of electrolytes and acid-base balance. The use of adrenaline should be avoided in the treatment of hypotension because of the possibility of a reverse adrenaline effect. Close medical supervision is necessary for at least 5 days because of the possibility of delayed reactions.

For further advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Antipsychotic agent (ATC code N05A H02)

Mechanism of action

Clozapine has been shown to be an antipsychotic agent that is different from classic antipsychotics. In pharmacological experiments, the compound does not induce catalepsy or inhibit apomorphine- or amphetamine-induced stereotyped behaviour. It has only weak dopamine receptor-blocking activity at D₁, D₂, D₃ and D₅ receptors, but shows high potency for the D₄ receptor, in addition to potent anti-alpha-adrenergic, anticholinergic, antihistaminic, and arousal reaction-inhibiting effects. It has also been shown to possess antiserotonergic properties.

Pharmacodynamic effects

Clinically clozapine produces rapid and marked sedation and exerts antipsychotic effects in patients with schizophrenia resistant to other antipsychotic agents. In such cases, Clozapine has proven effective in relieving both positive and negative schizophrenic symptoms in short- and long-term trials

Clozapine is unique in that it produces virtually no major extrapyramidal reactions such as acute dystonia and tardive dyskinesia. Furthermore, parkinsonian-like side effects and akathisia are rare. In contrast to classical antipsychotics, clozapine produces little or no prolactin elevation, thus avoiding adverse effects such as gynaecomastia, amenorrhoea, galactorrhoea, and impotence.

Potentially serious adverse reactions caused by clozapine therapy are granulocytopenia and agranulocytosis occurring at an estimated incidence of 3% and 0.7% respectively (*see section 4.4*).

Clinical efficacy and safety

In a double-blind clinical trial performed in 319 treatment-resistant patients, clinically relevant improvement was observed within 6 weeks in about 30% of the clozapine-treated patients (see Clozapine Study 30 below).

Two open-label trials in which patients were treated for 12 months, showed clinically relevant improvement in 37% of patients within the first 6 weeks of treatment and in an additional 39%-44% of patients by the end of 12 months. The improvement was defined as a reduction of more than 20% from baseline in Brief Psychiatric Rating Scale Score. In addition, improvement in some aspects of cognitive dysfunction has been described.

See sections 4.4 and 4.8 for safety-related information.

Clozapine Study 30

The efficacy of clozapine was evaluated in a randomized, double-blind, multicentre, parallel-group, 6-week, comparative study of clozapine versus chlorpromazine plus benztropine. The study population included 319 treatment-resistant schizophrenic patients, between the ages of 18 - 60 years, who met DSM-III criteria for schizophrenia, with a well-documented history of being refractory to treatment.

Eligible patients were randomly assigned to receive clozapine alone (up to 900 mg/day) or chlorpromazine plus benztropine (up to 1800 mg/day of chlorpromazine, plus 6 mg/day of benztropine).

Efficacy was assessed using the BPRS score, Clinical Global Impression (CGI) scale, and Nurses' Observation Scale for Inpatient Evaluation (NOSIE-30) Scale.

At the end of 6 weeks, clozapine was significantly superior to chlorpromazine in all "Positive", "Negative" and general symptoms of BPRS ($p < 0.001$) except 'Grandiosity' and 'BPRS total score'. Clozapine showed a significantly superior change in CGI scale compared to chlorpromazine starting at week 1 ($p < 0.001$). Clozapine was superior to chlorpromazine on all six NOSIE-30 factors and total assets starting at either week 1 or 2 (p -value ranging from $p < 0.05$ to 0.001). Clozapine was statistically significant in the following NOSIE factors, social competence, social interest and personal neatness, and total assets ($p < 0.001$), as well as irritability and motor retardation ($p < 0.01$ and $p < 0.05$, respectively).

In summary, the superiority of clozapine was not confined to a particular aspect or dimension of psychopathology; clozapine demonstrated broad-spectrum therapeutic effect on all major psychotic signs and symptoms.

5.2. Pharmacokinetic properties

Absorption

The absorption of orally administered clozapine is 90% to 95%; neither the rate nor the extent of absorption is influenced by food. Clozapine is subject to moderate first-pass metabolism, resulting in an absolute bioavailability of 50% to 60%.

Distribution

In steady-state conditions, when given twice daily, peak blood levels occur on an average at 2.1 hours (range: 0.4 to 4.2 hours), and the volume of distribution is 1.6 L/kg. Clozapine is approximately 95% bound to plasma proteins.

Biotransformation/metabolism

Clozapine is almost completely metabolised before excretion by CYP1A2 and 3A4, and to some extent by CYP2C19 and 2D6. Of the main metabolites, only the desmethyl metabolite was found to be active. Its pharmacological actions resemble those of clozapine but are considerably weaker and of short duration.

Elimination

Its elimination is biphasic, with a mean terminal half-life of 12 hours (range: 6 to 26 hours). After single doses of 75 mg, the mean terminal half-life was 7.9 hours; it increased to 14.2 hours when steady-state conditions were reached by administering daily doses of 75 mg for at least 7 days.

Only trace amounts of unchanged drug are detected in the urine and faeces, approximately 50% of the administered dose being excreted as metabolites in the urine and 30% in the faeces.

Linearity/non-linearity

Dosage increases from 37.5 mg to 75 mg and 150 mg given twice daily were found to result during steady-state in linearly dose-proportional increases in the area under the plasma concentration/time curve (AUC) and in the peak and minimum plasma concentrations.

5.3. Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential

Mutagenicity

Clozapine and/or its metabolites were devoid of genotoxic potential when investigated for induction of gene mutations, chromosome aberrations and primary DNA-damage in a spectrum of *in vitro* mutagenicity tests. No clastogenic activity was observed *in vivo* (bone marrow micronucleus test in mice).

Carcinogenicity

In Sprague-Dawley (CD) rats treated in the diet for 24 months, maximum tolerated doses of 35 mg/kg per day revealed no carcinogenic potential of clozapine. Likewise, no evidence of tumorigenic effects was obtained in two 78-week feeding studies in Charles River (CD) mice. In the first study, oral dose levels of up to 64 mg/kg were administered to males, and of up to 75 mg/kg to females respectively. In the second study, the drug intake achieved for both sexes was 61 mg/kg per day.

Reproductive toxicity

No embryotoxic or teratogenic potential of clozapine was observed in rats or rabbits at daily oral doses of up to 40 mg/kg. In male rats treated for 70 days prior to mating, fertility was unaffected.

In female rats, fertility as well as pre- and postnatal development of the offspring was not adversely affected by oral clozapine treatment prior to mating (up to 40 mg/kg per day). When rats were treated during the later part of pregnancy and during lactation, survival rates of the young from lactating dams, treated at dose levels up to 40 mg/kg body weight, were lowered and the youngs were hyperactive. However, there was no lasting effect on pup development after weaning.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sorbitol, povidone, sodium dihydrogen phosphate dihydrate, sodium hydroxide, hydrochloric acid, methylparaben sodium, propylparaben sodium, xanthan gum, glycerine, water.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

Unopened: 24 months

Opened: 100 days

6.4. Special precautions for storage

Store at or below 25°C. Protect from light. Do not refrigerate or freeze.

6.5. Nature and contents of container

Amber glass bottle, and child-resistant, tamper-evident cap packaged with graduated oral dispenser.

One bottle contains 100 mL of oral suspension.

6.6. Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

Douglas Pharmaceuticals Ltd

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Auckland 0651

New Zealand

Phone: (09) 835 0660

9. DATE OF FIRST APPROVAL

19 November 2019

10. DATE OF REVISION OF THE TEXT

27 August 2024

Summary table of changes

Section Changed	Summary of new information
Introductory Section	Aligned text with text on Medsafe's website regarding prescribing restrictions.