Composition
Diazepam: 7-chloro-1,3-dihydro-1 methyl-5-phenyl-2H-1,4-benzodiazepin-2-one.

Properties
The active ingredient of Valium Roche is a member of the group of benzodiazepine tranquilizers, which exert anxiolytic, sedative, muscle-relaxant and anticonvulsant effects. This is now known to be the result of facilitating the action of gamma-aminobutyric acid (GABA), the most important inhibitory neurotransmitter in the brain.

Pharmacokinetics
Absorption
The active ingredient of Valium Roche is rapidly and completely absorbed from the digestive tract, peak plasma concentrations appearing 30-90 minutes after oral intake. On intramuscular injection, absorption is also complete, though not always more rapid than with oral administration.

Distribution
Diazepam and its metabolites are highly bound to plasma proteins (diazepam: 98%).

Metabolism
Diazepam is metabolized to the pharmacologically active nordiazepam ($t_{1/2}$=96 hours), hydroxy-diazepam and to oxazepam.

Elimination
The elimination curve of diazepam is biphasic, an initial rapid and extensive distribution phase with a half-life of up to three hours being followed by a prolonged terminal elimination phase (half-life up to 48 hours).

The product is excreted mainly (about 70%) in the urine in the form of free or (predominantly) conjugated metabolites.

Pharmacokinetics in Special Clinical Situations
The elimination half-life may be prolonged in the newborn, the elderly and patients with liver or kidney disease, and it should be noted that the plasma concentration may take correspondingly longer to reach the steady state. Diazepam and its metabolites cross the blood-brain and placental barriers. They are also found in breast milk in concentrations approximately one tenth those in the maternal plasma.

Indications
Valium Roche is indicated for the symptomatic relief of anxiety, agitation and tension due to psychoneurotic states and transient situational disturbances. It can also be useful adjunctively in major mental and organic disorders. Anxiety may be expressed by manifest anxious mood or apprehensive behavior, and/or by functional, autonomic or motor equivalents such as palpitation, sweating, insomnia, tremor, restlessness, etc.

Valium Roche is a useful adjunct for the relief of reflex muscle spasm due to local trauma (injury, inflammation). It can also be used to combat spasticity arising from damage to spinal and supraspinal interneurons such as cerebral palsy and paraplegia, as well as in athetosis and stiff-man syndrome.

Contraindications
Valium Roche is contraindicated in patients with a known history of hypersensitivity to benzodiazepines or dependence on other substances including alcohol. An exception to the latter is the management of acute withdrawal reactions. In severe chronic hypercapnia, Valium Roche is contraindicated.

Side Effects
The most commonly reported side effects are fatigue, drowsiness and muscle weakness; they are usually dose-related. Effects encountered infrequently are confusion, constipation, depression, diplopia, dysarthria, headache, hypotension, incontinence, increase or decrease in libido, nausea, dry mouth or hypersalivation, skin rash, slurred speech, tremor, urinary retention, vertigo, respiratory depression, anterograde amnesia, bradycardia and blurred vision; very rarely,
elevated transaminases and alkaline phosphatase as well as cases of jaundice have been observed. Paradoxical reactions such as acute excitation, anxiety, sleep disturbances and hallucinations have been reported; should these occur, use of the drug should be discontinued. Respiratory depression and anterograde amnesia are most frequently seen following intravenous doses of the drug.

The physical dependence potential of benzodiazepines is very low in persons taking recommended doses. After longterm treatment, however, abrupt discontinuation of the drug can give rise of withdrawal symptoms (e.g. restlessness, excitation, tremor, in rare cases convulsions). Gradual reduction of the dose is therefore recommended.

**Precautions**

Patients taking Valium Roche should be warned against engaging in hazardous occupations requiring complete mental alertness such as operating dangerous machinery or driving a motor vehicle. They should also be cautioned about the concomitant consumption of alcohol as such a combination may potentiate the undesirable effects of both agents.

In the presence of known cardiorespiratory insufficiency, care should be exercised, since sedative drugs like Valium Roche can lead to further respiratory depression. However, the sedative effect can, on the contrary, benefit some patients by reducing respiratory effort. In patients with myasthenia gravis who are prescribed Valium Roche care should be taken on account of preexisting muscle weakness. Valium Roche should also be used with caution in patients with sleep apnea syndrome. The concomitant use of barbiturates, alcohol or other central nervous depressants increases the risk of cardiac or respiratory depression.

**Dependence**

Benzodiazepines have the potential to induce dependence. The risk of dependence increases with long-term therapy and higher doses. Predisposed patients are also at increased risk. Abrupt discontinuation of the drug, in particular, can provoke withdrawal symptoms. In mild cases these are restricted to tremor, restlessness, sleep disturbances, anxiety, headache and poor concentration. In more serious cases, symptoms such as sweating, muscle cramps, abdominal cramps, impaired sensory perceptions and, rarely, delirium and convulsions may result. Depending on the drug’s duration of action, symptoms may appear a few hours to one week or more after cessation of therapy.

In order to reduce the risk of dependence to a minimum, benzodiazepines should be prescribed only after careful evaluation of the indication, and therapy should be restricted to the shortest possible duration (for example, no more than four weeks for the treatment of sleep disturbances). The physician must periodically reevaluate the necessity for therapy. Long-term therapy is indicated only in certain patients, for example, those suffering from panic attacks; the risk/benefit ratio is uncertain.

To prevent withdrawal symptoms, abrupt discontinuation should be avoided and the dosage gradually tapered off. Close medical supervision and patient support are required should withdrawal symptoms develop.

**Pregnancy and Lactation**

There is strong evidence of risks to the human fetus, but these may be outweighed by the therapeutic benefits for the mother. (This is the case, for example, with life-saving drugs or when no therapeutic alternative with a more favourable risk profile is available for a serious illness.) Diazepam and its metabolites pass through the placental barrier and into the breast milk. In pregnant women and nursing mothers, therefore, the use of Valium Roche should be avoided whenever possible.

**Overdosage**

Intentional or accidental overdosage with Valium Roche alone is rarely life threatening. The symptoms are mainly an intensification of the therapeutic effects (sedation, muscle weakness, profound sleep) or paradoxical excitation. In most cases only observation of vital functions is required. Extreme overdosage, particularly in combination with other centrally acting drugs, may lead to coma, areflexia,
higher doses may, where appropriate, be given by parenteral route.

Duration of Treatment: the usual long-term treatment of anxiety with Valium Roche may last, depending on the type of condition and on the causal factors involved, as long as several weeks. After about 6 weeks’ treatment, no further improvement of the patient’s anxious state is to be expected; further treatment may be regarded purely as maintenance therapy. During prolonged maintenance therapy, drug-free periods should be introduced at regular intervals to assess the need for continuation. Treatment with Valium Roche should not be stopped abruptly, however, the dosage should be gradually tapered off. The effectiveness of long-term treatment (i.e. more than 6 months) with Valium Roche has not been assessed by systematic clinical studies.

Special Dosage Instructions
Dosage for elderly patients: treatment should begin with half the usual adult dosage and be increased gradually as needed and tolerated.

Children’s dosage: 0.1-0.3 mg per kg bodyweight daily.

In liver or kidney disorders, special attention must be paid to individual dosing.

Newborn infants: see Contraindications.

cardiorespiratory depression and apnea, requiring appropriate countermeasures (ventilation, cardiovascular support, gastric lavage). As specific therapy is recommended the administration of Anexate (active ingredient: flumazenil), benzodiazepine antagonist.

Stability
This medicine should not be used after the expiry date (EXP) shown on the pack.

Drug Interactions
The clearance of diazepam can be delayed in association with cimetidine (but not ranitidine), omeprazole or fluvoxamine. This may be clinically significant, particularly in the case of fluvoxamine, and necessitates adjustment of the Valium Roche dose. There have also been reports that the metabolic disposal of phenytoin is affected by diazepam. On the other hand, there is no known interference with commonly used antidiabetic, anticoagulant or diuretic substances.

If Valium Roche is to be combined with other centrally acting agents, such as neuroleptics, tranquilizers, antidepressants, hypnotics, anticonvulsants, analgesics and anesthetics, it should be borne in mind that their effects may potentiate or be potentiated by the action of Valium Roche. If Valium Roche is given in combination with opiates known to depress respiration, it should be kept in mind that this effect may be enhanced.

Dosage and Administration
For optimal effect, the dosage should be carefully individualized. The usual daily doses given below will meet the needs of most patients, though there will be cases requiring higher doses.

Usual adult dosage for oral administration: depending on severity of symptoms, 5-20 mg daily. The single oral dose should not normally exceed 10 mg. They should be taken at a time that meets the needs of the patient in question-usually the evening is the most suitable time.

In acute cases or life threatening situations, or when the response to enteral administration is insufficient,