<table>
<thead>
<tr>
<th>Lidocaine hydrochloride</th>
<th>Lidocaine treatment may aggravate arrhythmias. The potassium concentration should be normalised before lidocaine treatment is started. In patients with bradycardia complicated by ventricular tachyarrhythmia, lidocaine may have to be combined with atropine or atropine-like drugs or pacemaker treatment. Cardiac arrhythmia: Therapeutic plasma concentration range 1.5-6 µg/ml (6.5-26 µmol/l). Adults: In the treatment of ventricular arrhythmias, an intravenous injection should be given initially, followed by an intravenous infusion. Normally, 2-4 mg/minute is given by continuous intravenous infusion. In order to achieve a rapid antiarrhythmic effect, a bolus injection of 50-100 mg i.v. should be given initially. In order to maintain an adequate blood level, intravenous injection of 50-100 mg Xylocard may be repeated twice at 15-20 minutes intervals. If no bolus injection is given, it will take several hours for therapeutic blood concentrations to be reached with continuous intravenous infusion using the above dose. In certain cases doses higher than 4 mg/minute may be needed to achieve antiarrhythmic effect. The risk of side-effects increases with higher doses, however. Not more than 200-300 mg should be given during one hour. In shock, manifest heart failure or pronounced liver failure the dose should be reduced considerably. The infusion is normally given for two or more days. It should normally not be discontinued until 24 hours after the last signs of ventricular tachyarrhythmias. If the dose needs to be raised during intravenous infusion, a slow intravenous injection of 25-100 mg of lidocaine is given first in order to produce the desired blood concentration. The infusion rate should then be adjusted. Preparation of infusion solutions: A concentration of 2 mg of lidocaine per ml is normally used. With higher doses, and in cases in which it is desired to limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiarrhythmic agent</td>
<td></td>
</tr>
<tr>
<td>Sterile solution (disposable syringe for preparation of infusion solutions)</td>
<td></td>
</tr>
<tr>
<td><strong>Composition</strong></td>
<td></td>
</tr>
<tr>
<td>Each sterile syringe contains: 5 ml of lidocaine hydrochloride anhydrous 200 mg/ml, sodium hydroxide q.s. to pH 6.0, water for injection to 5 ml.</td>
<td></td>
</tr>
<tr>
<td><strong>Pharmaceutical form</strong></td>
<td></td>
</tr>
<tr>
<td>Xylocard 20% (200 mg/ml) contains a sterile solution without added preservative. The syringe is specially designed to ensure addition of the right quantity to infusion solutions, to prevent overdosage and to avoid the risk of confusion with other preparations of Xylocard for cardiological use. The solution is suitable for the preparation of the usual concentrations of Xylocard in infusion solutions. For safety reasons, the syringe has a short, broad plastic needle which is suitable only for the perforation of the rubber membrane of infusion bottles. A label is enclosed with each syringe for marking the infusion bottle with the concentration of lidocaine in the infusion solution.</td>
<td></td>
</tr>
<tr>
<td><strong>Indications</strong></td>
<td></td>
</tr>
<tr>
<td>Cardiac arrhythmias: Prophylaxis and treatment of ventricular tachyarrhythmias, especially in connection with myocardial infarction, mechanical irritation of the myocardium during cardiac surgery or diagnostic procedures (e.g. heart catheterisation and angiocardiography), digitalis intoxication and intoxication with tricyclic antidepressants. Facilitation of defibrillation of ventricular fibrillation and prevention of recurrence.</td>
<td></td>
</tr>
<tr>
<td>Status epilepticus</td>
<td></td>
</tr>
<tr>
<td>Posology and method of administration</td>
<td></td>
</tr>
<tr>
<td>The dosage is individual. When high doses are used and the patients myocardial function is impaired, combination with other drugs which reduce the excitability of cardiac muscle requires caution.</td>
<td></td>
</tr>
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</table>
the administration of fluid, a higher concentration may be used (see tables below).

Xylocard is miscible with 5.5% glucose, invertose, dextrane, physiological saline, Ringer’s and sodium bicarbonate solution.

The addition of drugs to infusion solutions always means an added risk with regard to sterility, stability and incompatibility. As a rule, infusion solutions with approved additions should therefore be used within 12 hours. (See Table Below).

Approximate infusion time for 500 ml infusion solution at different dose levels

<table>
<thead>
<tr>
<th>Conc. lidocaine in the infusion solution</th>
<th>No of disposable syringes</th>
<th>Xylocard 200 mg/ml per 500 ml</th>
<th>2 mg/min</th>
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<tr>
<td>2 mg/ml</td>
<td>1</td>
<td>8½ h</td>
<td>5½ h</td>
<td>4 h</td>
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<tr>
<td>4 mg/ml</td>
<td>2</td>
<td>16½ h</td>
<td>11 h</td>
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Approximate infusion rate (drops per minute), determined with an infusion unit for which 1 ml is equivalent to 15, 20 and 60 drops respectively

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<tr>
<th>Concentration of lidocaine in the infusion solution</th>
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<td>30</td>
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<td>8</td>
<td>11</td>
<td>15</td>
</tr>
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Normal drip rate Drops/min Lidocaine hydrochloride mg/min

| Adults (70 kg) | 35 | 7 |

Normal dose 6 mg/kg body weight per hour.

Children: One disposable syringe of Xylocard 200 mg/ml sterile solution (1000 mg lidocaine hydrochloride) is added to 500 ml of infusion solution (5.5% glucose or physiological saline). The infusion solution then contains 2 mg of lidocaine hydrochloride per ml.

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Normal drip rate Drops/min Lidocaine hydrochloride mg/min

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<th>5 kg</th>
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<th>15 kg</th>
<th>20 kg</th>
<th>25 kg</th>
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<th>50 kg</th>
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<td>35</td>
<td>40</td>
<td>45</td>
<td>50</td>
</tr>
</tbody>
</table>

Normal dose 6 mg/kg body weight per hour.

Note During infusion therapy with lidocaine the rate of administration must be carefully checked, preferably by means of a drop counter or the use of a special infusion pump. The total amount of lidocaine added to the infusion solution may be lethal if infused too rapidly.

Impaired renal function

Status epilepticus: Initially an intravenous injection should be given. See Xylocard 20 mg/ml single-dose syringe. For continued treatment, a continuous intravenous infusion for a maximum of 5 hours should be given.

Adults: Two disposable syringes of Xylocard 200 mg/ml sterile solution (2000 mg lidocaine hydrochloride) are added to 500 ml of infusion solution (5.5% glucose or physiological saline). The infusion solution then contains 4 mg of lidocaine hydrochloride per ml.

Impaired hepatic function

Liver disease means a risk of accumulation of lidocaine. Caution should be observed during repeated treatment with lidocaine in patients with impaired renal function.

Elderly

A reduction in dosage may be necessary for elderly patients, particularly those with compromised cardiovascular and/or hepatic function and/or prolonged
infusion. Elderly patients should be given reduced
doses corresponding to their age and physical status.

Contraindications
Known hypersensitivity to lidocaine (extremely rare).
Known hypersensitivity to other local anaesthetics of
the amide type, such as prilocaine, mepivacaine or
bupivacaine.
Second or third degree AV-block in the absence of
pacemaker.

Special warnings and precautions for use
ECG-monitoring should be instituted when lidocaine
is administered as an intravenous infusion.
Caution should be observed in patients with cardiac
decompensation and hypotension or posterior dia-
phragmal infarction with a tendency towards heart
block.

Lidocaine should be administered with caution to
patients with bradycardia, untreated first-degree
AV-block with bifascicular block or hypokalaemia.
Severely impaired liver or kidney function may
mean a risk of accumulation and toxic reactions as
lidocaine is mainly metabolised in the liver and the
metabolites are excreted by the kidneys. Caution
should be observed during repeated treatment with
lidocaine in patients with these functional disorders.
Through their lower enzyme capacity, neonates are at
risk of methaemoglobinemia. Methaemoglobinemia
can become clinically overt (cyanosis), and treatment
with methylene blue may be considered necessary.

Interactions
It is possible to explain observed drug-drug inter-
actions or even in certain cases predict the potent-
tial for drug-drug interactions based on the site of
metabolism/excretion or other pharmacologic effects
of a drug. Lidocaine is completely metabolised.

Potential for influence of lidocaine on the plas-
ma levels/effect of other drugs
Lidocaine is metabolised by cytochrome P4503A4
(CYP3A4) and thus has the potential to inhib-
it the metabolism of other drugs metabolised by
this enzyme, resulting in increased plasma levels
of these. This has so far not been reported for any
CYP3A substrate.

Potential for influence of other drugs on the
plasma levels/effect of lidocaine
Concomitant treatment with drugs that are sub-
strates, inhibitors, or inducers of CYP3A4 has the
potential to influence the metabolism and hence the
plasma levels and effect of lidocaine. Concomitant
administration with the substrate amiodarone has
resulted in increased plasma levels of lidocaine
resulting in toxic effects.

During concomitant administration with carbam-
azeine, phenobarbitone, and phenytoin which are
inducers of CYP3A4, decreased plasma levels of
lidocaine have been reported. Primidone has also
been reported to induce the metabolism of lidocaine.
Furthermore, the plasma levels of lidocaine have
been reported to increase, resulting in toxic effects,
during concomitant administration with cimeti-
dine, which has an unspecific inhibitory effect on
CYP (including CYP3A4) mediated metabolism.
Concomitant treatment with metoprolol, nadolol, and
propranolol have also been reported to increase the
plasma levels of lidocaine resulting in toxic effects.

Pregnancy and lactation
It is reasonable to assume that lidocaine has been
used, mainly as a local anaesthesia, by a large
number of pregnant women and women of child-
bearing age. No specific disturbances to the repro-
ductive process have so far been reported, e.g. an
increased incidence of malformations or direct or
indirect harmful effects on the fetus.
Enters breast milk but is not likely to affect the infant
when therapeutic doses are used.

Effects on ability to drive and use machines
Not applicable.

Undesirable effects
Most frequent are adverse reactions from the cen-
tral and peripheral nervous system. They occur in
5-10% of the patients and are mostly dose-related.
Central and peripheral nervous system: Dizziness,
paraesthesia and drowsiness.
Rarely persistent dizziness, tinnitus, confusion,
blurred vision, tremor, convulsions, loss of con-
sciousness and respiratory depression.
Cardiovascular: Rarely hypotension and bradycardia, which may lead to cardiac arrest. Arrhythmias including ventricular tachycardia/ventricular fibrillation.

Blood and lymphatic system disorders: Very rarely neonatal methaemoglobinemia.

Overdosage
Symptoms
The most serious effects of lidocaine intoxication are on the CNS and cardiovascular system and overdose can result in severe hypotension, asystole, apnoea, seizures, coma, respiratory arrest, and death.

Treatment
The administration of Xylocard should be discontinued immediately. Adequate ventilation should be ensured by checking that the airways are free and administering oxygen.

Hypotension may be counteracted by giving sympathomimetic drugs (e.g. adrenaline). Adrenergic agents of both β-adrenoceptors stimulating (e.g. metaraminol) and β-adrenoceptor stimulating type (e.g. isoprenaline) are generally effective.

The bradycardia may be treated with parasympatholytic agents (e.g. atropine).

Convulsions may be treated with small doses of a short-acting barbiturate (e.g. methohexital 50-120 mg i.v.) or diazepam (10-15 mg i.v.).

Pharmacodynamic properties
Lidocaine is the model class 1B substance according to Vaughan Williams and Harrison. Lidocaine blocks the sodium channels in the cell membranes of the heart and reduces the rate of the rise of the action potential and hence the conduction velocity in, above all, the His-Purkinje system and the atrial ventricular musculature. The automaticity and excitability are also reduced by lidocaine. The duration of the action potential (APD) and the effective refractory period (ERP) are reduced but the ratio ERP/APD is increased. The sinus node and AV-node are not influenced by therapeutic plasma concentrations of lidocaine.

The electrophysiological effects of lidocaine are strongly dependent on the extracellular potassium concentration (probably secondary to the change of the resting potential of the cells) and may be almost completely blocked by hypokalaemia. The effects are also frequency-dependent and are negligible at normal or low heart rates but pronounced at high rates. The effect of lidocaine may therefore be enhanced during tachyarrhythmias in connection with acute myocardial ischaemia, when leakage of potassium to the extracellular space occurs.

Lidocaine does not normally cause changes in the ECG. The QT-time is sometimes somewhat shortened.

In animal experiments, high doses of lidocaine have caused a negative inotropic effect. However, at therapeutic plasma concentrations, the risk of provocation of heart failure is small.

In the recommended doses, lidocaine is practically lacking in hypotensive and vasodilating effects.

Pharmacokinetic properties
Absorption and distribution
Treatment with lidocaine is easily managed, owing to rapid distribution, metabolism and excretion. During the first half-hour after an intravenous injection, the plasma concentration falls with a half-life of 10-15 minutes (alpha-phase), owing to the rapid distribution to different body tissues, including the heart. The therapeutic plasma concentration range is 1.5-6 µg/ml (6.5-26 µmol/l). The plasma protein binding is about 70%. The apparent distribution volume is approximately 1 l/kg.

Metabolism and elimination
Lidocaine is mainly metabolised by the liver (70-90%) through cytochrome P4503A4 (CYP3A4). The metabolites have a weaker antiarrhythmic action and are excreted by the kidneys. The half-life in the elimination phase (ß-phase) is 90-120 minutes. Less than 10% of the dose of lidocaine is excreted unchanged in the urine. There is a risk of accumulation of metabolites if the renal function is impaired.

Heart failure and liver disease also mean a risk of accumulation of lidocaine.

During continuous infusion, steady-state conditions are not reached until after 6-8 hours. In order to reach an adequate plasma concentration rapidly and maintain a therapeutic concentration, one or more intravenous injections must be given initially.
Pharmaceutical particulars
List of excipients
Sodium hydroxide
Water for injection

Incompatibilities
Not applicable.

Shelf Life
Please see outer pack.

Special precautions for storage
Do not store above 25°C. Do not freeze.

Pack Size
Please see outer pack.

Instructions for the mixing of Xylocard 20% (200 mg/ml) in inf. sol.
1 syringe Xylocard 20% (200 mg/ml) mixed with 500 ml of 5.5% glucose, invertose, dextrane, physiological saline, Ringer’s or sodium bicarbonate solution, provides a 0.2% solution for infusion. This concentration may be recommended for most cases. As a rule, infusion solutions should be used within 12 hours after mixing.

Instructions for use of the syringe:
1. Place the rear end of the glass cartridge against a firm horizontal surface. DO NOT remove the needle cover.
2. Support the syringe with one hand and press downwards, on the needle cover flange, until the rubber membrane of the cartridge is penetrated.
3. Unscrew the needle cover and perforate the rubber membrane of the infusion bottle. A turning movement facilitates perforation.
4. Assemble the needle cover to the cartridge.
5. Attach a label to the bottle to show that Xylocard has been added.

Date of revision
July 2003