

B SUMMARY OF PRODUCT CHARACTERISTICS**1 NAME OF THE MEDICINAL PRODUCT****OMNIPAQUE™ 140, 180, 240, 300, 350 mg I/ml****2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

Active ingredient	Strength	Content per. ml.
Iohexol (INN)	140 mg I/ml	302 mg equiv. 140 mg I
Iohexol (INN)	180 mg I/ml	388 mg equiv. 180 mg I
Iohexol (INN)	240 mg I/ml	518 mg equiv. 240 mg I
Iohexol (INN)	300 mg I/ml	647 mg equiv. 300 mg I
Iohexol (INN)	350 mg I/ml	755 mg equiv. 350 mg I

Iohexol is a non-ionic, monomeric, triiodinated, water-soluble X-ray contrast medium. Omnipaque in the concentration of 140 mg I/ml is isotonic with blood and tissue fluid. The osmolality and viscosity values of Omnipaque are as follows:

Concentration	Osmolality * Osm/kg H ₂ O 37°C	Viscosity (mPa·s)	
		20°C	37°C
140 mg I/ml	0.29	2.3	1.5
180 mg I/ml	0.36	3.2	2.0
240 mg I/ml	0,51	5.6	3.3
300 mg I/ml	0.64	11.6	6.1
350 mg I/ml	0.78	23.3	10.6

* in aqueous solutions of iohexol

3 PHARMACEUTICAL FORM

Solution for injection.

4 CLINICAL PARTICULARS

4.1 INDICATIONS

X-ray contrast medium for use in adults and children for urography, phlebography, i.v. DSA, CT, arteriography, cardioangiography and i.a. DSA. Myelography. For use in body cavities: Arthrography, ERP/ERCP, herniography, hysterosalpingography, sialography and use in the G-I tract.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

The dosage depends on the type of investigation and the technique used. Usually the same iodine concentration and volume is used as for other iodinated X-ray contrast media in current use.

Adequate hydration should be assured before and after administration as for other contrast media.

For intravenous, intra-arterial and intrathecal use, and use in body cavities.

The following dosages may serve as a guide:

**Guidelines for
Intravenous use**

Indication	Concentration	Volume	Comments
<p>Urography</p> <p><u>adults:</u> 300 mg I/ml or 350 mg I/ml</p> <p><u>children < 7 kg</u> 240 mg I/ml or 300 mg I/ml</p> <p><u>children > 7 kg</u> 240 mg I/ml or 300 mg I/ml</p>		<p>40 - 80 ml 40 - 80 ml 4 ml/kg b.w. 3 ml/kg b.w. 3 ml/kg b.w. 2 ml/kg b.w.</p>	
Phlebography (leg)	<p>or 240 mg I/ml or 300 mg I/ml</p>	20 - 100 ml/leg	
<p>Digital subtraction angiography</p> <p><u>adults:</u> 140 mg I/ml 300 mg I/ml or 350 mg I/ml</p> <p><u>children:</u> 140 mg I/ml</p>		<p>Up to 3 ml per kg body weight 20 - 60 ml/inj. 20 - 60 ml/inj.</p> <p>dependent upon age, weight and pathology</p>	
<p>CT-enhancement</p> <p><u>adults:</u> 140 mg I/ml or 240 mg I/ml or 300 mg I/ml or 350 mg I/ml</p>		<p>100 - 400 ml 100 - 250 ml 100 - 200 ml 100 - 150 ml</p>	

**Guidelines for
Intra-arterial use**

Indication	Concentration	Volume	Comments
<p>Arteriographies</p> <p>arch aortography selective cerebral aortography femoral</p> <p>various</p>	<p>300 mg I/ml 300 mg I/ml 350 mg I/ml 300 mg I/ml or 350 mg I/ml</p> <p>300 mg I/ml</p>	<p>30 - 40 ml/inj. 5 - 10 ml/inj. 40 - 60 ml/inj. 30 - 50 ml/inj.</p> <p>depending on type of examination</p>	
<p>Cardioangiography</p> <p><u>adults:</u> left ventricle and aortic root inj.</p> <p>selective coronary arteriography</p> <p><u>children:</u></p>	<p>350 mg I/ml</p> <p>350 mg I/ml</p> <p>300 mg I/ml or 350 mg I/ml</p>	<p>30 - 60 ml/inj.</p> <p>4 - 8 ml/inj.</p> <p>depending on age, weight and pathology (max 8 ml/kg b.w.)</p>	
<p>Digital subtraction angiography</p> <p><u>adults:</u></p> <p><u>children:</u></p>	<p>140 mg I/ml or 240 mg I/ml or 300 mg I/ml</p> <p>140 mg I/ml</p>	<p>4 - 10 ml/inj. 1 - 15 ml/inj. 1 - 15 ml/inj.</p> <p>Dependent upon age, weight and pathology</p>	

**Guidelines for
Intrathecal use**

Indication	Concentration	Volume	Comments
Lumbar and thoracic myelography (lumbar injection)	180 mg I/ml or 240 mg I/ml	10 - 15 ml 8 - 12 ml	
Cervical myelography (lumbar injection)	240 mg I/ml or 300 mg I/ml	10-12 ml 7 - 10 ml	
Cervical myelography (lateral cervical injection)	240 mg I/ml or 300 mg I/ml	6 - 10 ml 6 - 8 ml	
CT cisternography (lumbar injection)	180 mg I/ml or 240 mg I/ml	5 - 15 ml 4 - 12 ml	
Paediatric myelography <2 years 2-6 years >6 years	180 mg I/ml 180 mg I/ml 180 mg I/ml	2 - 6 ml 4 - 8 ml 6 - 12 ml	

To minimize possible adverse reactions a total dose of 3 g iodine should not be exceeded.

**Guidelines for
Body cavities**

Indication	Concentration	Volume	Comments
Arthrography	240 mg I/ml or 300 mg I/ml or 350 mg I/ml	5 - 20 ml 5 - 15 ml 5 - 10 ml	
ERP/ERCP	240 mg I/ml	20 - 50 ml	
Herniography	240 mg I/ml	50 ml	
Hysterosalpingography	240 mg I/ml or 300 mg I/ml	15 - 50 ml 15 - 25 ml	
Sialography	240 mg I/ml or 300 mg I/ml	0.5 - 2 ml 0.5 - 2 ml	
<u>Gastrointestinal studies</u>	180 mg I/ml or 350 mg I/ml	10-200ml 10-20ml	

4.3 CONTRA INDICATIONS

Manifest thyrotoxicosis. History of serious reaction to Omnipaque.

4.4 SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE.Special precautions for use of non-ionic monomeric contrast media in general:

A positive history of **allergy**, **asthma**, or untoward **reactions** to iodinated contrast media indicates a need for special caution. Premedication with corticosteroids or histamine H₁ and H₂ antagonists might be considered in these cases.

The risk of serious reactions in connection with use of Omnipaque is regarded as minor. However, iodinated contrast media may provoke **anaphylactoid** reactions or other manifestations of **hypersensitivity**. A course of action should therefore be planned in advance, with necessary drugs and equipment available for immediate treatment, should a serious reaction occur. It is advisable always to use an indwelling cannula or catheter for quick intravenous access throughout the entire X-ray procedure.

When performing vascular catheterization procedures one should pay meticulous attention to the angiographic technique and flush the catheter frequently (e.g.: with heparinized saline) so as to minimize the risk of *procedure-related* thrombosis and embolism.

Adequate **hydration** should be assured before and after contrast media administration. This applies especially to patients with multiple myeloma, diabetes mellitus, renal dysfunction, as well as to infants, small children and elderly patients. Young **infants** (age < 1 year) and especially **neonates** are susceptible to electrolyte disturbance and haemodynamic alterations. Care should also be taken in patients with **serious cardiac disease** and **pulmonary hypertension** as they may develop haemodynamic changes or arrhythmias.

Patients with **acute cerebral pathology**, tumours or a history of **epilepsy** are predisposed for seizures and merit particular care. Also **alcoholics** and **drug addicts** have an increased risk for seizures and neurological reactions. A few patients have experienced a temporary **hearing loss** or even deafness after myelography, which is believed to be due to a drop in spinal fluid pressure by the lumbar puncture per se.

To prevent acute renal failure following contrast media administration, special care should be exercised in patients with preexisting **renal impairment** and **diabetes mellitus** as they are at risk. Patients with **paraproteinemias** (myelomatosis and Waldenström's macroglobulinemia) are also at risk.

Preventive measures include:

- Identification of high risk patients
- Ensuring adequate hydration. If necessary by maintaining an i.v. infusion from before the procedure until the contrast medium has been cleared by the kidneys.
- Avoiding additional strain on the kidneys in the form of nephrotoxic drugs, oral cholecystographic agents, arterial clamping, renal arterial angioplasty, or major surgery, until the contrast medium has been cleared.
- Postponing a repeat contrast medium examination until renal function returns to pre-examination levels.

Diabetic patients receiving metformin.

There is a risk of the development of lactic acidosis when iodinated contrast agents are administered to diabetic patients treated with metformin, particularly in those with impaired renal function. To reduce the risk of lactic acidosis, the serum creatinine level should be measured in diabetic patients treated with metformin prior to intravascular administration of iodinated contrast media and the following precautions undertaken in the following circumstances:

Normal serum creatinine (<130µmol/litre)/normal renal function: Administration of metformin should be stopped at the time of administration of contrast medium and should not be resumed for 48 hours and only be restarted if renal function/serum creatinine remains in the normal range.

Abnormal serum creatinine (>130µmol/litre)/impaired renal function: Metformin should be stopped and the contrast medium examination delayed for 48 hours. Metformin should only be

restarted 48 hours later if renal function is not diminished (if serum creatinine is not increased) compared to pre-contrast values.

Emergency cases: In emergency cases where renal function is impaired or unknown, the physician should evaluate the risk/benefit of the contrast medium examination, and the following precautions should be implemented: Metformin should be stopped. It is particularly important that the patient is fully hydrated prior to contrast medium administration and for 24 hours afterwards. Renal function (e.g. serum creatinine), serum lactic acid and blood pH should be monitored. A pH <7.25 or a lactic acid level of >5 mmol/litre are indicative of lactic acidosis. The patient should be observed for symptoms of lactic acidosis. These include vomiting, somnolence, nausea, epigastric pain, anorexia, hyperpnoea, lethargy, diarrhoea and thirst.

A potential risk of transient hepatic dysfunction exists. Particular care is required in patients with severe disturbance of both renal and hepatic function as they may have significantly delayed contrast medium clearance. Patients on **haemodialysis** may receive contrast media for radiological procedures. Correlation of the time of contrast media injection with the haemodialysis session is unnecessary.

The administration of iodinated contrast media may aggravate the symptoms of **myasthenia gravis**. In patients with **phaeochromocytoma** undergoing interventional procedures, alpha blockers should be given as prophylaxis to avoid a hypertensive crisis. Special care should be exercised in patients with **hyperthyroidism**. Patients with multinodular **goiter** may be at risk of developing hyperthyroidism following injection of iodinated contrast media. One should also be aware of the possibility of inducing transient hypothyroidism in premature infants receiving contrast media.

Extravasation of contrast media occurs rarely and gives local pain and oedema, which usually recedes without sequela. However, inflammation and even tissue necrosis have been seen. Elevating and cooling the affected site is recommended as routine measures. Surgical decompression may be necessary in cases of compartment syndrome.

Observation-time:

Patients must be kept under close observation for 15 minutes following the last injection as the majority of severe reactions occur at this time. The patient should remain in the hospital environment (but not necessarily the radiology department) for one hour after the last injection, and should return to the radiology department if any symptoms develop.

Intrathecal use:

Following **myelography** the patient should rest with the head and thorax elevated by 20° for one hour. Thereafter he/she may ambulate carefully but bending down must be avoided. The head and thorax should be kept elevated for the first 6 hours if remaining in bed. Patients suspected of having a low seizure threshold should be observed during this period. Outpatients should not be completely alone for the first 24 hours.

4.5 INTERACTIONS WITH OTHER MEDICAMENTS AND OTHER FORMS OF INTERACTION

Use of iodinated contrast media may result in a transient impairment of renal function and this may precipitate lactic acidosis in diabetics who are taking **metformin** (see Section 4.4 Special warnings and special precautions for use).

Patients treated with **interleukin-2** less than two weeks previously have been associated with an increased risk for delayed reactions (flu-like symptoms or skin reactions).

All iodinated contrast media may interfere with tests on thyroid function, thus the iodine binding capacity of the thyroid may be reduced for up to several weeks.

High concentrations of contrast media in serum and urine can interfere with **laboratory tests** for bilirubin, proteins or inorganic substances (e.g. iron, copper, calcium and phosphate). These substances should therefore not be assayed on the day of examination.

4.6 PREGNANCY AND LACTATION

The safety of Omnipaque for use in human pregnancy has not been established. An evaluation of experimental animal studies does not indicate direct or indirect harmful effects with respect to reproduction, development of the embryo or fetus, the course of gestation and peri- and postnatal development.

Since whenever possible, radiation exposure should be avoided during pregnancy, the benefits of an X-ray examination, with or without contrast media, should be carefully weighed against the possible risk. Omnipaque should not be used in pregnancy unless the benefit outweighs risk and it is considered essential by the physician.

Contrast media are poorly excreted in human breast milk and minimal amounts are absorbed by the intestine. Breast feeding may be continued normally when iodinated contrast media are given to the mother. The amount of iohexol in breast milk excreted in 24 hours after injection was 0.5% of the weight adjusted dose in a trial. The amount of iohexol ingested by the baby in the first 24 hours after injection corresponds to only 0.2% of the paediatric dose.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There is no known effect on the ability to drive or operate machines. However, because of the risk of reactions, driving or operating machinery is not advisable for one hour after the last injection or for 6 hours following intrathecal procedure (see Section 4.4). Individual judgement must be performed if persistent post myelography symptoms.

4.8 UNDESIRABLE EFFECTS

General (applies to all uses of iodinated contrast media):

Below are listed possible general side effects in relation with radiographic procedures which include the use of non-ionic monomeric contrast media. For side effects specific to mode of administration, please refer to these specific sections.

Undesirable effects associated with the use of iodinated contrast media are usually mild to moderate and transient in nature, and less frequent with non-ionic than with ionic contrast media. Serious reactions as well as fatalities are only seen on very rare occasions.

The most frequent adverse event is a **mild, general sensation** such as a feeling of warmth or a transient metallic taste.

Abdominal discomfort/pain and gastrointestinal reactions like nausea, vomiting and diarrhoea may occur.

Hypersensitivity reactions are rare and usually present as mild respiratory or cutaneous symptoms like dyspnoea, rash, erythema, urticaria, pruritus and angioedema. They may appear either immediately after the injection or up to a few days later. The most common delayed reactions are pruritus and urticaria. Severe manifestations such as laryngeal oedema, bronchospasm or pulmonary oedema are very rare. Severe and even toxic skin reactions have been reported.

Anaphylactoid reactions may occur irrespectively of the dose and mode of administration and mild symptoms of hypersensitivity may represent the first signs of a serious reaction. Administration of the contrast medium must be discontinued immediately and, if necessary, specific therapy instituted via the vascular access. In patients using **beta blockers** the bradycardia may not respond to shock and thereby these patients present with atypical symptoms of anaphylaxis which may be misinterpreted as a vagal reaction.

Vagal reactions giving hypotension and bradycardia are seen on very rare occasions.

Headache or **fever** may occur. Episodes of **hypertension** may also occur. **Pyrexia** with rigors are seen on rare occasions.

Iodism or "**iodide mumps**" is a very rare complication of iodinated contrast media resulting in swelling and tenderness of the salivary glands for up to approximately 10 days after the examination.

Intravascular use (Intraarterial and Intravenous use)

Please first read the section labelled "General". Below, only undesirable events with frequency during intravascular use of non-ionic monomeric contrast media are described.

The nature of the undesirable effects specifically seen during intraarterial use depends on the site of injection and dose given. Selective arteriographies and other procedures in which the contrast medium reaches a particular organ in high concentrations may be accompanied by complications in that particular organ.

Distal **pain or heat sensation** in peripheral angiography is common (incidence >1:10).

A transient increase in S-creatinine is common after iodinated contrast media, but usually of no clinical relevance. Renal failure is very rare. However, renal failure may occur in high risk patients and among such patients fatalities have been reported.

Arterial spasm may follow injection into coronary, cerebral or renal arteries and result in transient ischaemia.

Neurological reactions are very rare. They may include seizures or transient motor or sensory disturbances. On very rare occasions the contrast medium may cross the blood-brain barrier resulting in uptake of contrast medium in the cerebral cortex being visible on CT-scanning until the day following examination, sometimes associated with transient confusion or cortical blindness.

Serious cardiac complications, including cardiac arrest, arrhythmia, depression or signs of ischaemia are very rare. Lactic acidosis and acute renal failure may occur in risk patients, see Section 4.4 Special warnings and special precautions for use.

Post phlebographic thrombophlebitis or thrombosis is very rare. A very few cases of **arthralgia** have been reported.

Severe respiratory symptoms and signs (including dyspnoea, bronchospasm, laryngospasm, non-cardiogenic pulmonary oedema) and cough may occur.

Thyrotoxicosis may occur. Flushing may occur. Injection site reactions may occur.

Intrathecal use

Please first read the section labelled "General". Below, only undesirable events with frequency during intrathecal use of non-ionic monomer contrast media are described.

Undesirable effects following intrathecal use may be delayed and present some hours or even days after the procedure. The frequency is similar to lumbar puncture alone.

Headache, nausea, vomiting or dizziness are common and may largely be attributed to pressure loss in the subarachnoid space resulting from leakage at the puncture site. Some of these patients may experience a severe headache lasting for several days. Excessive removal of cerebrospinal fluid should be avoided in order to minimize pressure loss.

Mild local **pain**, **paraesthesia** and **radicular pain** occasionally (incidence <1:10, but >1:100) occur at the site of injection. **Cramping and pain** in the lower limbs are seen on very rare occasions.

Meningeal irritation giving photophobia and meningism happens occasionally. Frank chemical meningitis appears on very rare occasions. The possibility of an infective meningitis should also be considered.

On very rare occasions, manifestations of **transient cerebral dysfunction** are seen. These include seizures, transient confusion or transient motor or sensory dysfunction. Changes in the EEG may be noted in a few of these patients.

Transient blindness may occur. Neck pain may occur. Injection site reaction may occur.

Use in Body Cavities

Please first read the section labelled "General". Below, only undesirable events with frequency during use of non-ionic monomeric contrast media in body cavities are described.

Systemic hypersensitivity reactions are rare.

Endoscopic Retrograde Choleangio Pancreatography (ERCP): Some elevation of amylase levels is common. Post ERCP renal opacification is seen on rare occasions and is associated with an increased risk of post ERCP **pancreatitis**. Rare cases of necrotizing pancreatitis have also been described.

Oral use: Gastrointestinal upset occasionally occurs.

Hysterosalpingography (HSG): Transient **pain** in the lower abdomen is common.

Arthrography: Post procedural **pain** is common. Frank arthritis is rare. The possibility of infective arthritis should be considered in such cases.

Herniography: Mild postprocedural pain is common.

4.9 OVERDOSE

Preclinical data indicate a high safety margin for Omnipaque and no fixed upper dose level has been established for routine intravascular use. Symptomatic overdosing is unlikely in patients with normal renal function unless the patient has received an excess of 2000 mg I/kg body-weight over a limited period of time. The duration of the procedure is important for the renal tolerability of high doses of contrast media ($t_{1/2} \sim 2$ hours). Accidental overdosing is most likely following complex angiographic procedures in children, particularly when multiple injections of contrast medium with high-concentration are given.

In cases of overdose, any resulting water- or electrolyte imbalance must be corrected. Renal function should be monitored for the next 3 days. If needed, haemodialysis may be used for clearance of excessive contrast medium. There is no specific antidote.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

For most of the haemodynamic, clinical-chemical and coagulation parameters examined following intravenous injection of iohexol in healthy volunteers, no significant deviation from preinjection values has been found. The few changes observed in the laboratory parameters were minor and considered to be of no clinical importance.

5.2 PHARMACOKINETIC PROPERTIES

Close to 100 per cent of the intravenously injected iohexol is excreted unchanged through the kidneys within 24 hours in patients with normal renal function. The maximum urinary concentration of iohexol appears within approximately 1 hour after injection. No metabolites have been detected. The protein binding of Omnipaque is very low (less than 2 %).

5.3 PRECLINICAL SAFETY DATA

Iohexol has a very low acute intravenous toxicity in mice and rats. Animal studies have shown that iohexol has a very low protein binding, and is well tolerated by the kidneys.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The following excipients are included:

Trometamol
Sodium calcium edetate
Hydrochloric acid (pH adjustment)
Water for injections.

The pH of the product is 6.8 - 7.6.

6.2 INCOMPATIBILITIES

Omnipaque should not be directly mixed with other drugs. A separate syringe should be used.

6.3 SHELF LIFE

Glass bottles: 3 years

Polypropylene bottles: 3 years

The expiry date is indicated on the label.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Omnipaque should be stored at or below 30°C protected from light and secondary X-rays. Furthermore, the product in glass vials and bottles can be stored at 37°C for up to 3 months prior to use.

The product in polypropylene bottles: 40, 50, 75, 100, 150, 175 and 200 ml volumes may be stored at 37°C for up to 1 month prior to use.

6.5 NATURE AND CONTENT OF CONTAINER

Glass bottles:

The product is filled in infusion vials (10 and 20 ml) and infusion bottles (50, 75 and 100 ml). Both containers are made of colourless highly resistant borosilicate glass (Ph. Eur. Type I), closed with chlorobutyl rubber stoppers (Ph. Eur. Type I), and sealed with combined "flip off seal/tear off seal - flat plast disc".

Polypropylene bottles:

The product is filled in polypropylene bottles. Bottles of 40 and 50 ml are rigid stand-up bottles with a twist-off top. Bottles of 50, 75, 100, 150, 175 and 200 ml are supplied with a plastic screw cap, which is provided with a tamper proof ring

The product is supplied as:

Glass vials/bottles:

140 mg I/ml	180 mg I/ml	240 mg I/ml	300 mg I/ml	350 mg I/ml
10 bottles of 50ml 6 bottles of 200ml	10 vials of 10ml 10 vials of 15ml 10 bottles of 50ml	10 vials of 10ml 6 vials of 20ml 25 vials of 20ml 10 bottles of 50ml 6 bottles of 200ml	10 vials of 10ml 6 vials of 20ml 25 vials of 20ml 10 bottles of 50ml 10 bottles of 75ml 6 bottles of 100ml	6 vials of 20ml 25 vials of 20ml 10 bottles of 40ml 10 bottles of 50ml 10 bottles of 75ml 10 bottles of 100ml 6 bottles of 200ml

Polypropylene bottles:

140 mg I/ml	180 mg I/ml	240 mg I/ml	300 mg I/ml	350 mg I/ml
10 bottles of 50 ml		10 bottles of 50 ml	10 bottles of 40ml	10 bottles of 40ml
1 bottle of 100ml		1 bottle of 100ml	10 bottles of 50ml	10 bottles of 50ml
10 bottles of 100ml		10 bottles of 100ml	1 bottle of 75ml	1 bottle of 75ml
1 bottle of 200ml		1 bottle of 200ml	10 bottles of 75ml	10 bottles of 75ml
10 bottles of 200ml		10 bottles of 200ml	1 bottle of 100ml	1 bottle of 100ml
			10 bottles of 100ml	10 bottles of 100ml
			1 bottle of 150ml	1 bottle of 150ml
			10 bottles of 150ml	10 bottles of 150ml
			1 bottle of 175ml	1 bottle of 175ml
			10 bottles of 175ml	10 bottles of 175ml
			1 bottle of 200ml	1 bottle of 200ml
			10 bottles of 200ml	10 bottles of 200ml

6.6 INSTRUCTIONS FOR USE/HANDLING

Like all parenteral products, Omnipaque should be inspected visually for particulate matter, discolouration and the integrity of the container prior to use.

The product should be drawn into the syringe immediately before use. Vials and bottles are intended for single use only, any unused portions must be discarded.

Omnipaque may be warmed to body temperature (37°C) before administration.

7. MARKETING AUTHORISATION HOLDER

GE Healthcare AS
Nycoveien 1-2
P.O.Box 4220 Nydalen
NO-0401 Oslo, Norway

Tel.: +47 23 18 50 50

Fax: +47 23 18 60 00

8. MARKETING AUTHORIZATION NUMBER

PL 00637/0038, 0037, 0034, 0035, 0036

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

20 April 1983

10. DATE OF REVISION OF THE TEXT

26 July 2006 (Company Name Change)

January 2007 (New safety information according to CCSI)