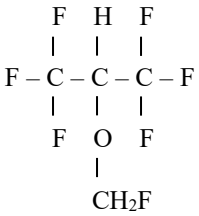
SEVORANE®
SEVOFLURANE

Inhalation Anaesthetic

Description and Composition
Sevoflurane is a non-flammable, pleasant smelling, volatile liquid. It is 1, 1, 1, 3, 3, 3-hexafluoro-2-fluoromethoxypropane and has the following structural formula:



Some physical constants of Sevoflurane are:

Relative molecular mass	200.05
Boiling point at 760mmHg	58.6°C
Refractive index n^{20}	1.2740 - 1.2760
Specific gravity at 20°C	1.520 - 1.525

Vapour pressure

Temp°C	mmHg
20	157
25	197
36	317

Partition coefficients at 37°C

Water/gas	0.36
Blood/gas	0.63-0.69
Olive Oil/gas	47.2-53.9

Mean Partition coefficients at 25°C - component/gas

Conductive rubber	14.0
Butyl rubber	7.7
Polyvinylchloride	17.4
Polyethylene	1.3

Purity by gas chromatography	99.975% or better
Flammability	Not flammable

Sevoflurane contains only Sevoflurane, no additives are included.

Sevoflurane Degradation
Sevoflurane is stable when stored under normal room lighting conditions. No discernible degradation of sevoflurane occurs in the presence of strong acids or heat. Sevoflurane is not corrosive to stainless steel, brass, aluminum, nickel-plated brass, chrome-plated brass, or copper beryllium alloy.

Chemical degradation can occur upon exposure of inhaled anaesthetics to CO_2 absorbent within the anaesthesia machine. When used as directed with fresh absorbents, degradation of sevoflurane is minimal, and degradants are undetectable or non-toxic, Sevoflurane degradation and subsequent degradant formation are enhanced by increasing absorbent temperature desiccated CO_2 absorbent (especially potassium hydroxide-containing), increased sevoflurane concentration and decreased fresh gas flow.

Sevoflurane can undergo alkaline degradation by two pathways. The first results from the loss of

hydrogen fluoride with the formation of pentafluoroisopropanyl fluoromethyl ether (PIFE or more commonly know as Compound A). The second pathway for degradation of sevoflurane occurs only in the presence of desiccated CO_2 absorbents and leads to the dissociation of sevoflurane into hexafluoroisopropanol (HFIP) and formaldehyde. HFIP is inactive, non-genotoxic, rapidly glucoronidated, cleared, and has toxicity comparable to sevoflurane. Formaldehyde is present during normal metabolic processes. Upon exposure to a highly desiccated absorbent, formaldehyde can further degrade into methanol and formate. Formate can contribute to the formation of carbon monoxide, in the presence of high temperature. Methanol can react with Compound A to form the methoxy addition product Compound B. Compound B can undergo further HF elimination to form Compounds C, D, and E. With highly desiccated absorbents, especially those containing potassium hydroxide, the formation of formaldehyde, methanol, carbon monoxide, Compound A and perhaps some of its degradants, Compounds B, C, and D may occur.

Indications

For induction and maintenance of general anaesthesia for in-patient and out-patient surgery in both adults and children.

Actions: The depth of anaesthesia changes rapidly following changes in the inspired concentration of Sevoflurane. Emergence and recovery are particularly rapid. Therefore, patients may require early post-operative pain relief.

As with all other inhalation agents Sevoflurane depresses cardiovascular function in a dose related fashion. In one volunteer study, increases in Sevoflurane concentration resulted in decrease in mean arterial pressure, but there was no change in heart rate. Sevoflurane did not alter plasma noradrenaline concentrations in this study.

No evidence of seizure was observed during the clinical development programme.

Dosage and Administration

Vaporisers specifically calibrated for use with Sevoflurane should be used so that the concentration delivered can be accurately controlled. MAC (minimum alveolar concentration) values for Sevoflurane decrease with age and with the addition of nitrous oxide. The table below indicates average MAC values for different age groups.

EFFECT OF AGE ON MAC OF SEVOFLURANE

AGE OF PATIENT (YEARS)	SEVOFLURANE IN OXYGEN	SEVOFLURANE IN 65% N_2O / 35% O_2*
<3	3.3 - 2.6%	2.0%
3 - <5	2.5%	Not available
5 - 12	2.4%	Not available
25	2.5%	1.4%
35	2.2%	1.2%
40	2.05%	1.1%
50	1.8%	0.98%
60	1.6%	0.87%
80	1.4%	0.70%

* In paediatric patients 60% N_2O / 40% O_2 was used.

Premedication: Premedication should be selected according to the need of the individual patient, and at the discretion of the anaesthetist. The use of anticholinergic drugs is a matter of choice.

Induction: Anaesthesia can be induced in adults and children with Sevoflurane. Dosage should be individualised and titrated to the desired effect according to the patient's age and clinical status. A short acting barbiturate or other intravenous induction agent may be administered followed by inhalation of Sevoflurane. (See also "Interactions"). Induction with Sevoflurane may be achieved in oxygen or in combination with oxygen-nitrous oxide mixtures. In adults inspired concentrations of up to 5% Sevoflurane usually produce surgical anaesthesia in less than 2 minutes. In children, inspired concentrations of up to 7% Sevoflurane usually produce surgical anaesthesia in less than 2 minutes. Alternatively, for induction of anaesthesia in unpremedicated patients, inspired concentrations of up to 8% Sevoflurane may be used.

Maintenance: Surgical levels of anaesthesia may be sustained with concentrations of 0.5 -3% Sevoflurane with or without the concomitant use of nitrous oxide (see also "Drug Interactions").

Elderly: As with other inhalation agents, lesser concentrations of Sevoflurane are normally required to maintain surgical anaesthesia. See above for MAC values.

Emergence: Emergence times are generally short following Sevoflurane anaesthesia. Therefore, patients may require early post-operative pain relief.

Contraindications

Sevoflurane should not be used in patients with known or suspected sensitivity to Sevoflurane or to other halogenated inhalational anaesthetics (e.g. history of hepatotoxicity, usually including elevated liver enzymes, fever, leukocytosis and/or eosinophilia temporally related to anaesthesia with one of these agents).

Sevoflurane is also contraindicated in patients with known or suspected genetic susceptibility to malignant hyperthermia.

Warnings and Precautions

Sevoflurane may cause respiratory depression, which may be augmented by narcotic premedication or other agents causing respiratory depression. Respiration should be supervised and if necessary, assisted.

Sevoflurane should be administered only by persons trained in the administration of general anaesthesia. Facilities for maintenance of a patent airway, artificial ventilation, oxygen enrichment and circulatory resuscitation must be immediately available. The concentration of sevoflurane being delivered from a vaporizer must be known exactly. As volatile anaesthetics differ in their physical properties, only vaporizers specifically calibrated for sevoflurane must be used. The administration of general anaesthesia must be individualized based on the patient's response. Hypotension and respiratory depression increase as anaesthesia is deepened.

During the maintenance of anaesthesia, increasing the concentration of Sevoflurane produces dose-dependent decreases in blood pressure. Excessive decrease in blood pressure may be related to depth of anaesthesia and in such instances may be corrected by decreasing the inspired concentration of Sevoflurane. The recovery from general anaesthesia should be assessed carefully before patients are discharged from the recovery room.

Isolated reports of QT prolongation, very rarely associated with torsade de pointes (in exceptional cases, fatal), have been received. Caution should be exercised when administering sevoflurane to susceptible patients.

Isolated cases of ventricular arrhythmia were reported in paediatric patients with Pompe's disease.

Caution should be exercised in administering general anaesthesia, including sevoflurane, to patients with mitochondrial disorders.

Hepatic: Very rare cases of mild, moderate and severe post-operative hepatic dysfunction or hepatitis with or without jaundice have been reported from postmarketing experiences.

Clinical judgment should be exercised when sevoflurane is used in patients with underlying hepatic conditions or under treatment with drugs known to cause hepatic dysfunction (see **Adverse Reactions**).

It has been reported that previous exposure to halogenated hydrocarbon anaesthetics, especially if the interval is less than 3 months, may increase the potential for hepatic injury.

Malignant Hyperthermia: In susceptible individuals, potent inhalation anaesthetic agents may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. The syndrome may include non-specific features such as muscle rigidity, tachycardia, tachypnoea, cyanosis, arrhythmias and unstable blood pressure. Some of these nonspecific signs may also appear during light anaesthesia, acute hypoxia, hypercapnia and hypovolemia.

In clinical trials, one case of malignant hyperthermia was reported. In addition, there have been postmarketing reports of malignant hyperthermia. Some of these reports have been fatal.

Treatment of malignant hyperthermia includes discontinuation of triggering agents (eg Sevoflurane), administration of intravenous dantrolene sodium (consult prescribing information for intravenous dantrolene sodium for additional information on patient management), and application of supportive therapy. Such therapy includes vigorous efforts to restore body temperature to normal, respiratory and circulatory support as indicated,

and management of electrolyte-fluid-acid-base abnormalities. Renal failure may appear later, and urine flow should be monitored and sustained if possible.

Perioperative Hyperkalemia: Use of inhaled anaesthetic agents has been associated with rare increases in serum potassium levels that have resulted in cardiac arrhythmias and death in paediatric patients during the postoperative period. Patients with latent as well as overt neuromuscular disease, particularly Duchenne muscular dystrophy, appear to be most vulnerable. Concomitant use of succinyl-choline has been associated with most, but not all, of these cases. These patients also experienced significant elevations in serum creatine kinase levels and, in some cases, changes in urine consistent with myoglobinuria. Despite the similarity in presentation to malignant hyperthermia, none of these patients exhibited signs or symptoms of muscle rigidity or hypermetabolic state. Early and aggressive intervention to treat the hyperkalemia and resistant arrhythmias is recommended, as is subsequent evaluation for latent neuromuscular disease.

Renal Impairment: Because of the small number of patients with renal insufficiency (baseline serum creatinine greater than 133 micromol / litre) studied, the safety of Sevoflurane administration in this group has not been fully established. Therefore, Sevoflurane should be used with caution in patients with renal insufficiency.

Sevoflurane produces low levels of Compound A (pentafluoroisopropenyl fluoromethyl ether (PIFE)) and trace amounts of Compound B (pentafluoromethoxy isopropyl fluoromethyl ether (PMFE)), when in direct contact with CO_2 absorbents. Levels of Compound A increase with:- increase in canister temperature; increase in anaesthetic concentration; decrease in gas flow rate and increase more with the use of Baralyme rather than Soda lime. (See also Pharmaceutical Precautions.)

In some studies in rats, nephrotoxicity was seen in animals exposed to levels of Compound A in excess of those usually seen in routine clinical practice. The mechanism of this renal toxicity in rats is unknown and its relevance to man has not been established.

Experience with repeat exposure to Sevoflurane is very limited. However, there were no obvious differences in adverse events between first and subsequent exposures.

General: During maintenance of anaesthesia, increasing the concentration of sevoflurane produces dose-dependent decreases in blood pressure. Excessive decrease in blood pressure may be related to depth of anaesthesia and in such instances may be corrected by decreasing the inspired concentration of sevoflurane.

As with all anaesthetics, maintenance of hemodynamic stability is important to the avoidance of myocardial ischemia in patients with coronary artery disease.

The recovery from general anaesthesia should be assessed carefully before patients are discharged from the post-anaesthesia care unit.

Although recovery of consciousness following sevoflurane administration generally occurs within minutes, the impact on intellectual function for two or three days following anaesthesia has not been studied. As with other anaesthetics, small changes in moods may persist for several days following administration. (see **Effects on driving ability and operation of machinery**)

Neurosurgery: In patients with normal intracranial pressure (ICP), Sevoflurane had minimal effect on ICP and preserved CO2 responsiveness. The safety of Sevoflurane has not been investigated in patients with a raised ICP. In patients at risk for elevations of ICP, Sevoflurane should be administered cautiously in conjunction with ICP-reducing manoeuvres such as hyperventilation.

Seizures: Rare cases of seizures have been reported in association with sevoflurance use (see **Warnings and Precautions – Paediatric Use** and **Adverse Reactions**).

Pediatric Use: The use of sevoflurane has been associated with seizures. Many of these have occurred in children and young adults starting from 2 months of age, most of whom had no predisposing risk factors. Clinical judgment should be exercised when using sevoflurane in patients who may be at risk for seizures. (see **Adverse Reactions**).

Bradycardia in Down Syndrome: Episodes of severe bradycardia and cardiac arrest, not related to underlying congenital heart disease, have been reported during anesthesia induction with sevoflurane in pediatric patients with Down syndrome. In most cases, bradycardia improved with decreasing the concentration of sevoflurane, manipulating the airway, or administering an anticholinergic or epinephrine.

During induction, closely monitor heart rate, and consider incrementally increasing the inspired sevoflurane concentration until a suitable level of anesthesia is achieved. Consider having an anticholinergic and epinephrine available when administering sevoflurane for induction in this patient population.

Replacement of Desiccated CO_2 Absorbents: Rare cases of extreme heat, smoke, and/or spontaneous fire in the anaesthesia machine have been reported during sevoflurane use in conjunction with the use of desiccated CO_2 absorbent, specifically those containing potassium hydroxide. An unusually delayed rise or unexpected decline of inspired sevoflurane concentration compared to the vaporizer setting may be associated with excessive heating of the CO_2 absorbent canister.

An exothermic reaction, enhanced sevoflurane degradation, and production of degradation products (see "Description and Composition") can occur when the CO_2 absorbent becomes desiccated, such as after an extended period of dry gas flow through the CO_2 absorbent canisters. Sevoflurane degradants (methanol, formaldehyde, carbon monoxide, and Compounds A, B, C, and D) were observed in the respiratory circuit of an experimental anaesthesia machine using desiccated CO_2 absorbents and maximum sevoflurane concentrations (8%) for extended periods of time ($\geq$ 2 hours). Concentrations of formaldehyde observed at the anaesthesia respiratory circuit (using sodium hydroxide containing absorbents) were consistent with levels known to cause mild respiratory irritation. The clinical relevance of the degradants observed under this extreme experimental model is unknown.

When a clinician suspects that the CO_2 absorbent may be desiccated, it should be replaced before administration of sevoflurane. The color indicator of most CO_2 absorbents does not necessarily change as a result of desiccation. Therefore, the lack of significant color change should not be taken as an assurance of adequate hydration. CO_2 absorbents should be replaced routinely regardless of the state of the color indicator.

Drug Interactions

Beta-sympathomimetic agents like isoprenaline and alpha- and beta- sympathomimetic agents like adrenaline and noradrenaline should be used with caution during Sevoflurane narcosis, due to a potential risk of ventricular arrhythmia.

Non-selective MAO-inhibitors: Risk of crisis during the operation. It is generally recommended that treatment should be stopped 2 weeks prior to surgery.

Sevoflurane may lead to marked hypotension in patients treated with calcium antagonists, in particular dihydropyridine derivates.

Caution should be exercised when calcium antagonists are used concomitantly with inhalation anesthetics due to the risk of additive negative inotropic effect.

Concomitant use of succinylcholine with inhaled anesthetic agents has been associated with rare increases in serum potassium levels that have resulted in cardiac arrhythmias and death in pediatric patients during the post-operative period.

The action of non-depolarising muscle relaxants is markedly potentiated with Sevoflurane, therefore, when administered with Sevoflurane, dosage adjustments of these agents should be made.

Sevoflurane is similar to isoflurane in the sensitisation of the myocardium to the arrhythmogenic effect of exogenously administered adrenaline.

MAC values for Sevoflurane decrease with the addition of nitrous oxide as indicated in the table on 'Effect of Age on MAC of Sevoflurane' (see "Dosage and Administration").

As with other agents, lesser concentrations of Sevoflurane may be required following use of an intravenous anaesthetic e.g. propofol.

Medicinal products and compounds that increase the activity of cytochrome P450 isoenzyme CYP2E1 such as isoniazid and alcohol, may increase the metabolism of sevoflurane and lead to significant increases in plasma fluoride concentration. Concomitant use of sevoflurane and isoniazid can potentiate the hepatotoxic effects of isoniazid.

Sevoflurane administration is compatible with barbiturates as commonly used in surgical practice.

Pregnancy and Lactation

Use in pregnancy: With the exception of one study in Caesarean Section, there are no other studies in pregnant women, including in labour and delivery. Experience in Caesarean Section is limited to one trial in a small number of patients. The safety of sevoflurane in labour and vaginal delivery has not been demonstrated.

Sevoflurane, like other inhalational agents, has relaxant effects on the uterus with the potential risk for uterine bleeding. Clinical judgment should be observed when using sevoflurane during obstetric anaesthesia.

Reproduction studies have been performed in rats and rabbits at doses up to 1 MAC. No effects on male and female reproductive capabilities were observed. Reduced foetal body weights concomitant with increased skeletal variations were noted in rats only at maternally toxic concentrations. No adverse foetal effects were observed in rabbits. Sevoflurane was not teratogenic. Therefore, Sevoflurane should be used during pregnancy only if clearly needed.

Published animal studies of some anesthetic/sedation drugs have reported adverse effects on brain development in early life and late pregnancy.

Published studies in pregnant and juvenile animals have demonstrated that anesthetic and sedation drugs that block N-methyl-D-aspartate (NMDA) receptors and/or potentiate gamma-aminobutyric acid (GABA) activity during the period of rapid brain growth or synaptogenesis may result in neuronal and oligodendrocyte cell loss in the developing brain and alterations in synaptic morphology and neurogenesis when used for longer than 3 hours. These studies included anesthetic agents from a variety of drug classes. The clinical significance of these nonclinical findings is yet to be determined (see **Further Information**). However, based on comparisons across species, the window of vulnerability to these changes is believed to correlate with exposures in the third trimester through the first several months of life, but may extend out to approximately 3 years of age in humans.

Use in nursing mothers: It is not known whether Sevoflurane or its metabolites is excreted in human milk. Due to the absence of documented experience, women should be advised to skip breast-feeding for 48 hours after administration of sevoflurane and discard milk produced during this period.

Effects on driving ability and operation of machinery

As with other anaesthetic agents, patients should be advised that performance of activities requiring mental alertness, such as operating a motor vehicle or hazardous machinery, may be impaired for some time after general anaesthesia. Patients should not be allowed to drive for a suitable period after Sevoflurane anaesthesia. (see **Warnings and Precautions**)

Adverse Reactions

As with all potent inhaled anaesthetics, Sevoflurane may cause dose-dependent cardiorespiratory depression. Most adverse events are mild to moderate in severity and transient. Nausea, vomiting and delirium are commonly observed in the postoperative period, at a similar incidence to those found with other inhalation anaesthetics. These effects are common sequelae of surgery and general anaesthesia, which may be due to the inhalational anaesthetic, other agents administered intraoperatively or post-operatively and to the patient's response to the surgical procedure.

Adverse Reaction Data Derived from Clinical Trials

The most commonly reported adverse reactions were as follows:

In adult patients: hypotension, nausea and vomiting

In elderly patients: bradycardia, hypotension and nausea

In paediatric patients: agitation, cough, vomiting and nausea.

All events, at least possibly related to sevoflurane from clinical trials, are displayed in the Table below by MedDRA System Organ Class, Preferred Term and frequency. The following frequency groupings are used: very common (≥1/10); common (≥1/100 and <1/10); uncommon (≥1/1,000 and <1/100); rare (≥1/10,000 and <1/1,000); very rare (<1/10,000), including isolated reports. The type, severity, and frequency of adverse events in sevoflurane patients were comparable to adverse events in reference-drug patients.

Summary of Most Frequent Adverse Drug Reactions in Sevoflurane Clinical Trials		
System Organ Class	**Frequency**	**Adverse Reactions**
Psychiatric disorders	Very common	Agitation
Nervous system disorders	Common	Somnolence Dizziness Headache
Cardiac disorders	Very common Common Uncommon Unknown	Bradycardia Tachycardia Atrioventricular block complete QT prolongation associated with Torsade
Vascular disorders	Very common Common	Hypotension Hypertension
Respiratory, thoracic and mediastinal disorders	Very common Common	Cough Respiratory disorder Laryngospasm
Gastrointestinal disorders	Very common Common	Nausea Vomiting Salivary hypersecretion
General disorders and administration site conditions	Common	Chills Pyrexia
Investigations	Common	Blood glucose abnormal Liver function test abnormal* White blood cell count abnormal Fluoride increased**
Injury, poisoning and procedural complications	Common	Hypothermia
*Occasional cases of transient changes in hepatic function tests were reported with sevoflurane and reference agents. **Transient increases in serum inorganic fluoride levels may occur during and after sevoflurane anaesthesia. Concentrations of inorganic fluoride generally peak within two hours of the end of sevoflurane anaesthesia and return within 48 hours to pre-operative levels. In clinical trials, elevated fluoride concentrations were not associated with impairment of renal function.		

Post-marketing Experience
Adverse events have been spontaneously reported during post-approval use of sevoflurane. These events are reported voluntarily from a population of an unknown rate of exposure. Therefore, it is not possible to estimate the true incidence of adverse events or establish a causal relationship to sevoflurane exposure.

Summary of Post-Marketing Adverse Drug Events	
System Organ Class	**Adverse Events**
Immune system disorders	Anaphylactic reaction* Anaphylactoid reaction Hypersensitivity*
Nervous system disorders	Convulsion Dystonia
Cardiac disorders	Cardiac arrest** Bradycardia in patients with Down syndrome
Respiratory, thoracic and mediastinal disorders	Bronchospasm

	Dyspnoea* Wheezing*
Hepato-biliary disorders	Hepatitis Hepatic failure Hepatic necrosis
Skin and subcutaneous tissue disorders	Rash* Urticaria Pruritus Dermatitis contact* Swelling face*
Musculoskeletal and connective tissue disorders	Muscle twitching
Renal and Urinary disorders	Renal failure acute
General disorders and administration site conditions	Hyperthermia malignant Chest discomfort*
* May be associated with hypersensitivity reactions, particularly in association with long-term occupational exposure to inhaled anaesthetic agents. ** There have been very rare postmarketing reports of cardiac arrest in the setting of sevoflurane use.	

Overdosage

In the event of overdosage, the following action should be taken: Stop drug administration, establish a clear airway and initiate assisted or controlled ventilation with pure oxygen and maintain adequate cardiovascular function.

Pharmaceutical precautions: Sevoflurane is chemically stable. As with some halogenated anaesthetics, minor degradation occurs through direct contact with CO_2 absorbents. The extent of degradation is clinically insignificant and no dose adjustments or change in clinical practice is necessary when rebreathing circuits are used. Higher levels of Compound A are obtained when using Baralyme rather than Soda lime.

Instructions for use: Some halogenated anaesthetics have been reported to interact with dry carbon dioxide absorbent to form carbon monoxide. To date there is no evidence that this can occur with Sevoflurane. However, in order to minimise the risk of formation of carbon monoxide in re-breathing circuits and the possibility of elevated carboxy-haemoglobin levels, carbon dioxide absorbents should not be allowed to dry out.

Package quantities: Bottles of 250ml.

Further information: The low solubility of Sevoflurane in blood should result in alveolar concentrations which rapidly increase upon induction and rapidly decrease upon cessation of the inhaled agent.

In humans <5% of the absorbed Sevoflurane is metabolised. The rapid agnd extensive pulmonary elimination of Sevoflurane minimises the amount of anaesthetic available for metabolism. Sevoflurane is defluorinated via cytochrome p450(CYP)2E1 resulting in the production of hexafluoroisopropanol (HFIP) with release of inorganic fluoride and carbon dioxide (or a one carbon fragment). HFIP is then rapidly conjugated with glucuronic acid and excreted in the urine.

The metabolism of Sevoflurane may be increased by known inducers of CYP2E1 (e.g. isoniazid and alcohol), but it is not inducible by barbiturates.

Transient increases in serum inorganic fluoride levels may occur during and after Sevoflurane anaesthesia. Generally, concentrations of inorganic fluoride peak within 2 hours of the end of Sevoflurane anaesthesia and return within 48 hours to pre-operative levels.

Pediatric

Some published studies in children have observed cognitive deficits after repeated or prolonged exposures to anesthetic/sedative agents early in life. These studies have substantial limitations, and it is not clear if the observed effects are due to the anesthetic/sedation drug administration or other factors such as the surgery or underlying illness. In addition, more recent published registry studies did not confirm these findings.

Published animal studies of some anesthetic/sedation drugs have reported adverse effects on brain development in early life (see **Pregnancy and Lactation**).

For use in pediatric patients with Down syndrome, see **Warnings and Precautions – Bradycardia in Down Syndrome**.

Special Precautions for storage: Store below 30°C. Do not refrigerate. Keep cap tightly closed.

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CCDS02190617
Date of Issue: DD MMM YYYY