ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ablavar 0.25 mmol/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml Ablavar solution for injection contains 244 mg (0.25 mmol) gadofosveset trisodium equivalent to 227 mg gadofosveset.

Each vial of 10 ml solution contains a total of 2.44 g (2.50 mmol) of gadofosveset trisodium equivalent to 2.27 g of gadofosveset
Each vial of 15 ml solution contains a total of 3.66 g (3.75 mmol) of gadofosveset trisodium equivalent to 3.41g of gadofosveset.
Each vial of 20 ml solution contains a total of 4.88 g (5.00 mmol) of gadofosveset trisodium equivalent to 4.54g of gadofosveset.

Excipient
This medicinal product contains 6.3 mmol sodium (or 145 mg) per dose.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear, colourless to pale yellow liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.
Ablavar is indicated for contrast-enhanced magnetic resonance angiography (CE-MRA) for visualisation of abdominal or limb vessels in adults only, with suspected or known vascular disease.

4.2 Posology and method of administration

This medicinal product should only be used by physicians experienced in the field of diagnostic imaging.

Posology
Adults: 0.12 ml/kg body weight (equivalent to 0.03 mmol/kg)

Imaging time points
Dynamic imaging begins immediately upon injection. Steady state imaging can begin after the dynamic scan has been completed. In clinical trials, imaging was completed up to approximately one hour following injection.

No clinical information is available about repeated use of this medicinal product.

Special populations

Elderly (aged 65 years and above)

No dose adjustment is considered necessary. Caution should be exercised in elderly patients (see section 4.4).

Renal impairment
Use of Ablavar should be avoided in patients with severe renal impairment (GFR < 30 ml/min/1.73 m^2) and in patients in the perioperative liver transplantation period unless the diagnostic information is essential and not available with non-contrast enhanced magnetic resonance imaging (MRI) (see section 4.4). If use of Ablavar cannot be avoided, the dose should not exceed 0.03 mmol/kg body weight. More than one dose should not be used during a scan. Because of the lack of information on repeated administration, Ablavar injections should not be repeated unless the interval between injections is at least 7 days.

Hepatic impairment
Dose adjustments in hepatic impairment are not necessary (see section 5.2).

Paediatric population
Use is not recommended in neonates, infants, children and adolescents. No clinical experience is yet available for patients younger than 18.

Method of administration
This medicinal product should be administered as a single intravenous bolus injection, manually, or by magnetic resonance injector (MR injector) over a period of time up to 30 seconds followed by a 25-30 ml normal saline flush.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

Diagnostic procedures involving the use of MRI contrast agents should be carried out under the supervision of a physician with the prerequisite training and a thorough knowledge of the procedure to be performed. Appropriate facilities should be available for coping with any complication of the procedure, as well as for emergency treatment of potential severe reactions to the contrast agent itself. The usual safety precautions for magnetic resonance imaging must be observed, e.g., exclusion of cardiac pacemakers and ferromagnetic implants.
As with other contrast enhanced diagnostic procedures, post-procedure observation of the patient is recommended, in particular in patients with a history of allergy, renal insufficiency, or adverse reaction.

Hypersensitivity warning
The possibility of a reaction, including serious, life-threatening, fatal, anaphylactoid, or cardiovascular reactions, or other idiosyncratic reactions should always be considered especially in those patients with a known clinical hypersensitivity, previous reaction of contrast media, a history of asthma, or other allergic disorders. Experience with other contrast media shows that the risk of hypersensitivity reactions is higher in those patients. Delayed reactions may occur (after hours to days).

Caution should also be exercised in the following cases:

Hypersensitivity reactions
If hypersensitivity reactions occur (see section 4.8), administration of the contrast medium must be discontinued immediately and - if necessary - specific therapy instituted via a venous access. It is therefore advisable to use a flexible indwelling cannula for intravenous contrast medium administration. Due to the possibility of severe hypersensitivity reactions after intravenous contrast administration, preparedness for institution of emergency measures is necessary, e.g., appropriate medicinal products, an endotracheal tube, and a respirator should be at hand.

Renal impairment
Since gadofosveset is cleared from the body primarily by urinary excretion, caution should be exercised in patients with impaired renal function (see section 4.2 and 5.2).

Prior to administration of Ablavar, it is recommended that all patients are screened for renal dysfunction by obtaining laboratory tests.

There have been reports of nephrogenic systemic fibrosis (NSF) associated with use of some gadolinium-containing contrast agents in patients with acute or chronic severe renal impairment (GFR < 30 ml/min/1.73 m^2). Patients undergoing liver transplantation are at particular risk since the incidence of acute renal failure is high in this group. As there is a possibility that NSF may occur with Ablavar, it should therefore be avoided in patients with severe renal impairment and in patients in the perioperative liver transplantation period unless the diagnostic information is essential and not available with non-contrast enhanced MRI.

Haemodialysis shortly after Ablavar administration may be useful at removing Ablavar from the body. There is no evidence to support the initiation of haemodialysis for prevention or treatment of NSF in patients not already undergoing haemodialysis.

Elderly
As the renal clearance of gadofosveset may be impaired in the elderly, it is particularly important to screen patients aged 65 years and older for renal dysfunction.

Haemodialysis shortly after Ablavar administration in patients currently receiving haemodialysis may be useful at removing Ablavar from the body. In a clinical trial it was shown that gadofosveset can effectively be removed from the body by dialysis using high flux filters.

There is no evidence to support the initiation of haemodialysis for prevention or treatment of NSF in patients not already undergoing haemodialysis.

Electrocardiographic changes
Elevated levels of gadofosveset (e.g. repeated use in the short term [within 6-8 hours], or an inadvertent overdose > 0.05 mmol/kg) may be associated with mild QT prolongation (8.5 msec by Fridericia correction). In the situation of elevated levels of gadofosveset or underlying QT prolongation the patient should be carefully observed including cardiac monitoring.

Vascular stents
It has been shown in published studies that MRA in the presence of metallic stents causes artefacts. The reliability of lumen visualisation in a stented vessel with Ablavar has not been evaluated.

Sodium
This medicine contains 6.3 mmol sodium (or 145 mg) per dose.
To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Because gadofosveset is bound to albumin, an interaction with other plasma protein bound active substances (e.g., ibuprofen and warfarin) is generally possible, i.e., a competition for the protein binding site can occur. However, in a series of *in vitro* drug interaction studies (in 4.5 % human serum albumin and human plasma), gadofosveset demonstrated no adverse interaction with digitoxin, propranolol, verapamil, warfarin, phenprocoumon, ibuprofen, diazepam, ketoprofen, naproxen, diclofenac and piroxicam at clinically relevant concentrations. *In vitro* studies using human liver microsomes did not indicate any potential to inhibit the cytochrome P 450 enzyme system.

In a clinical study, it was shown that gadofosveset does not affect the unbound fraction of warfarin in plasma. The anticoagulant activity of warfarin was not altered and the efficacy of the medicinal product was not influenced.

Laboratory test interactions
In clinical trials using Ablavar, no specific trends were observed that would signify a potential interaction of the medicinal product with laboratory test methods.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data from the use of Ablavar in pregnant women. Animal studies have shown reproductive toxicity at repeated high doses (see section 5.3). Ablavar should not be used during pregnancy unless the clinical condition of the woman requires use of the medicinal product.

Breast-feeding
Gadolinium containing contrast agents are excreted into breast milk in very small amounts (see section 5.3). At clinical doses, no effects on the infant are anticipated due to the small amount excreted in milk and poor absorption from the gut. Continuing breastfeeding or discontinuing Ablavar for a period of 24 hours after administration should be at the discretion of the physician and breast-feeding mother.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machine have been performed. Uncommonly, dizziness or vision problems may occur with this medicine. If a patient experiences these effects he/she should not drive or use machines

4.8 Undesirable effects

The most common adverse reactions were pruritus, paresthesia, headache, nausea, vasodilatation, burning sensation and dysgeusia. Most of the adverse reactions were mild to moderate in intensity. Most of the adverse reactions (80%) occurred within 2 hours. Delayed reactions (after hours to days) may occur.
Clinical trial data
Based on clinical trial experience in more than 1,800 patients, the following adverse reactions have been observed.

The table below reports adverse reactions by MedDRA system organ classes (MedDRA SOCs).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System Organ Class (MedDRA)	**Common (≥ 1/100)**	**Uncommon (≥ 1/1,000 to < 1/100)**	**Rare (≥ 1/10,000 to < 1/1,000)**
Infections and infestations		Nasopharyngitis	Cellulitis Urinary tract infection
Immune system disorders		Hypersensitivity	
Metabolism and nutrition disorders		Hyperglycaemia Electrolyte imbalance (incl. Hypocalcemia)	Hyperkalemia Hypokalemia Hypernatremia Appetite decreased
Psychiatric disorders		Anxiety Confusion	Hallucination Abnormal dreams

System Organ Class (MedDRA)	Common (≥ 1/100)	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1,000)
Nervous system disorders	Headache Paraesthesia Dysgeusia Burning sensation	Dizziness (excl. Vertigo) Tremor Hypoesthesia Parosmia Ageusia Muscle contractions involuntary	
Eye disorders		Vision abnormal Lacrimation increased	Abnormal sensation in eye Asthenopia
Ear and labyrinth disorders			Ear pain
Cardiac disorders		Atrioventricular block first degree, Electrocardiogram QT prolonged, Tachycardia Electrocardiogram abnormal	Cardiac flutter Myocardial ischaemia Bradycardia Atrial fibrillation Palpitations Electrocardiogram ST segment depression, Electrocardiogram T wave amplitude decreased
Vascular disorders	Vasodilatation (incl. Flushing)	Phlebitis Hypertension Peripheral coldness	Anaphylactoid reaction Hypotension Arteriosclerosis
Respiratory, thoracic and mediastinal disorders		Dyspnea Cough	Respiratory depression
Gastrointestinal disorders	Nausea	Vomiting Retching Diarrhea Abdominal pain Pharyngolaryngeal pain Abdominal discomfort Flatulence Hypoesthesia lips Salivary hypersecretion Dyspepsia Dry mouth Pruritus ani	
Skin and subcutaneous tissue disorders	Pruritus	Urticaria Rash Erythema Sweating increased	Swelling face Clamminess

System Organ Class (MedDRA)	Common (≥ 1/100)	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1,000)
Musculoskeletal and connective tissue disorders		Pain in limb Neck pain Muscle cramps Muscle spasms	Muscle tightness Sensation of heaviness
Renal and urinary disorders		Haematuria, Microalbuminuria, Glycosuria	Micturition urgency Renal pain Urinary frequency
Reproductive system and breast disorders		Genital pruritus, Genital burning sensation	Pelvic pain
General disorders and administration site conditions	Feeling cold	Pain, Chest pain Groin pain Fatigue Feeling abnormal Feeling hot Injection site pain, Injection site erythema, Injection site coldness	Pyrexia Rigors Weakness Chest pressure sensation Injection site thrombosis Injection site bruising Injection site inflammation Injection site burning Injection site extravasation Injection site haemorrhage Injection site pruritus Sensation of pressure
Injury, poisoning and procedural complications			Phantom limb pain

Cases of nephrogenic systemic fibrosis (NSF) have been reported with other gadolinium-containing contrast agents (see section 4.4).

As with other intravenous contrast agents, this medicinal product can be associated with anaphylactoid / hypersensitivity reactions characterised by cutaneous, respiratory and/or cardiovascular manifestations which may lead to shock.

4.9 Overdose

Ablavar can be removed by haemodialysis. However, there is no evidence that haemodialysis is suitable for prevention of nephrogenic systemic fibrosis (NSF).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Contrast media, paramagnetic contrast media, ATC code: V08CA.

Ablavar is a formulation of a stable gadolinium diethylenetriaminepentaacetic acid (GdDTPA) chelate substituted with a diphenylcyclohexylphosphate group (gadofosveset trisodium), for use in magnetic resonance imaging (MRI).

Gadofosveset binds reversibly to human serum albumin. Protein binding enhances T1 relaxivity of gadofosveset up to 10 fold compared to non-protein bound gadolinium chelates. In human studies, gadofosveset substantially shortens blood T1 values for up to 4 hours after intravenous bolus injection. Relaxivity in plasma was measured to be 33.4 to 45.7 $mM^{-1}s^{-1}$ over the dose range of up to 0.05 mmol/kg at 20 MHz. High resolution MRA scans of vascular structures are obtained up to one hour after administration of the medicinal product. The extended vascular imaging window for gadofosveset is attributed to enhanced relaxivity and extended residence in vascular space resulting from its plasma protein binding. No comparative studies with extracellular gadolinium contrast agents have been conducted.

The safety and effectiveness of Ablavar in patients under 18 years of age have not been established.

5.2 Pharmacokinetic properties

Distribution

The plasma concentration-time profile of intravenously administered gadofosveset conforms to a two-compartment open model. After intravenous administration of 0.03 mmol/kg dose the mean half-life of the distribution phase ($t_{1/2}\alpha$) was 0.48 ± 0.11 hours and the volume of distribution at steady state was 148 ± 16 ml/kg, roughly equivalent to that of extracellular fluid. Plasma protein binding was in a range 80% to 87% for up to the first 4 hours after injection.

Biotransformation

The results from various evaluations of plasma and urine samples indicated that gadofosveset does not undergo measurable metabolism.

Elimination

In healthy volunteers, gadofosveset was predominantly eliminated in the urine with 84% (range 79 – 94%) of the injected dose (0.03 mmol/kg) excreted in the urine in 14 days. Ninety-four percent (94%) of the urinary excretion occurred in the first 72 hours. A small portion of gadofosveset dose was recovered in the faeces (4.7%, range 1.1 – 9.3%), indicating a minor role of biliary excretion in the disposition of gadofosveset. After intravenous administration of 0.03 mmol/kg dose renal clearance (5.51 ± 0.85 ml/h/kg) and total clearance (6.57 ± 0.97 ml/h/kg) were similar, and mean terminal elimination half-life was 18.5 ± 3.0 hours.

Characteristics in patients

Renal impairment

In patients with moderate to severe renal impairment the half-life is markedly prolonged and the AUC increased by 2-3fold.

Hemodialysis patients

Gadofosveset can be removed from the body by hemodialysis. After bolus intravenous administration of 0.05 mmol/kg dose in patients requiring three times a week haemodialysis using high-flux filter, at the end of third dialysis session, the plasma concentration had declined to less than 15 % of the Cmax. During the dialysis sessions the mean half-life of plasma concentration decline was in the range 5-6 hours. The mean dialysis clearance was between the range of 16-32 ml/h/kg. The high-flux dialysis filter was more efficient compared to the low-flux filter, therefore, use of a high-flux dialysis filter is recommended.

Hepatic impairment

Plasma pharmacokinetics and protein binding of gadofosveset were not significantly influenced by moderate hepatic impairment (Child Pugh B). A slight decrease in faecal elimination of gadofosveset was seen for the hepatic impaired subjects (2.7%) compared to normal subjects (4.8%). In one subject with moderate hepatic impairment and abnormally low serum albumin, total clearance and half-life of gadofosveset was indicative of faster clearance compared to subjects with moderate hepatic impairment and normal serum albumin levels.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, acute toxicity, local tolerance, contact-sensitising potential, and genotoxicity.

No carcinogenicity studies were performed.

Repeated dose toxicity
Repeated-dose toxicity studies revealed vacuolation of the tubular cells of the kidneys, with strong evidence for reversibility of the effect. No functional impairment was observed and electron microscopic investigations of the rat kidneys indicated that the observed vacuolation was primarily a storage phenomenon. Effects were of higher severity in rats than in monkeys, probably because of the higher renal clearance in rats. In monkeys, no renal effects were observed after single use even at a dose 100-times higher than the clinical dose.

Reproduction toxicity
In rabbits, an increased number of early resorptions and a slight but significant increase in the number of foetal anomalies (in particular hydrocephalus and malrotated limbs) were observed at doses at which no or slight maternal toxicity was observed (exposure was 2 and 5 times the expected human exposure, respectively). In an animal study, it was shown that less than 1% of the dose of gadofosveset administered enters breast milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Fosveset
Sodium hydroxide
Hydrochloric acid
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years.
After first opening, the medicinal product should be used immediately.

6.4 Special precautions for storage

Keep the injection vial in the outer carton in order to protect from light.

6.5 Nature and contents of container

10 and 20 ml colourless type I glass vials with chloro- or bromobutyl elastomer stopper and aluminium bordered cap (plastic disk).
Pack sizes:
1, 5, or 10 vials × 10 ml (in 10-ml glass vial)
1, 5, or 10 vials × 15 ml (in 20-ml glass vial)
1, 5, or 10 vials × 20 ml (in 20-ml glass vial)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

This medicinal product is supplied ready to use as a clear, colourless to pale yellow aqueous solution. Contrast media should not be used in case of severe discolouration, the occurrence of particulate matter, or defective container.
Vials are not intended for the withdrawal of multiple doses. The rubber stopper should never be pierced more than once. After withdrawal of the solution from the vial, it should be used immediately.

The peel-off tracking label included with the vials should be stuck onto patient record to enable accurate recording of the gadolinium contrast agent used.

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

7. MARKETING AUTHORISATION HOLDER

TMC Pharma Services Ltd., Finchampstead, Berkshire RG40 4LJ, UK

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/313/001 - 009

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 3 October 2005
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Bayer Schering Pharma AG
D – 13342 Berlin
Germany

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to restricted medicinal prescription (See Annex 1: Summary of Product Characteristics, section 4.2)

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

- **OTHER CONDITIONS**

Risk Management Plan
The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 2.0 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, any updated RMP should be submitted at the same time as the following Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:
- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency

PSURs
The MAH will continue to submit yearly PSURs unless otherwise specified by the CHMP.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER PACKAGING - BOX

1. NAME OF THE MEDICINAL PRODUCT

Ablavar 0.25 mmol/ml solution for injection

Gadofosveset

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml Ablavar solution for injection contains 244 mg (0.25 mmol) gadofosveset trisodium equivalent to 227 mg gadofosveset..
Each vial of 10 ml solution contains 2.44 g (2.50 mmol) of gadofosveset trisodium equivalent to 2.27g gadofosveset.
Each vial of 15 ml solution contains 3.66 g (3.75 mmol) of gadofosveset trisodium equivalent to 3.41g gadofosveset .
Each vial of 20 ml solution contains 4.88 g (5.00 mmol) of gadofosveset trisodium equivalent to 4.54g gadofosveset.

3. LIST OF EXCIPIENTS

Excipients: fosveset, sodium hydroxide, hydrochloric acid, water for injections
See the leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 vial
5 vials
10 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use and diagnostic use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

The peel-off tracking label included with the vials should have the dose recorded on it and be stuck onto patient record

8. EXPIRY DATE

EXP
After first opening use immediately.

9. SPECIAL STORAGE CONDITIONS

Keep the injection vial in the outer carton in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard any unused medium after each investigation.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

TMC Pharma Services Ltd., Finchampstead, Berkshire, RG40 4LJ, UK

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/313/001 Ablavar-0.25 mmol/ml-Solution for injection-Intravenous use-Vial (glass)-10 ml-1 vial
EU/1/05/313/002 Ablavar-0.25 mmol/ml-Solution for injection-Intravenous use-Vial (glass)-10ml-5 vials
EU/1/05/313/003 Ablavar-0.25 mmol/ml-Solution for injection-Intravenous use-Vial (glass)-10ml-10 vials
EU/1/05/313/004 Ablavar-0.25 mmol/ml-Solution for injection-Intravenous use-Vial (glass)-15ml-1 vial
EU/1/05/313/005 Ablavar-0.25 mmol/ml-Solution for injection-Intravenous use-Vial (glass)-15ml-5 vials
EU/1/05/313/006 Ablavar-0.25 mmol/ml-Solution for injection-Intravenous use-Vial (glass)-15ml-10 vials
EU/1/05/313/007 Ablavar-0.25 mmol/ml-Solution for injection-Intravenous use-Vial (glass)-20ml-1 vial
EU/1/05/313/008 Ablavar-0.25 mmol/ml-Solution for injection-Intravenous use-Vial (glass)-20ml-5 vials
EU/1/05/313/009 Ablavar-0.25 mmol/ml-Solution for injection-Intravenous use-Vial (glass)-20ml-10 vials

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Vial 15 and 20ml

1. NAME OF THE MEDICINAL PRODUCT

Ablavar 0.25 mmol/ml solution for intravenous use

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml Ablavar solution contains 244 mg (0.25 mmol) gadofosveset trisodium equivalent to 227 mg of gadofosveset.

Each vial of 15 ml solution contains 3.66 g (3.75 mmol) of gadofosveset trisodium equivalent to 3.41 g of gadofosveset.
Each vial of 20 ml solution contains 4.88 g (5.00 mmol) of gadofosveset trisodium equivalent to 4.54 g of gadofosveset.

3. LIST OF EXCIPIENTS

Fosveset
Sodium hydroxide
Hydrochloric acid
Water for injection

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection.
15 ml
20 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Ablavar should be administered as a single intravenous bolus injection, manually, or by magnetic resonance injector over a period of time up to 30 seconds followed by a 25-30 ml normal saline flush.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

After first opening use immediately

9. SPECIAL STORAGE CONDITIONS

Keep the injection vial in the outer carton in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard any unused medium after each investigation.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

TMC Pharma Services Ltd., Finchampstead, Berkshire, RG40 4LJ, UK

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/313/004 Ablavar-0.25 mmol/ml-Solution for injection-Intravenous use-Vial (glass)-15ml-1 vial
EU/1/05/313/005 Ablavar-0.25 mmol/ml-Solution for injection-Intravenous use-Vial (glass)-15ml-5 vials
EU/1/05/313/006 Ablavar-0.25 mmol/ml-Solution for injection-Intravenous use-Vial (glass)-15ml-10 vials
EU/1/05/313/007 Ablavar-0.25 mmol/ml-Solution for injection-Intravenous use-Vial (glass)-20ml-1 vial
EU/1/05/313/008 Ablavar-0.25 mmol/ml-Solution for injection-Intravenous use-Vial (glass)-20ml-5 vials
EU/1/05/313/009 Ablavar-0.25 mmol/ml-Solution for injection-Intravenous use-Vial (glass)-20ml-10 vials

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

10 ML

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Ablavar 0.25 mmol/ml solution for injection
Gadofosveset
Intravenous use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use

3. EXPIRY DATE

EXP
After first opening: the medicinal product should be used immediately.

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 ml

6. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Ablavar 0.25 mmol/ml solution for injection
Gadofosveset

Read all of this leaflet carefully before you are given this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask the doctor giving you Ablavar (the radiologist) or the hospital/MRI-centre personnel
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or radiologist.

In this leaflet:

1. WHAT ABLAVAR IS AND WHAT IT IS USED FOR

Ablavar is an injectable contrast medium for making a diagnostic image of the body's blood vessels in the abdomen or limb clearer. It is for use in adults only.

Ablavar is for diagnostic use only. It is used to help detect changes in the blood vessels which are known or suspected to be abnormal. The diagnosis can be made with greater accuracy than without using this medicine.

This medicine, a contrast agent with magnetic properties, helps to visualise the passage of blood through the vessels by brightening the blood for an extended period. This medicine is used together with an imaging technique called magnetic resonance imaging (MRI).

If you have any questions or are not sure about something, ask the doctor or MRI-centre personnel.

2. BEFORE YOU ARE GIVEN ABLAVAR

Do not use Ablavar
You must not be given Ablavar if you are allergic (hypersensitive) to gadofosveset or any of the other ingredients of this medicine (see section 6 of this leaflet).

Take special care with Ablavar
You will need special medical attention if allergy-like reactions occur. Tell your doctor immediately if you notice itching, a feeling of mild swelling in your throat or tongue, which might be a first sign of some allergy-like reaction. Your doctor will be mindful of other signs as well.

Tell your doctor if:
- **you have a cardiac pacemaker** or **any ferromagnetic implant or a metallic stent in your body**
- **you suffer from allergy (e.g. hay fever, hives) or asthma**
- **you had any reactions to previous injections of contrast media**
- **your kidneys do not work properly**
- **you have recently had, or soon expect to have, a liver transplant**

If any of these apply to you, your doctor will decide whether the intended examination is possible or not.

Your doctor may decide to take a blood test to check how well your kidneys are working before making the decision to use this medicine, especially if you are 65 years of age or older.

Children or adolescents under 18 years
This medicine should not be used in children or adolescents under 18 year of age.

Using other medicines
Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.
Your doctor will advise you what to do.

Pregnancy and breast-feeding
Ask your doctor for advice before taking any medicine.
You must tell your doctor if you think you are or might become pregnant.
It has not been proven that this medicine is safe to use during pregnancy. Your doctor or radiologist will consider this with you. This medicine must not be used in pregnant women unless strictly necessary.
Tell your doctor if you are breast-feeding or about to start breast-feeding. Your doctor will discuss whether you should continue breast-feeding or interrupt breast-feeding for a period of 24 hours after you receive this medicine.

Driving and using machines
There are no studies on the effects on the ability to drive and use machines.
This medicine can uncommonly cause dizziness or vision problems. If you get these effects you should not drive or use machines

Important information about some of the ingredients of Ablavar
This medicine contains 6.3 mmol sodium (or 145 mg) per dose. To be taken into consideration by patients on a controlled sodium diet.

3. HOW TO USE ABLAVAR

You will be asked to lie down on the MRI scanning bed. Scanning may start immediately after the Ablavar injection. After the injection you will be observed in case there might be any initial side effects.

<u>The usual dose</u>

The dose of this medicine varies depending on your weight. The doctor will decide how much medicine is needed for your examination. The dose is: 0.12 ml/kg body weight (equivalent to 0.03 mmol/kg of body weight).
Further information regarding the administration and handling of this medicine is given at the end of the leaflet.

<u>Method of administration</u>
This medicine is given as a rapid injection into a vein by a medical professional only. The usual injection site is the back of your hand or just in front of your elbow.

<u>Dose in special patient groups</u>

The use of this medicine is not recommended in patients with severe kidney problems and patients who have recently had, or soon expect to have, a liver transplant. However if use is required you should only receive one dose of this medicine during a scan and you should not receive a second injection for at least 7 days.

Elderly
It is not necessary to adjust your dose if you are 65 years of age or older but you may have a blood test to check how well your kidneys are working.

If you receive more Ablavar than you should have received:
If you think you may have had an overdose talk to your doctor immediately. Your doctor will treat you should overdose occur. If necessary, this medicine can be removed from the body by haemodialysis using high-flux filters.

If you have any further questions on the use of this medicine, please consult your doctor, the radiologist or MRI-centre personnel.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Ablavar can cause side effects, although not everybody gets them.

If you have any of the following symptoms you should tell a doctor immediately:

Ablavar can be associated with allergy-like reactions (anaphylactoid / hypersensitivity reactions) characterised by:-

- skin reactions, (cutaneous reactions)
- breathing difficulties and/or heart/ pulse-rate/ blood pressure disturbances which may lead to consciousness disorders respiratory reactions, and /or cardiovascular manifestations which may lead to shock).

Most of the side effects were mild to moderate in intensity. Most of the side effects (80%) occurred within 2 hours. Delayed effects (after hours to days) may occur.

Below are listed the reported/experienced side effects by frequency): Very common: affects more than 1 user in 10
Common: affects 1 to 10 users in 100
Uncommon: affects 1 to 10 users in 1,000
Rare: affects 1 to 10 users in 10,000
Very rare: affects less than 1 user in 10,000
Not known: frequency cannot be estimated from the available data.

The following is a list of side-effects observed in clinical trials:

Common:
Headache
Tingling or numbness of the hands or feet
Change of taste in mouth
Burning sensation
Warm feeling (vasodilatation) including flushing
Nausea
Itching
Feeling cold.

Uncommon:

Runny nose
Sore throat
Feeling anxious
Confusion
Allergy-like reaction
Impairment of taste
Dizziness
Shaking
Decreased feeling or sensitivity (especially of the skin)
Sense of smell distortion
Involuntary muscle contractions
Abnormal vision
Tear secretion increased
Disturbed nerve signals in the heart (first degree)
Fast heart beat
Problems with the electrical rhythm of the heart (long QT)
High blood pressure
Swelling and clotting in a vein
Coldness in the fingers and toes
Shortness of breath
Cough
Vomiting
Attempting to vomit
Diarrhoea
Stomach discomfort
Stomach pain
Pain in the throat
Indigestion
Dry mouth
Wind
Decreased feeling or sensitivity of the lips
Increased production of saliva
Anal itching
Hives
Reddening of the skin
Rash
Sweating increased
Muscle cramps
Muscle spasms
Neck pain
Pain in arms or legs
Genital itching
Genital burning sensation
Pain
Chest pain
Tiredness
Feeling abnormal
Groin pain
Feeling hot
Injection site pain
Injection site coldness
Reddening of skin at the injection site
Blood in the urine
Proteins in the urine
Sugar in the urine
High sugar levels in the blood

Low calcium levels in the blood
Unusual amount of salt in the body.

Rare:
Inflammation of the skin
Urinary tract infection
Abnormal dreams
Seeing, feeling or hearing things that is not there
Appetite decreased
Eyesight disorders
Abnormal eye sensation
Ear pain
Heartbeat irregularity/disturbed heart-chamber contractions (cardiac flutter, atrial fibrillation)
problems with the electrical rhythm of the heart (ST segment/T wave abnormalities)
Chest pain
Slow heart beat
Palpitations
Thickening of the arteries due to cholesterol deposits
Low blood pressure
Shallow breathing
Face swelling
Sweatiness
Muscle tightness
Sensation of heaviness
Urge to pass urine
Kidney pain
Passing urine frequently
Lower abdominal pain
Fever
Shivering
Weakness
Chest pressure sensation
Injection site blood clot
Injection site bruising
Injection site inflammation
Injection site burning
Fluid escaping from injection site into the surrounding tissue
Injection site bleeding
Injection site itching
Sensation of pressure
Phantom pain in the arms or legs
Low or high potassium levels in the blood
High sodium levels in the blood.

There have been reports of nephrogenic systemic fibrosis (which causes hardening of the skin and may affect also soft tissue and internal organs) associated with use of other gadolinium-containing contrast agents.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or radiologist.

5. HOW TO STORE ABLAVAR

Keep out of the reach and sight of children.

Do not use this medicine after the expiry date which is stated on the label after EXP. The expiry date refers to the last day of the month.

Keep the injection vial in its outer carton in order to protect from light.

After first opening, the medicine should be used immediately.

Do not use this medicine if you notice severe discolouration, the occurrence of particulate matter or a defective container.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Ablavar contains

- The active substance is gadofosveset. 1 ml contains 227 mg gadofosveset equivalent to 244 mg/ml (0.25 mmol/millilitre) gadofosveset trisodium.
  10 ml solution contains 2.27 g, 15 ml solution contains 3.41g and 20 ml solution contains 4.54 g of gadofosveset in a vial.

- The other ingredients are fosveset, sodium hydroxide, hydrochloric acid, and water for injections.

What Ablavar looks like and contents of the pack

Ablavar is a clear, colourless to pale yellow liquid supplied in a rubber stoppered glass vial, with an aluminium seal, in individual cartons. The contents of the packs are:

1, 5 or 10 injection vials with 10 ml solution for injection (in 10-ml glass vial)
1, 5 or 10 injection vials with 15 ml solution for injection (in 20-ml glass vial)
1, 5 or 10 injection vials with 20 ml solution for injection (in 20-ml glass vial)
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

TMC Pharma Services Ltd., Finchampstead, Berkshire RG40 4LJ , UK
Tel:01252 842255

This leaflet was last approved in

Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu
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The following information is intended for medical or healthcare professionals only:

Prior to administration of Ablavar it is recommended that all patients are screened for renal dysfunction by obtaining laboratory tests.

There have been reports of nephrogenic systemic fibrosis (NSF) associated with use of some gadolinium-containing contrast agents in patients with acute or chronic severe renal impairment (GFR< 30 ml/min /1.73 m^2). Patients undergoing liver transplantation are at particular risk since the

incidence of acute renal failure is high in this group. As there is a possibility that NSF may occur with Ablavar, it should therefore be avoided in patients with severe renal impairment and in patients in the perioperative liver transplantation period unless the diagnostic information is essential and not available with non-contrast enhanced MRI. If use of Ablavar cannot be avoided, the dose should not exceed 0.03 mmol/kg body weight. More than one dose should not be used during a scan. Because of the lack of information on repeated administration, Ablavar injections should not be repeated unless the interval between injections is at least 7 days.

As the renal clearance of gadofosveset may be impaired in the elderly, it is particularly important to screen patients aged 65 years and older for renal dysfunction.

Haemodialysis shortly after Ablavar administration may be useful at removing Ablavar from the body. There is no evidence to support the initiation of haemodialysis for prevention or treatment of NSF in patients not already undergoing haemodialysis.

Ablavar should not be used during pregnancy unless the clinical condition of the woman requires use of gadofosveset.

Continuing breast feeding or discontinuing Ablavar for a period of 24 hours after administration, should be at the discretion of the doctor and lactating mother.

The peel-off tracking label included on the vials should be stuck onto the patient record to enable accurate recording of the gadolinium contrast agent used. The dose used should also be recorded.

Ablavar is supplied ready to use as a clear, colourless to pale yellow aqueous solution.
Contrast media should not be used in case of severe discolouration, the occurrence of particulate matter, or defective container.

Vials containing Ablavar are not intended for the withdrawal of multiple doses. The rubber stopper should never be pierced more than once. After withdrawal of the solution from the vial, this medicinal product should be used immediately.

Any remaining solution not used in one examination must be discarded.