PARAMAGNETIC CONTRAST AGENT IN MR STUDY OF CEREBRAL GLIOMAS

DOTAREM 0.5 mmol/mL, solution for injection. **Composition:** For 100 mL of solution: active ingredient: Gadoteric Acid 27.932 g corresponding to: DOTA 20.246 g corresponding to gadolinium oxide 9.062 g. **Indications (*):** Medicinal product for diagnostic use only: Magnetic Resonance Imaging for cerebral and spinal disease, diseases of the vertebral column, and other whole-body pathologies (including angiography). **Posology and method of administration:** The recommended dose is 0.1 mmol/kg, i.e. 0.2 mL/kg in adults and children. In angiography, depending on the results of the examination being performed, a second injection may be administered during the same session if necessary. Angiography with Gadoteric acid is not recommended in children (0-18 years). In Encephalic and spinal MRI, in some exceptional cases, as in the confirmation of isolated metastases or the detection of leptomeningeal tumours, a second injection of 0.2 mmol/kg may improve tumor characterisation and facilitate therapeutic decision making. For patients with impaired renal function and paediatric population (0-18 years) more than one dose should not be used during a scan, injections should not be expected unless the interval between injections is at least 7 days. The product must be administered by strict intravenous injection. Depending on the amount of gadoteric acid to be given to the child, it is preferable to use gadoteric acid vials with a single use syringe of a volume adapted to this amount in order to have a better precision of the injected volume. In neonates and infants the required dose should be administered by hand. **Contraindications:** Hypersensitivity to gadoteric acid, to meglumine or to any medicinal products containing gadolinium. **Special warnings and precautions for use:** Dotarem must not be administered by subarachnoid (or epidural) injection. The usual precaution measures for MR examination should be taken such as exclusion of patients with pacemakers, ferromagnetic vascular clips, infusion pumps, nerve stimulators, cochlear implants or suspected intraorganic metallic foreign bodies, particularly in the eye. **General particulars corresponding to all gadolinium contrast agents:** All gadolinium based contrast media can cause minor or major hypersensitivity reactions that can be life-threatening. These can occur immediately (within 60 minutes) or be delayed (within 7 days) and are often unpredictable. Because of the risk of major reactions, emergency resuscitation equipment should be available for immediate use. Hypersensitivity reactions can be aggravated in patients on betablockers and particularly in the presence of bronchial asthma. These patients may be refractory to standard treatment of hypersensitivity reactions with beta agonists. Impaired renal function. Prior to administration of gadoteric acid, 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 severe renal impairment (GFR < 30 ml/min/1.73 m²). As there is a possibility that NSF may occur with Dotarem, it should only be used in these patients after careful consideration. CNS disorders: As with other contrast agents containing gadolinium, special precautions should be taken in patients with a low seizure threshold. Precautionary measures, e.g. dose monitoring, should be taken. All equipment and drugs necessary to counter any convulsions which may occur must be made ready for use beforehand. **Interactions with other medicinal products and other forms of interaction:** No interactions with other medicinal products have been observed. Formal drug interaction studies have not been carried out. **Fertility, pregnancy and lactation:** Gadoteric acid should not be used during pregnancy unless the clinical condition of the woman requires use of gadoteric acid. Continuing or discontinuing breast feeding for a period of 24 hours after administration of gadoteric acid, should be at the discretion of the doctor and lactating mother. **Effects on ability to drive and use machines:** No studies on the effects on the ability to drive and use machines have been performed. Ambulant patients while driving vehicles or operating machinery should take into account that nausea may incidentally occur. **Undesirable effects:** Uncommon (≥ 1/1000 to < 1/100): hypersensitivity, headache, dysgeusia, dizziness, somnolence, paraesthesia (including burning sensation), hypotension, hypertension, nausea, abdominal pain, rash, feeling hot, feeling cold, asthenia, injection site reactions (extravasation, pain, discomfort, oedema, inflammation, coldness). Rare (≥ 1/10 000 to < 1/1 000): anxiety, presyncope, eyelid edema, palpitations, sneezing, throat tightness, vomiting, diarrhea, salivary hypersecretion, Urticaria, pruritis, hyperhidrosis, chest pain, chills. Very rare (< 1/10 000): anaphylactic reaction, anaphylactoid reaction, agitation, coma, convulsion, syncope, tremor, parosmia, conjunctivitis, ocular hyperaemia, vision blurred, lacrimation increased, tachycardia, cardiac arrest, arrhythmia, bradycardia, flushing, pallor, vasodilatation, hot flush, cough, dyspnoea, nasal congestion, respiratory arrest, bronchospasm, throat irritation, laryngospasm, pharyngeal oedema, dry throat, pulmonary oedema, erythema, angioedema, eczema, muscle cramps, muscular weakness, back pain, arthralgia, malaise, chest discomfort, pyrexia, face oedema, injection site necrosis (in case of extravasation), phlebitis superficial, decreased oxygen saturation, Not known : nephrogenic systemic fibrosis. **Overdose:** Gadoteric acid can be removed by haemodialysis. However there is no evidence that haemodialysis is suitable for prevention of nephrogenic systemic fibrosis. **Please note:** The peel-off tracking label on the vials or syringes should be stuck onto the patient record to enable accurate recording of the gadolinium contrast agent used. The dose used should also be recorded. If electronic patient records are used, the name of the product, the batch number and the dose should be entered into the patient record. **Pharmacological properties:** Pharmacotherapeutic group: paramagnetic contrast media for MRI, ATC code: V08CA02. **Presentation (*):** 5, 10, 15, 20, 60 & 100 mL in vial (glass) and 10, 15 & 20 mL in a prefilled syringe (glass). **Marketing authorization holder: (*) Information:** Guerbet - BP 57400 - F-95943 Roissy CdG cedex – FRANCE. Tel: 33 (0) 1 45 91 50 00. **Date of revision of this document:** September 2016.
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#3
MRI PROTOCOLS

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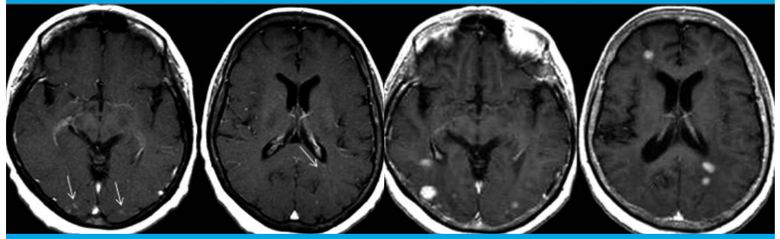

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INTRODUCTION

The diagnosis of a cerebral tumor includes the following steps: a) detection; b) characterization and malignancy grading; c) assessment of extension; d) differential diagnosis; e) post-therapeutic control.

a) DETECTION

Magnetic Resonance (MR) imaging allows to detect the majority of cerebral neoplastic lesions as they induce both brain signal and morphology changes (in several sequences), so it may not be necessary to inject intravenously (IV) a paramagnetic contrast medium. T2-weighted (w) and FLAIR sequences are the most sensitive for lesion detection and for peri-lesional edema evaluation. On the contrary, for the assessment of small cerebral metastases, IV contrast agent injection is always needed, the lesions appearing as enhancing areas [1].

In most cases, standard MR protocols allow to determine the intra- or extra-cerebral location of the lesion, based on its anatomical relationship with adjacent cerebral structures (brain tissues, cortical vessels, etc). The contrast-enhanced (CE) MR study evaluates the relationship between the neoplastic lesion and the dura matter and its possible infiltration [2].

b) CHARACTERIZATION AND MALIGNANCY GRADING

Structural MR studies allow to identify the macroscopic features of the lesions and to assess their different appearance (cystic, necrotic, hemorrhagic or calcified).
Morphological features are useful criteria for tumor grading. Most low grade gliomas display a homogeneous pattern [3A] whereas for high grade gliomas a more heterogeneous appearance may observed: high cellularity results in T2 and FLAIR hypointensity, whereas necrosis generates T1 hypointensity, variable FLAIR and T2 hyperintensity [4A].

The CE-MR study provides important information about the grades of intracerebral tumors because signal enhancement correlates with the degree of blood brain barrier (BBB) disruption and with the grade of lesion malignancy. Lack of tumor enhancement suggests low grade glioma [3B], whereas presence of tumor enhancement suggests high grade glioma [4B]. However, there are some exceptions: low grade tumors, such as pilocytic astrocytomas, xantoastrocytomas and giant cellular subependymal astrocytomas, show intense signal enhancement in CE-MR studies [5]. On the contrary, it is known that in some cases anaplastic gliomas may appear as non-enhancing lesions. Therefore, even if neoplastic enhancement does not necessarily mean high grade of malignancy, a lack of enhancement is not necessarily associated with a low degree of tumor malignancy.

MR perfusion studies play a fundamental role in tumor grading because they allow to assess the degree of neoangiogenesis, which correlates with tumor malignancy.
The most frequently used MR technique in perfusion studies is Dynamic Susceptibility Contrast (DSC). This technique uses the gadolinium T2* effect, that correlates the signal drop to the Cerebral Blood Volume (CBV). Recently, T1-based techniques have been introduced, which allow both CBV and permeability evaluation.
Practically, if a tumor does not show any enhancement in a CE-MR study, but shows an increase in CBV in an MR perfusion study, the most probable diagnosis is of high grade tumor malignancy [6].

c) ASSESSMENT OF EXTENSION

The tumor growth within the cerebral tissue may be either «expanding» or «infiltrative». In tumors with «expanding growth», like pilocytic astrocytomas, the increase of the lesional area depicted by MR is consistent with real tumor extension. On the other hand, tumors with «infiltrative growth» do not show a true boundary at the periphery of the lesion because the edematous peri-lesional area contains tumor cells, and the enhancing neoplastic area does not systematically coincide with the area of tumor extension. This area is characterized by a high level of angiogenesis and BBB disruption [7]. Frequently, more than one small area is enhanced in a single lesion, which does not mean that the lesion is multifocal [8]. The MR perfusion study is especially useful to demonstrate the infiltrative pattern of the lesions and it helps to differentiate them from areas of edema and gliosis.

d) DIFFERENTIAL DIAGNOSIS

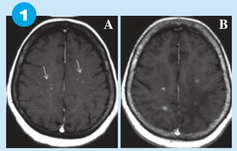
The MR standard study allows, in most cases, the identification of pathological abnormalities in terms of signal and morphology. Nevertheless, non-neoplastic lesions must be ruled out (e.g. stroke, multiple sclerosis, abscess, etc).

MR diffusion-weighted sequences may help in establishing a differential diagnosis between pyogenic abscesses and brain tumors (characterized by restricted diffusion). The IV injection of gadolinium-based contrast agent shows an «irregular ring enhancement» pattern in case of tumor, a «regular ring enhancement» pattern in case of abscess, and an «incomplete ring enhancement» pattern in case of pseudo-tumoral inflammatory lesion [9].

MR perfusion studies may be useful in ambiguous cases: neoplastic lesions show high relative CBV (rCBV) compared to the healthy brain tissue, whereas infectious-inflammatory lesions do not show this finding. Moreover, a differential diagnosis may be established between glioblastomas and metastases, based on the perfusion of the peri-tumoral area: in glioblastomas, high rCBV values are observed at the equilibrium phase, both in the pathological enhanced area and in the surrounding area of the tumor [10]; in metastases rCBV values are increased inside the lesion but not in the peri-lesional tissue where there is only edema [11]. MR perfusion studies of glioblastomas allow to differentiate between tumor subtypes based on rCBV values: each subtype is associated with a different prognosis. Finally, a correlation between rCBV values and the genetic profile of glioblastomas was recently demonstrated.

e) POST-THERAPEUTIC FOLLOW-UP

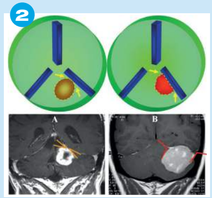
Patients with brain tumors who were treated surgically or with radiochemotherapy, have been traditionally checked by MR studies with and without contrast medium injection, and according to the Mc Donald criteria tumor grade was based on signal enhancement. However, it is not unusual to observe contrast enhancement even in neoplastic lesions which respond to therapy ("pseudo-progression"). On the other hand, a growing lesion may not show any pathological enhancement ("pseudo-answer"). Therefore, MR perfusion studies are mandatory for post-surgical control of brain tumors. They provide accurate information about the residual tumor activity and are useful to establish a differential diagnosis between tumor relapse and radionecrosis [12].



1 **Cerebral metastases**
MR study. Axial T1-w images following IV injection of contrast medium.

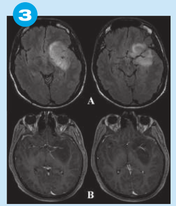
(A) Multiple pathologically enhanced punctuate areas in the white matter of both cerebral hemispheres (arrows).

(B) Three months later, the MR control study shows evident enlargement of the enhanced pathological areas.



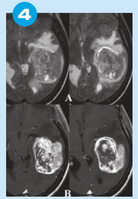
2 **Cerebellar metastasis (A) and meningioma (B)**
MR study. Coronal T1-w images following IV injection of contrast medium.

The posterior cranial fossa shows expansive processes, close to the tentorium: in **B** (meningioma), there is a clear meningeal expansion, with a higher degree angle in comparison to **A** (metastasis).



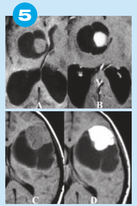
3 **Left fronto-temporal cerebral glioma**
MR study. Axial FLAIR **(A)** and T1-w post-contrast medium **(B)** MR images.

FLAIR sequence shows a glioma as an area of homogeneous hyperintensity **(A)**, without enhancement after IV contrast medium injection on T1-w images **(B)**.

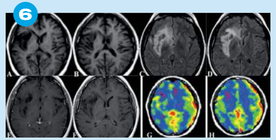


4 **Left temporo-parietal glioblastoma**
MR study. Axial T2-w **(A)** and T1-w images after IV injection of contrast medium **(B)**. The glioblastoma shows a patchy pattern, with hypointense areas on T2-w images due to hypercellularity, and hyperintense areas due to both necrosis and pathological vessels **(A)**.

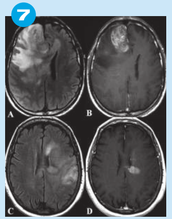
Contrast-enhanced T1-w images **(B)** show intense and patchy tumor enhancement.



5 **Pilocytic astrocytoma (A, B) and pleomorphic xantoastrocytoma (C, D)**
MR study. Axial T1-w images before **(A, C)** and after **(B, D)** IV contrast medium injection. The pilocytic astrocytoma appears as a cystic lesion with a solid nodule **(A)** on the tumor wall, homogenously enhancing after IV contrast medium administration **(B)**. The pleomorphic xantoastrocytoma **(C, D)** has a similar pattern, with a more peripheral location.

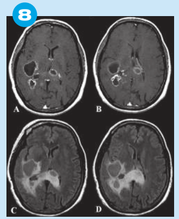


6 **Anaplastic glioma**
MR study. Axial pre-contrast T1-w **(A, B)**, T2-w **(C, D)**, post-contrast T1-w images **(E, F)**, and Dynamic Susceptibility Contrast enhanced (DSC) perfusion images **(G, H)**. Right fronto-insular T1 hypointense **(A, B)** and T2 hyperintense **(C, D)** infiltrative lesion without pathological enhancement after IV contrast medium injection **(E, F)**. The features lead toward the diagnosis of a grade II glioma. However, the MR perfusion study shows a high blood perfusion area in the lesion **(G, H)** characteristic of a higher grade glioma (anaplastic grade III).



7 **Cerebral glioma**
MR axial FLAIR **(A, C)** and post-contrast T1-w images **(B, D)**.
Glial infiltrative lesion located in the right hemisphere **(A, B)**, with controlateral extension through the callosal genu **(A)** into the fronto-parietal left side. The glioma spreads from the cortex to the deep periventricular white matter **(C)**.

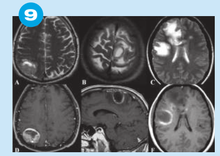
Areas of pathological enhancement after IV contrast agent injection **(B, D)** correlate with areas with BBB disruption and with high level of neoangiogenesis, but do not overlap with the real tumor extension.



8 **Glioblastoma**
MR axial T1-w post-contrast **(A, B)** and FLAIR **(C, D)** images.

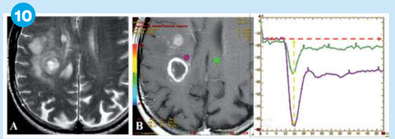
Presence of multiple enhancing pathological areas **(A, B)**, where BBB is disrupted and neoangiogenesis is highly developed.

Figures **C** and **D** demonstrate that the tumor is a single large glial lesion rather than focally spread multiple lesions.



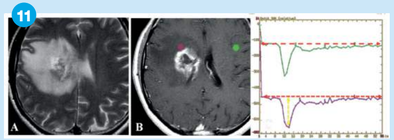
9 **Glioblastoma (A, D), abscess (B, E), and «pseudotumoral» plaque (C, F)** MR axial T2-w **(A, B, C)** and post-contrast T1-w axial **(D, F)** and sagittal **(E)** images.

The figures show lesions with different enhancing features: an «irregular ring» for the glioblastoma **(A, D)**, a «regular ring» for the abscess **(B, E)** and an «incomplete ring» in case of giant demyelinating plaque **(C, F)**.



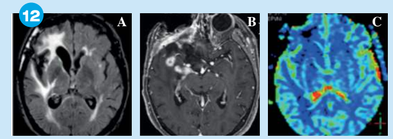
10 **Glioblastoma**
MR axial T2-w **(A)** and post-contrast T1-w **(B)** images.

The Dynamic Susceptibility Contrast (DSC)-enhanced T2*-w signal intensity-time curves shown on the graph demonstrate a quantification of the cerebral blood flow at the boundary of the glioblastoma enhancing area: these curves display a high T2* drop **(C)** in the vicinity of the tumor with respect to the controlateral area, related to an elevated blood perfusion.



11 **Cerebral metastasis**
MR axial T2-w **(A)** and post-contrast T1-w **(B)** images.

Dynamic Susceptibility Contrast (DSC)-enhanced MR T2*-w perfusion signal intensity-time curves are shown on the graph: the cerebral blood flow curve measured at the boundary of the enhanced area of the metastasis shows a similar pattern as in the controlateral side, which is interpreted as a normal blood perfusion **(C)**.



12 **Radionecrosis**
MR axial FLAIR **(A)**, post-contrast T1-w **(B)**, and Dynamic Susceptibility Contrast (DSC)-enhanced T2*-w MR perfusion **(C)** images.

The MR follow-up of post-surgery and post-radiochemotherapy shows a large pathological enhancement in the right fronto-temporal region **(A)** with diffuse and patchy post-contrast enhancement **(B)** suggesting intra-cerebral diffusion of the surgically-treated lesion.

The MR perfusion study **(C)** does not show any evidence of high cerebral blood flow, suggesting a radionecrosis more likely than a relapsing tumor.