1198818 CHN

核准日期：2006年12月
修改日期：2007年8月 2008年7月 2012年7月 2014年12月 2016年4月 2018年1月 2018年7月 2019年6月 2020年11月

GE Healthcare

钆双胺注射液

欧乃影®

钆双胺注射液说明书

请仔细阅读说明书并在医师指导下使用

警告

钆沉积：
线性和大环类含钆对比剂（GBCAs）均会在大脑及其他组织中发生痕量钆沉积。动物实验研究显示在重复使用GBCAs之后，线性GBCAs的沉积量比大环类高。本品为线性GBCA。

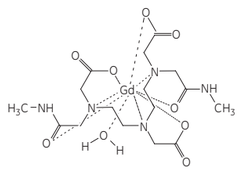
NSF：
含钆对比剂(GBCA)增加了药物清除受损患者的NSF风险。除非诊断信息是必要的，且无法用平扫MRI或其他方式获得，避免在这些患者中使用GBCA。NSF可导致影响皮肤、肌肉和内脏器官的致命的或严重的纤维化。

- 患有以下疾病的患者勿使用欧乃影：
  - 慢性、严重肾病(GFR < 30 mL/min/1.73m^2)，或
  - 急性肾损伤
- 筛查急性肾损伤和其他可能降低肾功能的情况。对于有慢性肾功能减退风险的患者(如年龄超过60岁，高血压或糖尿病)，通过实验室检测评估肾小球滤过率(GFR)。

不要超过推荐剂量使用欧乃影，并在再次给药前留出足够的时间使其从体内消除。

【药品名称】
通用名称：钆双胺注射液
商品名称：欧乃影® (Omniscan®)
英文名称：Gadodiamide Injection
汉语拼音：Gashuang'an Zhusheye

【成份】
本品活性成份为钆双胺，其化学名称为：[5,8-双(羧甲基)11-[2-(甲胺基)-2-氧代乙基]-3-氧代-2,5,8,11-四氮杂癸烷-13-氧代(3-)]钆
化学结构式：



分子式：$C_{16}H_{26}GdN_5O_8$
分子量：573.66
辅料：钙钠二酰胺，氢氧化钠或盐酸调节pH，注射用水。

【性状】
本品为无色或淡黄色澄明液体。
钆双胺注射液是非离子型顺磁性对比剂，它具有下列物化性质：

渗透压克分子浓度(mOsm/kg H_2O) 37℃时	780
粘度(mPa · s) 20℃时	2.8
粘度(mPa · s) 37℃时	1.9
密度(kg/l) 20℃时	1.15
容积克分子驰豫度	
r_1(mM^{-1} · s^{-1})，在20 MHz和37℃时	3.9
r_1(mM^{-1} · s^{-1})，在10 MHz和37℃时	4.6
r_2(mM^{-1} · s^{-1})，在10 MHz和37℃时	5.1
pH	6.0-7.0

钆双胺易溶于水。

【适应症】
静脉注射后，头颅、脊髓和身体一般磁共振成像(MRI)造影。
本品能增强对比，有利于全身不同部位包括中枢神经系统异常结构或病灶的显示。

【规格】
(1) 10ml: 2.87g (2) 15ml: 4.305g (3) 20ml: 5.74g

【用法用量】
病人无需特殊准备。本品必须在使用前才开瓶抽入注射器。一瓶药仅供一名病人使用。一次未用完的药品应丢弃。
静脉内注射，成人及儿童所需剂量须一次静脉注射完成。 为了保证对比剂完全注射，可以用0.9%NaCl注射液冲洗静脉注射用导管。
尽可能使用最低批准剂量。

中枢神经系统
成人和儿童（不包括四周以内的新生儿）的剂量
推荐剂量为按体重每公斤0.1mmol(相当于按体重0.2ml/kg)直至100kg。体重100kg以上者，通常用20ml就足以提供造影诊断所需剂量。

仅适用于成人
对怀疑脑中有转移性疾病的病人，注射剂量为按体重每公斤0.3mmol(相当于按体重0.6ml/kg)直至100kg。体重100kg以上者，通常用60ml就足够了。注射剂量为按体重每公斤0.3mmol(相当于按体重0.6ml/kg)可采用静脉团注。在注射按体重每公斤0.1mmol后进行后，如果扫描图像不明确，第一次注射后的20分钟内，可进行二次团注，剂量为按体重每公斤0.2mmol（相当于按体重0.4ml/kg），具有加和的诊断效果。

全身
成人的剂量
推荐剂量通常为按体重每公斤0.1mmol(相当于按体重0.2ml/kg)或0.3mmol(相当于按体重0.6ml/kg)直至100kg。体重100kg以上者，通常用20ml或60ml就足以提供造影诊断所需剂量。

6月以上儿童的剂量
推荐剂量为按体重每公斤0.1mmol(相当于按体重0.2ml/kg)。

中枢神经系统和全身
造影增强的MRI应在对比剂注射后的较短时间内开始，而此时间则取决于所用脉冲序列和检查方案。在注射后的最初数分钟(此时间取决于病灶或组织的类型)就可见显著的增强。一般增强持续时间为45分钟。T1加权成像序列特别适用于欧乃影的造影增强检查。在所研究的0.15至1.5特斯拉磁场强度范围内，发现相关的影像对比与所用磁场强度无关。

【不良反应】
在临床试验中，大约6%的患者出现了不良反应。钆双胺注射液给药后最常见的自发性不良反应是超敏反应、恶心和呕吐。

曾有肾源性系统纤维化（NSF）病例的报告。肾源性系统纤维化是一种以损害皮肤、肌肉和内脏器官为特征的，影响生命功能、有时也致命的进行性疾病，主要导致皮肤和内部器官中结缔组织增生，使得皮肤变厚、粗糙和僵硬，有时导致残疾性挛缩。

原产国说明书中，报告了以下频率的不良反应（非常常见 ≥1/10；常见(≥1/100, <1/10)；不常见(≥1/1,000, <1/100)；罕见(≥1/10,000, <1/1,000)；非常罕见<1/10,000）。未知（无法根据现有数据估计）

免疫系统疾病
不常见：过敏样皮肤和粘膜反应、超敏反应
未知：速发过敏反应/类速发过敏反应*

精神病类
罕见：焦虑

各类神经系统疾病
常见：头痛
不常见：头晕、异常感觉、一过性味觉倒错
罕见：惊厥、震颤、嗜睡、一过性瞁觉倒错

眼器官疾病
罕见：视觉障碍

心脏器官疾病
未知：心动过速

血管与淋巴管类疾病
不常见：潮红

呼吸系统、胸及纵隔疾病
罕见：呼吸困难、咳嗽
未知：支气管痉挛、呼吸窘迫、咽喉刺激、喷嚏

胃肠系统疾病
常见：恶心
不常见：呕吐、泄泻

皮肤和皮下组织类疾病
不常见：瘙痒症
罕见：水肿包括面肿及血管神经性水肿、荨麻疹、皮疹
未知：肾源性系统纤维化(NSF)、钆相关皮肤斑块

各种肌肉骨骼及结缔组织疾病
罕见：关节痛

肾脏及泌尿系统疾病
罕见：急性肾衰竭

全身性疾病及给药部位各种反应
常见：与注射有关的一过性温热感、冷感或局部压力感、注射部位一过性疼痛感。
罕见：胸痛、发热、寒战性发抖

*不论所给予的剂量及给药途径，可能发生的速发过敏反应/类速发过敏反应可能为休克的初期第一体征。

在欧乃影给药后数小时至数天可能发生迟发性不良反应。

已经在一些患者中观察到一过性血清铁改变，但所有这些患者均无症状。

上市后经验：
由于上市后反应是由样本量不确定的人群自发报告的，因此估计其发生的频率或建立与药物暴露的因果关系并不太可靠。
在上市后使用欧乃影时，发现了以下不良反应：
各类神经系统疾病：由于疏忽而进行鞘内给药可引起惊厥、昏迷、感觉异常和局部麻痹。在有或无抽搐或脑损伤史的患者中，也有在静脉使用（欧乃影）出现惊厥的报道。
全身性病症：肾源性系统纤维化(NSF)。
已有给予含钆对比剂后出现了起病时间和持续时间可变的不良事件的报道，包括疲乏、乏力、疼痛症状，以及神经系统、皮肤系统和肌肉骨骼系统中的异质性症状群。
肾脏及泌尿系统疾病：在已患肾损害的患者中：急性肾功能衰竭、肾损害、血肌酐增加。
皮肤：钆相关皮肤斑块。

【禁忌】
已知对本品组成成分有过敏的病人不得使用。
钆双胺禁用于严重肾损害的患者（GFR<30ml/min/1.73m^2）或急性肾损伤患者，进行过或正在接受肝移植的患者，以及不超过4周的新生儿。

【注意事项】
应谨慎使用GBCAs。在平扫磁共振成像（MRI）不能获得相应精确的诊断信息情况下，可使用GBCAs，尽可能使用最低批准剂量。
所有患者（尤其是60岁以上的患者），在使用含钆对比剂前应通过病史和/或实验室检查来评价其肾功能状况。
由于缺乏重复给药信息，不应重复欧乃影注射，注射间隔至少7天。

钆沉积
当前证据表明，即使是肾功能正常的患者，多次使用GBCAs后，痕量钆可沉积于脑部及其他身体组织中。在人体骨骼中发现的浓度比在皮肤和大脑中发现的浓度高。（研究报道显示）多次使用GBCAs后可引起脑部信号强度增加，特别是在齿状核和苍白球，目前线性GBCAs相关的平扫T1加权图像的信号增强报道较多，大环类GBCAs报道较少。动物试验研究显示在重复使用线性GBCAs之后钆沉积量高于重复使用大环类。
脑部钆沉积的临床意义尚不清楚。
在肾功能正常的病人中，包括钆相关的斑块在内的皮肤病理改变的报告很少。已收到肾功能正常患者涉及多个器官系统的不良事件的上市后报告。尚未确定与钆沉积的因果关系。这些事件包括疲乏、乏力、疼痛症状，以及神经系统、皮肤系统和肌肉骨骼系统中的异质性症状群。
虽然在肾功能正常的患者中尚未确定钆沉积的临床后果，但某些患者的风险可能较高。此类患者包括需要终身多次剂量的患者、孕妇和儿科患者。为了最大限度地降低钆沉积相关的潜在风险，必须严格按照适应症和批准剂量使用欧乃影，推荐使用满足诊断的最低批准剂量并在重复给药前进行仔细的获益风险评估和患者知情沟通。
肾损害与肝移植患者：有报告在严重肾损害的患者（GFR<30ml/min/1.73m^2），以及进行过或正在接受肝移植的患者中，发生与使用钆双胺及其他含钆对比剂有关的肾源性系统纤维化（NSF）。 因此在这些患者中不应该使用欧乃影（见禁忌部分）。在中度肾损害的患者（GFR<60ml/min/1.73m^2）中使用钆双胺，也有发生肾源性系统纤维化（NSF）的病例报告。欧乃影应慎用于这些患者。
钆双胺是可透析的。接受血液透析的患者，使用欧乃影后立即进行透析可能有助于欧乃影的体内清除。没有证据支持无需进行血液透析的患者可以用血液透析来预防或治疗NSF。

超敏反应
应考虑某些反应发生的可能性，包括严重的、危及生命的、致命的、类速发过敏反应或心血管反应或其他特异质反应，特别是对那些已知临床超敏反应或有哮喘病史或其他的过敏性呼吸系统疾病的病人。在欧乃影给药之前，接受过复苏技术和复苏设备培训的人员应到场。如果出现超敏反应，立即停止注射欧乃影并开始适当的治疗。在注射欧乃影期间或之后数小时内，密切观察患者，特别是那些有药物反应史、哮喘、过敏或其他超敏病症的患者。

服用β受体阻滞剂的患者
需要注意的是，服用β受体阻滞剂的患者不一定对通常用于治疗过敏反应的β激动剂有反应。

心血管疾病患者
在这组患者中，超敏反应可能更严重。尤其是严重心脏病(如重度心脏衰竭、冠状动脉疾病)患者，心血管反应可能加重。

中枢神经系统疾病：患癫痫或脑损伤的患者在检查期间出现惊厥的可能性增加。对这类患者在检查时必须采取一定的预防措施（如对患者进行监测），应备有对可能发生的惊厥进行快速处理所需要的设备和药物。

本品含钠量：0.62 mg/ml。对于控制钠饮食的患者，需要考虑这一点。

降低平扫MRI可检测病变的显示
顺磁性对比剂如全磁对比剂可能影响平扫MRI上可见的病灶的显示。这可能是由于顺磁对比剂或成像参数的影响。在没有平扫MRI的情况下解读欧乃影增强MRI扫描时需谨慎。
观察到血清铁离子无症状的短暂变化。临床意义尚不清楚。
欧乃影用医院常用的比色法（络合度法）干扰血钙测量，导致血钙浓度低于真实值。在肾功能正常的患者中，这种效应通常持续12-24小时。在肾功能下降的患者中，预计在长期消除欧乃影期间干扰钙测量。在患者接受欧乃影治疗后，应谨慎选择测量钙的方法类型。

对驾驶及操作机器能力的影响未知。

【孕妇及哺乳期妇女用药】
妊娠期用法
目前尚无妊娠期妇女使用欧乃影的经验。GBCAs可穿过胎盘，可导致胎儿暴露和钆沉积。关于GBCA与胎儿不良结局之间关系的人类数据有限，尚无定论。本品不应用于妊娠期妇女，除非MRI增强检查很有必要且无其它适当方法替代。
欧乃影对大鼠的生育能力或繁殖无影响，大鼠和兔子的畸变学研究也未见母体遗传毒性。

哺乳期用法
虽然预计分泌至人乳中的浓度极低，但分泌的程度仍未知。现有的动物数据显示钆双胺经乳汁排泄。不能排除对哺乳孩子的风险。欧乃影给药时及给药后至少24小时内不应哺乳。

【儿童用药】
钆沉积在儿童大脑中的数量和分布与成人相似。儿童大脑的发育可能更容易受到钆暴露的潜在影响。

新生儿与婴儿
欧乃影禁用于小于4周的新生儿。由于一岁以下婴儿肾功能未发育完全，只有在进行仔细的评估后才可在这些患者中使用欧乃影。
在患有严重肝或肾疾病的6个月以下儿童中，或4周以下的早产婴儿，以及妊娠期不足30周的早产婴儿中，尚无使用欧乃影的经验。

【老年用药】
根据临床使用经验，对65岁及以上年龄的老年患者不需要调整给药剂量。但是，考虑到老年患者发生肾，肝或心脏功能降低的可能性增加，以及伴随疾病或伴随其他药物治疗的可能性，老年患者在剂量选择时要加以注意，通常由剂量范围的低剂量开始。

【药物相互作用】
欧乃影不能直接与其它药物混和使用。
必须用单独的针头和针筒。

【药物过量】
目前尚无过量发生临床后果的报道。肾功能正常者似不可能发生急性中毒症状。如有需要当为对症处理。本品无拮抗剂。因肾功能不良或过量注射发生欧乃影排泄延缓时，进行血液透析治疗理论上可促使其排泄。
不应超过说明书推荐的剂量给药，若需再次给药，给药前也应有足够的间隔时间清除药物，以免增加NSF发生的潜在风险。

【药理毒理】
药理作用
在磁共振成像中，正常组织和病理组织的显影部分地取决于射频信号强度的变化。发生这些变化是由于：质子密度的变化；自旋点阵或纵向弛豫时间的改变（T1）；以及自旋-自旋或横向弛豫时间的变化（T2）。欧乃影是一种顺磁剂，具有不成对的电子自旋，这种自旋可产生局部磁场。当水质子穿过这个局部磁场时，质子所经历的磁场变化，与无顺磁剂时相比，可更快地使质子适应主磁场。通过提高弛豫率，欧乃影减少了其所在组织中的T1和T2弛豫时间。在临床剂量下，效果主要是在T1弛豫时间方面，并导致信号强度的增加。当存在血脑屏障破坏或血管异常时，欧乃影会在诸如肿瘤、脓肿和亚急性梗死等的病灶中蓄积。各种病变中的欧乃影药代动力学参数尚未得到阐明。

欧乃影的顺磁性使MRI的对比增强。健康志愿者接受静注钆双胺后，其血液动力学及血、尿的实验室参数与注射前相比都无临床意义上的明显偏差。但其血清铁离子浓度在注射钆双胺后8 - 48小时内有微小暂时的变化。
注射欧乃影后，疾病所致血脑屏障失常区域可以明显增强，从而使所提供的诊断信息超过了平扫MRI。由于某些恶性分化程度较低或非活动性多发性硬化斑是不增强的，所以MRI上不显示增强时并不表明没有病变。本品能用于不同疾病的鉴别诊断。
欧乃影作为MRI中造影增强剂的有效性在一系列动物实验中已得到证实。在狗和大鼠的安全性药理试验中表明：欧乃影对心血管系统无明显影响。体外试验还表明：本品对肥大细胞的组胺释放、血清补体激活、红细胞胆碱酯酶活性、溶酶体活性、红细胞脆性及形态、离体牛血管的血管张力等均无(显著)影响。在豚鼠的皮肤实验中未见它具有抗原性。
几种动物的药代动力学证明：欧乃影很快在细胞外液中扩散，通过肾小球滤过而定量地由肾脏排泄。人和猴子的排泄半衰期相似。分布体积约为身体的25%。

毒理研究
毒理学实验表明：欧乃影的急性耐受性高，大鼠的LD50约为大于30mmol/Kg。一次性高剂量或反复使用会引起可逆转的近曲小管的空泡形成，但不会引起肾功能改变。欧乃影在静脉内、动脉内、静脉旁、肌肉和皮下、皮肤、眼部给药无刺激。
在不产生母体毒性的剂量下，欧乃影对大鼠的生育能力或生殖行为无影响，大鼠和家兔的致畸敏感期试验中也未出现阳性结果。

GBCAs给怀孕的非人类灵长类动物(孕85和135天0.1 mmol/kg)使用后，其后代骨骼、大脑、皮肤、肝脏、肾脏和脾脏中的钆浓度至少在7个月内可测量到。对怀孕小鼠施用GBCA（在妊娠16至19日，每日2mmol/kg）导致在出生后1个月小鼠的骨、脑、肾、肝、血液、肌肉和脾中可测量到钆浓度。

【药代动力学】
钆双胺很快分布到细胞外液，其分布量与细胞外液中水量相等。其分布半衰期为4分钟，排泄半衰期约为70分钟。肾损害病人(GFR<30ml/min)排泄半衰期的延长程度与GFR值成反比。
钆双胺通过肾小球过滤而经肾脏排泄。对肾功能正常的病人注射钆双胺4小时后有约85%的注射剂量通过尿液排泄，静脉注射后24小时有95%-98%被排泄。钆双胺的肾脏清除率和其总清除率几乎相同，与其它主要经肾小球滤过排泄的物质相似。注射0.1和0.3mmol/kg时，未见与剂量有关的药代动力学变化。
本品无代谢物测出。未观察到与蛋白结合。

【贮藏】
2-30℃、遮光保存。

【包装】
玻璃瓶： 1瓶/盒；10瓶/盒

【有效期】
36个月

【执行标准】
进口药品注册标准： JX20190066

【批准文号】

浓度	规格	进口药品注册证号	分包装批准文号
287mg/ml × 10ml	10ml：2.87g	小包装：H20181149 大包装：H20181150	国药准字J20140162
287mg/ml × 15ml	15ml：4.305g	小包装：H20181153 大包装：H20181154	国药准字J20140163
287mg/ml × 20ml	20ml：5.74g	小包装：H20181151 大包装：H20181152	国药准字J20140164

【上市许可持有人】
名称： GE Healthcare AS
注册地址： P.O. Box 4220 Nydalen, NO-0401 Oslo, Norway

【生产企业】
企业名称： GE Healthcare Ireland Limited
生产地址： IDA Business Park
Carrigtohill
Co. Cork
爱尔兰
电话号码： +353 21 488 33 66
传真号码： +353 21 488 33 25

【贴签包装企业】
企业名称： 通用电气药业（上海）有限公司
生产地址： 中国（上海）自由贸易试验区牛顿路1号
邮政编码： 201203
电话号码： +86 21 38954500
传真号码： +86 21 38954502

欧乃影是GE医疗集团拥有的注册商标。
GE和GE Monogram是General Electric Company拥有的注册商标。

Document: 1198818 CHN Version: 2 Approved by: Tveten, Mette (100020471), 2020-11-12 14:22:07 Activated by: Gunnesen, Torun Kristin (100020425), 2020-11-13 05:05:11

1198818 CHN

1198818

Approved date: Dec. 2006
Revised date: Aug. 2007 Jul. 2008 Jul. 2012 Dec. 2014 Apr. 2016 Jan. 2018 Jul. 2018 Jun. 2019 Nov. 2020

GE Healthcare

GADODIAMIDE INJECTION

OMNISCAN®

Insert Sheet of Gadodiamide Injection

Please read the insert carefully and use under instruction by doctor

Warnings

Gadolinium retention:

Trace amount of Gadolinium will be retained in the brain and other tissues for both linear and macrocyclic GBCAs. Animal experimental study evidence suggests that the level of gadolinium retention is higher after repeat administration of linear than after repeat administration of macrocyclic agents. This product is linear GBCA.

NSF:

Gadolinium-based contrast agents (GBCAs) increase the risk for NSF among patients with impaired elimination of the drugs. Avoid use of GBCAs in these patients unless the diagnostic information is essential and not available with non-contrasted MRI or other modalities. NSF may result in fatal or debilitating fibrosis affecting the skin, muscle and internal organs.

- **Do not administer OMNISCAN to patients with:**
  - **chronic, severe kidney disease (GFR <30mL/min/1.73m^2), or**
  - **acute kidney injury**
- **Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (e.g., age > 60 years, hypertension or diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing.**

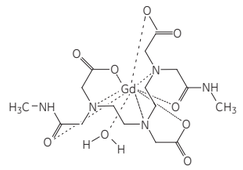
Do not exceed the recommended OMNISCAN dose and allow a sufficient period of time for elimination of the drug from the body prior to any readministration.

【Drug Name】

Generic Name: Gadodiamide Injection
Brand Name: Omniscan®
Chinese Phonetic Alphabet: Gashuang’an Zhusheye

【Composition】

The main ingredient of this drug is Gadodiamide and its chemical name is: [5,8-bis(carboxymethyl)11-[2-(methylamino)-2-oxoethyl]-3-oxo-2,5,8,11-tetraazatridecan-13-oato(3-)] gadolinium
Structure:



Molecular Formula: $C_{16}H_{20}GdN_5O_8$
Molecular Weight: 573.66
Excipients: Caldiamide Sodium, Sodium Hydroxide or Hydrochloric Acid to adjust pH, Water for Injection.

【Properties】

The product is a clear, colourless to slightly yellow aqueous solution. Gadodiamide injection is a non-ionic paramagnetic contrast medium with the following physicochemical properties:

Osmolarity (mOsm/kg H_2O) at 37°C	780
Viscosity (mPa · s) at 20°C	2.8
Viscosity (mPa · s) at 37°C	1.9
Density at 20°C (kg/l)	1.15
Molar relaxivity	
r_1 (mM^{-1} · s^{-1}) at 20 MHz and 37°C	3.9
r_1 (mM^{-1} · s^{-1}) at 10 MHz and 37°C	4.6
r_2 (mM^{-1} · s^{-1}) at 10 MHz and 37°C	5.1
pH	6.0-7.0

Gadodiamide is freely soluble in water.

【Indications】

Contrast medium for cranial and spinal magnetic resonance imaging (MRI) and for general MRI of the body after intravenous administration.
The product provides contrast enhancement and facilitates visualisation of abnormal structures or lesions in various parts of the body including the CNS.

【Strength】

(1)10ml: 2.87g (2)15ml: 4.305g (3)20ml: 5.74g

【Dosage and Administration】

No special preparation of the patient is required. The product should be drawn into the syringe immediately before use. Each bottle is intended for one patient only. Contrast medium not used in one examination must be discarded.

For intravenous use. For both adults and children the required dose should be administered as a single intravenous injection. To ensure complete injection of the contrast medium, the intravenous line may be flushed with sodium chloride injection 0.9%.
The lowest approved dose shall be used as far as possible.

CNS

Dosage for adults and children (No including neonates up to 4 weeks of age)
The recommended dosage is 0.1mmol/kg body weight (equivalent to 0.2ml/kg BW) up to 100 kg. Above 100kg body weight 20ml is usually sufficient to provide diagnostically adequate contrast.

Adults only
When brain metastases are suspected, a dosage of 0.3mmol/kg BW (equiv. to 0.6ml/kg BW) can be administered up to 100kg. Above 100kg BW a total of 60ml is usually sufficient. The dose of 0.3mmol/kg BW (equiv. to 0.6ml/kg BW) can be administered as a bolus intravenous injection.
In patients with equivocal scans after administration of the 0.1mmol/kg BW injection, a second bolus injection of 0.2mmol/kg BW (equiv. to 0.4ml/kg BW) may be of additional diagnostic value when administered within 20 minutes of the first injection.

Whole body

Dosage for adults
The recommended dosage is usually 0.1mmol/kg BW (equiv. to 0.2ml/kg BW) or occasionally 0.3mmol/kg BW (equiv. to 0.6ml/kg BW) up to 100kg. Above 100kg BW 20ml resp. 60ml is usually sufficient to provide diagnostically adequate contrast.

Dosage for children from 6 months of age
The recommended dosage is 0.1mmol/kg BW (equiv. to 0.2ml/kg BW).

CNS and whole body only

Contrast-enhanced MRI should start shortly after administration of the contrast medium, depending on the pulse sequences used and the protocol for the examination.
Optimal enhancement is observed within the first minutes after injection (time depending on type of lesion/tissue). Enhancement is generally lasting up to 45 minutes after contrast medium injection. T_1-weighted scanning sequences are particularly suitable for contrast-enhanced examinations with OMNISCAN.
In the investigated range of field strengths, from 0.15 Tesla up to 1.5 Tesla, the relative image contrast was found to be independent of the applied field strength.

【Adverse Reaction】

Adverse reactions have been reported in approximately 6 % of the patients in clinical trials. The most commonly reported spontaneous adverse effects after administering gadodiamide injection are hypersensitivity reactions, nausea and vomiting. Cases of nephrogenic systemic fibrosis (NSF) have been reported.

Nephrogenic systemic fibrosis, which is debilitating and sometimes fatal progressive disease characterized by affecting the skin, muscle and internal organs, leads to excessive formation of connective tissue in the skin and internal organs, causes skin thickening, coarseness and hardening and sometimes leads to disabling contractures.

In Ireland SmPC, adverse reactions have been reported with the following frequencies given (very common ≥1/10; common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare <1/10,000). Not known (cannot be estimated from the available data).

Immune system disorders
Uncommon: Allergy-like skin and mucous membrane reactions, hypersensitivity
Not known: Anaphylactic/anaphylactoid reactions*

Psychiatric disorders
Rare: Anxiety

Nervous system disorders
Common: Headache
Uncommon: Dizziness, paraesthesia, transient perverted sensation of taste
Rare: Convulsions, tremor, somnolence, transient perverted sensation of smell

Eye disorders
Rare: Visual disturbance

Cardiac disorders
Not known: Tachycardia

Vascular disorders
Uncommon: Flushing

Respiratory, thoracic and mediastinal disorders
Rare: Dyspnoea, coughing
Not known: Bronchospasm, respiratory distress, throat irritation, sneezing

Gastrointestinal disorders
Common: Nausea
Uncommon: Vomiting, diarrhoea

Skin and subcutaneous tissue disorders
Uncommon: Pruritus
Rare: Oedema including face swelling and angioneurotic oedema, urticaria, rash
Not known: Nephrogenic systemic fibrosis (NSF), Gadolinium associated skin plaques

Musculoskeletal and connective tissue disorders
Rare: Arthralgia

Renal and urinary system disorders
Rare: Acute renal failure

General disorders and administration site condition
Common: Transient sensation of warmth, coolness or local pressure in connection with injection. Transient sensation of pain at the injection site.
Rare: Chest pain, fever, shivering

* Anaphylactic/anaphylactoid reactions which may occur irrespective of the dose given and the method of administration, may be the first signs of an incipient shock.

Late adverse reactions can occur hours to days after administration of Omniscan.

Transient changes in serum iron have been observed in some patients, but all these patients remained asymptomatic.

Postmarketing Experience as per US Package Insert:
Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
The following adverse reactions have been identified during the postmarketing use of OMNISCAN:
Nervous System Disorders: Inadvertent intrathecal use causes convulsions, coma, paresthesia, paresis. Convulsions have also been reported with intravenous use in patients with and without a history of convulsions or brain lesions.
General Disorders: Nephrogenic Systemic Fibrosis (NSF)
Adverse events with variable onset and duration have been reported after GBCA administration. These include fatigue, asthenia, pain syndromes, and heterogeneous clusters of symptoms in the neurological, cutaneous, and musculoskeletal systems.
Renal and Urinary System Disorders: In patients with pre-existing renal insufficiency: acute renal failure, renal impairment, blood creatinine increased.
Skin: Gadolinium associated plaques.

【Contraindications】

OMNISCAN must not be used in patients known to have hypersensitivity to constituents of the product.
Gadodiamide is contraindicated in patients with severe renal impairment (GFR <30ml/min/1.73m^2), or acute kidney injury, those who have had or are undergoing liver transplantation and in neonates up to 4 weeks of age.

【Precautions】

GBCAs shall be used with caution. GBCAs should be used only when diagnostic information is essential and not available with unenhanced magnetic resonance imaging (MRI). The lowest dose shall be used as far as possible.
Prior to administering a Gadolinium-Based Contrast Agents, evaluate all patients (especially patients over 60 years) for renal dysfunction by assessing their renal function by obtaining a medical history and/or conducting laboratory tests.
Because of the lack of information on repeated administration, Omniscan injections should not be repeated unless the interval between injections is at least 7 days.

Gadolinium retention
Current evidence suggest that trace amounts of gadolinium will be retained in the brain and other body tissues after repeated administrations, even in patients with normal renal function. Higher concentrations have been identified in human bone than in skin and brain. Repeated administrations of GBCAs will subsequently cause signal enhancement in the brain, particularly in the dentate nucleus and globus pallidus. To date, signal enhancement of non-contrast T1 weighted images following repeated administration of linear GBCAs have been more frequently reported than for macrocyclic GBCAs. Animal experimental studies suggests that the level of gadolinium retention is higher after repeat administration of linear agents than after repeat administration of macrocyclic agents.
The clinical significance of gadolinium retention in brain is unknown.
There are rare reports of pathologic skin changes including gadolinium associated plaques in patients with normal renal function. Postmarketing reports of adverse events involving multiple organ systems in patients with normal renal function have been received. A causal link to gadolinium retention has not been established. These events include fatigue, asthenia, pain syndromes, and heterogeneous clusters of symptoms in the neurological, cutaneous, and musculoskeletal systems.
While clinical consequences of gadolinium retention have not been established in patients with normal renal function, certain patients might be at higher risk. These include patients requiring multiple lifetime doses, pregnant and paediatric patients. In order to minimize the potential risks associated with gadolinium retention, Omniscan must be used strictly according to the approved indication and approved dose. It is recommended to use the lowest approved dose to achieve a diagnosis, to carefully perform a risk assessment and to implement patient-informed communication before repeated administrations.
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 or a history of asthma or other allergic respiratory disorders. Personnel trained in resuscitation techniques and resuscitation equipment should be present prior to OMNISCAN administration. If a hypersensitivity reaction occurs, stop OMNISCAN Injection and immediately begin appropriate therapy. Observe patients closely, particularly those with a history of drug reactions, asthma, allergy or other hypersensitivity disorders, during and up to several hours after OMNISCAN Injection.

Renal impairment and liver transplant patient:
There have been reports of nephrogenic systemic fibrosis (NFS) associated with use of gadodiamide and some other gadolinium-containing contrast agents in patients with severe renal impairment (GFR <30ml/min/1.73m^2) and those who have had or are undergoing liver transplantation. Therefore OMNISCAN should not be used in these populations (see section for Contraindications). Cases of NSF have also been reported in patients with moderate renal impairment (GFR <60ml/min/1.73m^2) with gadodiamide. The risk, if any, for the development of NSF among patients with moderate renal insufficiency is unknown. Omniscan should be used in these patients with caution.
Gadodiamide is dialyzable.
Haemodialysis shortly after Omniscan administration in patients currently receiving haemodialysis may be useful at removing Omniscan 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.

Patients taking beta-blocker
It should be noted that patients using beta-blockers do not necessarily respond to the beta-agonists usually used for the treatment of hypersensitivity reactions.

Patients with cardiovascular disease
In this group of patients hypersensitivity reactions may be more severe. Especially in patients with serious heart diseases (e.g. severe heart failure, coronary artery disease) cardiovascular reactions may deteriorate.

Central nervous system disorders: In patients suffering from epilepsy or brain lesions the likelihood of convulsions during the examination may be increased. Precautions are necessary when examining these patients (e.g. monitoring of the patient) and the equipment and medicinal products needed for the rapid treatment of possible convulsions should be available.

This medicinal product contains sodium: 0.62mg/ml. This needs to be taken into consideration for patients on a controlled sodium diet.

Impaired Visualization of Lesions Detectable with Non-contrast MRI
Paramagnetic contrast agents such as OMNISCAN might impair the visualization of lesions which are seen on the non-contrast MRI. This may be due to effects of the paramagnetic contrast agent, or imaging parameters. Exercise caution when OMNISCAN MRI scans are interpreted in the absence of a companion non-contrast MRI.
Asymptomatic, transitory changes in serum iron have been observed. The clinical significance is unknown.
OMNISCAN interferes with serum calcium measurements with some colorimetric (complexometric) methods commonly used in hospitals, resulting in serum calcium concentrations lower than the true values. In patients with normal renal function, this effect lasts for 12-24 hours. In patients with decreased renal function, the interference with calcium measurements is expected to last during the prolonged elimination of OMNISCAN. After patients receive OMNISCAN, careful attention should be used in selecting the type of method used to measure calcium.

Effects on ability to drive and use machines
None known.

【Drugs for use by Women during Pregnancy or Lactation Period】

Use during pregnancy
There is no experience of the use of OMNISCAN during human pregnancy.
GBCAs cross the placenta and result in fetal exposure and gadolinium retention. Human data on the association between GBCA and adverse fetal outcomes are limited and inconclusive. The product should not be used during pregnancy, unless an enhanced MR investigation is essential, and no suitable alternative is available. OMNISCAN had no effects on fertility or reproductive performance in rats or in teratology studies in rats and rabbits at doses that did not cause maternal toxicity.

Use during lactation
The degree of excretion into human milk is not known, although expected to be low. Available data in animals have shown excretion of gadodiamide in milk. A risk to the suckling child cannot be excluded. Breast feeding should be discontinued prior to administration and should not be recommenced until at least 24 hours after the administration of OMNISCAN.

【Drugs for Children use】

Gadolinium is retained in pediatric brains similar in amount and distribution to adults. Developing pediatric brains may be more susceptible to the potential effects of gadolinium exposure.

Neonates and infants:
Omniscan is contraindicated in neonates up to 4 weeks of age. Due to immature renal function in infants up to 1 year of age, OMNISCAN should only be used in these patients after careful consideration.
Experience with Omniscan in children below 6 months with severe liver or renal disease in pre-term new-born infants below 4 weeks of age or with gestational age below 30 weeks is not available.

【Drugs for Elderly Patients】

According to experience from clinical trial, no dose adjustment in patients ≥65 years of age is warranted. However, dose selection for an elderly patient should be cautious usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

【Interactions】

OMNISCAN should not be directly mixed with other drugs.
A separate syringe and needle should be used.

【Overdose】

Clinical consequences of overdose have not been reported and acute symptoms of toxicity are unlikely in patients with a normal renal function. Treatment is symptomatic. There is no antidote for this contrast medium. In patients with delayed elimination due to renal insufficiency and in patients who have received excessive doses, the contrast medium can be eliminated by haemodialysis.
In order to reduce the potential risk of NSF, when administering, do not exceed the recommended dose in this leaflet and allow sufficient time for elimination of the agent prior to any readministration if it is necessary.

【Pharmacological and Toxicological Properties】

Pharmacological Properties

In magnetic resonance imaging, visualization of normal and pathologic tissue depends in part on variations in the radiofrequency signal intensity. These variations occur due to: changes in proton density; alteration of the spin-lattice or longitudinal relaxation time (T1); and variation of the spin-spin or transverse relaxation time (T2). OMNISCAN is a paramagnetic agent with unpaired electron spins which generate a local magnetic field. As water protons move through this local magnetic field, the changes in magnetic field experienced by the protons reorient them with the main magnetic field more quickly than in the absence of a paramagnetic agent. By increasing the relaxation rate, OMNISCAN decreases both the T1 and T2 relaxation times in tissues where it is distributed. At clinical doses, the effect is primarily on the T1 relaxation time, and produces an increase in signal intensity. Disruption of the blood-brain barrier or abnormal vascularity allows accumulation of OMNISCAN in lesions such as neoplasms, abscesses, and subacute infarcts. The pharmacokinetic parameters of OMNISCAN in various lesions are not known.

The paramagnetic properties of OMNISCAN provide contrast enhancement during MRI. There were no clinically significant deviations from preinjection values in haemodynamic and blood and urine laboratory parameters following intravenous injection of gadodiamide in healthy volunteers. However, a minor transient change in serum iron levels 8 to 48 hours after gadodiamide injection was observed.
Administration of OMNISCAN causes signal enhancement from areas where blood-brain barrier dysfunction has been induced by pathological processes, and may provide greater diagnostic yield than unenhanced MRI. Lack of enhancement need not indicate absence of pathology since some types of low grade malignancies or inactive MS-plaques fail to enhance; it can be used for differential diagnosis between different pathologies. The efficacy of OMNISCAN as a contrast enhancing agent during MRI has been demonstrated in a series of animal studies. Safety pharmacology studies in dogs and rats have demonstrated that OMNISCAN has no significant effects on the cardiovascular system. In vitro studies have demonstrated no or insignificant effects on mast cell histamine release, human serum complement activation factors, human erythrocyte cholinesterase activity, lysozyme activity, human erythrocyte fragility and morphology, and on tension in isolated bovine blood vessels. No evidence of antigenicity was seen in a dermal test in Guinea pigs.
Pharmacokinetic studies in several animal species have demonstrated OMNISCAN to be rapidly distributed in the extracellular volume, and quantitatively excreted via the kidneys by glomerular filtration. The elimination half-lives in man and monkey are similar. The calculated distribution volume is approximately 25% of body size.

Toxicological Properties

Toxicological studies have demonstrated a high acute tolerance of OMNISCAN, the approximate LD_{50} in mice was >30mmol/kg. The common finding after high single doses or repeated dosing was proximal tubular vacuolation, which was reversible, and was not associated with altered renal function. OMNISCAN was found to be non-irritating after intravenous, intra-arterial, paravenous, intramuscular and subcutaneous administration, or when applied to the skin or the eye.
OMNISCAN had no effects on fertility or reproductive performance in rats or in the teratology studies in rats and rabbits at doses that did not cause maternal toxicity. GBCAs administered to pregnant non-human primates (0.1mmol/kg on gestational days 85 and 135) result in measurable gadolinium concentration in the offspring in bone, brain, skin, liver, kidney, and spleen for at least 7 months. GBCAs administered to pregnant mice (2mmol/kg daily on gestational days 16 through 19) result in measurable gadolinium concentrations in the pups in bone, brain, kidney, liver, blood, muscle, and spleen at one month postnatal age.

【Pharmacokinetic Properties】

Gadodiamide is rapidly distributed in the extracellular fluid. The volume of distribution is equivalent to that of extracellular water. The distribution half-life is approximately 4 minutes and the elimination half-life is approximately 70 minutes. In patients with impaired renal function (GFR <30ml/min) the elimination half-life will be prolonged to an extent inversely proportional to GFR.
Gadodiamide is excreted through the kidneys by glomerular filtration. In patients with normal renal function approximately 85% of the administered dose is recovered in the urine by 4 hours and 95-98% by 24 hours after intravenous injection. The renal and total clearance rates of gadodiamide are nearly identical, and are similar to that of substances excreted primarily by glomerular filtration. No dose dependent kinetics have been observed after injection of 0.1 and 0.3mmol/kg.
No metabolites have been detected. No protein binding has been observed.

【Storage】

Stored at 2-30°C protected from light.

【Package】

Glass vials: 1 bottle/box; 10 bottles/box

【Shelf life】

36 months

【Specification】

Specification number: JX20190066

【 Approval Number 】

Concentration	Strength	Import Drug License Number	Approval Number
287mg/ml × 10ml	10ml: 2.87g	Finished product: H20181149 Semi-finished product: H20181150	国药准字J20140162
287mg/ml × 15ml	15ml: 4.305g	Finished product: H20181153 Semi-finished product: H20181154	国药准字J20140163
287mg/ml × 20ml	20ml: 5.74g	Finished product: H20181151 Semi-finished product: H20181152	国药准字J20140164

【Marketing Authorization Holder】

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

【Manufacturer】

GE Healthcare Ireland Limited
IDA Business Park
Carrigtohill
Co. Cork
Ireland
Telephone: + 353 21 488 3366
Fax: + 353 21 488 3325

【Labelled and Packed by】

GE Healthcare (Shanghai) Co., Ltd.
No.1 Niudun Road, China (Shanghai) Pilot Free Trade Zone
Postal Code: 201203
Telephone: + 86 21 38954500
Fax: + 86 21 38954502

Omniscan is a trademark of GE Healthcare.
GE and GE Monogram are trademarks of General Electric Company.

Document: 1198818 CHN Version: 2 Approved by: Tveten, Mette (100020471), 2020-11-12 14:22:07 Activated by: Gunnesen, Torun Kristin (100020425), 2020-11-13 05:55:11