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GE Healthcare

碘克沙醇注射液

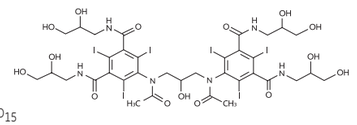
威视派克®

碘克沙醇注射液说明书

请仔细阅读说明书并在医师指导下使用

【药品名称】
通用名称：碘克沙醇注射液
商品名称：威视派克® (Visipaque®)
英文名称：Iodixanol Injection
汉语拼音：Diankeshachun Zhusheye

【成份】
本品活性成分为碘克沙醇，其化学名称为：5,5'-[(2-羟基-1,3-丙二基)-双（乙酰基氨基)]-双 (N,N'-双(2,3-二羟基丙基)-2,4,6-三碘-1,3-苯二甲酰胺)
化学结构式：



分子式:$C_{35}H_{44}I_6N_6O_{15}$
分子量:1550.20
辅料：氨丁三醇，氯化钠，氯化钙，EDTA钙钠，盐酸调节pH，注射用水

【性状】
本品为无色或淡黄色的澄明液体。
碘克沙醇是一非离子型、双体、六碘、水溶性的X线对比剂。
与全血和其它相应规格的非离子型单体对比剂相比，所有临床使用浓度的纯碘克沙醇水溶液具有较低的渗透压。通过加入电解质，本品和正常的体液等渗。
本品的渗透压和粘度值如下：

浓度	渗透压* mOsm/kg H_2O 37°C	粘　度 (mPa · s) 20°C	37°C
270 mgI/ml	290	11.3	5.8
320 mgI/ml	290	25.4	11.4

*方法：蒸汽压渗透压测定法。

本品的pH值为6.8-7.6。

【适应症】
X-线对比剂，用于成人的心血管造影、脑血管造影（常规的与i.a.DSA)，外周动脉造影(常规的与i.a.DSA)、腹部血管造影（常规的与i.a.DSA)，尿路造影，静脉造影以及CT增强检查；儿童心血管造影、尿路造影和CT增强检查。

【规格】
(1) 50ml:13.5g(I)　(2) 50ml:16g(I)　(3) 100ml:27g(I)　(4) 100ml:32g(I)

【用法用量】
给药剂量取决于检查的类型、年龄、体重、心输出量和病人全身情况及所使用的技术。通常使用的碘浓度和用量与其它当今使用的含碘X线对比剂相似，但在一些研究中使用较低碘浓度的碘克沙醇注射液也得到足够的诊断信息。与其它对比剂一样，在给药前后应给病人充足的水分。

下列推荐的剂量可作为指导，用于动脉内注射的单次剂量，可重复使用。

适应症/检查	浓度	用量
动脉内使用		
动脉造影		
选择性脑动脉造影	270/320 (1)mgI/ml	一次注射5 - 10ml
选择性脑 i.a.DSA	150mgI/ml	一次注射5 - 10ml
主动脉造影	270/320mgI/ml	一次注射40 - 60ml
外周动脉造影	270/320mgI/ml	一次注射30 - 60ml
外周i.a.DSA	150mgI/ml	一次注射30 - 60ml
选择性内脏i.a.DSA	270mgI/ml	一次注射10 - 40ml
心血管造影		
左心室与主动脉根注射	320mgI/ml	一次注射30 - 60ml
选择性冠状动脉造影	320mgI/ml	一次注射4 - 8ml
儿童	270/320mgI/ml	根据年龄、体重和病理情况|推荐最大总剂量为按体重10ml/kg)
静脉内使用		
尿路造影		
成人	270/320mgI/ml	40-80ml (2)
儿童<7kg	270/320mgI/ml	按体重2-4ml/kg
儿童>7kg	270/320mgI/ml	按体重2-3ml/kg
		所有剂量均根据年龄、体重及病理情况|最大剂量为50ml)
静脉造影	270mgI/ml	每腿50-150ml
CT增强		
成人：头部CT	270/320mgI/ml	50-150ml
成人：体部CT	270/320mgI/ml	75-150ml
儿童：头、体部CT	270/320mgI/ml	按体重2-3ml/kg可至50ml
		(少数病例可至150ml)

(1) 两种规格都有文献记载，但是多数病例推荐使用270mgI/ml。
(2) 在高剂量的尿路造影中可以使用较高剂量。
老年人：与其他成年人剂量相同。

【不良反应】
下面列举了使用本品进行放射学检查而可能产生的不良反应。
与碘克沙醇相关的副作用通常是轻度至中度的，并且是一过性的。严重反应以及死亡仅在非常罕见的情况下才观察到，包括慢性肾病急性加重、急性肾脏衰竭、速发过敏反应性休克或类速发过敏反应性休克、超敏反应后出现心脏反应(Kounis综合征）、心脏或心脏呼吸骤停和心肌梗死，心脏反应可能由基础疾病或手术诱发。超敏反应可能表现为呼吸系统或皮肤症状，如呼吸困难、皮疹、红斑、荨麻疹、瘙痒症、重度皮肤反应、血管神经性水肿、低血压、发热、喉水肿、支气管痉挛或肺水肿。在自身免疫疾病患者中，观察到血管炎和史蒂文斯-约翰逊样综合征病例。以上反应可能会在注射后立即出现或长达几天后出现。超敏反应可能与剂量和给药方式无关的情况下发生，轻度症状可能为严重速发过敏反应/休克的首发迹象。出现以上症状后应立即停止对比剂给药，必要时，通过血管通路采取特定疗法。使用β阻滞剂的患者可能出现超敏反应的非典型症状，其可能会被误诊为迷走神经反应。碘对比剂给药后，血清肌酐的微小一过性升高是常见的，但通常没有临床相关性。
不良反应的发生频率定义如下：非常常见(≥ 1/10)、常见(≥ 1/100且<1/10)、不常见(≥ 1/1000且<1/100)、罕见(≥ 1/10000且<1/1000)、非常罕见(<1/10000)和不详(根据现有数据无法估计)。
列出的频率是基于内部临床文件和发表的研究，包括超过57,705名患者。

血管内给药:
血液及淋巴系统疾病:
不详：血小板减少症

免疫系统疾病:
不常见：超敏反应
不详：速发过敏反应性休克/类速发过敏反应性休克、速发过敏反应/类速发过敏反应，包括危及生命或致命的速发过敏反应。

内分泌系统疾病:
不详：甲状腺功能亢进，甲状腺功能减退

精神病类:
非常罕见：激越、焦虑
不详：意识模糊状态

各类神经系统疾病
不常见：头痛
罕见：头晕、感官异常，包括味觉障碍、异常感觉、瞋觉异常
非常罕见：脑血管意外、遗忘症、晕厥、震颤(短暂性)、感觉减退
不详：昏迷、意识障碍、惊厥、对比剂外渗引起的一过性对比剂脑病(包括失忆症、幻觉、瘫痪、局部麻痹、暂时性言语障碍、失语、构音不良)、可表现为感觉、运动或全身神经功能障碍

眼器官疾病:
非常罕见：皮质盲(一过性)、视觉损害(包括复视、视物模糊、眼睑水肿。

心脏器官疾病:
罕见：心律不齐(包括心动过缓、心动过速)、心肌梗死
非常罕见：心脏停搏、心悸
不详：心室运动功能减退、冠状动脉痉挛、心脏呼吸骤停、传导异常、冠状动脉血栓形成、心绞痛

血管类疾病:
不常见：潮红
罕见：低血压
非常罕见：高血压、缺血
不详：休克、动脉痉挛、血栓形成、血栓性静脉炎

呼吸系统、胸及纵隔疾病:
罕见：咳嗽、喷嚏
非常罕见：呼吸困难、咽喉刺激、喉水肿
不详：非心源性肺水肿、呼吸停止、呼吸衰竭、支气管痉挛、咽喉缩紧感、咽部水肿

胃肠系统疾病:
不常见：恶心、呕吐
非常罕见：腹痛/腹部不适、腹泻
不详：急性胰腺炎、胰腺炎加重、腮液腺增大

皮肤和皮下组织类疾病
不常见：皮疹或药疹、瘙痒症、荨麻疹
非常罕见：血管神经性水肿、红斑、多汗
不详：大疱性皮炎或剥脱性皮炎，史蒂文斯-约翰逊综合征、多形性红斑、中毒性表皮坏死松解症、急性全身发疹性脓包性皮病，伴有嗜酸性粒细胞增多症和全身症状的药疹

各种肌肉骨骼及结缔组织疾病:
非常罕见：背痛、肌肉痉挛
不详：关节痛

肾脏及泌尿系统疾病:
不常见：急性肾损伤或肾病毒性(对比剂诱发的肾病CIN)
不详：血肌酐升高

全身性疾病及给药部位各种反应:
不常见：胸痛、体温感觉改变
罕见：寒战性发抖(寒战)、发热、疼痛和不适、给药部位各种反应(包括外渗)
非常罕见：虚弱状态(如不适、疲乏)、面部水肿、局部水肿
不详：肿胀

各类损伤、重度及手术并发症
不详：碘中毒

【禁忌】
未经控制症状的甲亢患者及既往对本品有严重不良反应史的患者。
对药物的活性物质或任何辅料有超敏反应者禁用。
本品禁止鞘内使用(详见【注意事项】“意外鞘内给药”内容)。

【注意事项】
意外鞘内给药
本品仅用于血管内使用，不得用于鞘内使用，误行鞘内注射可导致死亡、惊厥/癫痫发作、脑出血、昏迷、瘫痪、蛛网膜炎、急性肾功能衰竭、心脏骤停、横纹肌溶解、高热和脑水肿。
超敏反应:
对碘对比剂有过敏、哮喘或非预期反应阳性病史的患者需要特别谨慎。在这些病例中下可能要考虑皮质类固醇或组胺H1和H2受体拮抗剂的术前用药。
一般使用本品后发生严重不良反应发生风险较小。但是，碘对比剂可能会引起类速发过敏反应或其他超敏反应症状。
还应考虑到过敏反应的可能性包括严重的、危及生命的、致命的速发过敏反应/类速发过敏反应。大多数严重副作用出现在前30分钟内。可能发生迟发型(用药后1小时或更长时间)超敏反应。因此应事先制定处理方法，应备好必要的药物和设备以便发生严重反应时立即治疗。在整个X线操作中使用留置管或导管以保持静脉输液通路通畅。
使用β-肾上腺素能阻滞剂可降低对比反应的阈值并增加对比反应的严重性，并降低肾上腺素治疗过敏反应的反应性。
哮喘患者同时接受β受体阻滞剂治疗的风险更高(见【药物相互作用】)
鉴于预试验对由非离子型对比剂引起的过敏反应预测的准确性极低，以及预试验本身也可能导致严重过敏反应，因此不建议采用预试验来预测碘过敏反应。
本品给药后至少30分钟内应当对患者进行观察。

凝血:
在体外，非离子碘对比剂与离子型对比剂相比，抑制凝血效应较弱。曾报告血液与含非离子介质的对比剂注射器保持接触时，会发生凝血。
已经报告使用塑料注射器代替玻璃注射器降低了体外凝血的可能性，但并没有消除这种可能性。

血栓栓塞的风险:
已经报告了在使用离子和非离子对比剂的心血管造影过程中导致心肌梗死和卒中的严重、罕见情况下致死的血栓栓塞事件。
因此，有必要进行细致的血管内给药技术操作，特别是在血管造影术中，以最小化血栓栓塞事件。许多因素，包括操作时长、导管和注射器材料、基础疾病状态以及伴随用药，都可能导致血栓栓塞事件的发生。由于这些原因，推荐使用细致的血管造影技术，包括密切关注导丝和导管操作，用肝素化盐水溶液频繁冲洗导管，并尽量缩短操作时间，应备有高级生命支持设施。
避免患有同型半胱氨酸尿症的患者进行血管造影，以降低血栓形成和栓塞的风险。

水化:
在对比剂给药前后，应确保经过适当的水化。这尤其适用于多发性骨髓瘤、糖尿病、肾功能不全，以及婴儿、幼儿和老年患者。小婴儿(年龄<1岁)尤其是新生儿对电解质紊乱和血流动力学改变易感。

心脏-循环系统反应:
应该对严重心脏病和肺动脉高压患者给予特别关注，因为其可能发生血流动力学变化或心律失常，曾发生罕见重度危及生命的反应及从心血管疾病原因的死亡，如心脏停搏、心脏呼吸骤停和心肌梗死。

中枢神经系统紊乱:
有急性脑病、脑瘤、或癫痫病史的病人要预防癫痫发作并需特别注意。另外，酗酒及药物成瘾者其癫痫发作和神经病理学改变的危险大为增加。

肾脏反应:
对比剂肾病的主要风险因素是基础肾功能不全。
在存在肾功能不全的情况下，糖尿病和碘对比剂剂量是诱发因素。其他问题包括脱水、晚期动脉硬化、肾灌注不佳和存在可能具有肾毒性的其他因素，例如某些用药或大手术。
为防止在对比剂给药后出现急性肾脏衰竭，应特别关注已有肾损害和糖尿病的患者，因其具有风险。
异常蛋白血症患者（浆细胞骨髓瘤和瓦尔登斯特伦巨球蛋白血症）也有风险。

预防措施包括：
- 明确高风险患者
- 确保适当水化。如有必要，在该操作前维持静脉内输注，直到对比剂被肾脏清除。
- 在将对比剂清除之前，避免额外向肾脏施加压力，例如肾毒性药物、口服胆囊对比剂、动脉钳闭、肾动脉血管成形术或大手术。
- 尽量减少对比剂使用剂量。
- 推迟反复对比剂检查，直至肾功能恢复到检查前水平。

正在接受二甲双胍治疗的糖尿病患者：
为防止乳酸性酸中毒，在碘对比剂血管内给药前，应对二甲双胍治疗的糖尿病患者的血清肌酐水平进行测定。在接受二甲双胍治疗的肾功能受损患者中，使用碘对比剂进行血管内造影研究可导致肾功能的急性改变，并与乳酸性酸中毒有关。对于血清肌酐/肾功能正常的患者：在注射对比剂时必须停用二甲双胍并在48小时内不能恢复用药，或直至肾功能/血清肌酐达正常值。对于血清肌酐/肾功能不正常的患者：必须停用二甲双胍并将对比剂检查推迟至48小时后。只有在肾功能/血清肌酐水平恒定后才能恢复二甲双胍的用药。对有些肾功能不正常或未知的急救病例，医生必须评估使用对比剂检查的利弊，并需采取预防措施：停用二甲双胍、给病人充足的水分、监测肾功能和仔细观察乳酸性酸中毒的症状。
肾功能和肝功能受损:
具有重度肾肝功能紊乱的患者需要特别护理，因为其体内的对比剂清除可能会显著延迟。血液透析患者可能由于放射检查而接受对比剂。对比剂注射与血液透析操作没必要时间关联，因为没有证据表明血液透析可保护肾功能受损患者免于发生对比剂肾病。

重症肌无力:
碘对比剂的给药可能会加重重症肌无力的症状。

嗜铬细胞瘤:
在进行介入治疗的嗜铬细胞瘤患者中应给予α-阻滞剂作为预防，以避免高血压危象。

甲状腺功能紊乱:
具有甲状腺毒症风险的患者应在使用碘对比剂之前进行谨慎评价。应对甲状腺功能亢进患者给予特别护理。多节性甲状腺肿患者在注射碘对比剂后可能具有发生甲状腺功能亢进的风险。
在成人和儿科患者(包括婴儿）使用碘对比剂后，已报告表明甲状腺功能减退或暂时性甲状腺抑制的甲状腺功能测试。有些病人因甲状腺功能减退而接受治疗。

外渗:
本品由于其等渗特性，相较于高渗对比剂，局部疼痛和血管外水肿更轻。发生外渗时，建议将患肢抬高并冷敷受累部位作为常规措施。在间隔综合征的病例中，可能需要手术减压。
本品的渗透压摩尔浓度为270-310mOsmol/kg。
根据适应证，每剂本品可能含有超过23mg的钠。控制钠饮食的患者必须考虑这点。

观察时间:
给予对比剂后，应至少观察患者30分钟，因为大部分严重副作用都出现在此时间内。但是，经验显示注射后数小时或数天内可能出现超敏反应。

镰状细胞病患者的镰状细胞危象:
血管内注射碘对比剂可促进纯合型镰状细胞病患者镰变，碘克沙醇给药前后，应对患者进行水化，只有当使用其他替代显像检查无法获得所需显像信息时，才使用碘克沙醇。
重度皮肤不良反应:
血管内对比剂给药后1小时至数周会发生重度皮肤不良反应(SCAR)，这些反应包括史蒂文斯-约翰逊综合征与中毒性表皮坏死松解症(SJS/TEN)、急性全身发疹性脓包性皮病(AGEP)以及药物反应伴嗜酸性粒细胞增多和全身性症状(DRESS)。反复使用对比剂后，反应严重程度可能升高，至不良事件发生时间可能缩短：预防性给药可能不会预防或减轻重度皮肤不良反应。使用碘克沙醇有上述重度皮肤不良反应史的患者避免使用碘克沙醇。

【孕妇及哺乳期妇女用药】
妊娠:
在妊娠女性中使用碘克沙醇的安全性尚未确立。一项针对实验动物研究的评价未表明该对比剂对生殖、胚胎或胎仔发育、妊娠期间和围产期、产后发育产生直接或间接的有害影响。因为在可能的情况下，在妊娠期间应避免辐射暴露，有或无对比剂的任何X线检查的获益应相对于可能风险进行仔细权衡。本产品不应该在妊娠期间使用，除非获益大于风险并且医师认为是必要的。
若母亲妊娠期使用过碘对比剂，则应在新生儿初生一周内检测其甲状腺功能。
推荐在2至6周龄时重复检测甲状腺功能，特别是低出生体重的新生儿或早产新生儿中。
哺乳:
对比剂在人类乳汁中的排出量未知，虽然估计很少，但在使用本品前应停止母乳喂养，并持续到至少24 小时后。

【儿童用药】
一般而言，碘克沙醇在儿科群体中所报告的不良反应类型与成年人类似。研究结果显示，与年纪大的患者相比，小于1岁的患儿出现不良反应的数量更多，可能与该年龄组药物消除较慢有关。
患儿(包括婴儿）在使用碘对比剂后指示甲状腺功能减退或甲状腺功能暂时性抑制的报道不常见。一些患者会接受甲状腺功能减退治疗(详见不良反应“国外不良反应监测情况”)。
患有脾瞒、其他药物和/或过敏原过敏症、青光眼和焦虑性心脏病、充血性心力衰竭或血清肌酐大于1.5mg/dL的患儿在使用任何对比剂期间和之后出现不良反应的风险更高。由于碘对比剂的消除较慢，肾功能不全或脱水的患儿可能出现不良事件的风险增加。

【老年用药】
在碘克沙醇的临床研究中，254/757(34 %)例患者为65岁及以上。这些患者和较年轻患者之间观察到的安全性和有效性没有总体差异。根据报告的其他临床经验，未确定老年患者与年轻患者中的缓解存在差异，但不能排除有些老年患者的敏感性更高。一般而言，应谨慎选择老年患者的用药剂量，通常应以剂量范围中的最低剂量开始，要考虑到肝、肾或心脏功能减退以及伴发疾病或其他药物治疗的频率均更高。

【药物的相互作用】
所有碘对比剂都可能影响甲状腺的碘结合能力，使甲状腺的碘结合能力可能降低长达数周，因此测量碘摄取（使用放射性碘）的测试将受到影响，使用碘对比剂可能会导致一过性的肾功能损害，这可能会在服用二甲双胍的糖尿病患者中导致乳酸性酸中毒(见【注意事项】)。
脾瞒患者同时接受β受体阻滞剂治疗的风险更高(见【注意事项】)。
接受白细胞介素-2治疗的患者，如果在少于两周的时间后接受碘对比剂注射，其出现延迟反应（流感样症状或皮肤反应）的风险升高。
有证据表明，β阻滞剂是X线对比剂类速发过敏反应的一个风险因素(β阻滞剂治疗时，X线对比剂给药可引起重度低血压)。
对甲状腺检查的影响
蛋白结合碘和放射性碘摄取研究的结果(取决于碘估值)将无法准确反映碘对比剂给药至少16天后的甲状腺功能。不依赖于碘估值(例如T3树脂摄取和总甲状腺素或游离甲状腺素T4测定)的甲状腺功能检查则可能不受影响。
对尿检的影响
与其它对比剂的报道相同，本品会导致使用尿浸试验检测尿液中的蛋白质出现假阳性结果。但考马斯蓝法可准确检测使用本品后的尿液蛋白。此外，如果尿液中含有高水平本品和其它对比剂，应谨慎解释尿比重测量结果，可以替换为折光测定法或尿渗透压法。

配伍禁忌
未发现有配伍禁忌。但是本品不能直接和其他药物混用。必须使用单独的注射器。

【药物过量】
用药过量在肾功能正常的患者中不大可能发生。该操作的持续时间在肾脏对高剂量对比剂的耐受性方面是十分重要的($t_{1/2}$约为2小时)。在偶然用药过量的情况下，水和电解质损耗必须通过输注进行补偿。肾功能应该在接下来的至少3天内进行监测，如果需要，血液透析可用于从患者身体系统中去除碘克沙醇。没有特异性的解毒剂。对用药过量的处理依症状而定。

【药理毒理】
注射时，有机结合碘在血管/组织中吸收射线。

在对健康志愿者静脉内注射碘克沙醇后进行检查，大多数的血液动力学、临床化学和血凝参数与注射前的数值比较，未发现显著偏差。所观察到的少量实验室参数的改变是极小的且无临床意义。
碘克沙醇注射液对病人肾功能只产生轻微的影响。对于血清肌酐水平在1.3-3.5mg/dl的糖尿病患者，使用本品后仅3%病人肌酐水平的上升≥0.5mg/dl，而无肌酐水平上升≥1.0mg/dl的病人。从邻近的管状细胞释放的酶（碱性磷酸酶和N-乙酰-β-葡萄糖亚酰胺酶）较注射非离子型单体对比剂要少，与离子单体型对比剂比较也有相同的趋势。碘克沙醇注射液还有很好的肾脏耐受性。
注射碘克沙醇注射液与其它对比剂比较，对心血管参数，如:LVEDP、LVSP、心率和QT-时间以及股血管血流的影响较少。
临床前安全性数据
在大鼠与兔子的生殖研究中没有证据显示由碘克沙醇引起的繁殖力损害或致畸。

【药代动力学】
碘克沙醇在体内快速分布，平均分布半衰期约为21分钟。表观分布容积与细胞外液量(0.26l/kg 体重)相同，这表明碘克沙醇仅分布在细胞外液。
没有检测到代谢物，蛋白结合率低于2%。
平均排泄半衰期约为2小时。碘克沙醇主要由肾小球滤过经肾脏排泄，健康志愿者经静脉注射后，约80%的注射量在4小时内以原形从尿中排出，97%在24小时内排出。只有约1.2%的注射量在72小时内从粪便中排泄，最大尿药浓度在注射后约1小时内出现。
在所推荐的剂量范围内未观察到有剂量依赖性的动力学特征。

【贮藏】
本品应遮光，低于30°C室温贮藏。本品在使用前37°C的条件下最多可贮存1个月。

【包装】
本品包装在注射用聚丙烯塑料瓶内。1塑料瓶/盒。

【有效期】36个月

【执行标准】进口药品注册标准JX20190104

【批准文号】

浓度/体积	规格	进口药品注册证号	分包装批准文号
270 mgI/ml-50 ml	50ml:13.5g(I)	小包装：H20181164 大包装：H20181163	国药准字J20140156
320 mgI/ml-50 ml	50ml:16g(I)	小包装：H20181166 大包装：H20181165	国药准字J20140157
270 mgI/ml-100 ml	100ml:27g(I)	小包装：H20181170 大包装：H20181169	国药准字J20140158
320 mgI/ml-100 ml	100ml:32g(I)	小包装：H20181168 大包装：H20181167	国药准字J20140159

【使用与操作指导】
如所有的非胃肠道药品，在使用本品前应进行目检，以检查是否有微粒、变色和容器的损坏现象。打开包装后即刻使用。每瓶仅供一人使用，用剩药液弃去。
在使用本品前可加热至体温(37°C)。

【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

威视派克是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

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Approved Date: Dec. 2006

Revised Date: Jul. 2009 Aug.2010 Nov. 2014 Apr. 2016 Jul.2018 Jul. 2019 Oct.2020

GE Healthcare

IODIXANOL INJECTION

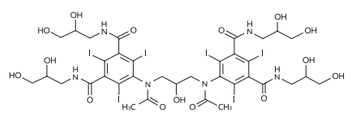
VISIPAQUE®

Insert Sheet of Iodixanol Injection

Please read the insert carefully and use under instruction by doctor

【Drug Name】
Generic Name: Iodixanol Injection
Brand Name: Visipaque®
Chinese Phonetic Alphabet: Diankeshachun Zhusheye

【Composition】
The main ingredient of this drug is Iodixanol and its chemical name is 5,5'-[(2-Hydroxy-1,3-propanediyl)-bis (acetyliminol)]-bis[N,N'-bis (2,3-dihydroxypropyl)-2,4,6-triiodo-1,3-benzenedicarboxamide]
Chemical structure:



Molecular Formula: $C_{35}H_{44}I_6N_6O_{15}$
Molecular Weight: 1550.20
Excipients: Trometamol, Sodium Chloride, Calcium Chloride, Sodium Calcium Edetate, Hydrochloric Acid to adjust pH, Water for Injection

【Properties】
The product is clear, colourless to pale yellow aqueous solutions.
Iodixanol is a non-ionic, dimeric, hexaiodinated, water-soluble X-ray contrast medium.
Pure aqueous solutions of iodixanol in all clinical relevant concentrations have a lower osmolality than whole blood and the corresponding strengths of the non-ionic monomeric contrast media.
The product is made isotonic with normal body fluids by addition of electrolytes. The osmolality and viscosity values of the product are as follows:

Concentration	Osmolality* mOsm/kg H_2O 37°C	Viscosity (mPa.s) 20°C	37°C
270 mgI/ml	290	11.3	5.8
320 mgI/ml	290	25.4	11.4

*Method: Vapour- pressure osmometry.
The pH of the product is 6.8-7.6

【Indications】
X-ray contrast medium for use in adults for cardioangiography, cerebral angiography (conventional and i.a. DSA), peripheral arteriography (conventional and i.a. DSA), abdominal angiography (i.a. DSA), urography, venography, CT-enhancement. Cardioangiography, urography and CT-enhancement for Children.

【Presentation】
(1) 50ml:13.5g(I) (2) 50ml:16g(I) (3) 100ml:27g(I) (4) 100ml:32g(I)

【Dosage and Administration】
The dosage may vary depending on the type of examination, the age, weight, cardiac output and general condition of the patient and the technique used. Usually approximately the same iodine concentration and volume is used as with other iodinated X-ray contrast media in current use, but adequate diagnostic information has also been obtained in some studies with iodixanol injection with somewhat lower iodine concentration. Adequate hydration should be assured before and after administration as for other contrast media.

The following recommendation for an average dose for a normal adult may serve as a guide. The doses given for intra-arterial use are for single injections that may be repeated.

Indication/Investigation	Concentration	Volume
Intra-arterial use		
Arteriographies		
selective cerebral	270/320 (1) mgI/ml	5 - 10 ml per inj.
selective cerebral i.a. DSA	150 mgI/ml	5 - 10 ml per inj.
aortography	270/320 mgI/ml	40 - 60 ml per inj.
peripheral	270/320 mgI/ml	30 - 60 ml per inj.
peripheral i.a. DSA	150 mgI/ml	30 - 60 ml per inj.
selective visceral i.a. DSA	270 mgI/ml	10 - 40 ml per inj.
Cardioangiography		
Left ventricle and aortic root inj.	320 mgI/ml	30 - 60 ml per inj.
Selective coronary arteriography	320 mgI/ml	4 - 8 ml per inj.
Children:	270/320 mgI/ml	Depending on age, weight and pathology (recommended max total dose 10 ml/kg)
Intravenous use		
Urography		
Adults	270/320 mgI/ml	40 - 80 ml (2)
Children < 7 kg	270/320 mgI/ml	2-4 ml/kg (2)
Children > 7 kg	270/320 mgI/ml	2-3 ml/kg
		All doses depending on age, weight and pathology (max. 50 ml)
Venography	270 mgI/ml	50 - 150 ml/leg
CT-enhancement		
CT of the head, adults	270/320 mgI/ml	50 - 150 ml
CT of the body, adults	270/320 mgI/ml	75 - 150 ml
Children, CT of the head and body	270/320 mgI/ml	2 - 3 ml/kg up to 50 ml (in a few cases up to 150 ml may be given)

(1) Both strengths are documented, but 270 mg I/ml is recommended in most cases.
(2) In high-dose urography higher doses can be used.
Elderly: As for other adults.

【Adverse Reaction】
Below are listed possible side effects in relation with radiographic procedures which include the use of VISIPAQUE.
Undesirable effects associated with VISIPAQUE are usually mild to moderate and transient in nature. Serious reactions as well as fatalities are only seen on very rare occasions, these may include acute-on-chronic renal failure, acute renal failure, anaphylactic or anaphylactoid shock, hypersensitivity reaction followed by cardiac reactions (Kounis' syndrome), cardiac or cardio-respiratory arrest and myocardial infarction. Cardiac reaction may be promoted by the underlying disease or the procedure. Hypersensitivity reactions may present as respiratory or cutaneous symptoms like dyspnoea, rash, erythema, urticaria, pruritus, severe skin reactions, angioneurotic oedema, hypotension, fever, laryngeal oedema, bronchospasm or pulmonary oedema. In patients with autoimmune diseases cases of vasculitis and SJS-like syndrome were observed. They may appear either immediately after the injection or up to a few days later. Hypersensitivity reactions may occur irrespectively of the dose and mode of administration and mild symptoms may represent the first signs of a serious anaphylactoid reaction/shock. Administration of the contrast medium must be discontinued immediately and, if necessary, specific therapy instituted via the vascular access.
Patients using beta blockers may present with atypical symptoms of hypersensitivity which may be misinterpreted as a vagal reaction. A minor transient increase in serum creatinine is common after iodinated contrast media, but is usually of no clinical relevance.
The frequencies of undesirable effects are defined as follows: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data). The listed frequencies are based on internal clinical documentation and published studies, comprising more than 57,705 patients.

Intravascular administration:
Blood and lymphatic system disorders
Not known: Thrombocytopenia

Immune system disorders:
Uncommon: Hypersensitivity
Not known: Anaphylactic/anaphylactoid shock, anaphylactic/anaphylactoid reaction including life-threatening or fatal anaphylaxis

Endocrine disorders:
Not known: Hyperthyroidism, transient hypothyroidism

Psychiatric disorders:
Very rare: Agitation, anxiety
Not known: Confusional state

Nervous system disorders:
Uncommon: Headache
Rare: Dizziness, sensory abnormalities including dysgeusia paraesthesia, parosmia
Very rare: Cerebrovascular accident, amnesia, syncope, tremor (transient), hypoaesthesia
Not known: Coma, disturbance in consciousness, convulsion, transient contrast-induced encephalopathy caused by extravasation of contrast media (including amnesia, hallucination, paralysis, paresis, transient speech disorder, aphasia, dysarthria), which can manifest as sensory, motor or global neurological dysfunction .

Eye disorders:
Very rare: Cortical blindness (transient), visual impairment (including diplopia, blurred vision), eyelid oedema

Cardiac disorders:
Rare: Arrhythmia (including bradycardia, tachycardia), myocardial infarction
Very rare: Cardiac arrest, palpitations
Not known: Ventricular hypokinesia, spasms of coronary arteries, cardio-respiratory arrest, conduction abnormalities, coronary artery thrombosis, angina pectoris

Vascular disorders:
Uncommon: Flushing
Rare: Hypotension
Very rare: Hypertension, ischaemia
Not known: Shock, arterial spasm, thrombosis, thrombophlebitis

Respiratory, thoracic and mediastinal disorders:
Rare: Cough, sneezing
Very rare: Dyspnoea, throat irritation, laryngeal oedema,
Not known: Non-cardiogenic pulmonary oedema, respiratory arrest, respiratory failure, bronchospasm, throat tightness, pharyngeal oedema

Gastrointestinal disorders:
Uncommon: Nausea, vomiting
Very rare: Abdominal pain/ discomfort, diarrhoea
Not known: Acute pancreatitis, pancreatitis aggravated, salivary gland enlargement

Skin and subcutaneous system disorders
Uncommon: Rash or drug eruption, pruritus, urticaria
Very rare: Angioedema, erythema, hyperhidrosis
Not known: Bullous or exfoliative dermatitis, Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, acute generalised exanthematous pustulosis, drug rash with eosinophilia and systemic symptoms

Musculoskeletal and connective tissue disorders:
Very rare: Back pain, muscle spasm
Not known: Arthralgia

Renal and urinary disorders:
Uncommon: Acute kidney injury or nephropathy toxic (contrast induced nephropathy-CIN)
Not known: Increased blood creatinine

General disorders and administration site conditions:
Uncommon: chest pain, feeling of body temperature change
Rare: Shivering (chills), pyrexia, pain and discomfort, administration site reactions including extravasation,
Very rare: Asthenic conditions (e.g. malaise, fatigue), face oedema, localised oedema
Not known: Swelling

Injury, poisoning and procedural complications:
Not known: Iodism

【Contraindications】
Manifest thyrotoxicosis. History of serious hypersensitivity reaction to VISIPAQUE. Hypersensitivity to the active substance or to any of the excipients. NOT FOR INTRATHECAL USE . [See the contents of 【Precautions】 "Accidental intrathecal administration" for details.]

【Precautions】
Accidental intrathecal administration
VISIPAQUE is for intravascular use only and is contraindicated for intrathecal use [see Contraindications (4) and Dosage and Administration (2.1)]. Inadvertent Intrathecal administration can cause death, convulsions/seizures, cerebral hemorrhage, coma, paralysis, arachnoiditis, acute renal failure, cardiac arrest, rhabdomyolysis, hyperthermia, and brain edema.
Hypersensitivity:
A positive history of allergy, asthma, or untoward reactions to iodinated contrast media indicates a need for special caution. Premedication with corticosteroids or histamine H_1 and H_2 antagonists might be considered in these cases.
The risk of serious reactions in connection with use of VISIPAQUE is regarded as minor. However, iodinated contrast media may provoke anaphylactoid reactions or other manifestations of hypersensitivity.
The possibility of hypersensitivity including serious, life-threatening, fatal anaphylactic/ anaphylactoid reactions should always be considered. The majority of serious undesirable occur within the first 30 minutes. Late onset (that is 1 hour or more after application) hypersensitivity reactions can occur.
A course of action should therefore be planned in advance, with necessary drugs and equipment available for immediate treatment, should a serious reaction occur. It is advisable always to use an indwelling cannula or catheter for quick intravenous access throughout the entire X-ray procedure.
The use of beta-adrenergic blocking agents lowers the threshold for and increases the severity of contrast reactions and reduces the responsiveness of treatment of anaphylactoid reactions with adrenaline. Asthmatic patients are at higher risk on concomitant beta blocker therapy (see 【Interaction】 Because the predict value of iodinate hypersensitivity pretest before administration of non-ionic contrast medium is very low and the pretest itself may cause severe hypersensitivity reaction, it is not suggested to use pretest to predict the iodinate hypersensitivity reaction. Patients should be observed for at least 30 minutes after administration of VISIPAQUE.
Coagulopathy:
Non-ionic, iodinated contrast media inhibit blood coagulation in vitro less than ionic contrast media. Clotting has been reported when blood remains in contact with syringes containing contrast media including non-ionic media. The use of plastic syringes in place of glass syringes has been reported to decrease but not eliminate the likelihood of in vitro clotting.
Risk for thromboembolism:
Serious, rarely fatal, thromboembolic events causing myocardial infarction and stroke have been reported during angio-cardiographic procedures with both ionic and non-ionic contrast media. Therefore, meticulous intravascular administration technique is necessary, particularly during angiographic procedures, to minimize thromboembolic events. Numerous factors, including length of procedure, catheter and syringe material, underlying disease state, and concomitant medications, may contribute to the development of thromboembolic events. For these reasons, meticulous angiographic techniques are recommended, including close attention to guidewire and catheter manipulation, frequent catheter flushing (e.g. with heparinized saline solutions), and minimizing the length of the procedure. Advanced life support facilities should be readily available. Avoid blood remaining in contact with syringes containing iodinated contrast agents, which increases the risk of clotting. Avoid angiocardiography in patients with homocystinuria because of the risk of inducing thrombosis and embolism.
Hydration:
Adequate hydration should be assured before and after contrast media administration. This applies especially to patients with multiple myeloma, diabetes mellitus, renal dysfunction, as well as to infants, small children and elderly patients. Young infants (age < 1 year) and especially neonates are susceptible to electrolyte disturbance and haemodynamic alterations.
Cardio-circulatory reactions:
Care should also be taken in patients with serious cardiac disease and pulmonary hypertension as they may develop haemodynamic changes or arrhythmias. Rarely severe life-threatening reactions and fatalities of cardiovascular origin such as cardiac-, cardio-respiratory arrest and myocardial infarction have occurred.
CNS disturbances:
Patients with acute cerebral pathology, tumours or a history of epilepsy are predisposed for seizures and merit particular care. Also alcoholics and drug addicts have an increased risk for seizures and neurological reactions
Renal reactions:
Major risk factor for contrast medium-induced nephropathy is underlying renal dysfunction. Diabetes mellitus and the volume of iodinated contrast medium administered are contributing factors in the presence of renal dysfunction. Additional concerns are dehydration, advanced arteriosclerosis, poor renal perfusion and the presence of other factors that may be nephrotoxic, such as certain medications or major surgery.

To prevent acute renal failure following contrast media administration, special care should be exercised in patients with pre-existing renal impairment and diabetes mellitus as they are at risk. Patients with paraproteinemias (myelomatosis and Waldenström's macroglobulinemia) are also at risk.
Preventive measures include:
- Identification of high risk patients
- Ensuring adequate hydration. If necessary by maintaining an i.v. infusion from before the procedure until the contrast medium has been cleared by the kidneys.
- Avoiding additional strain on the kidneys in the form of nephrotoxic drugs, oral cholecystographic agents, arterial clamping, renal arterial angioplasty, or major surgery, until the contrast medium has been cleared.
- Dose reducing to a minimum.
- Postponing a repeat contrast medium examination until renal function returns to pre-examination levels.

Diabetic patients receiving metformin:
To prevent lactic acidosis, serum creatinine level should be measured in diabetic patients treated with metformin prior to intravascular administration of iodinated contrast medium.
Intravascular contrast studies with iodinated contrast media can lead to acute alteration of renal function and have been associated with lactic acidosis in patients with impaired renal function receiving metformin. Normal serum creatinine/renal function: Administration of metformin should be stopped at the time of administration of contrast medium and not resumed for 48 hours or until renal function/serum creatinine is normal. Abnormal serum creatinine/renal function: Metformin should be stooped and the contrast medium examination delayed for 48 hours. Metformin should only be restarted if renal function/serum creatinine is unchanged. In emergency cases where renal function is abnormal or unknown, the physician should evaluate the risk/benefit of the contrast medium examination, and precautions should be implemented: Metformin should be stopped, patient hydrated, renal function monitored and patient observed for symptoms of lactic acidosis.
Impaired renal and hepatic function:
Particular care is required in patients with severe disturbance of both renal and hepatic function as they may have significantly delayed contrast medium clearance. Patients on haemodialysis may receive contrast media for radiological procedures. Correlation of the time of contrast media injection with the haemodialysis session is unnecessary because there is no evidence that haemodialysis protects patients with impaired renal function from contrast medium induced nephropathy.
Myasthenia gravis:
The administration of iodinated contrast media may aggravate the symptoms of myasthenia gravis.
Phaeochromocytoma:
In patients with phaeochromocytoma undergoing interventional procedures, alpha blockers should be given as prophylaxis to avoid a hypertensive crisis.
Disturbances in thyroid function:
Patients at risk of thyrotoxicosis should be carefully evaluated before any use of iodinated contrast medium. Special care should be exercised in patients with hyperthyroidism. Patients with multinodular goitre may be at risk of developing hyperthyroidism following injection of iodinated contrast media.

Thyroid function tests indicative of hypothyroidism or transient thyroid suppression have been reported following iodinated contrast media administration to adult and paediatric patients, including infants. Some patients were treated for hypothyroidism.
Extravasation:
VISIPAQUE due to its isotonicity gives rise to less local pain and extravascular oedema than hyperosmolar contrast media. In case of extravasation, elevating and cooling the affected site is recommended as routine measures. Surgical decompression may be necessary in cases of compartment syndrome.
The osmolality should be between 270 to 310 mOsmol/kg. Visipaque may, dependent on the indication, contain more than 23 mg sodium per dose. This must be taken into consideration in patients on a controlled sodium diet.
Observation-time
After contrast medium administration, the patient should be observed for at least 30 minutes, since the majority of serious side effects occur within this time. However, experience shows that hypersensitivity reactions may appear up to several hours or days post injection.
Sickle Cell Crisis in Patients with Sickle Cell Disease.
Iodinated contrast agents when administered intravascularly may promote sickling in individuals who are homozygous for sickle cell disease. Hydrate patients prior to and following VISIPAQUE administration and use VISIPAQUE only if the necessary imaging information cannot be obtained with alternative imaging modalities.
Severe Cutaneous Adverse Reactions
Severe cutaneous adverse reactions (SCAR) may develop from 1 hour to several weeks after intravascular contrast agent administration. These reactions include Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN), acute generalized exanthematous pustulosis (AGEP) and drug reaction with eosinophilia and systemic symptoms (DRESS). Reaction severity may increase and time to onset may decrease with repeat administration of contrast agents; prophylactic medications may not prevent or mitigate severe cutaneous adverse reactions. Avoid administering VISIPAQUE to patients with a history of a severe cutaneous adverse reaction to VISIPAQUE

【Drugs for use by women during Pregnancy and Lactation Period】
Pregnancy:
The safety of VISIPAQUE for use in human pregnancy has not been established. An evaluation of experimental animal studies does not indicate direct or indirect harmful effects with respect to reproduction, development of the embryo or foetus, the course of gestation and peri- and postnatal development. Since, wherever possible, radiation exposure should be avoided during pregnancy, the benefits of any X-ray examination, with or without contrast media, should be carefully weighed against the possible risk. The product should not be used in pregnancy unless benefit outweighs risk and it is considered essential by the physician.
Thyroid function should be checked in neonates during the first week of life, following administration of iodinated contrast agents to the mother during pregnancy.

Repeat testing of thyroid function is recommended at 2 to 6 weeks of age, particularly in low birth weight newborn or premature newborn.

Lactation: The degree of excretion into human milk is not known, although expected to be low. Breast feeding should be discontinued prior toadministration of VISIPAQUE and should not be recommended until at least 24 hours after the administration of VISIPAQUE.

【Drugs for Children Use】
In general, the types of adverse reactions reported are similar to those of adults. A higher number of adverse events in patients less than 1 year of age compared to older patients were observed in a study of VISIPAQUE. The elimination of VISIPAQUE is slower in this age group. Pediatric patients at higher risk of experiencing an adverse reaction during and after administration of any contrast agent may include those with asthma, hypersensitivity to other medication and/or allergens, cyanotic and acyanotic heart disease, congestive heart failure, or a serum creatinine greater than 1.5 mg/dL. Pediatric patients with immature renal function or dehydration may be at increased risk for adverse events due to slower elimination of iodinated contrast agents.

【Drugs for Elderly Patients】
In clinical studies of VISIPAQUE, 254/757 (34%) of patients were 65 and over. No overall differences in safety or effectiveness were observed between these patients and younger patients. Other reported clinical experience has not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. In general, 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.

【Interaction】
All iodinated contrast media may affect the iodine binding capacity of the thyroid which may be reduced for up to several weeks, thus tests that measure iodine uptake (using radioactive iodine) will be affected. Use of iodinated contrast media may result in a transient impairment of renal function and this may precipitate lactic acidosis in diabetics who are taking **metformin** (see 【Precautions】). Asthmatic patients are at higher risk on concomitant beta blocker therapy (see 【Precautions】). Patients treated with **interleukin-2** less than two weeks prior to an iodinated contrast medium injection have an increased risk for delayed reactions (flu-like symptoms or skin reactions). There is some evidence that use of beta blockers is a risk factor for anaphylactoid reactions to X-ray contrast media (severe hypotension has been seen with X-ray contrast media on beta blocker therapy).
Effect on Thyroid tests
The results of protein bound iodine and radioactive iodine uptake studies, which depend on iodine estimation, will not accurately reflect thyroid function for at least 16 days following administration of iodinated contrast agents. However, thyroid function tests which do not depend on iodine estimations (e.g., T3 resin uptake and total or free thyroxine T4 assays) are not affected.
Effect on Urine Tests
As reported with other contrast agents, VISIPAQUE may produce a false-positive result for protein in the urine using urine dip tests However, the Coomassie blue method has been shown to give accurate results for the measurement of urine protein in the presence of VISIPAQUE. In addition, care should be used in interpreting the results of urine specific gravity measurements in the presence of high levels of VISIPAQUE and other contrast agents in the urine. Refractometry or urine osmolality may be substituted.

Incompatibilities:
No incompatibility has been found. However, VISIPAQUE should not be directly mixed with other drugs. A separate syringe should be sued.

【Overdose】
Overdose is unlikely in patients with a normal renal function. The duration of the procedure is important for the renal tolerability of high doses of contrast media ($t_{1/2}$~2 hours). In the event of accidental overdosing, the water and electrolyte losses must be compensated by infusion. Renal function should be monitored for at least the next 3 days. If needed, haemodialysis may be used to remove iodixanol from the patient's system. There is no specific antidote. Treatment of overdose is symptomatic.

【Pharmacological and Toxicological Properties】
The organically bound iodine absorbs radiation in the blood vessels/tissues when it is injected.
For most of the haemodynamic, clinical-chemical and coagulation parameters examined following intravenous injection of iodixanol in healthy volunteers, no significant deviation from preinjection values has been found. The few changes observed in the laboratory parameters were minor and considered to be of no clinical importance.
Iodixanol Injection induces only minor effects on renal function in patients. In diabetic patients with serum creatinine levels of 1.3-3.5mg/dl, VISIPAQUE use resulted in 3% of patients experiencing a rise in creatinine of ≥0.5mg/dl and 0% of patients with a rise of ≥1.0mg/dl. The release of enzymes (alkaline phosphatase and N-acetyl-ß-glucosaminidase) from the proximal tubular cells is less than after injections of non-ionic monomeric contrast media and the same trend is seen compared to ionic dimeric contrast media. Iodixanol Injection is also well tolerated by the kidney.
Cardiovascular parameters such as LVEDP, LVSP, heart rate and QT-time as well as femoral blood flow were less influenced after the injection of Iodixanol than after other contract media, where measured.
Preclinical safety data.
Reproduction studies in rats and rabbits have revealed no evidence of impaired fertility or teratogenicity due to iodixanol.

【Pharmacokinetic Properties】
Iodixanol is rapidly distributed in the body with a mean distribution half-life of approximately 21 minutes. The apparent volume of distribution is of the same magnitude as the extracellular fluid (0.26 l/kg b.w.), indicating that iodixanol is distributed in the extra-cellular volume only.
No metabolites have been detected. The protein binding is less than 2%.
The mean elimination half-life is approximately 2 hours. Iodixanol is excreted mainly through the kidneys by glomerular filtration. Approximately 80% of the administered dose is recovered unmetabolized in the urine within 4 hours and 97% within 24 hours after intravenous injection in healthy volunteers. Only about 1.2% of the injected dose is excreted in faeces within 72 hours.
The maximum urinary concentration appears within approximately 1 hour after injection.
No dose dependent kinetics have been observed in the recommended dose range.

【Storage】
VISIPAQUE should be stored at room temperature up to 30°C protected from light. The product bottles may be stored at 37°C for up to 1 month prior to use.

【Package】
The product is filled in polypropylene bottles, 1 bottle/box

【Shelf life】
36 months

【Specification】
Specification number: JX20190104

【Approval Number】

Strength-Volume	Presentation	Import Drug License Number	Repackaging Approval Number
270 mgI/ml-50 ml	50ml:13.5g(I)	Finished product: H20181164 Semi-finished product: H20181163	国药准字J20140156
320 mgI/ml-50 ml	50ml:16g(I)	Finished product: H20181166 Semi-finished product: H20181165	国药准字J20140157
270 mgI/ml-100 ml	100ml:27g(I)	Finished product: H20181170 Semi-finished product: H20181169	国药准字J20140158
320 mgI/ml-100 ml	100ml:32g(I)	Finished product: H20181168 Semi-finished product: H20181167	国药准字J20140159

【Instructions for use/handling】
Like all parenteral products, VISIPAQUE should be inspected visually for particulate matter, discolouration and the integrity of the container prior to use.
The product should be drawn into the syringe immediately before use. Bottles are intended for single use only, any unused portions must be discarded.
VISIPAQUE may be warmed to body temperature (37°C) before administration.

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