Reports of Cases

JUDGMENT OF THE GENERAL COURT (Fourth Chamber)

19 September 2019*

(Medicinal products for human use — Suspension of the marketing authorisation for gadolinium-containing contrast agents — Articles 31 and 116 of Directive 2001/83/EC — Precautionary principle — Equal treatment — Proportionality — Impartiality)

In Case T-783/17,

GE Healthcare A/S, established in Oslo (Norway), represented by D. Scannell, Barrister, G. Castle and S. Oryszczuk, Solicitors,

applicant,

v

European Commission, represented by M. Wilderspin and A. Sipos, acting as Agents,

defendant,

ACTION based on Article 263 TFEU seeking annulment of Commission Implementing Decision C(2017) 7941 final of 23 November 2017, concerning, in the framework of Article 31 of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ 2001 L 311, p. 67), the marketing authorisations for gadolinium-containing contrast agents for human use which contain one or more of the active substances 'gadobenic acid, gadobutrol, gadodiamide, gadopentetic acid, gadoteric acid, gadoteridol, gadoversetamide and gadoxetic acid', in so far as that decision concerns Omniscan,

THE GENERAL COURT (Fourth Chamber),

composed of H. Kanninen, President, L. Calvo-Sotelo Ibáñez-Martín (Rapporteur) and I. Reine, Judges,

Registrar: P. Cullen, Administrator,

having regard to the written part of the procedure and further to the hearing on 29 January 2019,

gives the following

* Language of the case: English.

Judgment

I. Background to the dispute

1 The applicant, GE Healthcare A/S, is a Norwegian wholly owned subsidiary of GE Healthcare Inc. The applicant is a member of the GE Healthcare group of companies, engaged in various medical and pharmaceutical activities worldwide.

2 The applicant is the manufacturer of Omniscan (gadodiamide) and the marketing authorisation ('MA') holder for that product in fifteen Member States.

3 Omniscan is a contrast agent with a linear structure based on gadolinium ('linear gadolinium'), as opposed to contrast agents also based on gadolinium but with a macrocyclic structure ('macrocyclic gadolinium'). It is administered intravenously and is used to provide contrast image enhancement, in order to improve images obtained in magnetic resonance imaging ('MRI') and in magnetic resonance angiography imaging. Gadolinium-containing contrast agents improve the visualisation of tumours and lesions in patients and optimise the accurate diagnosis of chronic conditions such as cancer and heart disease. They are classed as medicinal products.

4 In the course of 2010, the Committee for Medicinal Products for Human Use ('CHMP') found a link between gadolinium-containing contrast agents and nephrogenic systemic fibrosis in patients with severe renal impairment. That finding led to the adoption of risk-management measures. Those measures include warnings in the product information, restrictions on use in patients with impaired renal function and contraindication in patients with severe or acute renal impairment.

5 On 14 January 2016, a common assessment was made of documents analysing the adverse effects caused by medicinal products, in other words periodic safety update reports ('PSUR'). During that assessment of the PSUR on gadolinium-containing contrast agents, the Pharmacovigilance Risk Assessment Committee ('PRAC') observed that studies had shown that gadolinium is retained in the human body, including in the brain, but that no clinical consequences of that retention had been identified to date. At that stage, the PRAC considered that the risk-benefit balance of Omniscan remained positive. Nevertheless, the PRAC recommended adding the accumulation and retention of gadolinium in the brain to the risk management plan and to state in that plan that there was no information on the clinical implications of that retention. Finally, the PRAC suggested that there should be an in-depth review of that accumulation and its clinical consequences.

6 On 9 March 2016, the European Commission triggered a referral as provided under Article 31 of Directive 2001/83 on the ground that a review of gadolinium-containing contrast agents would allow a more in-depth assessment of the evidence of their accumulation in the brain. The Commission added that such a review would also enable a re-evaluation of the risk-benefit balance of those products in order to determine whether the MA should be maintained, varied, suspended or revoked.

7 The first subparagraph of Article 31(1) of Directive 2001/83 sets out a procedure whereby 'the Member States, the Commission, the applicant or the marketing authorisation holder shall, in specific cases where the interests of the Union are involved, refer the matter to the [CHMP] for application of the procedure laid down in Articles 32, 33 and 34 before any decision is reached on an application for an [MA] or on the suspension or revocation of an [MA], or on any other variation of the [MA] which appears necessary'. Furthermore, the second subparagraph of Article 31(1) of Directive 2001/83 provides that 'where the referral results from the evaluation of data relating to pharmacovigilance of an authorised medicinal product, the matter shall be referred to the [PRAC] … . The [PRAC] shall issue a recommendation … . The final recommendation shall be forwarded to the [CHMP]'.

8 At the end of the first recommendation of 9 March 2017, the PRAC recommended, inter alia, the suspension of the MA for Omniscan.

9 On 20 March 2017, the applicant requested a re-examination of the first PRAC recommendation. In that request for re-examination, the applicant claimed that that first recommendation was based on errors and omissions, that a fair assessment of the risk-benefit balance of Omniscan had not been carried out and that the precautionary principle had not been applied correctly. Moreover, the applicant took issue with the composition of the expert group consulted by the PRAC. Lastly, the applicant took the view that the suspension of the MA for Omniscan was disproportionate given that it was possible to adopt other measures to minimise the risks.

10 The PRAC issued its second recommendation on 6 July 2017. It was very similar to the first.

11 The PRAC thus acknowledged that gadolinium could be detected in the brain after being administered. It also observed that the long-term clinical consequences of gadolinium retention in the brain remained unknown and that, although no adverse neurological effects had yet been demonstrated to be caused by that accumulation, long-term safety data was limited. The PRAC considered, nevertheless, that absent or limited information in case studies on the effects of gadolinium could not be regarded as evidence of the absence of gadolinium toxicity in the brain. In view, in particular, of data supporting dechelation of linear agents in vivo and of the affected regions of the brain, the PRAC considered that harmful effects, such as impairment of fine motor skills or cognitive impairment, as well as potential interaction with disease processes, were plausible. The PRAC therefore considered that there were reasonable and serious concerns raised as to the potential of neurological harm associated with the accumulation of gadolinium in the brain. Nonetheless, the PRAC issued the opinion that, although both linear and macrocyclic gadolinium-containing agents had the ability to distribute to the brain, linear agents are retained and persist in the brain for up to 1 year or longer, whereas macrocyclic agents show only a transient increase in the concentration of gadolinium in the brain and undergo early washout.

12 Moreover, and while the applicant claimed that Omniscan had a unique indication in myocardial perfusion imaging in four Member States as it was of special benefit to that type of imaging, the PRAC called into question that special benefit. The PRAC observed that Omniscan was also indicated for whole-body MRI, which encompassed imaging of the heart, including myocardial perfusion imaging. The PRAC also recalled that Omniscan was contraindicated for use in patients with severe or acute renal impairment, but noted that, following the introduction of risk minimisation measures in 2010, there had been no new confirmed cases of nephrogenic systemic fibrosis. The PRAC also described the appearance of skin plaques following injection of linear gadolinium. Finally, as regards hypersensitivity reactions, the PRAC acknowledged that the summary of product characteristics for Omniscan already included appropriate warnings and risk minimisation measures, and that the claimed differences between Omniscan and other gadolinium-containing contrast agents were, in that respect, too subtle to influence the risk-benefit balance.

13 In the light of the foregoing, and taking into account the existence of alternative products and the serious concerns regarding potential neurological harm, as well as the risks already associated with the use of linear gadolinium-containing contrast agents, including the significant risk of nephrogenic systemic fibrosis and skin plaques, the PRAC considered that patients could not bear those risks until conclusive scientific evidence on the long term neurotoxic effects of Omniscan became available, and that the benefit of that product in terms of contrast enhancement in MRI did not outweigh those risks.

14 Ultimately, in its second recommendation, the PRAC reiterated its conclusion that the risk-benefit balance of linear gadolinium-containing contrast agents was no longer favourable, and that, with exceptions, the MA for those products should be suspended, while the MA for other macrocyclic products should be merely varied. As in its first recommendation, the PRAC recommended that that

suspension could be lifted only if MA holders were able to provide data indicating either that there were clinically important benefits which were not established at that time, and which would outweigh the risks related to the product, or that the product did not lead to retention of gadolinium in tissues, including in the brain.

15 The second PRAC recommendation was sent to the CHMP. The CHMP issued its opinion on 20 July 2017. Despite the divergent positions of the representatives from 12 Member States and the Norwegian and Icelandic representatives, the CHMP agreed, in essence, with the PRAC recommendations. In particular, it considered that the risk-benefit balance of Omniscan was no longer favourable.

16 Nevertheless, the CHMP differed on certain points of the second PRAC recommendation.

17 First of all, the CHMP disagreed with the PRAC's assertion that macrocyclic agents showed only a transient increase in gadolinium in the brain and were rapidly eliminated. The CHMP considered it sufficient to observe that 'measurements of gadolinium in the brain … showed differences between linear and macrocyclic agents in terms of accumulation over time'.

18 Next, given the extensive use of gadolinium and the absence of data on the adverse effects of gadolinium accumulation in the brain, the CHMP considered that those harmful effects and the potential interaction of that product with disease were 'possible' rather than 'plausible' because 'plausible' would imply a higher risk of harm.

19 Finally, the CHMP considered that the PRAC's conclusion regarding the risk of skin plaques upon exposure to linear gadolinium was based on only a limited number of cases and could not, therefore, constitute a relevant ground for the suspension of the MA.

20 Following the CHMP's opinion, the Commission sent its draft decision to the Standing Committee on Medicinal Products for Human Use on
1 September 2017, setting a deadline for the Member States to submit their observations. The Czech Republic, Italy and Poland raised objections to that draft decision.

21 From August to November 2017, there was an exchange of correspondence between the applicant and the Commission on the subject of the CHMP's opinion.

22 On 23 November 2017, the Commission adopted Implementing Decision C(2017) 7941 final concerning, in the framework of Article 31 of Directive 2001/83/EC, the marketing authorisations for gadolinium-containing contrast agents for human use which contain one or more of the active substances 'gadobenic acid, gadobutrol, gadodiamide, gadopentetic acid, gadoteric acid, gadoteridol, gadoversetamide and gadoxetic acid' ('the contested decision').

23 Under the first paragraph of Article 3 and Annex IB to that decision, the Member States are required to suspend MAs for linear gadolinium-containing contrast agents, including Omniscan. According to the second paragraph of Article 3, and Annex IV to the same decision, the suspension of the MAs may be lifted only if the MA holder provides data showing either that there are clinically important benefits which were not established at that time or which outweigh the risks related to the product in question, or that the product does not undergo significant dechelation and does not lead to retention of gadolinium in tissues. Nevertheless, it follows from the third and fifth paragraphs of Article 3 of the decision in question that Member States may defer the suspension of the MA for a period not exceeding 12 months, if they consider that the medicinal products in question are critical.

24 It is clear from recitals 4 and 5 of the contested decision that the reasons for the decision are to be found in the CHMP's scientific assessment appended to it.

II. Procedure and forms of order sought

25 By application lodged at the Court Registry on 1 December 2017, the applicant brought the present action.

26 By separate document lodged at the Court Registry on 1 December 2017, the applicant submitted an application for interim measures. That application was dismissed by order of 11 July 2018, *GE Healthcare* v *Commission* (T-783/17 R, EU:T:2018:503) and the costs were reserved.

27 On 20 February 2018, the Commission lodged the defence.

28 On 17 April 2018, the applicant lodged the reply.

29 On 4 June 2018, the Commission lodged the rejoinder.

30 On a proposal from the Judge-Rapporteur, the Court (Fourth Chamber) decided to open the oral part of the procedure.

31 By letter of 6 November 2018, the Court informed the Commission of a measure of organisation of procedure to which the Commission replied on 23 November 2018.

32 The parties presented oral arguments and answered the questions put to them by the Court at the hearing on 29 January 2019. At that hearing, the applicant confirmed that its action is limited to the annulment of the contested decision in so far as it concerns Omniscan.

33 The applicant claims that the Court should:

– annul the contested decision;

– order the Commission to pay the costs;

34 The Commission contends that the Court should:

– dismiss the action;

– order the applicant to pay the costs.

III. Law

A. Whether the action could have been brought on behalf of all the Omniscan MA holders

35 According to the Commission, in the applicant's application, it states that it is acting not only on its own behalf, but also on behalf of the other Omniscan MA holders in the GE Healthcare group. In those circumstances, the Commission points out that the applicant has provided evidence in that regard only in the annex to its reply and therefore late, therefore the action may not be extended to those other holders. Moreover, the applicant is not directly concerned by the suspension of MAs held by other companies.

36 The applicant replies that it is directly and individually concerned by the contested decision in so far as that decision affects the MAs for Omniscan held by other companies in the GE Healthcare group and by two other distributors in Cyprus and Germany, because it is the sole manufacturer of Omniscan and that decision prevents it from placing that product on the market. In the annex to its reply, the

applicant also provides documents from those companies showing that it is also acting on their behalf. Lastly, in response to a question put by the Court at the hearing, the applicant confirmed that it was acting on behalf of all the Omniscan MA holders, a note of which was made in the minutes of the hearing.

37 In that regard, it should be recalled that, in accordance with the first paragraph of Article 21 of the Statute of the Court of Justice of the European Union and point (a) of the first paragraph of Article 76 of the Rules of Procedure of the General Court, the application must contain the applicant's name and address.

38 In the present case, the application has been brought expressly only in the applicant's name. Furthermore, the mandate attached to the application and issued to the applicant's advisers was drawn up by only the applicant and in its sole name. In addition, the fact that, in order to establish the admissibility of its action the applicant indicated in passing in its application that the contested decision also adversely affects the interests of its parent company and of the other companies in the GE Healthcare group, cannot establish that it was acting not only in its own name but also on behalf of other entities which, moreover, were not identified in the application initiating proceedings. In those circumstances, the application must be considered to have been brought only in the applicant's name.

39 The production, at the stage of the reply, of documents drafted during the procedure showing that the applicant is also acting on behalf of other companies cannot alter the scope of the action. Nor can it, as the applicant pleads in vain, be regarded as a clarification of the position adopted in the application, as a refining of the arguments in that application, or as a reply to new elements. To give effect to such a production, first, would infringe the first paragraph of Article 21 of the Statute of the Court of Justice of the European Union, point (a) of the first paragraph of Article 76 of the Rules of Procedure, and the nature of the reply and, second, would make it possible to circumvent the rules on intervention set out in Articles 142 to 144 of the Rules of Procedure.

40 Consequently, without there being any need to question whether the applicant is able to represent other companies before the Court, it must be held that the application has been brought in the applicant's sole name.

B. Pleas in law

41 In support of its action, the applicant relies on five pleas in law alleging, first, infringement of Article 116 of Directive 2001/83, second, infringement of the precautionary principle, third, infringement of the principle of equal treatment and non-discrimination, fourth, infringement of the principle of proportionality and, fifth, infringement of the principle of sound administration.

42 In response to a question put by the Court at the hearing, the applicant agreed that the first two pleas in law are connected. It is therefore appropriate to examine them together.

1. The first and second pleas in law alleging, respectively, infringement of Article 116 of Directive 2001/83 and of the precautionary principle

(a) Preliminary observations

43 Since the applicant is relying on, in particular, Article 116 of Directive 2001/83, it should be recalled, as a preliminary point, that that article provides that the competent authorities are to suspend, revoke or vary an MA if the view is taken that the medicinal product is harmful or where its therapeutic efficacy is lacking, or that the risk-benefit balance is not favourable, or where its qualitative and quantitative composition is not as declared.

44 Those conditions of variation, suspension or revocation of an MA are alternative and not cumulative (judgment of 11 December 2014, *PP Nature-Balance Lizenz* v *Commission*, T-189/13, not published, EU:T:2014:1056, paragraph 41). They must also be interpreted in accordance with the general principle, set out in the case-law, that the protection of public health must unquestionably take precedence over economic considerations (judgment of 19 April 2012, *Artegodan* v *Commission*, C-221/10 P, EU:C:2012:216, paragraph 99).

45 Furthermore, the precautionary principle, which is a general principle of EU law, authorises the competent authorities, where there is uncertainty, to take appropriate measures in order to prevent certain potential risks for public health, safety and the environment without having to wait until the reality and seriousness of those risks become fully apparent (see, to that effect, judgment of 10 April 2014, *Acino* v *Commission*, C-269/13 P, EU:C:2014:255, paragraph 57 and the case-law cited).

46 Consequently, in accordance with the precautionary principle, the health risks which the grounds set out in the first paragraph of Article 116 of Directive 2001/83 aim to prevent need not be specific, but only potential (see, to that effect, judgments of 10 April 2014, *Acino* v *Commission*, C-269/13 P, EU:C:2014:255, paragraph 59, and of 3 December 2015, *PP Nature-Balance Lizenz* v *Commission*, C-82/15 P, not published, EU:C:2015:796, paragraph 23).

47 In that system, the first paragraph of Article 116 of Directive 2001/83 confers rights on undertakings which are holders of MAs, since it ensures the retention of MAs as long as the existence of one of the conditions to vary, suspend or revoke them is not established (see, to that effect, judgment of 19 April 2012, *Artegodan* v *Commission*, C-221/10 P, EU:C:2012:216, paragraph 96). It follows that, as regards the burden of proof, it is for the competent authority, in this case the Commission, to establish that the conditions relating to the revocation, suspension or modification of an MA, set out in Article 116 of Directive 2001/83, are met (judgment of 7 March 2013, *Acino* v *Commission*, T-539/10, not published, EU:T:2013:110, paragraph 79).

48 In view of the precautionary principle, the Commission may nevertheless merely provide serious and conclusive evidence which, without ruling out scientific uncertainty, gives reasonable grounds for doubting the harmlessness of the medicinal product concerned, its therapeutic effect, the existence of a favourable risk-benefit balance or the qualitative and quantitative composition declared (judgments of 3 December 2015, *PP Nature-Balance Lizenz* v *Commission*, C-82/15 P, not published, EU:C:2015:796, paragraph 23, and of 7 March 2013, *Acino* v *Commission*, T-539/10, not published, EU:T:2013:110, paragraph 66).

49 However, the decision to vary, suspend or revoke an MA for a medicinal product is justified only where that decision is substantiated by new, objective, scientific or medical data (judgments of 26 November 2002, *Artegodan and Others* v *Commission*, T-74/00, T-76/00, T-83/00 to T-85/00, T-132/00, T-137/00 and T-141/00, EU:T:2002:283, paragraphs 174, 177 and 191 to 194, and of 11 December 2014, *PP Nature-Balance Lizenz* v *Commission*, T-189/13, not published, EU:T:2014:1056, paragraphs 44 and 75).

50 In that respect, the competent authority is obliged to refer to the main reports and scientific expert opinions on which it relies and to explain, in the event of a significant discrepancy, the reasons why it has departed from the conclusions of the reports or expert opinions supplied by the undertakings concerned. That obligation is particularly strict in cases of scientific uncertainty. The consultation is to be *inter partes* and transparent in order to ensure that the substance considered has undergone an in-depth and objective scientific assessment, based on using the most representative scientific theories and scientific positions put forward by the relevant pharmaceutical laboratories (see, to that effect, judgments of 26 November 2002, *Artegodan and Others* v *Commission*, T-74/00, T-76/00, T-83/00 to T-85/00, T-132/00, T-137/00 and T-141/00, EU:T:2002:283, paragraph 200, and of 11 December 2014, *PP Nature-Balance Lizenz* v *Commission*, T-189/13, not published, EU:T:2014:1056, paragraph 52).

51 That being so, it should be recalled, as the applicant accepted at the hearing, that the Court cannot substitute its own assessment for that of the PRAC and the CHMP. Its power of judicial review is exercised only over the lawfulness of their operation, and over the internal consistency and reasoning of the PRAC's recommendation and the CHMP's opinion. With regard to the latter element, the courts may only examine whether the recommendation and the opinion contain a statement of reasons from which it is possible to ascertain the considerations on which the recommendation and opinion are based, and whether they establish a comprehensible link between the medical or scientific findings and their conclusions (see, to that effect, judgment of 11 December 2014, *PP Nature-Balance Lizenz* v *Commission*, T-189/13, not published, EU:T:2014:1056, paragraph 52).

52 It is in the light of those considerations that the applicant's arguments should be examined. Those arguments concern the assessment, forming the basis of the contested decision, both of the risks and of the benefits of linear gadolinium and of Omniscan in particular.

(b) The assessment of the risks of linear gadolinium and of Omniscan in particular

53 First of all, the applicant criticises the assessment of the risks of adverse neurological effects associated with the use of linear gadolinium, then the assessment of other risks associated with that use. The applicant states, in that context, that the precautionary principle requires a public health risk to be plausible and not simply hypothetical or theoretical. That plausibility is not apparent from the analysis forming the basis of the contested decision.

(1) Neurological risks

54 As regards neurological risks, the applicant disputes, in turn, the assessments by the PRAC and by the CHMP.

(i) The assessment by the PRAC

55 The applicant submits that no new evidence substantiates the PRAC's assessment that Omniscan causes patients neurological risks and that the PRAC unlawfully reversed the burden of proof which it bore in that regard.

– As regards the absence of new evidence

56 The applicant submits that the precautionary principle does not exempt the authority from its obligation to provide serious and conclusive evidence which would give rise to doubt as to the safety or efficacy of the medicinal product at issue. In particular, following the grant of an MA, the authority bears the burden of proof and it may suspend an MA only on the basis of new data and not on the basis of a simple reassessment of the risks already examined earlier.

57 In the present case, according to the applicant, there is no solid, persuasive and new evidence of the risk of neurological harm to patients caused by the use of linear gadolinium and its accumulation in the brain. Studies on gadolinium retention in the body and gadolinium toxicity were already available at the time of the single assessment procedure for the periodic safety update reports. The PRAC had already reviewed the studies available at that time and concluded that, in the absence of any evidence of harm, the risk-benefit balance of Omniscan remained favourable. The latest data had not advanced the state of knowledge, except in so far as they indicated the persistence of macrocyclic gadolinium in the brain, with only partial elimination. Furthermore, a study by the M. Clinic in the United States found that cognitive disorders or other neurological disorders could not be associated with Omniscan.

58 The argument advanced by the applicant is not however convincing.

59 First of all, according to the case-law cited in paragraphs 45, 48 and 49 above, in accordance with the precautionary principle, the suspension of an MA does not have to be based on solid and persuasive evidence as argued by the applicant. It is sufficient for it to be based on serious and conclusive evidence as a result of new scientific or medical data, not necessarily ruling out any scientific uncertainty, provided that it gives reasonable grounds for doubting, in particular, that there is a favourable risk-benefit balance.

60 Next, it should be observed that, according to Article 107(e)(2) and (3) of Directive 2001/83, the single assessment procedure for PSURs includes the preparation of a report by a rapporteur within 60 days of receipt of the PSURs; the possibility for Member States and the MA holder to submit comments within 30 days following receipt of the report; the update of that report by the rapporteur within fifteen days of receipt of those comments; and the adoption by the PRAC of the final report and a recommendation at the meeting following that update. The single assessment procedure for the PSURs thus requires a critical analysis of the risk-benefit balance of a medicinal product which takes into account any new information on the medicinal product and which may lead to the variation, suspension or revocation of the MA. However, that procedure remains relatively short. Also, a more in-depth scientific analysis may be necessary and require the opening of another procedure, such as that set out in Articles 31 and 32 of Directive 2001/83. In essence, that procedure, which is more complex, includes the preparation of a preliminary report by one or two rapporteurs, as in the present case; the sending of that report to the MA holders and to the Member States for their comments; the preparation of an updated report in the light of those comments; the adoption of a recommendation by the PRAC, all of this within 150 days; the possibility for MA holders being able to request a review; the option to call on experts; the adoption of a new recommendation by the PRAC; the forwarding of that new recommendation to the CHMP; the adoption of an opinion by the CHMP; and the forwarding of that opinion to the Commission, to the MA holders and to the Member States, before the Commission takes a decision.

61 In the light of recent data, the PRAC found, in the context of the single assessment procedure for the PSURs, that the risk-benefit balance of Omniscan remained positive, but also that there was no information on the clinical significance of the retention of gadolinium in the brain and that that retention, and its clinical consequences, required an in-depth examination. That suggestion led the Commission to open the procedure under Article 31 of Directive 2001/83, which led to the contested decision.

62 In those circumstances, the data available at the stage of the single assessment procedure for the PSURs cannot be regarded as already fully assessed data which would not justify a suspension of the MA for Omniscan following the procedure at issue.

63 In any event, it is apparent from the PRAC's second recommendation that the PRAC relied in particular on about fifty studies published in 2016 and 2017, that is, after the single assessment procedure for the PSUR.

64 It is true that the PRAC also argued in its second recommendation that, as already had been proven since 2010, linear gadolinium-containing contrast agents have been associated with a significant risk of nephrogenic systemic fibrosis. However, that finding is not the decisive ground of the PRAC's second recommendation and of the contested decision. As the Commission argues, that risk was used as an example of the adverse effect of releasing linear gadolinium into tissues and its subsequent accumulation, increasing the fear that gadolinium released into the brain might also have a toxic effect. Data already known previously may be taken into account without infringing the precautionary principle and Article 116 of Directive 2001/83, in so far as it is used only to support the authority's opinion on the basis of new data.

65 In the light of the foregoing, it must be held that PRAC's second recommendation was based on new scientific or medical data.

– *As regards the reversal of the burden of proof*

66 The applicant alleges that the PRAC based its second recommendation on the fact that the absence or insufficient amount of data could not be considered to be evidence that there was no risk of adverse neurological effects associated with the retention of gadolinium in the brain. The PRAC thus unlawfully transferred to the applicant the burden of proof which falls on the competent authorities.

67 After examining the available observational data, the PRAC found that, although the clinical consequences of the retention of gadolinium in the brain are unknown or remain obscure, the absence or insufficient amount of data following the case reports could not be considered to be evidence that there was no risk of adverse neurological effects.

68 The PRAC's recommendation cannot, however, be reduced to that single finding.

69 The PRAC first of all relied on studies showing that gadolinium, whether linear or macrocyclic, was able to cross the blood-brain barrier and reach the brain.

70 The PRAC then cited authors stating that linear gadolinium-containing contrast agents release more gadolinium into their tissue environment than macrocyclic agents as a result of their lower stability, and therefore were more prone to accumulation in the tissue environment. It was thus observed that linear agents were retained in the brain at a 10-fold higher magnitude than macrocyclic agents and remained there for up to 1 year or even more.

71 The PRAC also noted that, in spite of wide use of gadolinium, there was no study showing clinical signs of neurotoxicity following exposure to gadolinium beyond 50 weeks after being administered intravenously, nor histopathological signs beyond a certain concentration. Nevertheless, the PRAC drew attention to the fact that data on the long-term effects of the retention of gadolinium in the brain was still limited and that the adverse effects which might be associated with that accumulation could be delayed and subtle and so the spontaneous reporting of adverse effects is subject to various unknown factors. In particular, the PRAC took into consideration the study by the M. clinic produced by the applicant in support of its product, but rejected it, inter alia because its results were limited by the size of the patient sample taken into consideration, by the relatively short follow-up with regard to potential long-term effects and by a lack of detailed information of the statistical methods used and their reliability. Similarly, the PRAC found that the studies based on experiments carried out on healthy animals having received intravenous doses of gadolinium could not be considered to cover the various illnesses which might be found in a human and which could be exacerbated by the retention of gadolinium in the brain. Furthermore, the PRAC noted a few other studies which suggested a link between exposure to gadolinium and various adverse effects, such as headaches, vision or hearing problems, digestive, respiratory or musculo-skeletal symptoms or even fine motor problems or cognitive impairments depending on the areas of the brain affected by the accumulation of gadolinium and its dechelation. The PRAC also noted that the toxicity of gadolinium had been demonstrated in cases in which it had been injected directly into the central nervous system of rats, in that it caused changes in morphology and behaviour depending on the dose received. Lastly, as has already been stated, the PRAC noted, as evidence of the toxicity of linear gadolinium in tissues, that it has been associated with a significant risk of nephrogenic systemic fibrosis.

72 The PRAC finally relied on the findings of an expert group which it had instructed and which itself concluded, first, that linear gadolinium accumulates in the brain due to its propensity to dechelate, and, second, that that accumulation could plausibly have adverse effects.

73 It must be stated that the PRAC thus relied on an assessment of objective scientific or medical data which definitely do not rule out any scientific uncertainty, but which could nevertheless be serious and conclusive evidence, first, of the accumulation of linear gadolinium in the brain in a greater proportion and for a longer duration than macrocyclic gadolinium and, second, of potential toxic effects of that accumulation.

74 In those circumstances, the PRAC was able, without reversing the burden of proof, to find that the absence of, or insufficient amount of data from the case reports could not be considered to be evidence that there is no risk of adverse neurological effects, since it had sufficient information giving rise to reasonable doubt in that regard.

75 The applicant's complaints regarding the PRAC's assessment of the neurotoxic effects associated with the retention of gadolinium in the brain are therefore unfounded.

(ii) The assessment by the CHMP

76 The applicant submits, in essence, that the CHMP did not essentially carry out its own assessment and that, in any event, by departing from some of the PRAC's assessments, it undermined the PRAC's recommendation.

– As regards the allegation that the CHMP did not carry out its own assessment

77 The applicant submits that, with regard to adverse neurological effects, in the CHMP's opinion, it agreed, in essence, with the PRAC's recommendation without carrying out its own assessment.

78 However, it should be recalled that, it is only where there is sufficient corroborative evidence supporting the applicant's arguments on the absence of a proper examination that the authority is required to prove that such an examination took place (see, to that effect, judgment of 28 September 2004, *Tenreiro* v *Commission*, T-216/03, EU:T:2004:276, paragraph 59).

79 The fact that the CHMP broadly shared the PRAC's opinion does not mean that it did not carry out its own assessment of the available medical or scientific data. That is particularly true because the MA holders were able to argue their position before the CHMP on 18 July 2017 and because, after setting out the content of the PRAC's second recommendation and indicating that it agreed overall with the PRAC's conclusions, the CHMP qualified them before providing its own conclusions. Finally, the different opinions of the representatives of 12 Member States and of the Norwegian and Icelandic representatives, together with the CHMP's opinion, show that there was a discussion within the CHMP.

80 It is therefore not established that the CHMP did not carry out its own assessment of the neurological risks which could be caused by exposure to gadolinium.

– As regards the alleged departure by the CHMP from some of the PRAC's assessments

81 The applicant submits that the CHMP departed from some of the assessments by the PRAC, whose recommendation it thus 'undermined'. According to the applicant, it follows that the information forming the basis of the CHMP's own opinion and the contested decision is neither solid nor persuasive.

82 The applicant points out, in the first place, that, as regards the fact that a distinction should be drawn between linear gadolinium-containing contrast agents and macrocyclic gadolinium-containing contrast agents, the CHMP considered it necessary to correct the PRAC's conclusion that 'macrocyclic agents

show only a transient increase in [gadolinium] in the brain and undergo early washout'. The CHMP considered it sufficient to observe that 'measurements of gadolinium in the brain over longer periods showed differences between linear and macrocyclic agents in terms of accumulation over time'.

83 However, the qualification made by the CHMP does not call into question the finding that linear gadolinium dechelates more than macrocyclic gadolinium and that it is retained for longer in the brain. It is on the basis, in particular, of those findings that the PRAC and the CHMP drew a distinction between contrast agents according to whether they belong to those two types of gadolinium and that the Commission suspended, without exceptions, some MAs but not others. Therefore, contrary to the applicant's argument, the different wording adopted by the CHMP does not undermine the grounds supporting the contested decision.

84 The applicant submits, in the second place, that, in the CHMP's opinion, it found that it could not be argued, as the PRAC had argued, that the adverse effects and the potential interactions of gadolinium with illnesses are 'plausible'. The applicant also notes that the CHMP considered it preferable to use the adjective 'possible' rather than the adjective 'plausible' because 'plausible' implied 'a stronger potential for harm'. The applicant points out that, for the same reason, the CHMP considered it appropriate to omit the word 'yet' from the PRAC's conclusion that 'no adverse neurological effects, such as cognitive or movement disorders have yet been demonstrated to be caused by gadolinium accumulation in the brain'.

85 In the light of 300 million doses of gadolinium-containing contrast agents administered since 1988 and the absence of data concerning the effects of its accumulation in the brain, the applicant submits that the CHMP thus disowned the PRAC's theory forming the basis of the contested decision.

86 However, it should be recalled that, in order to justify the adoption of a measure under Article 116 of Directive 2001/83, a potential risk is sufficient (see paragraph 46 above). Furthermore, contrary to the applicant's argument, the suspension of a MA does not necessarily have to be based on solid and persuasive evidence; it may be based only on serious and conclusive evidence, even if that evidence does not rule out any scientific uncertainty (see paragraph 59 above).

87 Furthermore, as has already been set out (see paragraph 45 above), the precautionary principle authorises the competent authorities, where there is uncertainty, to take appropriate measures in order to prevent certain potential risks for public health, safety and the environment without having to wait until the reality and seriousness of those risks become fully apparent.

88 Furthermore, although, as the applicant submits, the risk assessment cannot be based on purely hypothetical considerations, the Court of Justice has, however, held that the precautionary principle justifies the adoption of restrictive measures, even when it proves to be impossible to determine with certainty the existence or extent of the alleged risk because of the insufficiency, inconclusiveness, or imprecision of the results of studies conducted, but the likelihood of real harm to public health persists should the risk materialise (judgments of 10 April 2014, *Acino* v *Commission*, C-269/13 P, EU:C:2014:255, paragraph 58, and of 3 December 2015, *PP Nature-Balance Lizenz* v *Commission*, C-82/15 P, not published, EU:C:2015:796, paragraph 22).

89 In the present case, the CHMP did not fundamentally dispute the existence of a risk by making the above-mentioned two qualifications to the PRAC's second recommendation. The CHMP, as the PRAC before it, admittedly conceded that no adverse effects in humans had been proven to have been caused by the accumulation of gadolinium in the brain, in spite of the fact that gadolinium has been widely used. Nevertheless, the CHMP did not challenge the PRAC's point of view that, first, the long-term safety data was limited, second, the adverse effects which could be associated with that accumulation could be delayed and subtle, and, third, the spontaneous reporting of adverse effects was subject to various unknown factors. Whilst acknowledging that adverse neurological effects, such as cognitive or

motor disorders, had not been demonstrated, the CHMP accepted that there was a risk of adverse effects and interactions with illnesses in the light of the data indicating that linear agents dechelate in vivo and non-clinical data revealing the toxicity of dechelated gadolinium.

90 By way of further detail, it must be held, as the Commission argued in its written statements, that the purpose of the CHMP's use of the adjective 'possible' rather than the adjective 'plausible' used by the PRAC, was to avoid creating a state of anxiety in patients, and not to depart from, as regards the substance, the PRAC's position, since the CHMP endorsed the PRAC's recommendation to suspend MAs for linear gadolinium-containing contrast agents.

91 In the light of all of the grounds above, the CHMP's substitution of the word 'possible' for the adjective 'plausible' and its removal of the adverb 'yet' from the PRAC's recommendation cannot be regarded as being significant for the application of Article 116 of Directive 2001/83 and the precautionary principle. Thus, they do not affect the lawfulness of the contested decision.

(2) Risks other than neurological risks

92 As regards risks other than neurological risks associated with the use of gadolinium as a contrast agent, the applicant points out that the CHMP departed from the PRAC's finding that the appearance of skin plaques is the result of exposure to linear gadolinium, on the ground that that finding was based on a limited number of cases. The applicant also submits that the fact that gadolinium may lead to nephrogenic systemic fibrosis in patients with severe renal impairment is insufficient to validate the conclusion that the risk-benefit balance is unfavourable to Omniscan because the CHMP had already concluded in 2010 that the risk of nephrogenic systemic fibrosis in patients had been sufficiently taken into account and negated by warnings and by restrictions on use, because that opinion was supported 6 years later by the PRAC in the context of the single assessment procedure for PSURs and because, as has already been stated, the precautionary principle can be implemented to suspend an MA only when there is new data, of which there is none in the present case. It follows that adverse effects other than neurological effects could not constitute a relevant ground for suspending the MA for Omniscan.

93 In the PRAC's second recommendation, however, the risk of skin plaques appearing following exposure to gadolinium is a ground of secondary importance. Furthermore, the contested decision draws its grounds from the CHMP's opinion and not from the PRAC's recommendation. That opinion is itself fundamentally based on the accumulation of linear gadolinium in the brain and on the risk of neurotoxic effect which that accumulation may entail. Therefore, the fact that the CHMP did not for its part share the PRAC's opinion regarding the risk of skin plaques appearing cannot affect the lawfulness of that decision.

94 As regards the risk of nephrogenic systemic fibrosis, that matter is only put forward in so far as it corroborates the toxicity of gadolinium in tissues and it is not a decisive ground of the contested decision. Moreover, it has already been stated (see paragraph 64 above) that previously known data may be taken into account without infringing the precautionary principle and Article 116 of Directive 2001/83 when it is used only, as in the present case, to support the authority's opinion on the basis of new data.

95 In the light of the foregoing, the complaints raised by the applicant relating to risks other than neurological risks do not render the contested decision unlawful.

(c) The assessment of the benefits of linear gadolinium and of Omniscan in particular

96 The applicant submits that it was for the competent authorities to take account of the benefits which Omniscan brings to myocardial perfusion imaging and hypersensitivity reactions.

(1) The benefit of Omniscan for myocardial perfusion imaging

(i) Medical arguments

97 The applicant submits that Omniscan has a specific benefit compared to other contrast agents for myocardial perfusion imaging, but that the PRAC dismissed that benefit by stating, in its second recommendation, that the whole-body MRI indication which most other gadolinium-based agents have, covered heart imaging, including myocardial perfusion imaging.

98 According to the applicant, there are significant differences between whole-body MRI and myocardial perfusion imaging, the latter being more accurate and efficient for identifying people at risk of a cardiac event, for managing patients and preventing any fatal conditions. Furthermore, the posology and administration instructions are different for whole-body MRI and myocardial perfusion imaging. Consequently, the PRAC's finding that the whole-body MRI indication encompasses imaging of the heart invites medical specialists to ignore MAs that have been granted by Member States which have expressly authorised Omniscan as a unique gadolinium-containing contrast agent for myocardial perfusion imaging. Nevertheless, the decision whether to prescribe off-label rests with the prescribing physician alone.

99 It must, however, be observed that the applicant bases its arguments relating to the benefit of Omniscan for myocardial perfusion imaging on medical considerations, which the Commission disputes with similar arguments, and on scientific literature. As has already been recalled (see paragraph 51 above), the Court cannot substitute its own assessment for that of the PRAC and the CHMP, and its power of judicial review is exercised only over the lawfulness of their operation, and over the internal consistency and reasoning of their recommendations and opinions. Consequently, the Court cannot examine whether the applicant's statements are well-founded.

100 Therefore, the Court cannot moreover rule on the applicant's argument that the position adopted by the PRAC and the CHMP as regards myocardial perfusion imaging invites medical specialists to ignore MAs that have been granted by Member States which have expressly authorised Omniscan as a unique gadolinium-containing contrast agent for that imaging. The applicant's argument is based on the premiss, upon which the Court is not able to rule, that the indication for myocardial perfusion imaging is independent and cannot be considered to be a sub-set of whole-body indication.

101 In any event, the Commission rightly points out that when questions which are relevant to the EU are brought before a committee, such as the PRAC or the CHMP, in the context of the procedure set out in Article 31(1) of Directive 2001/83, it is for that committee to carry out, at European level, its own assessment of the relevant medicinal product, which is independent of the assessment by the national authorities, and this assessment cannot be used to challenge the committee's assessment (see, to that effect, judgment of 3 December 2015, *PP Nature-Balance Lizenz* v *Commission*, C-82/15 P, not published, EU:C:2015:796, paragraphs 36 and 37).

(ii) Arguments other than medical arguments

102 After putting forward arguments calling for a scientific assessment, the applicant sets out other complaints regarding compliance with guidelines, infringement of the obligation to carry out a full assessment and an error of fact which it is for the Court to examine.

– *As regards the benefit of Omniscan for myocardial perfusion imaging*

103 The applicant submits, in the first place, that by dismissing the significance of the Omniscan indication in myocardial perfusion imaging, the PRAC and the CHMP disregarded guidelines on good pharmacovigilance practice, according to which the risk-benefit balance must be evaluated for each indication.

104 However, the PRAC and the CHMP clearly did take into account the specific indication which Omniscan had in certain countries for myocardial perfusion imaging. Nevertheless, when assessing that indication, the PRAC and the CHMP found that, in so far as, from a medical point of view, that imaging was covered by the whole-body indication, which it is not for the Court to examine as has just been noted, that indication could not tip the scales in favour of the risk-benefit balance based on the accumulation of linear gadolinium in the brain and the risk of toxicity of that accumulation.

105 The applicant claims, in the second place, that there is nothing to indicate that the PRAC, in its second recommendation, and then the CHMP, took into account the observations on the Omniscan indication in myocardial perfusion imaging which the applicant had put forward in its request for a re-examination.

106 In its first recommendation, the PRAC had considered that the 'unique' Omniscan indication for myocardial perfusion imaging was irrelevant on the ground that a whole-body MRI indication encompassed imaging of the heart, including myocardial perfusion imaging.

107 In its request for a re-examination, the applicant stated, first of all, that it was not claiming that Omniscan has a 'unique' indication for myocardial perfusion imaging, since Multihance (gadobenic acid) had received authorisation for that use in certain countries and Gadovist (gadobutrol) in Poland. The applicant then argued that, by considering that a whole-body MRI indication encompasses myocardial perfusion imaging, the PRAC had disregarded the fact that that imaging involves administering a stress agent and is a functional, not anatomic examination, essential for the diagnosis of ischemic heart disease.

108 In its second recommendation, the PRAC maintained that the applicant had claimed that Omniscan had a unique indication for myocardial perfusion imaging. However, even if that statement is ambiguous, it does not render the contested decision unlawful since the applicant itself states in its written pleadings that Omniscan has such a 'unique' indication in four Member States, namely in Croatia, Cyprus, Portugal and Romania.

109 It must be noted above all that, in its second recommendation, the PRAC accepted, as the applicant essentially argued, that the main objective of myocardial perfusion imaging is to diagnose ischemic heart disease by combining one imaging at rest and another under a stress agent and that, for that purpose, it used a dynamic imaging technique. Next, the PRAC noted that the documentation available stated that Omniscan is indicated for general MRI of the body, but also specifically for other examinations such as heart scans by myocardial perfusion imaging, which is confirmed in the product characteristics summary in the United Kingdom, provided by the applicant. The PRAC deduced from that that whole-body MRI actually encompassed myocardial perfusion imaging. The PRAC also observed that that finding was aligned with opinions of the experts consulted, according to whom linear and macrocyclic contrast agents could be used interchangeably for cardial imaging so that no difference in their clinical use was established.

110 Furthermore, the PRAC rapporteur noted that the applicant had not submitted any chemical or physiological evidence supporting its point of view that results similar to those which could be obtained with Omniscan could not be obtained with other contrast agents. The rapporteur pointed out, in that regard, that it had already been shown that similar results could be obtained with Multihance and Gadovist.

111 It follows that the applicant argues in vain that no account was taken of the observations on the Omniscan indication in myocardial perfusion imaging, as the applicant had contended in its request for re-examination.

112 The applicant submits, in the third place, that the PRAC and the CHMP dismissed the benefits of Omniscan by arguing that it was not the unique contrast agent indicated for myocardial perfusion imaging because, in Germany, Gadovist, a macrocyclic gadolinium-containing contrast agent, had a whole-body indication considered also to cover that type of imaging. According to the applicant, the applicant for the MA had in fact opted not to seek a specific authorisation for myocardial perfusion imaging due to concerns raised by some Member States. Consequently, it is not possible to infer from the fact that the Bundesinstitut für Arzneimittel und Medezinprodukte (Federal Institute for Medicinal and Medical Products, 'the German Institute') authorised Gadovist for the whole body, that it accepted that Gadovist is also suitable for myocardial perfusion imaging.

113 In that regard, it must be found that, in its preliminary assessment of the grounds for reviewing the PRAC's first recommendation, the PRAC's co-rapporteur actually considered that the Gadovist indication for myocardial perfusion imaging had been included in Germany under the 'whole-body' category.

114 It is apparent from the German Institute's evaluation report that Gadovist has a specific indication for magnetic resonance imaging of the skull, spinal cord, liver and kidneys, and that, on 13 September 2011, the holder of that MA requested that indication to be extended to the whole body.

115 In his debate on the scientific elements, the German Institute's rapporteur noted, in particular, that the use of Gadovist was not documented for certain parts of the body such as the pancreas, the colon, or even the prostate, that it was much debated for others, such as the uterus, but that it was sufficiently substantiated for cardiac magnetic resonance imaging, including perfusion imaging. Nevertheless, as the MA holder was seeking an extension of the indication for whole-body imaging, the rapporteur stated that those parts of the body would no longer be cited in the list of indications. Some Member States raised questions in that procedure. One Member State, in particular, took the view that among the indications requested for the 'whole-body', the indication for the heart deserved particular attention and especially a comparison of cardiac magnetic resonance imaging with other examination procedures. In the light of the responses provided by the MA applicant, that point was regarded as resolved.

116 Contrary to the applicant's argument, it is not therefore clear from that report that the holder of the MA for Gadovist withdrew the request for a specific authorisation for myocardial perfusion imaging due to concerns raised by some Member States. The applicant's claims in that regard are, moreover, formulated in the conditional. Furthermore, the Commission points out that, in his preliminary report on the grounds for reviewing the PRAC's first recommendation, the PRAC's co-rapporteur confirmed that, in the light of studies, the German Institute had accepted the Gadovist indication for myocardial perfusion imaging under the category 'whole body'. Since that co-rapporteur was a member of that institute, it is unlikely that he misinterpreted its position.

117 In view of the foregoing, it must be held that it is not proven that the PRAC and the CHMP dismissed the benefit of Omniscan as regards myocardial perfusion imaging, by wrongly finding that, in Germany, Gadovist had a whole-body indication which was regarded as also to covering that type of imaging.

– As regards the benefit of Omniscan in respect of hypersensitivity risks

118 The applicant also claims that the PRAC and the CHMP incorrectly assessed the benefit of linear gadolinium as regards the rate of hypersensitivity reactions to that type of contrast agent. The applicant submits that Omniscan, in particular, is, in that respect, better tolerated than macrocyclic agents.

119 However, as has already been stated in paragraph 51 above, it is not for the Court to substitute its assessment for those of the PRAC and the CHMP. Consequently, the Court cannot resolve the scientific debate between the applicant and the PRAC and the CHMP as regards any benefits of a contrast agent such as Omniscan in comparison with macrocyclic gadolinium-containing agents.

120 Nevertheless, the applicant submits that the PRAC, and subsequently the CHMP, did not examine a meta-analysis by Professor P. which the applicant had produced and which confirmed that linear gadolinium-containing contrast agents are better tolerated than macrocyclic agents.

121 However, it is apparent from the PRAC's second recommendation that the PRAC took that meta-analysis into account but dismissed it because, as with other studies, it had certain significant limitations relating to its design, its dependence with regard to the recording of adverse effects and the possibility of under-reporting or reporting brought about by changes in the use of the agents. More specifically, in his updated evaluation report of 30 June 2017, the PRAC's co-rapporteur observed that Professor P.'s meta-analysis was based on a selection of adverse effects pointed out retrospectively, when it is well known that only a small proportion of the adverse effects which occur are reported to the health authorities, therefore those spontaneous reports on adverse effects may not be used to carry out a quantitative analysis and a comparison of the agents.

(d) Conclusion on the first and second pleas in law

122 It follows from all of the foregoing that the applicant has not established that the PRAC's second recommendation and the CHMP's opinion were vitiated by errors or omissions.

123 Therefore the first and second pleas in law must be rejected as unfounded, without it being necessary to examine the applicant's last argument raised as part of the first plea in law, according to which the alleged errors and omissions by the PRAC and by the CHMP cannot be compensated by the fact that the suspension of the MA for Omniscan can be postponed for 12 months by the Member States under Article 3 of the contested decision.

2. The third plea in law alleging infringement of the principle of equal treatment and non-discrimination

124 The applicant submits that the contested decision infringes the principle of equal treatment and non-discrimination for four reasons based on the fact that its competitors received favourable treatment in respect of contrast agents for which they hold an MA.

125 As a preliminary point, it should be recalled that, according to settled case-law, the general principle of equal treatment requires that comparable situations must not be treated differently and that different situations must not be treated in the same way unless such treatment is objectively justified (see judgment of 12 June 2015, *Health Food Manufacturers' Association and Others* v *Commission*, T-296/12, EU:T:2015:375, paragraph 113 and the case -law cited).

(a) The first case of alleged discrimination

126 The applicant sees a first case of discrimination in the fact that linear gadolinium-containing contrast agents such as Omniscan had their MAs suspended, whereas a similar measure was not taken against macrocyclic gadolinium-containing contrast agents. The applicant submits that there is no objective reason for that difference in treatment since there is no evidence of harm caused by gadolinium retention in the brain and since, in addition, the CHMP found that such harm was not 'plausible'.

That difference in treatment is in fact based on the single premiss that linear gadolinium-containing contrast agents are retained for longer in the brain than macrocyclic gadolinium-containing contrast agents. However, that claim has not been substantiated.

127 However, it is apparent from paragraphs 69 to 71 above that the PRAC found that scientific data first showed that linear gadolinium-containing contrast agents was retained for longer in the brain than macrocyclic gadolinium-containing contrast agents and, second, supported the conclusion that exposure to linear gadolinium potentially created, due to its lower stability, a risk of toxicity unlike macrocyclic gadolinium.

128 Furthermore, it follows from paragraphs 86 and 91 above that the CHMP's substitution of the word 'possible' for the adjective 'plausible' used by the PRAC was not significant.

129 In those circumstances, the Commission was entitled to find that both types of gadolinium have sufficiently different characteristics to justify a difference in treatment. The Commission thus did not infringe the principle of equal treatment and non-discrimination.

(b) The second case of alleged discrimination

130 The applicant sees a second case of discrimination in the fact that, in the contested decision, the Commission suspended the MA for Omniscan and not the MA for Magnevist (gadopentetic acid), even though they are both linear gadolinium-containing contrast agents. As regards Magnevist, the contested decision merely states in Article 4 that the Member States must take into account the CHMP's scientific findings when evaluating the effectiveness and safety of contrast agents containing gadopentetic acid.

131 The applicant claims that, since there is no evidence that the retention of linear gadolinium in the brain causes harm, there is no objective justification for distinguishing between Magnevist and other linear gadolinium-containing contrast agents such as Omniscan, on the sole ground that Magnevist is prescribed in smaller doses.

132 As has already been stated in paragraphs 71 and 73 above, in the light of the scientific data, the PRAC was able to find that there is serious and conclusive evidence that the accumulation of linear gadolinium in the brain presents a risk of neurotoxicity. In its second recommendation, the PRAC also observed that studies had shown that Magnevist was, as with Omniscan, detected in the brain after being administered. Nevertheless, the PRAC also noted that Magnevist was used as a contrast agent in artierography at a dose 200 times lower than other agents injected intravenously, such as Omniscan. Furthermore, the PRAC noted that, in that case, patients were usually exposed to that product only once, whereas they may be exposed to Omniscan on several occasions.

133 On the basis of that difference in the administration of the two products, the PRAC, the CHMP and, after them, the Commission, were able to adopt different approaches, in particular distinguishing Magnevist and Omniscan, and to find, without infringing the principle of equal treatment and non-discrimination, that it was necessary only to invite Member States to take into account the finding that the risk-benefit balance of Magnevist remained positive in the event of an intra-articular injection.

(c) The third case of alleged discrimination

134 The applicant sees a third case of discrimination in the fact that, in the contested decision, the Commission suspended the MA for Omniscan and not the MA for Multihance and for Primovist (gadoxetic acid) even though they are all linear gadolinium-containing contrast agents. As regards

Multihance and Primovist, the contested decision merely provides, in Article 4, that the Member States must take into account the CHMP's scientific findings in order to assess the effectiveness and safety of contrast agents containing gadobenic acid or gadoxetic acid.

135 The applicant submits, in that regard, that in so far as the PRAC and the CHMP took the view that the risk-benefit balance of Multihance and Primovist is favourable due to their usefulness in hepatic imagery, it was discriminatory not to treat as similarly beneficial Omniscan's specific indication for myocardial perfusion imaging.

136 It must be observed that that complaint is based on the premiss that Omniscan is of particular importance for myocardial perfusion imaging. The PRAC and the CHMP disputed that and it must be recalled (see paragraph 99 above) that it is not for the Court to settle the scientific dispute between the parties as to whether, inter alia, there are significant differences between 'whole-body' imaging and myocardial perfusion imaging. Furthermore, it follows from the examination of the first two pleas in law (see paragraphs 113 to 117 above) that it is not established that the PRAC erred in finding that a 'whole-body' indication covered the indication for myocardial perfusion imaging granted to Omniscan in four Member States.

137 On the other hand, the PRAC noted that Multihance and Primovist were beneficial for delayed phase imaging of poorly vascularised hepatic lesions, which could not be achieved with other gadolinium-based products and thus allowed early diagnosis of potentially life threatening diseases. In those circumstances, and in spite of the risks caused by the accumulation of gadolinium in the brain, the PRAC considered that the risk-benefit balance of those two products remained favourable, provided that their use was limited to that type of liver imaging.

138 In that context, in the light of their different qualities, it does not appear that the principle of equal treatment and non-discrimination was infringed by the fact that Multihance and Primovist were treated differently to Omniscan.

(d) The fourth case of alleged discrimination

139 The applicant submits that there is a fourth case of discrimination in the fact that, although the purpose of the contested decision is to reduce the risk to human health, it favours macrocyclic gadolinium-containing contrast agents over linear gadolinium-containing contrast agents in the light of a hypothetical risk of neurotoxicity, without taking into account the fact that linear gadolinium-containing contrast agents, and Omniscan in particular, have a more favourable safety profile in respect of the risks of acute hypersensitivity reactions which, although slight, are nevertheless real.

140 However, first of all, it should be noted that neither the PRAC nor the CHMP, nor the Commission considered that the risk of neurotoxicity of linear gadolinium-containing contrast agents is hypothetical. In accordance with the CHMP's opinion, to which it refers in the contested decision, the Commission considered that the neurotoxicity of those contrast agents is possible.

141 Next, although the PRAC noted that studies indicated that there was a lower risk of hypersensitivity reactions, in particular with Omniscan, it nevertheless noted that 'there are some important limitations of studies [on hypersensitivity]: the retrospective or survey design, the reliance on adverse event recording, and potential for under-reporting or reporting stimulated by changes in use of the products'. The PRAC also found that 'the rate of serious adverse reactions is very low, and the studies which have evaluated the rate of hypersensitivity reactions with [gadolinium-containing contrast agents] have all reported that a very low proportion of patients experienced a severe hypersensitivity reaction'. In addition, the PRAC noted that 'the risk of hypersensitivity is appropriately addressed in the product information of gadolinium-containing contrast agents'.

142 It is true that the applicant produces a publication by the American College of Radiology of 4 April 2007 entitled 'Response to the PRAC Recommendations', a declaration by Professor A. and a meta-analysis by Professor P., from which it is apparent that linear gadolinium has a more favourable safety profile than macrocyclic gadolinium in respect of hypersensitivity risks.

143 However, it is not for the Court to reconsider the contested decision in the light of scientific elements (see paragraph 51 above). Furthermore, as has already been stated (see paragraph 121 above), the PRAC considered that Professor P.'s meta-analysis had certain significant limitations. Furthermore, the publication by the American College of Radiology merely broadly indicates that linear agents 'have a lower acute reaction risk than macrocyclic agents' without substantiating that conclusion. As regards the declaration by Professor A., it was made subsequent to the contested decision, therefore it could not be taken into account by the PRAC, the CHMP and the Commission. Furthermore, its objectivity and probative value have not been proven because it was prepared explicitly in support of the applicant's action.

144 Consequently, it does not appear that the Commission, in the contested decision, infringed the principle of equal treatment and non-discrimination by treating macrocyclic gadolinium-containing contrast agents differently to linear gadolinium-containing contrast agents, since the latter have different properties.

145 In the light of all of the foregoing, the third plea in law is unfounded.

3. The fourth plea in law, alleging infringement of the principle of proportionality

146 The applicant submits that the contested decision infringes the general principle of proportionality, even if it were to be found that the risk-benefit balance of linear gadolinium-containing contrast agents is not favourable.

147 It should be recalled at the outset, in that regard, that, according to settled case-law, the principle of proportionality, which is part of the general principles of EU law, requires that EU measures do not exceed the limits of what is appropriate and necessary in order to achieve the objectives legitimately pursued by the legislation in question; when there is a choice between several appropriate measures, recourse must be had to the least onerous, and the disadvantages caused must not be disproportionate to the aims pursued (see judgment of 7 March 2013, *Acino* v *Commission*, T-539/10, not published, EU:T:2013:110, paragraph 85 and the case-law cited).

148 In support of its plea in law, the applicant submits, in the first place, that the suspension of the MA for Omniscan was unnecessary. The applicant points out, in that regard, that the Commission took the view that labelling and warnings were sufficient to neutralise the real risks of nephrogenic systemic fibrosis and acute hypersensitivity reactions which all gadolinium-containing contrast agents entail, but that it ordered, in a contradictory manner, the suspension of the MAs for linear gadolinium-containing contrast agents in order to prevent a mere hypothetical risk associated with the retention of those agents in the brain.

149 It must however be found that the applicant once again incorrectly suggests (see paragraph 140 above) that the Commission found that there was a mere hypothetical risk of neurotoxicity of linear gadolinium as the basis for the contested decision.

150 Furthermore, in response to the applicant's suggestion, the PRAC contemplated other measures for minimising the risks which were less strict than the suspension of MAs for linear gadolinium-containing contrast agents, but considered those measures to be unfeasible or insufficient. The CHMP agreed with the PRAC.

151 As regards any updating of information on Omniscan, the PRAC took the view that, since the accumulation in the brain was an intrinsic property of gadolinium-containing contrast agents administered intravenously, information in that regard would not lead to a reduction of the risks associated with that accumulation.

152 The PRAC also noted that it was not possible to restrict the use of Omniscan to certain groups of patients, as has been the case for the risk of nephrogenic systemic fibrosis, or as proposed by 19 Member States, Iceland and Norway, given that no patient group with less risk of accumulation in the brain could currently be identified.

153 The PRAC also took the view that, in a clinical context, it was not realistic to wish to restrict the number of doses administered to a patient during his life or to take measures regarding the frequency and timing of the applications because exposure to gadolinium may not be recorded, in particular when there is a change of radiologist or general practitioner.

154 Lastly, the PRAC considered that restrictions on the use of Omniscan would still expose the population to a risk, without knowing the safe threshold level for retention in the brain and in other tissues and because it was not possible to define a period of time during which no potential adverse effect would have time to manifest.

155 In those circumstances, the contested decision cannot be found to be contradictory and disproportionate, on the ground that the Commission was satisfied with labelling and warnings in order to minimise the risks of nephrogenic systemic fibrosis and acute hypersensitivity reactions whilst ordering the suspension of MAs for most linear gadolinium-containing contrast agents in order to prevent a risk associated with the retention of those agents in the brain.

156 In support of its plea in law, the applicant submits, in the second place, that the suspension of the MA for Omniscan is not appropriate. It submits, in that regard, that the disproportionate nature of the contested decision is as a result of the fact that it leads to, first, the loss of its specific indication for myocardial perfusion imaging granted in four Member States and, second, the loss of a product which has a lower level of hypersensitivity reaction than other products.

157 That argument is however based on the premiss that Omniscan is of particular importance for myocardial perfusion imaging and in terms of major hypersensitivity risks. Since it is not for the Court to settle the scientific dispute between the parties on those two questions (see paragraphs 51, 99 and 119 above), the Court is also unable infer from that supposed particular importance that there is an infringement of the principle of proportionality.

158 The lack of foundation for the applicant's argument is further confirmed by the fact that it follows from the examination of the first plea in law (see paragraphs 113 to 117 above) that it is not established that the PRAC erred in finding that a 'whole-body' indication covered the myocardial perfusion imaging indication and when, as has been stated in paragraphs 121 and 141 above, the PRAC rejected Professor P.'s studies and meta-analysis relating to the risk of hypersensitivity on the ground that they had significant limitations.

159 The applicant also infers that the contested decision is inappropriate from the observation that, in view of the absence of evidence of neurological harm in spite of millions of prescriptions, the contested decision opens the entire market for gadolinium-containing contrast agents to a small group of manufacturers of macrocyclic gadolinium-containing agents, even though the latter agents are also retained in the brain.

160 However, it should be recalled that, according to a general principle, established by the case-law, the protection of public health must unquestionably take precedence over economic considerations (see paragraph 44 above). Furthermore, the PRAC and the CHMP noted that there is a difference between

linear gadolinium-containing contrast agents and macrocyclic gadolinium-containing contrast agents, the latter being retained in the brain at a 10-fold lower magnitude than linear agents and remaining there for less time (see paragraph 70 above). In addition, the PRAC and the CHMP noted that long-term safety data was limited, that the adverse effects which may be associated with accumulation in the brain could be delayed and subtle and that the spontaneous reporting of adverse effects was subject to various unknown factors. Lastly, the PRAC and the CHMP pointed out that there are studies suggesting a connection between exposure to gadolinium and various adverse effects (see paragraph 74 above). In those circumstances, the fact that contrast agents have been widely inoculated without adverse neurological effects being identified, does not support the conclusion that there has been an infringement of the principle of proportionality.

161 The applicant submits, in the third place, that conditions to which the contested decision makes lifting the suspension of the MAs subject are so restrictive that that suspension amounts to a revocation of authorisation. It is unlikely that benefits of linear gadolinium not yet established will emerge in the future and that the retention of linear gadolinium in tissues will be disproved in the future.

162 According to the second paragraph of Article 3 and Annex IV of the contested decision, the suspension of the MA for Omniscan may be lifted provided that its holder provides data indicating either that there are clinically important benefits that are currently not established and which outweigh the risks related to the product at issue, or that the product does not undergo significant dechelation and does not lead to retention of gadolinium in tissues.

163 The Commission submits, in that regard, that it is not unusual that a new indication for a product is developed some years after it is placed on the market. The risk-benefit balance of Omniscan could thus be re-evaluated. The Commission also suggests that the applicant could propose some changes to the structure or composition of its product that would make it more stable, which would reduce its accumulation in the brain.

164 The Court cannot, however, speculate either on the likelihood that a new Omniscan indication will be discovered or on the possibility of changing Omniscan's structure or composition.

165 Furthermore, the Commission concedes, in its written pleadings, that the results from observational studies conducted in order to address the concerns relating to the toxicity of linear gadolinium are unlikely to be available in a reasonable timeframe in view of the heterogeneity of the patient population that undergoes MRI, the number of patients needed for such studies and methodological limitations of those studies. The Commission also notes that interventional clinical studies comparing the effects of different products could be considered unethical.

166 Nevertheless, even if it is difficult to meet the conditions for lifting the suspension of the MA for Omniscan, the fact remains that that suspension does not appear disproportionate in the light of paragraphs 155 to 160 above.

167 The fourth plea in law is therefore unfounded.

4. The fifth plea in law, alleging infringement of the principle of sound administration

168 The applicant claims, in the first place, that the procedure was not impartial and, in the second place, that the relevant bodies did not carry out a full examination of all of the observations that the applicant had submitted.

(a) The impartiality of the procedure

169 The applicant submits that the principle of impartiality was infringed because Professor T. participated in an expert group whose opinion was used in the PRAC's first recommendation. Professor T. acted as a consultant in a class action brought inter alia against the applicant and was personally involved with the applicant in libel proceedings for his declarations regarding Omniscan.

170 Institutions, bodies, offices and agencies of the European Union are required to respect the fundamental rights guaranteed by EU law, which include the right to good administration enshrined in Article 41 of the Charter of Fundamental Rights of the European Union (see, to that effect, judgment of 11 July 2013, *Ziegler* v *Commission*, C-439/11 P, EU:C:2013:513, paragraph 154).

171 Article 41(1) of the Charter of Fundamental Rights states, in particular, that every person has the right to have his or her affairs handled impartially by the institutions, bodies, offices and agencies of the Union.

172 In that regard, it should be noted that the need for impartiality, required of institutions, bodies, offices and agencies in carrying out their missions, is intended to guarantee equality of treatment, which is at the heart of the European Union. That requirement is intended, inter alia, to avoid a situation where there could be a conflict of interest with regard to officials or agents acting on behalf of those institutions, bodies, offices and agencies. Having regard to the fundamental importance of ensuring the independence and probity of EU institutions and bodies as regards both their internal functioning and external reputation, the requirement of impartiality covers all circumstances in which an official or agent who is called upon to decide on an issue must reasonably consider that issue as being of such a nature as to be viewed by third parties as a possible source of impairment of his or her independence in that matter (see, to that effect, judgment 25 October 2007, *Komninou and Others* v *Commission*, C-167/06 P, not published, EU:C:2007:633, paragraph 57).

173 Therefore, it is incumbent upon those institutions, bodies, offices and agencies to comply with both components of the requirement of impartiality, which are, first, subjective impartiality, by virtue of which no member of the institution concerned may show bias or personal prejudice, and second, objective impartiality, under which there must be sufficient guarantees to exclude any legitimate doubt as to possible bias on the part of the institution concerned (see, to that effect, judgment of 20 December 2017, *Spain* v *Council*, C-521/15, EU:C:2017:982, paragraph 91 and the case-law cited).

174 In response to a question put by the Court at the hearing, the applicant stated that, in the present case, it specifically relied on an infringement of objective impartiality.

175 As regards, more particularly, the second component of the principle of impartiality, it should be made clear that, where a number of EU institutions or bodies are given separate responsibilities of their own in the context of a procedure that is liable to result in a decision adversely affecting a party, each of those institutions and bodies is required, in respect of its own activities, to comply with the requirement of objective impartiality. Consequently, even where only one of them has breached that requirement, such a breach is liable to render the decision adopted by the other at the end of the procedure at issue unlawful (see, to that effect, judgment of 20 December 2017, *Spain* v *Council*, C-521/15, EU:C:2017:982, paragraph 94).

176 Furthermore, the requirement of impartiality to which the institutions are subject also extends to experts consulted by the institutions. In particular, where an expert is requested to give an opinion on the effects of a potential medicinal product, it is necessary for that expert to perform his task impartially (judgment of 9 September 2010, *Now Pharm* v *Commission*, T-74/08, EU:T:2010:376, paragraph 88).

177 In the present case, the Commission does not dispute the facts presented by the applicant regarding Professor T. and acknowledges that those facts must be assessed with reference to the principle of impartiality rather than in relation to the policy of the European Medicines Agency (EMA) on dealing with the competing interests of members of scientific committees and experts, in the light of which the EMA examined those interests.

178 The Commission points out, however, that the Court held, in its judgment of 9 September 2010, *Now Pharm* v *Commission*, T-74/08, EU:T:2010:376, paragraph 93), that the obligation of impartiality cannot be construed as meaning that there is a legal impediment to an expert being consulted in a procedure relating to a medicinal product solely because he has already given an opinion on the same product in another procedure. According to the Commission, that was Professor T.'s role in the class action to which the applicant refers. The Commission also notes that Professor T. was not the initiator of the libel proceedings, but that he was only the defendant.

179 Nevertheless, it should be noted that, in the present case, the disagreement between the applicant and Professor T. is not merely a difference in scientific opinions between a pharmaceutical undertaking and an expert. That disagreement led to a conflict which stems in particular from the fact that, in 2010, Professor T. assisted lawyers in a class action for compensation brought inter alia against the applicant as a result of damage allegedly caused by gadolinium-containing contrast agents, and by Omniscan in particular. It follows that the solution adopted in the judgment of 9 September 2010, *Now Pharm* v *Commission*, T-74/08, EU:T:2010:376) cannot be applied in the present case. On the contrary, such involvement in legal proceedings can give rise to legitimate doubt as to Professor T.'s impartiality in the procedure which led to the adoption of the contested decision.

180 However, it is necessary to examine whether that fact had a decisive impact on either the conduct or the outcome of that procedure (see, to that effect, judgment of 20 December 2017, *Spain* v *Council*, C-521/15, EU:C:2017:982, paragraph 104).

181 It should be noted, in that regard, that Professor T. was neither a member of the PRAC nor the CHMP, but only a member of an expert group set up by the PRAC under Article 32 of Directive 2001/83. The PRAC designated those experts from a list of names provided by the Member States to the EMA under Article 62(2) of Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (OJ 2004 L 136, p. 1). In accordance with the abovementioned Article 32, that expert group's task was only to provide the PRAC with an opinion and the PRAC set out the specific matters on which the expert group was to take a view.

182 Admittedly, it is apparent from the minutes of the expert group's meeting of 5 September 2016 that, out of the thirteen members of which it was initially composed, six declared a conflict of interests for various reasons and were not able to take part in the final conclusions, therefore those conclusions were adopted only by the remaining members, including Professor T. Nevertheless, the expert group's conclusions were reached collegiately by seven members. Collegiality is a guarantee of impartiality (see, to that effect and by analogy, judgment of 19 February 2009, *Gorostiaga Atxalandabaso* v *Parliament*, C-308/07 P, EU:C:2009:103, paragraph 44). Furthermore, contrary to what the applicant suggests, nothing indicates that, because of his duties or his status, Professor T. had a dominant influence within that small group. In particular, he was not the president of that group.

183 Next, it is apparent from the minutes of the meeting of 5 September 2016 that the expert group did not specifically adopt a position on the risks and benefits of Omniscan, but on all molecules derived from gadolinium. The expert group thus merely examined, from a general point of view, the issue of gadolinium's ability to reach the brain and accumulate there, the risks associated with that accumulation, the issue of the possible interchangeability of linear and macrocyclic

gadolinium-containing contrast agents, whether or not it is possible to isolate patient groups for whom exposure to gadolinium has an increased risk, whether it is possible to change how contrast agents are used in order to minimise the risks and which studies could be undertaken.

184 In addition, on 19 June 2017, the PRAC consulted a second expert group which did not include Professor T. Even though that second group's mandate differed from the first group's mandate, as the applicant submits, the fact remains that the second group gave its view on the grounds for re-examination which the applicant had presented.

185 Furthermore, it should be noted that the PRAC relied inter alia on around fifty studies published in 2016 and 2017 (see paragraph 63 above) which it examined carefully, citing many of them on several occasions and assessing their merits and scope, as shown in the file.

186 Lastly, the grounds of the contested decision are to be found in the opinion of the CHMP which carried out its own assessment and qualified the PRAC's second recommendation, as has been noted in paragraph 79 above.

187 It follows from the foregoing considerations that Professor T.'s participation in the expert group was not decisive for either the conduct or the outcome of the procedure which led to the contested decision. Thus, that participation does not lead to a finding that the procedure, assessed as a whole, did not offer sufficient guarantees to exclude any legitimate doubt as to Professor T.'s impartiality.

188 Consequently, the complaint alleging infringement of the principle of impartiality must be rejected.

(b) The allegation that the relevant bodies did not carry out a full examination of all the observations submitted

189 The applicant claims, first, that the grounds which it had submitted in support of its request for re-examination were not taken into account. It submits, second, that the factual errors relating to the specific Omniscan indication for myocardial perfusion imaging, brain gadolinium levels, retention times for gadolinium in the brain and contrast agent posology were not corrected. It argues, third, that the competent bodies did not take a view on the issues relating to MRI study limitations, inconsistencies in the appraisal of data and the PRAC's apparently held belief that certain publications had been sponsored by MA holders.

190 The applicant does not, however, specify the grounds of its request for re-examination which were allegedly not taken into account, nor which factual errors were made relating to the specific Omniscan indication for myocardial perfusion imaging. The applicant also does not identify which factual errors were not corrected relating to brain gadolinium levels, retention times for gadolinium in the brain and contrast agent posology. Nor does it identify the issues relating to MRI study limitations and inconsistencies in the appraisal of data on which the PRAC, the CHMP and the Commission did not take a view. In respect of all those complaints, the applicant merely refers to the annexes to its application. It is not for the Court to seek and identify in the annexes the pleas and arguments on which the applicant may regard as providing the basis for the action, since the annexes have a purely evidential and instrumental function (see judgment of 31 May 2018, *Kaddour* v *Council*, T-461/16, EU:T:2018:316, paragraph 113 and the case-law cited). The complaints at issue are therefore merely set out without being substantiated by arguments, contrary to the rule in Article 76(d) of the Rules of Procedure. It follows that the applicant's complaints must be declared inadmissible. Furthermore, the fact that the applicant did not receive a particular response to its complaint regarding the PRAC's apparently held belief that certain publications had been sponsored by MA holders cannot lead to the annulment of the contested decision since, with effect from 16 August 2017, the EMA stated that sponsorship should not be considered per se to have an impact on study conclusions.

191 In any event, it is apparent from the file that the applicant's request for re-examination led to the convening of the meeting of an expert group. The grounds put forward by the applicant in support of that request were assessed and discussed by the rapporteur and co-rapporteur in their assessment reports of 28 June 2017. In particular, it has been found in paragraphs 111, 113 and 117 above that the PRAC had re-examined its first recommendation regarding the usefulness of Omniscan for myocardial perfusion imaging in the light of the grounds of the applicant's request for re-examination and that the alleged error made in that regard in the light of the MA issued by the German institute to Gadovist for the whole-body was not established. Furthermore, the CHMP also carried out an examination of the risk-benefit balance of gadolinium and did qualify the PRAC's second recommendation (see paragraph 79 above).

192 Furthermore, as the Commission submits, the existence of a scientific disagreement between the applicant and the PRAC or the CHMP does not mean that the applicant's observations relating to the specific Omniscan indication for myocardial perfusion imaging, brain gadolinium levels, retention times for gadolinium in the brain and contrast agent posology were not taken into account.

193 It follows that the applicant's complaint alleging that the relevant bodies did not carry out a full examination of all the observations which it had submitted must be rejected, as must all of the plea alleging infringement of the principle of sound administration.

194 In the light of all of the foregoing and as none of the pleas have been successful, the action must be dismissed in its entirety.

IV. Costs

195 Under Article 134(1) of the Rules of Procedure, the unsuccessful party is to be ordered to pay the costs if they have been applied for in the successful party's pleadings. Since the applicant has been unsuccessful, it must be ordered to pay the costs, in accordance with the form of order sought by the Commission, including the costs relating to the interlocutory proceedings.

On those grounds,

THE GENERAL COURT (Fourth Chamber)

hereby:

1. **Dismisses the action;**

2. **Orders GE Healthcare A/S to pay the costs, including the costs relating to the interlocutory proceedings.**

Kanninen Calvo-Sotelo Ibáñez-Martín Reine

Delivered in open court in Luxembourg on 19 September 2019.

E. Coulon
Registrar

A. M. Collins
President

Table of contents

I. Background to the dispute 1

II. Procedure and forms of order sought 5

III. Law 5

A. Whether the action could have been brought on behalf of all the Omniscan MA holders 5

B. Pleas in law 6

1. The first and second pleas in law alleging, respectively, infringement of Article 116 of Directive 2001/83 and of the precautionary principle 6

(a) Preliminary observations 6

(b) The assessment of the risks of linear gadolinium and of Omniscan in particular 8

(1) Neurological risks 8

(i) The assessment by the PRAC 8

– As regards the absence of new evidence 8

– As regards the reversal of the burden of proof 10

(ii) The assessment by the CHMP 11

– As regards the allegation that the CHMP did not carry out its own assessment 11

– As regards the alleged departure by the CHMP from some of the PRAC's assessments 11

(2) Risks other than neurological risks 13

(c) The assessment of the benefits of linear gadolinium and of Omniscan in particular 13

(1) The benefit of Omniscan for myocardial perfusion imaging 14

(i) Medical arguments 14

(ii) Arguments other than medical arguments 14

– As regards the benefit of Omniscan for myocardial perfusion imaging 15

– As regards the benefit of Omniscan in respect of hypersensitivity risks 16

(d) Conclusion on the first and second pleas in law 17

2. The third plea in law alleging infringement of the principle of equal treatment and non-discrimination 17

(a) The first case of alleged discrimination 17

(b) The second case of alleged discrimination 18

(c) The third case of alleged discrimination 18

(d) The fourth case of alleged discrimination 19

3. The fourth plea in law, alleging infringement of the principle of proportionality 20

4. The fifth plea in law, alleging infringement of the principle of sound administration 22

(a) The impartiality of the procedure 23

(b) The allegation that the relevant bodies did not carry out a full examination of all the observations submitted 25

IV. Costs 26