Intellectual Property Office

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01 December 2022

COUNCIL REGULATION (EC) 469/2009
CONCERNING THE CREATION OF A
SUPPLEMENTARY PROTECTION CERTIFICATE
FOR MEDICINAL PRODUCTS[1]

APPLICANT	Newron Pharmaceuticals S.p.A
ISSUE	Whether application for supplementary protection certificate SPC/GB15/046 meets the requirements of Article 3(b) of the Regulation
HEARING OFFICER	Dr L Cullen

DECISION

Introduction

1 This decision relates to the application for supplementary protection certificate ("SPC") SPC/GB15/046 ("the application"), filed in the name of Newron Pharmaceuticals S.p.A. ("the applicant")[1].

2 This SPC application was filed on 16 July 2015 and relies on basic patent EP(UK) 1613296 B1, entitled "*Methods for treatment of Parkinson's Disease*", and on centralised European marketing authorisation EU/1/14/984, covering the medicinal product XADAGO[2]. The marketing authorisation for XADAGO was granted following Commission Implementing Decision C(2015)1390 of 24 February 2015. As this was an authorisation granted under the centralised procedure by the European Medicine Agency (the "EMA"), it had to meet the requirements set down in Regulation (EC) 726/2004 (the "EMA Regulation") for a centralised approval that would cover all EU countries[3].

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[1] *This decision relates to a SPC that was applied for in 2014. Thus, it relates to the period when the UK was part of the European Union prior to its withdrawal on 31 Decembe2 2020. As such, it is necessary to apply the relevant law and case law that was in force at that time in the UK. This is set out in the decision below.*

[2] *Xadago is a registered trademark (RTM) in the UK. In this decision, I will use XADAGO (in uppercase) to refer to the medicinal product unless quoting from the text of the marketing authorisation and its annexes directly.*

[3] *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 (see here)*

3 The product that is the subject of this SPC application is identified on the associated form SP1 as "*Safinamide for use in combination with levodopa/PDI, and optionally with other PD medicinal products, for the treatment of Parkinson's Disease*".

4 Throughout the examination process, the examiner dealing with this application has maintained the view that, if the product is taken to be the combination of safinamide and levodopa/PDI, then the application is contrary to Article 3(b) of the SPC Regulation, because the marketing authorisation on which the application is based is for safinamide only, and not the combination. Alternatively, if the product is taken to be a single compound, i.e., safinamide, then it is contrary to Article 3(a) of Regulation (EC) 469/2009 ("the SPC Regulation")[4], because the basic patent protects only the combination of safinamide with levodopa/PDI.

5 Following several rounds of correspondence, the matter came before me at a hearing on 23 March 2022, which took place by videoconference. At the hearing, the applicant was represented by Richard Davis, of Hogarth Chambers, and Martin MacLean, of Mathys & Squire LLP. Senior examiner Gareth Prothero acted as Hearing Assistant for the Hearing Officer.

6 Prior to the hearing I raised some further issues on which I wished to be addressed, and I am grateful to the applicant for their supplemental Skeleton arguments in response, which I have referred to below.

7 Following the hearing there was an additional issue that arose relating to the significance of the term "PDI", which stands for '*peripheral decarboxylase inhibitor'*, and how the term "levodopa/PDI" should be understood with regard to the marketing authorisation. Again, I would like to express my thanks to the applicant for their further submissions in writing in response to this issue.

8 I apologise that I was not able to issue this decision to the timescale proposed at the hearing.

The Basic Patent

9 The basic patent, EP(UK) 1613296 B1, entitled *"Methods for the treatment of Parkinson's Disease"*, was filed on 8 April 2004, with an earliest priority date of 11 April 2003, and was granted on 1 September 2009. The expiry date of the patent is 7 April 2024.

10 The invention disclosed in the patent relates to the combination of safinamide and levodopa/PDI in the treatment of Parkinson's disease. Paragraphs [0002] and [0003] of the patent set out the background to the invention regarding Parkinson's disease

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[4] *Regulation (EC) No 469/2009 of the European Parliament and of the Council of 6 May 2009 concerning the supplementary protection certificate for medicinal products; see CELEX Document number: 32009R0469; published in Official Journal of the European Union L 152 on 16.06.2009.*

and the use of levodopa/PDI therapy in its treatment. These are reproduced below (my emphasis added in bold and underline):

> *"[0002] Parkinson's Disease (PD) currently affects about 10 million people world-wide. PD is a highly specific degeneration of dopamine-containing cells of the substantia nigra of the midbrain. Degeneration of the substantia nigra in Parkinson's disease causes a dopamine deficiency in the striatum. Effective management of a patient with PD is possible in the first 5-7 years of treatment, after which time a series of often debilitating complications, together referred to as Late Motor Fluctuations (LMF) occur (Marsden and Parkes, Lancet II: 345-349,1997).* ***It is believed that treatment with levodopa, or L-dopa, the most effective antiparkinson drug, may facilitate or even promote the appearance of LMF. Dopamine agonists are employed as a treatment alternative, but they do not offer the same degree of symptomatic relief to patients as L-dopa does*** *(Chase, Drugs, 55 (suppl.1): 1-9, 1998).*
>
> *[0003] Symptomatic therapies improve signs and symptoms without affecting the underlying disease state.* ***Levodopa*** *((-)-L-alpha-amino-beta-(3,4-dihydroxybenzene) propanoic acid)* ***increases dopamine concentration in the striatum, especially when its peripheral metabolism is inhibited by a peripheral decarboxylase inhibitor (PDI). Levodopa/PDI therapy is widely used for symptomatic therapy for Parkinson's disease, such as combinations with levodopa, with carbidopa ((-)-L-alpha-hydrazino-alpha-methyl-beta-(3,4-dibydroxybenzene) propanoic acid monohydrate), such as SINEMET®; levodopa and controlled release carbidopa (SINEMET-CR®), levodopa and benserazide (MADOPAR®, Prolopa), levodopa plus controlled release benserazide (2-Amino-3-hydroxy-propionic acid N'-(2,3,4-trihydroxybenzyl)-hydrazide), MADOPAR-HBS****."*

The role of the PDI is thus to inhibit the breakdown of levodopa by carboxylase enzymes in the body while the levodopa is being transported from its site of administration through the bloodstream to the brain where, once it crosses the blood-brain barrier which the PDI cannot, the levodopa exerts its therapeutic effect[5].

11 The specification of the patent explains that a combination of safinamide and levodopa/PDI has been found that leads to an improvement of symptoms and a delay of disease progression as compared to administration of either safinamide or levodopa/PDI on its own. This synergistic combination is discussed in more detail in paragraphs [0008] to [0013] of the patent, which are reproduced below (my emphasis added in bold and underline):

> *"[0008] The present invention is based, in part, on the unexpected finding that* ***the combination of safinamide, a safinamide derivative, or a MAO-***

[5] The carboxylase enzyme, aromatic L-amino acid decarboxylase (often referred to as AADC, AAAD or DOPA decarboxylase) is found in the blood. As its name implies, it will convert levodopa (or L-DOPA) to dopamine via a decarboxylation step. The use of a PDI with levodopa can significantly reduce the amount of levodopa that needs to be administered on its own to patients to achieve the same therapeutic impact.

B inhibitor and other Parkinson's Disease agents provides a more effective treatment for Parkinson's Disease (PD) than either component alone*. The invention includes methods of using such compounds to treat Parkinson's Disease and pharmaceutical compositions for treating PD which may be used in such methods.*

[0009] In one embodiment, ***the invention relates to methods for treating Parkinson's Disease through the administration of safinamide from 0.5 to 1, 2, 3, 4 or 5 mg/kg/day in combination with levodopa/PDI, COMT inhibitors, amantadine****. **When safinamide is used in combination with other types of drugs, an unexpected, synergistic effect is achieved. The improvement of symptoms and the delay of disease progression are more evident in patients treated with the combination of drugs than those treated with a single type of drug alone.** When safinamide was administered alone, patients improved only by an average 6.9% whereas when safinamide was added to a stabilized dose of a variety of dopamine agonists, the average improvement reached 27.8%.*

[0010] In one embodiment, ***methods of treating Parkinson's Disease are disclosed, wherein safinamide, and a Parkinson's Disease agent are administered to a subject having Parkinson's Disease, such that the Parkinson's Disease is treated or at least partially alleviated****. The safinamide, and Parkinson's Disease agent may be administered as part of a pharmaceutical composition, or as part of a combination therapy. The amount of safinamide, and a Parkinson's Disease agent is typically effective to reduce symptoms and to enable an observation of a reduction in symptoms.*

[0011] Safinamide is an anti-PD agent with multiple mechanisms of action. One mechanism of safinamide may be as a MAO-B inhibitor.

[0012] ***Parkinson's Disease agents which may be used with safinamide, include one or more of levodopa/PDIs.***

[0013] ***Levodopa/PDIs include, but are not limited to, levodopa plus carbidopa (SINEMET®), levodopa plus controlled release carbidopa (SINEMET-CR®), levodopa plus benserazide (MADOPAR®), and levodopa plus controlled release benserazide (MADOPAR-HBS).”***

12 There are two independent claims in the granted basic patent. These are claim 1 which relates to the therapeutic use and claim 7 which relates to a composition. Both are set out below:

“(1) The use of a first agent selected from safinamide from 0.5 to 1, 2, 3, 4 or 5 mg/kg/day in combination with levodopa/PDI, for the preparation of a medicament as a combined product for simultaneous, separated or sequential use for the treatment of Parkinson’s Disease.

……..

(7) A levodopa composition comprising effective amounts of safinamide from 0.5 to 1, 2, 3, 4 or 5 mg/kg/day and of levodopa/PDI."

13 Therefore, for the avoidance of doubt, and based on the description at paragraph [0013], I take the term "*levodopa/PDI*" as meaning specifically the combination of levodopa and a peripheral decarboxylase inhibitor ("PDI"). I do not consider that it can be construed as just levodopa on its own or just PDI on its own. Levodopa is the necessary active ingredient to treat Parkinson's disease as it is the precursor to dopamine and provides a source of dopamine to replace that which has been destroyed by the disease. As explained above, the PDI is an agent that inhibits the peripheral breakdown of levodopa which mean that a greater proportion of the levodopa administered to a patient makes it across the blood brain barrier to exert the necessary therapeutic effect to counteract the impact of Parkinson's disease. The patent gives examples of two PDIs in this paragraph (carbidopa and benserazide) but indicates that the term is not limited to these two active ingredients.

14 Therefore, I construe claim 1 as relating to a combination of three active ingredients for use to treat Parkinson disease and claim 7 as relating to a combination of three active ingredients. Claim 1 protects the simultaneous, separate or sequential administration of safinamide, levodopa, and a peripheral decarboxylase inhibitor (for example carbidopa or benserazide), in the treatment of Parkinson's Disease, and where the safinamide is administered at a dosage of from 0.5 to 1, 2, 3, 4 or 5 mg/kg/day.

15 Similarly, I construe claim 7 as relating to a composition comprising safinamide, in amounts for administration at a dosage rate of from 0.5 to 1, 2, 3, 4 or 5 mg/kg/day, in combination with levodopa and a PDI. It is noted that this claim is not restricted to the use of the composition in the treatment in Parkinson's Disease.

Issue to be Decided

16 There is a single issue to be decided in the present case. Does the present SPC application meet the requirements of Article 3(b) of the SPC Regulation? In effect, is the authorisation for the medicinal product XADAGO, which is provided in support of this SPC application, a valid authorisation to place the combination of active ingredients identified on form SP1 (i.e., "*safinamide for use in combination with levodopa/PDI*") onto the market in the UK?

17 At the hearing itself, Mr Davis submitted that it is the applicant's intention that the product is the combination of safinamide and levodopa. If there is any ambiguity on this point arising from the wording of the product definition on form SP1, then the applicant suggested that this could be resolved via amendment of the product definition so that the combination is unambiguously stated.

18 Although the product as defined on form SP1 accompanying the application is perhaps not clearly worded, I accept the applicant's proposal that the product that is the subject of the application is a combination. While I note that the applicant was seeking SPC protection for a combination of safinamide and levodopa, as I have explained above and, in light of the further submissions from the applicant following the hearing, I will

have to consider if the combination is a three component one rather than a two component one, i.e., a combination of safinamide, levodopa, and a peripheral decarboxylase inhibitor (PDI, such as carbidopa or benserazide).

19 Furthermore, I note also that there has been no argument from the examiner that the combination of safinamide and levodopa and a peripheral decarboxylase inhibitor (PDI) is not protected by the patent, and in my view, it is clear from a plain reading of claims 1 and 7 that the invention does indeed protect these compounds in combination. Claim 1 protects the use of safinamide in combination with levodopa/PDI for the preparation of a medicament for use in the treatment of Parkinson's Disease, whether that be sequential, separate, or combined; and claim 7 protects a composition that comprises safinamide and levodopa/PDI. Thus, for the avoidance of doubt, there is no article 3(a) issue to be decided (see paragraph 4 above).

20 Therefore, and as was clarified at the hearing, the matter I need to resolve is, in light of Article 3(b) of the SPC Regulation whether or not the marketing authorisation for XADAGO represents an authorisation for the combination of safinamide, levodopa and a peripheral decarboxylase inhibitor (PDI), such as carbidopa.

The Relevant Law

21 Article 1 of the SPC Regulation defines various terms, of which Articles 1(a) and 1(b) are relevant to this decision and are reproduced below:

Article 1

Definitions

For the purposes of this Regulation, the following definitions apply:

(a) 'medicinal product' means any substance or combination of substances presented for treating or preventing disease in human beings or animals and any substance or combination of substances which may be administered to human beings or animals with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in humans or in animals;

(b) 'product' means the active ingredient or combination of active ingredients of a medicinal product;

……..

22 Article 3 of the SPC Regulation concerns the conditions for obtaining an SPC; part (b) of this Article states that a certificate cannot be obtained if the product has not been the subject of a valid authorisation to place a medicinal product including this product onto the market in the EU (my emphasis added in bold):

Article 3

Conditions for obtaining a certificate

***A certificate shall be granted if**, in the Member State in which the application referred to in Article 7 is submitted and at the date of that application:*

(a) the product is protected by a basic patent in force;

*(b) **a valid authorisation to place the product on the market as a medicinal product has been granted** in accordance with Directive 2001/83/EC or ….., as appropriate;*

(c) ……..

(d) ……..

23 Article 10 of the SPC Regulation sets out the conditions for grant or rejection of an SPC application as follows:

Article 10

Grant of the certificate or rejection of the application for a certificate

1. Where the application for a certificate and the product to which it relates meet the conditions laid down in this Regulation, the authority referred to in Article 9(1) shall grant the certificate.

2. The authority referred to in Article 9(1) shall, subject to paragraph 3, reject the application for a certificate if the application or the product to which it relates does not meet the conditions laid down in this Regulation.

3. Where the application for a certificate does not meet the conditions laid down in Article 8, the authority referred to in Article 9(1) shall ask the applicant to rectify the irregularity, or to settle the fee, within a stated time.

4. If the irregularity is not rectified or the fee is not settled under paragraph 3 within the stated time, the authority shall reject the application.

5. ……..

6. ……..

Relevant Case Law

UK Court decisions

Yeda UK

24 The most relevant UK authority is *Yeda Research and Development Company Ltd v Comptroller General of Patents [2010] EWHC 1733 (Pat)* [6]. This case, which I shall refer to as *Yeda UK,* was a decision from the UK Patents High Court on appeal from a decision of the Intellectual Property Office (IPO)[7].

25 The applicant had filed two SPC applications: the first, the 037 application was for the active ingredients, cetuximab and irinotecan in combination and the second, the 038 application, concerned the active ingredient cetuximab alone. The same marketing authorisation (MA) was cited in support of both applications and this MA related to '*Erbitux-cetuximab'*. However, in this MA, there was discussion of how '*Erbitux-cetuximab'* could be used in conjunction with another therapeutically active compound, irinotecan, to treat certain types of cancer. The applicant argued that this was sufficient basis to provide support for a SPC for the combination of cetuximab with irinotecan. The court confirmed the view of the hearing officer at the IPO that the medicinal product ERBITUX and its single active ingredient cetuximab was clearly defined as the subject matter of the authorisation. Although there were brief references in the MA to the use of another therapeutically active compound, irinotecan, with cetuximab, the Court found that these references were wholly insufficient to amount to a marketing authorisation for a product consisting of both cetuximab and irinotecan. In this example, the cetuximab and irinotecan were administered separately.

26 I shall refer to issues discussed in this judgment as necessary at the relevant points in the decision below.

Arguments and Analysis

27 As we are concerned with whether the present SPC application relates to a combination of active ingredients, it is the discussion in *Yeda UK* relating to the '037 application that is particularly relevant to the present situation. It is necessary to consider what are the active ingredients in the medicinal product authorised for human use by the MA and whether these match the active ingredients protected by the patent.

28 As noted above, the *Yeda UK* judgement confirmed that there is indeed a difference between what the medicinal product containing the product is, i.e., the subject of the

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[6] *Yeda Research and Development Co Ltd v Comptroller General of Patents [2010] (EWHC) 1733 (Pat); For full text of this decision from the UK Patents Court, please see Yeda Research and Development Company Ltd v Comptroller General of Patents [2010] EWHC 1733 (Pat) (12 July 2010) (bailii.org) (http://www.bailii.org/ew/cases/EWHC/Patents/2010/1733.html).*

[7] *For text of the IPO decision, see Imclone Systems Inc. and Aventis Holdings Inc. SPC application (BL O/066/10) of 23.02.2010 here (on IPO patents decision database) relating to SPC applications SPC/GB04/037 and 04/038.*

MA as a whole, and what the medicinal product containing the product is used for – which is the subject usually of the section of the MA dealing with pharmaceutical particulars.

29 Paragraph 17 of *Yeda UK* provides a summary of the two applications that were the subject of the appeal as follows (my emphasis added in bold):

> "*17. The patentee applied for two SPCs.* ***The first (referred to as "037") specified the product to be protected as "cetuximab in combination with irinotecan". The Hearing Officer refused to grant the certificate on the ground that the marketing authorisation upon which the application was based was an authorisation for cetuximab alone. Accordingly, that application did not comply with article 3(b).*** *The second (referred to as "038") specified the product to be protected as "cetuximab". The Hearing Officer refused to grant the certificate on the ground that cetuximab (as opposed to the combination of cetuximab and irinotecan) was not protected by the patent. Accordingly, that application did not comply with article 3(a). Thus the patentee fell between two stools and was not entitled to any SPC. It is from those two decisions that the patentee now appeals."*

30 Referring to the earlier UK court decision in *Generics v Daiichi*[8] and also to recital 10 of the SPC regulation, the judge in *Yeda UK* indicated that the therapeutic use of the medicinal product containing the active ingredient is not part of the definition of the medicinal product for the purpose of the SPC regulation. This is a well-established principle from the case law of the CJEU which was most recently confirmed in the *Santen* judgement (C-673/18)[9] and was first elaborated in the *Yissum* judgment (C-202/05)[10] and the *MIT* judgment (C-431/04)[11]. Further, the product must have its own therapeutic effect and not just act as adjuvant or assist the delivery of the active ingredient to the place where it exerts its therapeutic effect (as confirmed in *GlaxoSmithKline* judgment (C-210/13) from the CJEU)[12]. The judgement in *Yeda UK* agreed with the approach adopted by the IPO and summarised the situation as follows:

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[8] *Generics (UK) Ltd v Daiichi Pharmaceutical Co. Ltd. [2009] RPC 23; [2009] EWCA Civ 646.,*

[9] *For full text of the C-673/18 Santen CJEU decision, see ECLI identifier: ECLI:EU:C:2020:531; CURIA - Documents (europa.eu); EUR-Lex - 62018CJ0673 - EN - EUR-Lex (europa.eu).*

[10] *For full text of the C-202/05 Yissum Research and Development Co. v Comptroller-General CJEU decision, see ECLI identifier: ECLI:EU:C:2007:214; CURIA - Documents (europa.eu); EUR-Lex - 62005CO0202 - EN - EUR-Lex (europa.eu).*

[11] *Massachusetts Institute of Technology (Re) [2004] RPC 3, Pat Ct; see also case C-431/04 Massachusetts Institute of Technology CJEU decision, see ECLI identifier: ECLI:EU:C:2006:291 CURIA - Documents (europa.eu); EUR-Lex - 62004CJ0431 - EN - EUR-Lex (europa.eu).*

[12] *For full text of the C-210/13 GlaxoSmithKline Biologicals SA and GlaxoSmithKline Biologicals, Niederlassung der Smithkline Beecham Pharma GmbH & Co. KG v Comptroller General of Patents, Designs and Trade Marks CJEU decision, see ECLI identifier: ECLI:EU:C:2013:762 EUR-Lex - 62013CB0210 - EN - EUR-Lex (europa.eu)*

“23. The Hearing Officer analysed the marketing authorisation as follows (§ 33):

> *"If, as Mr Powell asked me to do, I consider the MA as it was when the SPC application was filed, i.e., in decision C(2004)2509, the attached SmPC makes clear that the medicinal product that is the subject of the authorisation is Erbitux and that it contains cetuximab as the active ingredient. The title of the decision refers to "Erbitux – cetuximab" alone and not to a combination of Erbitux and Irinotecan. The medicinal product is clearly identified as Erbitux, the active ingredient is cetuximab, the physical form is a solution for infusion – see Sections 1, 2 & 3 of the SmPC. This data does not change and defines clearly what is the medicinal product and the active substance which is the subject of the MA.* ***This is in my view distinguishable from how this medicinal product is used****. **This can change on the basis of further clinical evidence and experience and this will happen over the life of an MA. It is only those parts of the MA that deal with the use of Erbitux in patients that mention Irinotecan****. The MA is otherwise silent on Irinotecan, its use, constituents, safety, etc. In those parts of the MA that define the medicinal product in terms of quality or safety, e.g. describing how it is prepared and what are its components, there is no mention of Irinotecan….* ***Section 6 of the SmPC, entitled "Pharmaceutical Particulars" does not make any mention of Irinotecan as being a component of this medicinal product. Thus, Irinotecan is not present in any way in the medicinal product that has been approved by this MA****."*

24. The Hearing Officer made further points (§ 40):

> *"In my view, the MA filed in support of this SPC application only comprises complete information regarding the quality, safety and efficacy of one medicinal product or substance – Erbitux – and one product or active ingredient in that substance – cetuximab. It is clear from the original MA for Erbitux that the other medicinal product – Irinotecan – is the subject of a different MA and the reader is directed to consult that MA for details. Thus, despite the view put forward by Mr Powell, I consider that the passages he referred me to in the SmPC, and the assessment report, do not tell the full story. They describe conditions under which Erbitux may be used clinically. I have to concern myself with determining what exactly is the medicinal product that has been approved and not just with its use or uses.* ***Furthermore, such a focus on what the product is, rather than what it does, is consistent with the fact that what it does can change in the life of the MA but the product itself does not****. In my view the MA for Erbitux is not one for a medicinal product that is a combination of substances rather it is one for a single substance. Thus the corresponding product which is approved in terms of Article 1(b)*

of the Regulation is a single active ingredient, cetuximab. The MA for "Erbitux" allows the holder to place this medicinal product on the market and so is the first for the active ingredient "cetuximab". It is not one for the combination of "cetuximab in combination with Irinotecan"."

25. Mr Powell had two points in rebuttal of this compelling analysis. The first point was that data about irinotecan were incorporated by reference into the marketing authorisation with the consequence that, on its true interpretation, it authorised the combination of cetuximab and irinotecan. The second point is that the Swiss authorities, acting on the same information that had been provided to the Community regulator, had approved Erbitux for the indication/possible use in combination with irinotecan. Thus the Community marketing authorisation should be construed as authorising the same combination. I am not persuaded by either point.

26. ***So far as the first point is concerned, article 1 of the decision plainly identifies the medicinal product, "Erbitux – cetuximab" as the subject-matter of the authorisation. No other medicinal product is identified. The direction to enter that product in the Community Register of Medicinal Products is to the same effect. Article 3 specifies the form of the labelling and package leaflet. The outer packaging makes no mention of irinotecan at all****. The package leaflet contains two brief mentions of irinotecan in explaining how cetuximab is used. The summary of the product characteristics likewise contains brief mentions of irinotecan in explaining how cetuximab is used.* ***But as the case law shows, how a medicinal product is used does not form part of the identification of the product itself.*** *In my judgment the brief references to irinotecan in explaining how cetuximab is used are wholly insufficient to amount to a marketing authorisation of a product consisting of both cetuximab and irinotecan. In short, I agree with the Hearing Officer for the reasons that he gave.*

27. So far as the second point is concerned, in the first place I am not convinced that the Swiss authorities gave a marketing authorisation for a combined product, as opposed to a combined use (or, to put the point another way, they attached a condition about use to their approval of cetuximab as a product). In the second place what is important for present purposes is not what the Swiss regulators have authorised but what the Community regulators have authorised. If they have authorised different things, so be it. Third, it may well have been open to the patentee to frame its application to the Community regulator for marketing authorisation in such a way as would have resulted in an authorisation for a combination of cetuximab and irinotecan. But it did not. I agree, therefore, with the Hearing Officer that there was a mismatch between the 037 application and the marketing authorisation. He was right to refuse the SPC. Consequently, the appeal against his determination on the 037 application must be dismissed."

Therefore, the appeal failed because, having considered the relevant caselaw[7-13], the judge concluded that how a medicinal product is used does not form part of the identification of the product itself. In the case of ERBITUX, the references to irinotecan in the MA were insufficient to amount to a marketing authorisation for the combination of cetuximab and irinotecan.

31 It is therefore relevant for me to identify what is the active ingredient or active ingredients in the medicinal product covered by the marketing authorisation for XADAGO; is it a single active ingredient, safinamide, or is it a combination of safinamide, levodopa and a PDI?

32 With these points in mind, I now turn to consider the MA for XADAGO in greater detail.

Granted Marketing Authorisation, EU/1/14/984 for "XADAGO-safinamide"

33 In considering the MA for XADAGO, I note that I am not interpreting a patent document or construing claims to determine what is the scope of the SPC based on those claims, I am reading the MA to find out what is/are the active ingredient/ingredients, what is the medicinal product that has been approved for use in humans, and does/do the active ingredient(s) from the MA match the product for which SPC protection is being sought. I am interested in the therapeutic uses of the medicinal product authorised by the MA only in so far as it helps me to answer the question what active ingredients are the subject of the marketing authorisation?

34 The MA has been granted by European Commission Decision C(2015)1390 (final) of 24/02/2015. It is entitled as follows:

> "*Commission Implementing Decision of 24.2.2015 granting marketing authorisation under Regulation (EC) No 726/2004 of the European Parliament and of the Council for "Xadago – safinamide", a medicinal product for human use*".

The name of the medicinal product "Xadago" is followed immediately by the name of the active ingredient "safinamide" – using the usual naming convention for MAs granted by the European Commission.

35 The decision itself comprises a total of 4 recitals and 5 articles. In the present case, recitals (1) and (2) and Articles 1-3 are most relevant. Recital (1) indicates that "*The medicinal product "Xadago – safinamide" complies with the requirements set out in 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*". As Recital (2) then makes clear "*it is therefore appropriate to authorise its placing on the market*". Thus, the product comprising the single active ingredient has met the requirement under the relevant legislation to be approved as a medicinal product for human use,

36 Article (1) of the decision states, "*The marketing authorisation provided for in Article 3 of Regulation (EC) No. 726/2004 is granted for the medicinal product "Xadago-safinamide", the characteristics of which are summarised in Annex 1 to this decision*".

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[13] *Takeda Chemical Industries Ltd.'s SPC Applications (No. 3) [2004] RPC 3; [2003] EWHC 649;.*

Annex 1 of the decision is also referred to as the Summary of Product Characteristics (SmPC). This article then goes on to list the MA identification number that "Xadago-safinamide" will be authorised under. Article (2) of the implementing decision makes clear that Annex II to this decision sets out the conditions that the medicinal product will have to comply with. It states that: "*The marketing authorisation concerning the medicinal product referred to in Article 1 shall be subject to compliance with the conditions set out in Annex II and, in particular, with those relating to manufacture and importation, control and issue*". Article 3 states that the "*labelling and package leaflet concerning the medicinal product referred to in Article 1 shall comply with the conditions set out in Annex III*".

37 On this basis, there appears to be only one active ingredient identified, safinamide.

38 Turning now to the Summary of Product Characteristics (SmPC) which is Annex I to the Commission Implementing decision for *"Xadago – safinamide"*. This describes the medicinal product and its characteristics in specific detail. I note that Section 1 and Section 2 of the SmPC describe the medicinal product and its composition as follows:

> *"1. NAME OF THE MEDICINAL PRODUCT*
> *Xadago 50 mg film-coated tablets*
> *Xadago 100 mg film-coated tablets*
>
> *2. QUALITATIVE AND QUANTITATIVE COMPOSITION*
> *Xadago 50 mg film-coated tablets*
> *Each film-coated tablet contains safinamide methansulfonate equivalent to 50 mg safinamide.*
> *Xadago 100 mg film-coated tablets*
> *Each film-coated tablet contains safinamide methansulfonate equivalent to 100 mg safinamide.*
> *For the full list of excipients, see section 6.1."*

39 The first reference to levodopa occurs when the therapeutic use of the medicinal product is being discussed, i.e., in Section 4 of Annex I entitled "CLINICAL PARTICULARS" as set out below (my emphasis added as **bold**):

:

> *"4. CLINICAL PARTICULARS*
>
> *4.1 Therapeutic Indications*
>
> ***Xadago is indicated for the treatment of adult patients with idiopathic Parkinson's disease (PD) as add-on therapy to a stable dose of Levodopa (L-dopa) alone or in combination with other PD medicinal products** in mid-to late-state fluctuating patients."*

So far as I have been able to establish, this is the only reference in the SmPC to the term "add-on therapy"

Further references are made as follows in this section:

> *"4.4 Special warnings and precautions for use:*
> *……...*

Dopaminergic side effects

*Safinamide used as an adjunct to **levodopa** may potentiate the side effects of levodopa, and pre-existing dyskinesia may be exacerbated, requiring a decrease of **levodopa**. This effect was not seen when safinamide was used as an adjunct to dopamine agonists in early-stage PD patients."*

40 The discussion is expanded further in Section 5 of Annex 1 which relates to the "PHARMACOLOGICAL PROPERTIES" of the medicinal product. There is a brief summary of the mechanism of safinamide which indicates that as an active ingredient it has both a dopaminergic and a non-dopaminergic mechanism of action.

"5.1 Pharmacodynamic properties
……..

Pharmacodynamic effects

*Population PK models developed from studies in patients with Parkinson's disease indicate that the pharmacokinetic and pharmacodynamics effects of safinamide were not dependent on age, gender, weight, renal function and exposure to **levodopa**, indicating that dose adjustments will not be required based on these variables.*

……..."

At section 5.3, there is the only reference to levodopa/carbidopa:

"5.3 Preclinical safety data
……..

In embryo-foetal developmental studies in rats and rabbits, malformations were induced at safinamide exposures of 2 and 3-fold above human clinical exposure, respectively. The combination of safinamide with levodopa/carbidopa resulted in additive effects in the embryo-foetal development studies with a higher incidence of foetal skeletal abnormalities than seen with either treatment alone."

41 There are no references to levodopa, or a PDI (such as carbidopa or benserazide), in Annex II to the authorisation which relates to the manufacturing conditions and conditions for safe use of the medical product.

42 A number of references to Levodopa are included in Annex III to the decision which is the Labelling and Packaging Leaflet. In particular, at part B (packaging leaflet) which is explaining what the active ingredient in the medicinal product is and how it works as follows:

- Section 1:

"1. What Xadago is used for

Xadago is a medicine that contains the active substance safinamide. It acts to increase the level of a substance called dopamine in the brain, which is involved in the control of movement and is present in reduced amounts in the brain of patients with Parkinson's disease. Xadago is used for the treatment of Parkinson's disease in adults.

In mid- to late-stage patients experiencing sudden switches between being "ON" and able to move and being "OFF" and having difficulties moving about, Xadago is added to a stable dose of the medicine called levodopa alone or in combination with other medicines for Parkinson's disease."

- Section 2:

"2. What you need to know before you take Xadago
……..

Warnings and precautions
……

- *Uncomfortable jerky movements may occur or worsen when Xadago is used together with levodopa."*

43 Taking the above points into account, I consider that this is highlighting the fact that safinamide is used to treat Parkinson disease at a stage when the levodopa is losing its impact. The safinamide is an additional medicinal product available to continue to treat Parkinson disease. Applying the same analytical approach as in the original office decision[7], which was approved on appeal[6], and is consistent with the approach adopted by the examiner dealing with the present case, to identify what the medicinal product is, as distinct from how it is used, leads me to the conclusion that this marketing authorisation is for safinamide alone and not for the combination of safinamide, levodopa and a PDI.

44 Firstly, article 1 of the marketing authorisation, which I think should not be downplayed or ignored, refers to safinamide only. As I have indicated above, the annexes to the authorisation do make reference as to how safinamide is used; however, as was concluded in *Yeda UK*, for the purposes of deciding whether an SPC can be granted, how a product is used is not part of that decision. In particular, it was confirmed at paragraph 19 of *Yeda UK* that:

> *"To my mind, it is clear from recital (10) and from the case law that what constitutes a "product" is to be strictly construed: Generics (UK) Ltd v Daiichi Pharmaceutical Co. Ltd. [2009] EWCA Civ 646, [2009] R.P.C. 23. CA. In deciding what is a "product" one must focus, as the hearing officer puts it, "on what the product is, rather than what it does". As the ECJ said in Case C-202/05 Yissum Research and Development Co v Comptroller General (§18):*
>
> *"It follows that the concept of a "product" cannot include the therapeutic use of an active ingredient protected by a basic patent"."*

45 At the hearing, I understood Mr Davis as arguing that this paragraph only states that the product does not relate to its therapeutic use but says nothing of its "use" in combination with another active (i.e., levodopa) or combination of active ingredients (i.e., levodopa and a PDI). In my view this is an artificial distinction. In this case, the product is safinamide. Based on the definition in Article 1(b) of the regulation and, as is clear from the case-law discussed above (see paragraph 30), the SPC is for the product and the therapeutic use of this product does not play a part in identifying the product that is the subject of the SPC.

46 In my view, the MA makes clear that what safinamide does is provide a means for effective treatment for Parkinson's disease to continue when a problem starts to arise with the usual treatment of levodopa on its own or with levodopa and a PDI. Thus, the safinamide works only with some Parkinson patients – and this is reflected in the SmPC and in the related European Public Assessment Report (EPAR) which provides a report from the relevant committee of the EMA on the risks and benefits of the safinamide as a medicine for human use based on the data provided by the applicant for the MA[14]. Safinamide is used to treat Parkinson's patients only when they start to show a reduction in the effect of the dose of levodopa in terms of having more OFF effects (when the patient has problems with mobility) than ON effects (when the patient is able to move around). Thus, on balance, I do not consider that it is appropriate to consider the use of safinamide with levodopa or safinamide with levodopa and a PDI as a combination product. Safinamide is not necessary for treatment of all Parkinson's patients that are treated with levodopa and/or levodopa and a PDI. This in my view is why the marketing authorisation refers to the use of safinamide as an add-on therapy – it is not used in all cases where patients are being treated for Parkinson's disease with levodopa and a PDI but it is used in some situations where certain clinical conditions merit it.

47 I have already noted that the claims of the basic patent specify the use of safinamide with levodopa and a PDI. As I have indicated above, the role of the PDI is to prevent breakdown of the levodopa before it crosses the blood brain barrier. Thus, the PDI is playing a supplementary role in a similar fashion to the polifeprosan component in the *MIT* case[10]. The PDI is making it easier for the levodopa to get from its site of administration (as a pill for oral consumption) via absorption from the small intestine into the bloodstream and then to the part of the body (i.e. the brain) where it exerts its therapeutic effect.

48 According to the SmPC and the EPAR, safinamide does have a direct therapeutic effect that is relevant to Parkinson's disease. Safinamide, in contrast to a PDI such as carbidopa, does cross the blood-brain barrier and enters into the brain where it exerts a therapeutic effect in an analogous fashion to the levodopa. Thus, it is clear that safinamide is treating the same disease as levodopa. However, I do think that I have to take into account that it is not being used in all cases with levodopa to treat Parkinson's disease. It is only used at the point where the on-going treatment with levodopa is no longer having the same impact and so the OFF effects are more

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[14] The European Medicines Agency (EMA) publishes detailed information on the medicines assessed by the Committee for Medicinal Products for Human Use (CHMP) in the European public assessment report (EPAR). This set of documents describe the evaluation of a medicine authorised via the centralised procedure and includes the product information and is published on the European Medicines Agency website. See EPAR for Xadago, INN-safinamide (europa.eu)

significant and treatment has to be adjusted to account for that. This, in my view, is the meaning of the reference to safinamide as an "*add-on therapy to a stable dose of levodopa*" in the SmPC (see para 35 above and SmPC, '*4.1 Therapeutic Indications' under '4. CLINICAL PARTICULARS'*). It is added to treat Parkinson's disease in certain specific circumstances – such as set out in the MA. For this reason, I do not think that I can accept the applicant's argument that the marketing authorisation for "*Xadago – safinamide*" is for a combination of safinamide and levodopa or safinamide and levodopa/PDI. I consider instead that it is a marketing authorisation that describes when safinamide is used to treat Parkinson disease. Thus I am not persuaded that I should consider this MA as anything other than an MA for safinamide on its own which describes the form of this active ingredient in a medicinal product and when it should be used to treat Parkinson disease. I am of the view that the MA filed in support of the present SPC application only comprises complete information regarding the quality, safety and efficacy of one medicinal product – XADAGO – which comprises the single active ingredient – safinamide.

49 At the hearing, Mr MacLean suggested that without the levodopa therapy there is no therapy, and that safinamide cannot be considered to work on its own without the levodopa or levodopa/PDI. However, in my opinion the basic patent itself seems to cast doubt on that view since it states, at paragraph [0009] (reproduced above), that although patients treated with safinamide combined with dopamine agonists showed greater improvement, there was, nevertheless, still an improvement seen in patients treated with safinamide alone. The SmPC also indicates that safinamide has an action against Parkinson's disease in its own right.

50 Mr MacLean also sought to distinguish the present situation from the one relevant to *Yeda UK* in that the marketing authorisation at issue in that earlier decision discusses two specific scenarios in the field of cancer treatment: one being the combination of ERBITUX with the chemotherapeutic irinotecan; the other being the combination of ERBITUX with radiation therapy. It follows, in Mr MacLean's view, that in order to make sense of the marketing authorisation for ERBITUX in the *Yeda UK* case, it can only be concluded that it relates to just the common component of these two treatments which is ERBITUX, by which I take him to mean, the active ingredient or product of ERBITUX which is cetuximab. According to Mr MacLean, this could be contrasted with the present situation, in which the authorisation is *only* concerned with the treatment of Parkinson's Disease.

51 I can find nothing in the decision of the Patent's Court in *Yeda UK* that suggests that such an approach was taken in reaching the conclusion that the authorisation related to the active ingredient cetuximab only. On the contrary, paragraph 26 of *Yeda UK* is clear in its finding that the reason the authorisation was found to relate to cetuximab alone was because the case law shows that how a medicinal product is used does not form part of the identification of the product itself, and that the few references to how the product was used in the marketing authorisation were insufficient to amount to an authorisation of the combination of cetuximab and irinotecan. In my opinion this applies whether the marketing authorisation mentions just a single use (as 'add-on therapy'), or whether it mentions several such uses.

52 The patent and the SmPC indicate that safinamide has an action against Parkinson's disease in its own right. While I accept that the effect is much better when it is given with levodopa, I do not consider that this is enough to conclude that safinamide and

levodopa and a PDI are a combination product and that the MA for XADAGO represents a MA for this combination product. The information in the MA is about how safinamide is used in therapy and the medicinal product XADAGO is used only in some Parkinson's patients.

53 In the supplemental skeleton arguments provided for the hearing, Mr Davis explained that safinamide has therapeutic activity through both dopaminergic and non-dopaminergic effects, which are discussed in the SmPC at paragraph 5.1 ("Pharmacological Properties"), under the sub-heading "Mechanism of action". This states that:

> *"Safinamide acts through both dopaminergic and non-dopaminergic mechanisms of action. Safinamide is a highly selective and reversible MAO-B inhibitor causing an increase in extracellular levels of dopamine in the striatum. Safinamide is associated with state-dependent inhibition of voltage-gated sodium (Na^+) channels, and modulation of stimulated release of glutamate. To what extent the non-dopaminergic effects contribute to the overall effect has not been established".*

54 However, while I accept that safinamide has its own dopaminergic effect, I note that this explanation as to the mechanism of action of safinamide makes absolutely no mention of any interaction between safinamide and levodopa/PDI, which might help suggest that the authorisation relates to a combination. Although I note that the same section of the SmPC also details the clinical efficacy of safinamide in two phase III clinical trials ("Study SETTLE" and "Study 016/018", discussed further below), and that one of the inclusion criteria for those trials was that participants were undergoing treatment with levodopa/carbidopa, this fact is not referred to or otherwise made clear in the authorisation itself. Furthermore, the inclusion criteria were not only for patients undergoing treatment with levodopa/carbidopa, but it was also open to patients undergoing treatment with levodopa. Thus, I do not think that one can read the MA as being for a combination of safinamide and levodopa and a PDI.

Levodopa v Levodopa/PDI

55 As I have mentioned above, following the hearing, I invited further comments from the applicant as regards how the marketing authorisation relates to safinamide in combination with both levodopa ***and*** a PDI. In response, the applicant's representative argues that the reference to "*treatment with a stable dose of levodopa*" (for instance at section 4.1 of the SmPC for XADAGO), would be taken by the skilled addressee as necessarily referring to levodopa in combination with a PDI, because (1) the use of a PDI is the only means of stabilising the peripheral concentration of levodopa, and (2) because without a stabilised, optimal concentration of levodopa on the blood side of the blood-brain barrier, efficacious delivery of dopamine to the dopaminergic neurons in the substantia nigra cannot be reliably maintained due to the degradation of levodopa. It is therefore argued that "stabilising" means avoiding the degradation through the administration of PDI.

56 In support of this argument the applicant refers to the phase III clinical trials that underpin the marketing authorisation. In particular, they refer to pages 7 and 39 of the trial referred to in the marketing authorisation for XADAGO as "Study SETTLE", as

indicating that a PDI must be present because this is necessary to avoid the degradation of levodopa.

57 However, on the evidence before me, I do not find the applicant's arguments regarding this point persuasive. Firstly, although it makes reference, as noted above, to safinamide being for "*use as an add-on therapy for*" levodopa, the MA makes no mention at all of the term "peripheral decarboxylase inhibitor" (PDI), which is specified in each of claims 1 and 7 of the basic patent. The only reference I can find in the MA is to a specific PDI, carbidopa, at section 5.3 of the SmPC (see above), where it is discussed with regard to preclinical safety data, that the combination of safinamide with levodopa/carbidopa resulted in higher incidence of foetal skeletal abnormalities than seen with either treatment alone.

58 Secondly, while I note that page 39 of "Study SETTLE" (at section 9.3.1 "Inclusion Criteria") makes it clear that participants in the study were "*levodopa responsive and receiving treatment with a stable dose of levodopa [three to ten doses per day of any levodopa preparation (including CR, IR, or a combination of CR/IR), plus benserazide/carbidopa; with or without addition of a COMT inhibitor*]", I do not think that it can be inferred from this that a "stable dose" of levodopa necessarily means it is always administered with a peripheral decarboxylase inhibitor. Based on the information in the MA for XADAGO and giving the words their usual meaning, I consider that the term "stable dose" would be well understood as meaning simply that the patient is receiving a consistent, non-varying dose over a period of time. The same sentence at page 39 for instance also mentions that participants in the study "…*may have been receiving concomitant treatment with <u>stable doses</u> of a dopamine agonist, an anticholinergic, and/or amantadine for at least four weeks prior to the screening visit*" (my emphasis added as underline). Thus I am of the view that it is not appropriate to interpret the word "stable" when used in connection with a dopamine agonist as meaning a combination of this agonist with a PDI.

59 Thirdly, I note that "Study SETTLE" states (at page 32, fourth paragraph) that "*The most effective medical treatment currently available is the dopamine precursor, levodopa, <u>usually</u> administered together with a peripheral decarboxylase inhibitor*" (my emphasis added as underline). This does not seem to me quite the same as saying that administration of levodopa with a PDI is mandatory.

Support from IPO decision BL O/711/22 (Roche Glycart AG's SPC Application.)

60 I find support from recent IPO decision concerning SPC application SPC/GB17/055 in the name of *Roche Glycart AG* (hereafter *Roche*)[15] for my conclusion above that the MA in the present case is for safinamide alone.

61 As a hearing officer, I need to consider each case based on its particular facts and circumstances. I am not bound by decisions from the IPO Tribunal in the same way as I am bound by decisions of the UK courts. However, where a similar situation has arisen, the matters discussed in the earlier IPO decision may well be relevant when considering the later case. Both *Roche* and the present case concern the question of

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[15] *For full text of the IPO decision, see Roche Glycart AG's SPC application (BL O/711/22) of 23.08.2022 here (on IPO patents decision database) relating to SPC applications SPC/GB17/055.*

whether the combination product for which SPC protection was being sought meet the requirements of Article 3(b) of the SPC Regulation. As in the present case, the approach set down in the *Yeda UK* judgement was adopted in *Roche* to determine what were the active ingredients in the medicinal product that was the subject of the marketing authorisation.

62 In *Roche* an application for an SPC for a combination of obinutuzumab and bendamustine was based on a type-II variation to the MA for medicinal product GAZYVARO comprising obinutuzumab only as active ingredient. This hearing officer came to the conclusion that, although the SmPC for GAZYVARO explicitly states that it is mandatory that the antibody obinutuzumab, the single active ingredient in the medicinal product GAZYVARO, is used in combination with the anti-neoplastic agent, bendamustine, for the treatment of non-Hodgkin lymphoma[16], this does not serve, under Article 3(b) of the SPC Regulation, as a suitable MA for the combination of obinutuzumab and bendamustine.

63 The information about the use of obinutuzumab with bendamustine in the MA for the authorised medicinal product GAZYVARO that contains obinutuzumab was at a similar level to that provided about levodopa in the present MA for the authorised medicinal product XADAGO that contains safinamide, i.e., the use in combination was really only mentioned in the discussion on clinical particulars.

64 The MA is more than just the section describing clinical use (often titled 'Clinical Particulars'), albeit that this is an important part. The SmPC in *Roche* also provided information on the composition and formulation of the medicinal product; the pharmacological properties of the active ingredient; what additional ingredients make up the medicinal product and what their purpose is; and what are the outcomes from all the testing that was carried out on obinutuzumab. It did not provide the same level of information about the other components in either of the combinations which are discussed in the clinical section of the SmPC for GAZYVARO – i.e., that with bendamustine or that with chlorambucil. It would appear to be necessary to go to some other source, e.g., a different marketing authorisation document, to find the same level of information about bendamustine or chlorambucil, that the MA in *Roche* provides about obinutuzumab. As a consequence, the MA provided in support of the SPC application in *Roche* was found not to be a valid authorisation to place the product, when defined as a combination of obinutuzumab and bendamustine, on the market in the UK.

65 In the present case, I note that the authorised use being discussed is not the result of a type-II variation to the MA (as occurred in *Roche*) but rather is the use that the MA was first authorised for. However, as I have explained above, the use to which the medicinal product is being put is not relevant to determining what are the active ingredients in the medicinal product.

Conclusion

66 Taking all of the above into account, I find that the marketing authorisation that forms the basis of SPC application SPC/GB15/046 in the name of Newron Pharmaceuticals

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[16] This is the result of a type-II variation to the marketing authorisation for GAZYVARO; see section 4.1 of SmPC, which deals with therapeutic use.

SpA is not a valid authorisation to place the product applied for on the market as required under Article 3(b) of the SPC Regulation. SPC protection is being sought for the combination of safinamide, levodopa and a PDI.

67 For the reasons I have outlined above I have concluded that the marketing authorisation provided in support of this application relates to the active ingredient safinamide alone and not to a combination of safinamide, levodopa and a PDI.

68 As I have found that this application does not meet the requirements of Article 3(b) of the SPC regulation, I refuse the application under Article 10(2) of this regulation.

Appeal

69 Any appeal must be lodged within 28 days after the date of this decision.

Dr L CULLEN
Deputy Director, acting for the Comptroller