OFFICE OF FAIR TRADING

Completed acquisition by Shire plc of Viropharma Incorporated

ME/6331/13

The OFT's decision on reference under section 22(1) given on 10 February 2014. Full text of decision published 8 April 2014.

Please note that the square brackets indicate figures or text which have been deleted or replaced in ranges at the request of the parties or third parties for reasons of commercial confidentiality.

PARTIES

1. **Shire plc** ('**Shire**') is an international pharmaceutical group which is incorporated in Jersey and headquartered in Dublin. It is listed on the London Stock Exchange and on the NASDAQ Global Select Market. Shire supplies a range of pharmaceutical products. Within the rare diseases segment, Shire offers Firazyr, a synthetic peptide therapy for the acute treatment of angioedema owing to hereditary C1-inhibitor deficiency ('hereditary angioedema or '**HAE**'). Its UK subsidiary is Shire Pharmaceuticals Limited. Shire's 2012 group turnover was $4,681 million and its 2012 UK turnover was £[ ] million.

2. **ViroPharma Incorporated** ('**ViroPharma**') is an international biopharmaceutical company incorporated in Delaware and headquartered in Pennsylvania (United States), and listed on the NASDAQ Global Select Market. Its UK subsidiary, ViroPharma Limited, sold three branded products in the UK, including Cinryze, a C1-inhibitor replacement therapy used primarily for the prophylactic treatment of HAE. Viropharma's 2012 group turnover was $428 million and its 2012 UK turnover was £[ ] million.

3. Shire and ViroPharma are referred to below as the '**Parties**'.

TRANSACTION

4. On 11 November 2013, Shire and ViroPharma entered into a merger agreement pursuant to which Shire acquired all the outstanding shares of ViroPharma for $50 per share in cash by way of a tender offer. The total consideration was approximately $4.2 billion (the '**Merger**').

5. The Merger was notified to the Office of Fair Trading ('**OFT**') on 9 December 2013. It completed on 24 January 2014. The administrative deadline is 10 February 2014 and the statutory deadline is 23 May 2014.

JURISDICTION

6. As a result of the Merger, the Parties have ceased to be distinct. ViroPharma constituted an 'enterprise' for the purposes of section 23 of the Enterprise Act 2002 (the '**Act**').

7. The Parties submit that the merged entity will have an increased share of supply of over 25 per cent in the supply of pharmaceutical products for acute treatment of HAE ([30-40] per cent with a [0-10] per cent increment (by value)) and that the share of supply test in section 23(3) of the Act is met.

8. The OFT therefore believes that it is or may be the case that a relevant merger situation has been created.

BACKGROUND

9. Prior to the completion of the Merger, Shire and ViroPharma each supplied pharmaceutical products for the treatment of HAE. HAE is a rare genetic disease characterised by attacks of swelling of the skin or the mucous membranes which can be disfiguring, painful, and potentially life-threatening in the case of laryngeal attacks.[1] It is estimated to affect between 1 in 10,000 and 1 in 50,000 people.

10. C1-inhibitor is a protease inhibitor that is found in human plasma. It primarily regulates activation of key inflammatory and coagulation biochemical pathways. It achieves this by limiting the production of bradykinin, a small protein (peptide) that causes blood vessels to leak fluid into the tissues, causing swelling.

11. Patients with HAE have a mutation in the gene that encodes C1-inhibitor, resulting in either low level production of C1-inhibitor ('**HAE 1**') or the production of dysfunctional C1-inhibitor ('**HAE 2**').[2] These patients have difficulty regulating

[1] See literature on HAE, Cicardi et al. on behalf of Hereditary Angioedema International Working Group ('**HAWK**'), 'Evidence-based recommendations for the therapeutic management of angioedema owing to hereditary C1 inhibitor deficiency: consensus report of an International Working Group', The European Journal of Allergy and Clinical Immunology 2012, pp. 147-157 ('**HAWK article on HAE**'); Craig et al., 'WAO Guideline for the Management of Hereditary Angioedema', WAO Journal 2012, pp. 182-199 ('**WAO guideline on HAE**').

[2] The Parties submit that around 85 per cent of patients diagnosed with HAE have HAE-1; the remaining 15 per cent have HAE-2. A third variant of HAE (HAE -3) has been identified in patients with normal levels of functional C1-inhibitor (this type of HAE is distinct from C1-inhibitor deficiency-associated forms of HAE, and therefore does not necessarily respond to therapies designed to treat HAE-1 or HAE-2. See also the literature on HAE listed at footnote 1.

bradykinin levels. Therefore, the flow of fluids into bodily tissue can become uncontrolled, leading to potentially severe swelling or oedema.[3]

12. Once a patient has been diagnosed with HAE, physicians consider which of the following options is best for the management of the condition:[4]

    - Acute treatment is used to remedy the symptoms of episodic attacks (once the patient is suffering an attack);
    - Long-term prophylactic therapy is used to help reduce the frequency of HAE attacks.[5]

Treatments for HAE available in the UK

13. Table 1 below sets out the various treatments for HAE available in the UK.

Table 1: HAE treatments in the UK[6]

Branded name (generic name)	**Function and mode of administration**	**Supplier**	**Indicated use (specifically approved) and prescribing practice in the UK**
Berinert (C1-inhibitor)	C1-inhibitor replacement therapy derived from human plasma. Treatment with a C1 inhibitor concentrate eliminates the underlying cause of HAE-1/2 by replacing the deficient protein. Plasma-derived C1-inhibitor binds irreversibly to proteins in the inflammation system. This slows bradykinin release causing fluid release to stop. It is administered intravenously.	CSL Behring	Indicated for acute treatment and used for both acute and prophylactic treatment
Cinryze (C1-inhibitor)		ViroPharma	Indicated and used for both acute and prophylactic treatment
Ruconest (Conestat alfa)[7]	This has an identical amino acid sequence and comparable biological activity to plasma-derived C1-inhibitor. It is administered intravenously.	Swedish Orphan Biovitrium AB	Indicated and used for acute treatment only
Firazyr (Icatibant)	Firazyr is a a synthetic peptide therapy which inhibits bradykinin activity through antagonism of the bradykinin type two receptor, thus	Shire	Indicated and used for acute treatment only

[3] http://www.viropharma.com/pipeline/c1-inh/hae.aspx
[4] Patients with HAE who have planned surgery or dental work may be prescribed a treatment to prevent the occurrence of an attack, so called 'short-term prophylaxis.' The Parties assert that this type of treatment is very rarely necessary. See also, Farkas et al., 'Short-term prophylaxis in hereditary angioedema due to deficiency of the C1-inhibitor – a long-term survey', The European Journal of Allergy and Clinical Immunology 2012, pp. 1586-1593.
[5] HAWK Article on HAE; WAO guideline on HAE, see footnote 1 above.
[6] See also the articles described in footnote 1 for further details on the treatments available for HAE.
[7] It is a recombinant C1-inhibitor that is made from the milk of genetically modified female rabbits which are able to produce human protein.

	preventing vasodilation and vascular permeability. (In other words, it temporarily blocks the bradykinin receptor rather than reducing bradykinin release).[8] It is administered subcutaneously.		
(Tranexamic acid)	This inhibits the fibrinolytic pathway, decreasing plasma-induced activation of C1-inhibitor and slowing the rate of usage of C1-inhibitor so that the protein is depleted less quickly. It is available in tablets.	Generics pharmaceuticals suppliers	Indicated and used for acute and prophylactic treatment
(Anabolic steroids, either Danazol or Stanozol; androgens)	These increase the hepatic production of C1-inhibitor. They are available in tablets.	Generics pharmaceuticals suppliers	Not indicated but used in practice for acute and prophylactic treatment
(Fresh frozen and solvent/detergent plasma)	Plasma contains C1-inhibitor. It is administered intravenously.	National blood transfusion services	Not indicated for acute or prophylactic treatment but used in practice for acute treatment

Source: the Parties, third parties and literature on HAE

14. Shire offers Firazyr, which is a synthetic peptide therapy. Firazyr was previously owned by Jerini.[9] It was first supplied by Shire in the UK in 2008. ViroPharma markets Cinryze, a C1-inhibitor replacement therapy derived from human plasma.[10] ViroPharma began marketing Cinryze in the UK in 2012.

Price regulation and procurement in the prescription channel

15. HAE treatments are only available in the UK on prescription. The Parties' HAE treatments are mostly sold to hospitals with immunology centres, and are reimbursed by national health services in the UK.[11]

16. In a previous decision in the pharmaceutical sector, the OFT noted that the pharmaceutical sector has certain specific features which need to be taken into account when defining the relevant markets as they can affect the extent to which demand for a product, and the behaviour of other suppliers, would

[8] Further information on the action of Firazyr is available at http://www.firazyr.com/hcp/about-hereditary-angioedema/bradykinin.
[9] Jerini did not market Firazyr in the EU before the acquisition of Jerini by Shire in July 2008. The EC authorised the marketing of Firazyr throughout the EU in July 2008.
[10] Other differences between Firazyr and Cinryze are described at paragraphs 46-54 below.
[11] They may also be delivered to certain patients at home when agreed with the ordering hospital. *See*, for example, documents published by the All Wales Medicines Strategy Group, the Scottish Medicines Consortium and the 'Clinical Commissioning Policy: Treatment of Acute Attacks in Hereditary Angioedema', dated April 2013 ('**NHS Commissioning Policy**') for England.

respond to a change in its price.[12] These features include the regulation of pricing and reimbursement of pharmaceutical products (including under the Pharmaceutical Price Regulation Scheme, **PPRS**) and the fact that doctors'[13] decisions (they are the main determinant of demand) as to which medicine to prescribe are not typically driven by price considerations but clinical needs.

17. The price and reimbursement of pharmaceutical products may be regulated under the PPRS. The PPRS is a non-contractual voluntary scheme between the Department of Health (acting on behalf of the Health Departments of England, Wales, Scotland and Northern Ireland) and the Association of the British Pharmaceutical Industry.[14] The PPRS aims to strike a balance on prices to ensure that the interests of patients, the NHS, industry, and the taxpayer are promoted for each other's mutual benefit. It provides for some pricing flexibility mechanisms to allow some variation in price. Shire has consented to be part of the 2014 PPRS.

18. The Parties submit that they offer each of Firazyr and Cinryze at a [ ] price [ ] to hospitals throughout the UK (Firazyr through a 'Patient Access Scheme'[15]) and that [ ]. The Parties explain that their products are offered at a [ ] price to ensure that each is priced competitively [ ].[16]

19. Although tender processes may have an impact on pricing for pharmaceutical products bought by hospitals, the OFT understands from third parties and the Parties that the Parties' products are sold at the same [ ] price throughout the UK.[17] The Parties and NHS England told the OFT that a new national tender is being set up, which will run from 1 July 2014. It is however unclear at this stage what effect it will have on prices for HAE treatments in the UK.[18]

20. In addition, the OFT notes that doctors may choose which medicine to prescribe based on clinical needs rather than prices. In relation to HAE treatments, most physicians told the OFT that they are mindful of the costs of medicines but that they ultimately give priority to a patient's clinical needs. Their prescribing behaviour may nevertheless be indirectly informed by price insofar

[12] OFT Decision No. CA98/02/2011, Abuse of a dominant position by Reckitt Benckiser Healthcare (UK) Limited and Reckitt Benckiser Group plc ('**Reckitt Benckiser decision**'), at paragraphs 4.19 *ff*.
[13] In this case, the Parties' products are mainly prescribed by consultants in hospitals.
[14] The 2014 PPRS is available at https://www.gov.uk/government/publications/pharmaceutical-price-regulation-scheme-2014
[15] 2014 PPRS, at paragraphs 5.25 *ff*.
[16] Shire submits that in the past, [ ].
[17] The OFT understands that national health services may perform tenders to purchase medicines to comply with EU procurement rules and to obtain better prices, particularly where a generic version of a branded pharmaceutical product is available. Shire has [ ]. ViroPharma has [ ]. These tenders were organised by the Commercial Medicines Unit of the Department of Health. The Parties [ ].
[18] The OFT understands that it is not compulsory for suppliers to participate in the tender and it will continue to be possible for physicians to prescribe treatments which are not part of the tender.

as they are encouraged to follow prescribing guidelines (which often take into account the cost-effectiveness of treatments) and to meet certain budgetary objectives.[19] This may provide pharmaceutical suppliers with some incentive to compete on prices and offer their medicine at a cost-effective price.

MARKET DEFINITION

21. The OFT considers that market definition is a useful tool, but not an end in itself. Market definition provides a framework for assessing the competitive effects of the merger and involves an element of judgement. The boundaries of the market do not determine the outcome of the analysis of the competitive effects of a merger in a mechanistic way, as it is recognised that there can be constraints on merging parties from outside the relevant market, segmentation within the relevant market, or other ways in which some constraints are more important than others.[20]

22. The Parties both supply pharmaceutical products for HAE treatment.[21] The OFT's review of the merger did not reveal further overlaps between the Parties' activities (including in relation to pharmaceutical products in the research and development phase, so-called 'pipeline products').

Product scope

23. With respect to market definition, in previous decisions in the pharmaceutical sector, the European Commission ('**EC**') and the OFT have referred to the 'Anatomical Therapeutic Chemical' ('**ATC**') classification, devised by the European Pharmaceutical Marketing Research Association ('**EphMRA**') and maintained by EphMRA and Intercontinental Medical Statistics.[22] The EC has traditionally used the third level of the EphMRA ATC classification (ATC 3) which groups medicines based on their therapeutic indication (that is, intended use) as a starting point. In some cases, it has also departed from ATC3 (instead using the fourth level of the classification)[23] or included medicines used for the treatment of a particular disease (irrespective of their ATC classification). In Sanofi-Aventis/ Genzyme, the EC stated that it is appropriate to diverge from ATC3 where the circumstances of a case show that sufficiently

[19] See for instance the NHS Commissioning Policy.
[20] *Merger Assessment Guidelines,* A joint publication of the Competition Commission and the Office of Fair Trading, OFT1254, September 2010, ('**Merger Assessment Guidelines**') at paragraph 5.2.2.
[21] The Parties outsource the production of Cinryze and Firazyr.
[22] This classification is based on finished dose pharmaceutical products and their approved indications in the various countries. *See* for example, European Commission decision of 5 October 2012, Case COMP/M.6613 - *Watson/Actavis*; European Commission decision of 3 August 2010, Case COMP/M.5865 – *Teva/Ratiopharm;* ME/4136/09 - OFT decision of 9 July 2009, Anticipated joint venture between GlaxoSmithKline plc and Pfizer Inc in relation to their respective HIV businesses; Reckitt Benckiser decision.
[23] The ATC4 level constitutes a further subdivision which may be based on therapeutic use or more frequently pharmacological criteria such as molecule class, formulation, or mode of action.

strong competitive constraints faced by the undertakings involved are situated at another level and there are indications that the ATC3 class does not lead to a correct market definition.[24] The market definition was ultimately left open in this case.

24. In the *Reckitt Benckiser* decision, the OFT also considered the ATC classification system compiled and updated by the World Health Organization ('**WHO ATC classification**').[25] In addition to evidence on product characteristics and intended use (referring for example to the ATC classification systems), the OFT considered guidelines and literature used by prescribers, as well as internal documents and sales trends.[26]

25. The Parties submit that there are separate relevant markets for (i) acute treatment and (ii) long-term prophylactic therapy for HAE. They state that there is no overlap between Cinryze and Firazyr on an EphMRA ATC3 basis. They add that leading international guidelines on the treatment of HAE support the distinction between acute treatment and long-term prophylactic therapy. The Parties also submit that although Cinryze is authorised in the European Union ('**EU**') for acute treatment, there is in practice only minimal usage of Cinryze for acute cases and that it is mainly used for prophylactic treatment.[27] They also state that, so far as they are aware, Firazyr is, on the other hand, used for acute treatment only.

Constraints between HAE products in different EphMRA ATC3 categories

26. The OFT understands that Firazyr and Cinryze are not in the same EphMRA ATC3 category.[28] Cinryze (like Berinert and Ruconest) is in the ATC3 category of B2C (proteinase inhibitors), while Firazyr is in the ATC3 category of C6A (other cardiovascular products). Tranexamic acid, anabolic steroids, and fresh frozen plasma are also in different EphMRA ATC3 categories. The OFT nevertheless notes that the Parties' products (together with Berinert and Ruconest) are in the same WHO ATC category entitled '*drugs used in*

[24] See Commission decision of 12 January 2011 - Case COMP/M.5999 – *Sanofi- Aventis/Genzyme* at paragraph 9; Commission decision of 6 February 2006, Case COMP/M.4049 - *Novartis/Chiron*.
[25] At paragraphs 4.38 *ff*.
[26] Reckitt Benckiser decision, at paragraphs 4.1 *ff*.
[27] See paragraphs 55 to 58 of the decision for further information.
[28] Available at http://www.ephmra.org/Classification.

hereditary angioedema' (B6AC).[29] Tranexamic acid, anabolic steroids, and fresh frozen plasma are in different WHO ATC categories.

27. In line with its *Reckitt Benckiser* decision, the OFT has also considered literature available to physicians, physicians' actual prescribing practices, Parties' internal documents, as well as pricing of HAE treatments.

28. Literature available to prescribers on the treatment of HAE includes articles published by HAWK and the WAO, as well as national prescribing policies.[30] These articles and national prescribing policies make a distinction between acute and prophylactic therapy[31] as they address different needs. Berinert, Cinryze, Firazyr and Ruconest are recommended for acute treatment, while Berinert, Cinryze, androgens and to a lesser extent, tranexamic acid are considered for prophylactic treatment. This approach is also consistent with the British Formulary ('**BNF**') Guidelines.[32]

29. The OFT notes that physicians' prescribing practices are largely in line with the literature on HAE. The OFT's market investigation shows that customers (prescribing physicians at NHS hospitals) and competitors of the Parties distinguish between acute and prophylactic treatment.

30. With respect to acute treatment, based on physicians' responses to the market investigation, Berinert appears as the first choice treatment for a number of physicians. Cinryze is also used by a smaller number of physicians for acute treatment; they mention that it is similar to Berinert. A few state that it is ('slightly') more expensive than Berinert (one physician however stated that it is less expensive). Firazyr is also widely used (in particular for patients who prefer subcutaneous rather than intravenous administration). Ruconest is used by fewer physicians, although a few refer to its cost advantage, especially for larger patients. The other HAE treatments are not used as frequently (fresh frozen plasma is not used at all based on physicians' responses). The OFT notes that this evidence shows some demand-side substitution between a number of HAE treatments.

31. In addition, internal documents of Shire suggest that Firazyr is competing mainly against [ ], as well as against [ ]. ViroPharma's internal documents suggest that Cinryze's strongest direct competitor is [ ]. ViroPharma's internal

[29] The WHO ATC classification system is based on the modified version of the EphMRA system. It is based on active ingredients and serves a scientific, rather than commercial purpose.
[30] HAWK article on HAE; WAO guideline on HAE; documents published by the All Wales Medicines Strategy Group, the Scottish Medicines Consortium and NHS Commissioning Policy.
[31] Some articles discuss long-term and short-term prophylaxis separately, some focus on a specific type of prophylaxis.
[32] The National Institute for Health and Clinical Excellence has not published guidelines in relation to the treatment of HAE.

documents also refer to the targeting of patients that use [ ] for prophylactic treatment. ViroPharma's internal documents also mentioned [ ] as competing with Cinryze.

32. In terms of pricing, the OFT notes that there are significant price differences between the various HAE treatments.[33] This indicates that the less costly HAE treatments do not effectively constrain the price of the more expensive HAE treatments. The OFT notes that HAE treatments can be divided into two main groups:

    - The first group includes branded and more costly products for which no generic version is available. This group includes all C1-inhibitors (Berinert, Cinryze, Ruconest) and icatibant (Firazyr).
    - The second group consists of medicines where generic products are available and the cost of a single treatment is about 1/1000 of the cost of a single treatment with any of the branded products. This group includes androgens and tranexamic acid.[34]

33. The Parties indicate that they offer a [ ] price for each of their HAE products throughout the UK to compete with [ ] prices.

34. The OFT considers that, assessed in the round, this evidence shows that there is some demand-side substitution manifesting itself in a degree of price constraints between some HAE treatments (Firazyr, Berinert, Cinryze and to a lesser extent Ruconest), which are not in the same EphMRA ATC3 categories. On a cautious basis, and based on the above, the OFT has therefore taken into account constraints between different HAE products which are not in the same EphMRA ATC3 category.

Products for the treatment of HAE vs. further segmentation

35. The OFT notes that although acute and prophylactic treatments address different patient needs, some of the products are used for both types of treatment (for instance, Cinryze or Berinert). In addition, the Parties and one of their competitors told the OFT that they are not able to price discriminate between products used for acute treatment and prophylactic therapy.

36. On a cautious basis, the OFT has assessed the Merger on the basis of the supply of pharmaceutical products for the acute treatment of HAE for which both of the Parties' products can be used. The OFT has also considered the

[33] See the BNF website and the NHS Commissioning Policy.
[34] The OFT has not received price information for plasma products. Since plasma products are not considered in any guidelines for the treatment of HAE and are not prescribed in practice by the physicians contacted during the market investigation, the OFT considers that they do not exert a significant competitive constraint on the other HAE treatments.

supply of pharmaceutical products for the treatment of HAE (including acute and prophylactic therapy) as a possible frame of reference. However, the OFT does not consider it necessary to determine conclusively the precise product scope given that, on the evidence presented to it, no competition concerns arise on any reasonable frame of reference.

Geographic scope

37. The Parties submit that the geographic scope for the supply of pharmaceutical products for HAE treatment is national due to the existence of different registration systems, safety standards, social security and pricing policies within each Member State. The OFT notes that this is in line with previous EC and OFT decisions.[35]

38. Third parties who replied to the OFT's market investigation stated that there were no differences in relation to the supply of HAE treatments within the UK.

39. As no competition concerns arise on any reasonable frame of reference, the OFT does not consider it necessary to conclude on the exact scope of the geographic frame of reference. The OFT has assessed the Merger on a UK-wide basis.[36]

HORIZONTAL ISSUES

40. Prior to the Merger, the Parties' activities overlapped in relation to the supply of pharmaceutical products for the treatment of HAE, in particular with regard to the acute treatment of HAE.

Shares of Supply

41. In the absence of any reliable independent third-party data, Shire provided shares of supply of pharmaceutical products for treatment of HAE in the UK and acute treatment based on internal estimates.

42. The shares of supply vary substantially when based on value and volume. This is due to substantial price differences between branded and generic HAE treatments. According to the Merger Assessment Guidelines, concentration can be measured using various data including sales revenue and production volume.[37] The measures used will depend on the facts of the case and the availability of information; for example, when products differ in quality it may be appropriate to use sales revenue as the basis. The OFT considers for the purpose of this case that the share of supply by value is more appropriate (than

[35] See footnotes 22 and 24 above.
[36] For the purposes of the Merger, the OFT has found that differences within the UK (for instance in terms of procurement) did not justify narrowing the geographic scope.
[37] *Merger Assessment Guidelines*, at paragraph 5.3.3.

by volume) to assess the effects of the Merger, in particular in light of the Parties' offerings consisting of branded, high-value products.

43. The Parties' estimated combined share of supply of pharmaceutical products for the acute treatment of HAE in the UK (by value) is [30-40] per cent with a [0-10] per cent increment.

Table 3: Shares of supply of pharmaceutical products for acute treatment of HAE in the UK by value (2010-2013) (per cent)

Products	FY 2010	FY 2011	FY 2012	First half 2013
Firazyr	[10-20]	[10-20]	[10-20]	[30-40]
Cinryze	-	-	[0-10]	[0-10]
Combined	[10-20]	[10-20]	[10-20]	[30-40]
Berinert	[90-100]	[90-100]	[80-90]	[60-70]
Ruconest	-	-	[0-10]	[0-10]
Androgens	[0-10]	[0-10]	[0-10]	[0-10]
Tranexamic acid	[0-10]	[0-10]	[0-10]	[0-10]
Plasma products	[0-10]	[0-10]	[0-10]	[0-10]

Source: Shire's estimates

Table 4: Shares of supply of pharmaceutical products for HAE treatments by value (2010-2013) (per cent)

Products	FY 2010	FY 2011	FY 2012	First half 2013
Firazyr	[0-10]	[0-10]	[0-10]	[10-20]
Cinryze	-	-	[0-10]	[0-10]
Combined	[0-10]	[0-10]	[10-20]	[20-30]
Berinert	[90-100]	[90-100]	[80-90]	[70-80]
Ruconest	-	-	[0-10]	[0-10]
Androgens	[0-10]	[0-10]	[0-10]	[0-10]
Tranexamic acid	[0-10]	[0-10]	[0-10]	[0-10]
Plasma products	[0-10]	[0-10]	[0-10]	[0-10]

Source: Shire's estimates

44. The Parties' estimated combined share of supply of pharmaceutical products for the treatment of HAE (acute and prophylactic) in the UK (by value) is [20-30] per cent with a [0-10] per cent increment.

45. The OFT notes that pharmaceutical products for the treatment of HAE are differentiated, in particular, due to the products' different characteristics. The OFT has therefore considered closeness of substitution between the Parties' products, as the share of supply is a less meaningful indicator of unilateral effects in the supply of differentiated products.[38]

[38] *Merger Assessment Guidelines*, at paragraphs 5.4.6 *ff*.

Closeness of competition

46. The Parties state that Firazyr and Cinryze have differentiated characteristics which mean that they are not closely substitutable. They explain that the two pharmaceutical products have different EphMRA ATC classifications, different active ingredients (icatibant vs. C1-inhibitor), different dosage forms (10mg/mL vs. 1000 units), different mechanisms of action[39], and different modes of administration (subcutaneous portable pre-filled syringe vs. powder that needs to be reconstituted and administered intravenously).

47. In addition, the Parties submit that Cinryze has minimal sales in the acute treatment sector since it is primarily marketed for the prophylactic treatment of HAE. [40]

48. The Parties also submit that the merged entity will continue to face intense competition in the acute market from suppliers of Berinert, conestat alpha (Ruconest), attenuated androgens, tranexamic acid and fresh frozen plasma. The Parties argue, in particular, that Berinert is the leading product indicated for acute treatment of HAE. They state that Berinert is popular with clinicians and patients because it performs well in terms of both efficacy and tolerability. With respect to Ruconest, the Parties state that it has a similar mechanism of action to C1-inhibitor products derived from human plasma and that it is safer in that it carries no risk of either pathogen transmission or thrombosis. The Parties also state that they ensured that each of their products is priced competitively [ ].

49. The OFT discusses the Parties' arguments in turn below.

Closeness of competition between Firazyr and Cinryze

50. The majority of third parties who replied to the OFT's market investigation and in particular physicians at NHS hospitals in the UK, indicated that Firazyr and Cinryze are not substitutable. They highlighted the products' different characteristics in terms of efficacy, side effects, mode of administration, and mode of action.

51. Most physicians who replied to the OFT's market investigation told the OFT that Cinryze is similar to Berinert. The OFT received mixed evidence as regards the price competitiveness of Cinryze compared to Berinert. A few physicians noted

[39] C1-inhibitors (Berinert, Cinryze and Ruconest) bind irreversibly to proteins in the inflammation system. This slows bradykinin release causing fluid release to stop. Capillary walls become less permeable and fluids are re-absorbed into the body. Icatibant (Firazyr) is a peptide therapy which inhibits bradykinin activity through antagonism of the bradykinin type two receptor, preventing vasodilatation and vascular permeability.

[40] The Parties explained that marketing for Cinryze is focused on long-term prophylactic treatment because of [ ]. For example, the OFT notes that the Food and Drug Administration (US) refused Cinryze's marketing authorisation for acute treatment.

that Cinryze may be 'slightly' more expensive than Berinert. One physician indicated that Cinryze might have a cost-advantage over Berinert depending on the patient's weight.

52. A lack of closeness of competition is supported by internal documents of each of Shire and ViroPharma which refer to [ ]. There are only few references to the other party's products.[41]

53. The OFT also notes that Cinryze's share of supply of pharmaceutical products for the (acute) treatment of HAE has remained relatively small since 2012. Firazyr's share, on the other hand, has increased in the same period while Berinert's share has decreased.

54. Together, this evidence suggests that the Parties' products are not close competitors and that Berinert is the closest competitor of each of the Parties' products.

Cinryze's position in acute treatment

55. The OFT found that ViroPharma's internal documents relating to Cinryze focus on prophylactic treatment, consistent with the Parties' statement that Cinryze is primarily marketed as a prophylactic product.

56. ViroPharma submits that clinical results suggesting that Cinryze is not [ ] in acute treatment in Europe.[42]

57. Some physicians who responded to the OFT's market investigation stated that they use Cinryze for acute treatment and that it is similar to Berinert. However, some other physicians who replied mentioned that they do not use Cinryze for acute treatment; they use it only for prophylactic therapy.

58. Cinryze's low market position in the supply of pharmaceutical products for HAE treatment (and in acute treatment) was confirmed by data held by some national health authorities in the UK.[43]

Remaining competition

59. Third parties who replied to the OFT's market investigation indicated that Berinert is a strong competitor of the Parties in the acute treatment of HAE. It has been on the market for many years and it has a very good reputation.

[41] With respect to prophylactic treatment, Viropharma's documents frequently refer to [ ] as a competitor.
[42] Zuraw et al.,'Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema', The New England Journal of Medicine 2010, pp. 513-22; Craig et al.,'Efficacy of human C1 esterase inhibitor concentrate compared with placebo in acute hereditary angioedema attacks', The Journal of Allergy and Clinical Immunology 2009, pp. 801-8.
[43] National Services Scotland, and data submitted by the Health and Social Care Information Centre (HSCIC) and collected by IMS Health for England.

Patients currently using Berinert may be reluctant to switch to another product. This is also in line with the relevant literature on HAE.

60. In addition, the price of a dose of tranexamic acid and attenuated androgens is substantially lower than the price of a dose for a branded acute treatment of HAE, such as Berinert, Cinryze, or Firazyr.[44] The OFT notes that the substantial price differences indicate that the competitive pressure exerted on the Parties' products by the generic products may be limited.

61. The Parties submit that Ruconest can only be used for acute treatment and has 'not recommended' status from the Scottish Medicines Consortium and 'not endorsed' status from the All Wales Medicines Strategy Group. Therefore, NHS funding for Ruconest in Scotland and Wales can only be obtained on an individual basis. The OFT received mixed evidence from third parties who replied to its market investigation as regards the price competitiveness of Ruconest depending on dosage and weight of the patient. One physician told the OFT that Ruconest is generally more expensive than comparable treatments.

62. Together this evidence suggests that Ruconest, tranexamic acid, androgens and plasma products do not exert as strong a constraint as Berinert on each of the Parties' products. A majority of physicians indicated that they do not often use any of Ruconest, tranexamic acid, androgens and plasma products for acute treatment.

Parties' research and development ('**R&D**') activity

63. One third party raised concerns regarding a possible reduction of the Parties' R&D activities post-Merger. The OFT reviewed the Parties' internal documents, including post-Merger strategic documents. The OFT notes that there was no indication that the Parties would limit their R&D activity for HAE post-transaction.

64. Moreover, the OFT has not identified any competition concerns in relation to the Parties' pipeline products. ViroPhama is currently conducting clinical trials of a low-volume formulation of Cinryze [ ]. Internal documents showed the merged entity's intent to [ ]. Shire [ ].

[44] The list price for a single acute treatment with a branded medicine ranges from £1,100 to £2,672 whereas the price range for a single acute treatment attenuated androgens or tranexamic acid, which are supplied by generic manufacturers is between £0.27 and £1.58. Please refer to the BNF website and the NHS Commissioning Policy.

65. The Parties are also investigating the use of their respective products for the treatment of children. Shire told the OFT that [ ] in respect of paediatric treatments.

66. The OFT has not identified competition concerns as a result of the merger in relation to the Parties' pipeline products for treatments other than HAE.

67. The OFT also notes that the Parties' pipeline products are differentiated, as the products they currently market for the treatment of HAE. Due to the high degree of differentiation of the Parties' pipeline products and the strong competitive constraint exerted by Berinert [ ], the OFT considers that the Parties' incentives for R&D will not decrease post-Merger.

Conclusion

68. Based on the above, and in particular the small increment brought by the Merger, the OFT's findings that the Parties' products are not close substitutes and the presence of Berinert as a strong constraint on both Parties' products, the OFT considers that the Merger does not give the merged entity the ability to increase prices or worsen non-price aspects of its competitive offering post-Merger.

Barriers to entry and expansion

69. Entry or expansion of existing firms can mitigate the initial effect of the acquisition on competition, and in some cases may mean that there is no substantial lessening of competition. In assessing whether entry or expansion might prevent a substantial lessening of competition, the OFT considers whether such entry or expansion would be timely, likely and sufficient.[17] In terms of timeliness, the OFT's guidance indicates that the OFT will look for entry to occur within two years.

70. The Parties argue that new entry into the acute market is a real possibility. They note that Dyax successfully markets a further acute treatment (Kalbitor) in other jurisdictions, including the United States and that it could submit an application to the European Medicines Agency in the future.

71. The Parties submit that Firazyr's patent protection expires on [ ]. It also benefits from regulatory protection as a result of its orphan drug status[45], which is valid until [ ]. There is no patent or regulatory protection for Cinryze.

[45] Authorised orphan medicines benefit from ten years of protection from market competition with similar medicines with similar indications once they are approved. Further information available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000029.jsp&mid=WC0b01ac05800240ce

72. Given the uncertainty around Dyax's possible entry into the UK market, the OFT has not given any material weight to its possible entry in its competitive assessment.[46] Moreover, following its market investigation, the OFT is not aware of plans for the entry of any other pharmaceutical product into the UK market for the supply of HAE treatment within the next two years.

Buyer power

73. In assessing buyer power, the OFT considers the extent to which the merger is likely to reduce customers' ability and incentive to exercise buyer power.[47] The Parties submit that the NHS is able to exert significant buyer power in respect of the Parties' products and that both Firazyr and Cinryze are subject to price regulation under the PPRS.

74. Given the outcome of the competition assessment above, the OFT has not found it necessary to assess or conclude on buyer power.

NON-HORIZONTAL ISSUES

75. The OFT has considered whether the Parties might engage in anti-competitive foreclosure through the bundling of their products. Generally, in competitive terms, conglomerate mergers are often benign or even efficiency-enhancing. However, in certain circumstances, a conglomerate merger of complementary products can result in the merged entity foreclosing rivals.[48] The OFT typically frames its analysis of such theories of harm by reference to the ability of the firm to harm its rivals, as well as the incentive for, and the effect of, doing so.[49]

76. The OFT's approach in examining the possibility of anti-competitive foreclosure through bundling involves analysing the:

    a) Ability of the merging parties to undertake such strategies (would the merged firm have the ability to harm rivals?);
    b) Incentive of the parties to do so (would the merged firm find it profitable to do so?); and
    c) The effect of this strategy (would the effect be sufficient to reduce competition, for example, by foreclosing access to customers of significant competitors?).

77. In assessing these, the OFT takes into account the following factors:[50]

[46] Dyax did not respond to the OFT's market investigation.
[47] *Merger Assessment Guidelines*, section 5.9.
[48] *Merger Assessment Guidelines*, at paragraph 5.6.5.
[49] *Merger Assessment Guidelines*, at paragraph 5.6.6.
[50] *Merger Assessment Guidelines*, paragraph 5.6.13.

a) whether customers have a demand for more than one of the products, and whether the products are complements (relevant to ability);
b) customer preferences for variety and one-stop shopping (relevant to incentive); and
c) the costs to rivals of providing variety and one-stop shopping at a scale to enable them to compete effectively with the merged firm (relevant to effect).

78. The Parties argue that Shire would have neither the ability nor the incentive to offer Firazyr and Cinryze for sale together at a reduced price. They state that there is no demand for products for acute and prophylactic treatment of HAE to be bundled together, which is evidenced by these products not being supplied as a bundle in practice. They also submit that the products are prescribed and administered separately and differently and the demand for each is distinct. The Parties add that CSL Behring (Berinert) is the market leader in acute treatment and attenuated androgens and tranexamic acid are also often prescribed. In prophylactic treatment, they state that attenuated androgens hold the highest volume share, and Berinert and tranexamic acid are also often used. The Parties also argue that competing suppliers (CSL Behring and suppliers of attenuated androgens and tranexamic acid) could easily replicate the bundle.

79. With regards to the ability to foreclose, the OFT notes that the results of the market investigation suggest that there is no demand for a bundle of HAE treatments. Although physicians prescribe both acute and prophylactic treatments, their decision to prescribe one or the other depends primarily on the individual's circumstances and the clinical needs of the patient. Acute and prophylactic treatments are not usually prescribed together[51] and even if patients might use both types of treatments, the respective quantities used will vary according to the patients' conditions. The market investigation also confirmed that suppliers do not offer products for acute and prophylactic treatment as a bundle in practice.

80. In addition, as set out above, the Parties' products face competition from a number of HAE treatments. Berinert is the main treatment prescribed by physicians for acute and for prophylactic treatment. Other treatments such as androgens and tranexamic acid are also prescribed for both treatments, although not to the same extent as Berinert. Together, this evidence suggests that the Parties would not have the ability to foreclose competing products through bundling.

[51] As a precaution, some patients under prophylactic treatment may also be prescribed one dose of an acute treatment to treat a possible acute attack.

81. Furthermore, given the strong position of Berinert and the presence of attenuated androgens and tranexamic acid on the markets for acute and prophylactic treatment, the OFT considers that such a strategy would not have a foreclosure effect on the merged entity's competitors.

82. Based on the above, the OFT considers on the basis of the evidence it has found that the merged entity would not have the ability to foreclose its competitors in either acute or prophylactic treatment. Furthermore, given the strong position of Berinert and the presence of attenuated androgens and tranexamic acid on the markets for acute and prophylactic treatment, the OFT considers that such a strategy would not have a foreclosure effect on the merged entity's competitors.

THIRD PARTY VIEWS

83. The OFT contacted customers and competitors of the Parties, as well as the Department of Health (including the Commercial Medicines Unit), NHS England, NHS National Services Scotland, NHS Wales Shared Services Partnership Procurement Sourcing, Health and Social Care Northern Ireland, and patient associations.

84. Some third parties raised concerns about a possible price increase as a result of the Merger. The OFT took these concerns into account in its competitive assessment, although it found that they were not substantiated for the reasons set out in the section on unilateral effects.

85. A third party mentioned that the price for Firazyr had increased since the acquisition of Jerini by Shire in 2008. As stated above, the OFT notes that Jerini did not market Firazyr prior to the acquisition of Jerini by Shire in July 2008.

86. Third party comments have been included where relevant in the decision.

ASSESSMENT

87. The OFT has assessed the Merger on the basis of the supply of pharmaceutical products for the treatment of HAE, and the acute treatment of HAE, in the UK.

88. The estimated increment in the combined share of supply for the Parties, by value, is small and the combined share of supply is moderate under any frame of reference. On the basis of the supply of pharmaceutical products for HAE treatment, it is approximately [20-30] per cent with an increment of [0-10] per cent. On the basis of the supply of pharmaceutical products for the acute treatment of HAE, it is approximately [30-40] per cent with an increment of [0-

10] per cent. On the basis of the evidence it has found, the OFT considers that the Parties' products (Firazyr and Cinryze) are not close substitutes and that they exert a limited constraint on each other. In addition, the OFT has not identified any competition concerns in relation to the Parties' pipeline products.

89. Moreover, the merged entity will continue to face competition from the incumbent product (Berinert), and to a lesser extent from other competing products including Ruconest and generic products (in particular, tranexamic acid and androgens).

90. A couple of customers of the Parties raised concerns that the merged entity might increase prices post-Merger. The OFT took these comments into account in its assessment but considers that they were not substantiated. Given that the Parties' products are not close substitutes, that Cinryze has a limited presence in acute treatment and that the merged entity will continue to face competition from a strong competitor and smaller competitors, the OFT considers that the merged entity will not be able to increase prices or worsen non-price aspects of its competitive offering post-Merger.

91. In addition, the OFT considers on the basis of the evidence it has found that the merged entity would not have the ability to foreclose its competitors in either acute or prophylactic treatment. Furthermore, given the strong position of Berinert and the presence of attenuated androgens and tranexamic acid on the markets for acute and prophylactic treatment, the OFT considers that such a strategy would not have a foreclosure effect on the merged entity's competitors.

92. Consequently, the OFT does not believe that it is or may be the case that the Merger has resulted or may be expected to result in a substantial lessening of competition within a market or markets in the United Kingdom.

DECISION

93. This Merger will therefore **not be referred** to the Competition Commission under section 22(1) of the Act.