

European Medicines Agency Pre-authorisation Evaluation of Medicines for Human Use

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COMMITTEE FOR ORPHAN MEDICINAL PRODUCTS

PUBLIC SUMMARY OF POSITIVE OPINION FOR ORPHAN DESIGNATION OF

OF

N-3[[4(aminoiminomethyl)benzoyl]amino]propyl]-1-[[2,4-dichloro-3-[[2,4-dimethyl-8quinolinyl)oxy]methyl] phenyl]sulphonyl]-(2S)-2-pyrrolidinecarboxamide, di(methanesulfonate) for the treatment of moderate and severe traumatic brain injury

On 23 February 2004, orphan designation (EU/3/04/188) was granted by the European Commission to Laboratoires Fournier, France, for N-3[[4(aminoiminomethyl)benzoyl]amino]propyl]-1-[[2,4-dichloro-3-[[2,4-dimethyl-8-quinolinyl) oxy]methyl] phenyl]sulphonyl]-(2S)-2-pyrrolidinecarboxamide, di(methanesulfonate) (anatibant) for the treatment of moderate and severe traumatic brain injury.

The sponsorship was transferred to Xytis Pharmaceutical Limited, United Kingdom, in April 2006.

What is moderate and severe traumatic brain injury?

Trauma to the head (head injuries) is a general term for an injury of the scalp, skull and/or brain. These injuries may be from direct force (e.g. club), from a rapid deceleration force (e.g. a fall or striking the windshield in a car accident) or from a penetrating missile such as bullets.

Head injuries are potentially dangerous and the outcome depends on the severity of the injury. Traumatic brain injury is classified as minor, moderate or severe according to the symptoms present following the injury. These symptoms are mainly impairment of speech, movements or vision (e.g. breathing problems; unequal pupil size; disturbed orientation in regard to time, place or person; loss of consciousness). These symptoms are often related to the fact that the brain injury caused a bleeding or a swelling of the brain tissue (oedema), which on itself causes an elevated pressure within the skull. People with moderate and severe traumatic brain injuries are almost always admitted to the hospital for observation and will undergo repeated examinations to assure that the condition does not worsen. A so-called "cat scan" (abbreviation: CT scan) is the test used most often to evaluate acute head injuries. The scan is a special radiographic technique, using a computer, to record internal body images. It is useful for identifying the localisation and extent of the injuries to the brain.

Moderate and severe traumatic brain injuries are chronically debilitating and life-threatening.

What are the methods of treatment available?

Various methods (e.g. medicinal products and surgery), which counteract elevated pressure within the skull, were used in the Community for the treatment of moderate and severe traumatic brain injury at the time of submission of the application for orphan drug designation.

Anatibant, as a new therapeutic class in the treatment of moderate and severe traumatic brain injury, might help to achieve better overall control of the condition in particular by decreasing oedema. These benefits will have to be confirmed at the time of marketing authorisation. This will be necessary to maintain the orphan status.

What is the estimated number of patients affected by the condition*?

According to the information provided by the sponsor, moderate and severe traumatic brain injury was considered to affect about 154,000 persons in the European Union.

How is this medicinal product expected to act?

Anatibant is an antagonist of the bradykinin B_2 receptor. An antagonist is a substance that tends to nullify the action of another most often by taking its place on its specific site of action. Bradykinin, which is the substance in the body that binds to the B_2 receptor, is spontaneously generated in the brain following a brain injury and causes the swelling of the brain tissue (oedema). Anatibant is expected to act by inhibiting the binding of the bradykinin to the B_2 receptors and thus to avoid further formation of brain oedema following trauma. The reduction in brain oedema might improve the long-term outcome of the patient.

What is the stage of development of this medicinal product?

The effects of anatibant were evaluated in experimental models. At the time of submission of the application for orphan designation, a clinical trial in patients with severe traumatic brain injury was ongoing.

Anatibant was not marketed anywhere worldwide for moderate and severe traumatic brain injury, at the time of submission.

According to Regulation (EC) No 141/2000 of 16 December 1999, the Committee for Orphan Medicinal Products (COMP) adopted on 14 January 2004 a positive opinion recommending the grant of the above-mentioned designation.

Opinions on orphan medicinal products designations are based on the following cumulative criteria: (i) the seriousness of the condition, (ii) the existence or not of alternative methods of diagnosis, prevention or treatment and (iii) either the rarity of the condition (considered to affect not more than five in ten thousand persons in the Community) or the insufficient return of development investments.

Designated orphan medicinal products are still investigational products which were considered for designation on the basis of potential activity. An orphan designation is not a marketing authorisation. As a consequence, demonstration of the quality, safety and efficacy will be necessary before this product can be granted a marketing authorisation.

For more information:

Sponsor's contact details: Xytis Pharmaceutical Limited 20-22 Bedford Row London, WC1R 4JS United Kingdom Telephone: +44 800 083 2234

^{*}Disclaimer: The number of patients affected by the condition is estimated and assessed for the purpose of the designation, for a European Community population of 385,000,000 (Eurostat 2002) and may differ from the true number of patients affected by the condition. This estimate is based on available information and calculations presented by the sponsor at the time of the application.

Translations of the active ingredient and indication in all EU languages

Language	Active Ingredient	Indication
English	N-	Treatment of moderate and severe traumatic
	3[[4(aminoiminomethyl)ben	brain injury
	zoyl] amino]propyl]-1-[[2,4-	
	dichloro-3-[[2,4-dimethyl-8-	
	quinolinyi)oxy]metnyi]	
	puenyi]suiphonyi]-(23)-2-	
	di(methanesulfonate)	
Danish	N-[3-[[4-	Behandling af moderat til svær traumatisk
	(aminoiminomethyl)benzoy	hjerneskade
	l]amino]propyl] -1-[[2,4-	3
	dichlor-3-[[(2,4-dimethyl-	
	8-	
	quinolinyl)oxy]methyl]phe	
	nyl]sulphonyl] (2S)-2-	
	pyrrolidincarboxamid-	
	di(methansulfonat)	
D 1		
Dutch	N-[3-[[4-	Behandeling van matig tot ernstig traumatisch
	(aminoiminomethyl)benzoy	nersenietsei
	dichloro 2 [[(2 4 dimethy]	
	8_	
	auinolinyl)oxylmethyl]nhe	
	nyllsulphonyll-(28)-2-	
	pyrrolidinecarboxamide	
	di(methanesulfonate)	
Finnish	N-[3-[[4-	Kohtalaisen ja vaikean traumaattisen
	(aminoiminometyyli)bentso	aivovaurion hoito
	yyli]amino]propyyli] -1-	
	[[2,4-dikloro-3-[[(2,4-	
	dimetyyli-8-	
	kinolinyyli)oksi]metyyli]fe	
	nyyli]sulfonyyli] (2S)-2-	
	pyrrolidiinikarboksamidi,	
T 1	di(metaanisultonaatti)	
French	Dimethane sulfonate de N-	I raitement de blessures traumatiques moderees
		et severes du cerveau
	laminolpropyll 1 [[2 4	
	dichloro-3-[[(2 4-diméthyl-	
	8-	
	aujnoljnyl)oxvlméthyl1phé	
	nvllsulfonvll-2(S)-	
	pyrrolidinecarboxamide	

German	N_[3_[[4_	Behandlung mittelschwerer und schwerer
German	(aminoiminomethyl)benzov	traumatischer Hirnverletzungen
	llaminolnronyll 1 [[2 4	
	diablana 2 [[(2,4 dim athrd	
	alchioro-3-[[(2,4-almethyl-	
	8-	
	quinolinyl)oxy]methyl]phe	
	nyl]sulphonyl]-(2S)-2-	
	pyrrolidinecarboxamide,	
	di(methanesulfonate)	
Greek	N-	Θεραπεία μέτριας και σοβαρής τραυματικής
	3[[4(αμινοϊμινομεθυλο)βεν	κάκωσης εγκεφάλου
	ζοϋλο]αμινο]προπυλο]-1-	
	[[2,4-διχλωρο-3-[[2,4-	
	διμεθυλο-8-	
	κινολινυλο])οξυ]μεθυλο]φα	
	ινυλοΙσουλφονυλο]-(2S)-2-	
	πυροολιδινοκαρβοξαμιδο	
	δι(μεθανοσουλφονικό)	
Italian	N-[3-[[4-	Trattamento delle lesioni cerebrali traumatiche
	(aminoiminometil)benzoilla	gravi e moderate
	minolpropil]-1-[[2 4-	
	dicloro-3-[[(2 4-dimetil-8-	
	quinolinil)ossilmetillfenills	
	ulfonill (28) 2	
	nimelidingerhaggemide	
	dimeter av lfor at a	
Dortuguaga		Tratamento de dense corebrais traumáticos
Polluguese	N-[3-[[4-	Tratamento de danos cerebrais traumaticos
	(annionninonetii)denzoiija	moderados a graves
	$\min_{i=1}^{i} propii_{i=1}^{i-1} - 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 $	
	dicioro-3-[[(2,4-dimetil-8-	
	quinolinil)oxi]	
	metil]fenil]sulfonil]-(2S)-2-	
	pirrolideno carboxamida,	
	di(metanosulfonato)	
Spanish	Dimetano sulfonato de N-	Tratamiento de lesiones traumáticas cerebrales
	[3-[[4-	moderadas y graves
	(aminoiminometil)benzoil]a	
	mino]propil]-1-[[2,4-	
	dicloro-3-[[(2,4-dimetil-8-	
	quinolinil)oxi]metil]fenil]su	
	lfonil]-(2S)-2-	
	pirrolidincarboxamida, de	
	(metanosulfonato)	
Swedish	N-[3-[[4-	Behandling av måttlig och svår traumatisk
	(aminoiminometvl)bensovl]	hiärnskada
	amino]propvl] -1-[[2 4-	
	diklor-3-[[(2 4-dimetvl-8-	
	kinolinyl)oxilmetvllfenvlle	
	ulfonvll (28) 2	
	nvrrolidinkarbovamid	
	di(matansulfonat)	
	un(metansunonat)	