1. 2.	**ANNOTATED AMENDED PROPOSED PROFESSIONAL INFORMATION**	
3.		
4.	**SCHEDULING STATUS: S5**	
5.		
6.	**1. NAME OF THE MEDICINE**	
7.	**XANOR® 0,25 mg tablets**	
8.	**XANOR® 0,5 mg tablets**	
9.	**XANOR® 1,0 mg tablets**	
10.	**XANOR® 2,0 mg tablets**	
11.	**XANOR® SR 0,5 mg tablets**	
12.	**XANOR® SR 1,0 mg tablets**	
13.	**XANOR® SR 2,0 mg tablets**	
14.		
15.	**2. QUALITATIVE AND QUANTITATIVE COMPOSITION**	
16. 17.	Each XANOR 0,25 mg tablet contains 0,25 mg alprazolam and 0,1125 mg sodium benzoate (preservative).	
18. 19.	Each XANOR 0,5 mg tablet contains 0,5 mg alprazolam and 0,1125 mg sodium benzoate (preservative).	
20. 21.	Each XANOR 1,0 mg tablet contains 1,0 mg alprazolam and 0,1125 mg sodium benzoate (preservative).	
22. 23.	Each XANOR 2,0 mg tablet contains 2,0 mg alprazolam and 0,225 mg sodium benzoate (preservative).	
24.	Each XANOR SR tablet contains 0,5 mg, 1,0 mg or 2,0 mg alprazolam.	
25.	For full list of excipients, see section 6.1.	
26.	Contains sugar (lactose).	Added as per recommendation
27.		
28.	**3. PHARMACEUTICAL FORM**	

29.	Tablets	
30. 31.	XANOR 0,25 mg tablets are white, ovoid shaped, embossed with "Upjohn 29" on the one side and scored on the other side.	
32. 33.	XANOR 0,5 mg tablets are pink, ovoid shaped, embossed with "Upjohn 55" on the one side and scored on the other side.	
34. 35.	XANOR 1,0 mg tablets are lavender, ovoid shaped, embossed with "Upjohn 90" on the one side and scored on the other side.	
36. 37.	XANOR 2,0 mg tablets are white capsule shaped, three scored tablets, embossed with "U94".	
38. 39.	XANOR SR 0,5 mg tablets are ~~light~~round, blue, ~~round deep oval shape~~convex tablets~~, embossed~~ with "P&U 57" on one side.	As per Type IA_{IN} overall variations dated 27 Sep 2019 (implemented 07 Oct 2019), the wording for Appearance of the SR tablet has been simplified for clarity in alignment to Module 3.2.P.5.1 Specifications.
40. 41.	XANOR SR 1,0 mg tablets are ~~white,~~ round, white ~~deep oval shape~~, convex tablets ~~embossed~~ with "P&U 59" on one side.	
42. 43.	XANOR SR 2,0 mg tablets are ~~light blue,~~ pentagonal ~~deep oval shape~~, blue tablets ~~embossed~~ with "P&U 66"on one side.	
44.		
45.	**4. CLINICAL PARTICULARS**	
46.	**4.1 Therapeutic indications**	
47.	XANOR is indicated for the treatment of:	
48.	• SHORT-TERM RELIEF OF SYMPTOMS OF ANXIETY	
49.	• TREATMENT OF ANXIETY DISORDERS	
50. 51. 52.	Anxiety disorder is a condition corresponding most closely to the latest APA Diagnostic and Statistical Manual (DSM) diagnosis of generalised anxiety disorder.	
53. 54.	Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.	
55.	*Diagnostic criteria for generalised anxiety disorder:*	
56.	A. Generalised, persistent anxiety is manifested by symptoms from	

57.	three of the following four categories:	
58.	1. Motor tension:	
59. 60. 61.	Shakiness, jitteriness, jumpiness, trembling, muscle aches, tension, eyelid twitch, inability to relax, furrowed brow, strained face, restlessness and easily startled.	
62.	2. Autonomic hyperactivity:	
63. 64. 65. 66.	Heart pounding or racing, sweating, cold clammy hands, dry mouth, light-headedness, dizziness, paraesthesias, upset stomach, diarrhoea, discomfort in the pit of the stomach, hot or cold spells, lump in the throat, flushing, pallor, high resting pulse and respiration rate.	
67.	3. Apprehensive expectation:	
68. 69.	Fear, anxiety, worry, rumination, and anticipation of misfortune to self and others.	
70.	4. Vigilance and scanning:	
71. 72.	Hyper attentiveness resulting in distractibility, difficulty in concentrating, insomnia, feeling "on edge", impatience and irritability.	
73.	B. The anxious mood has been continuous for at least one month.	
74. 75.	C. Not due to another mental disorder, such as depressive disorder or schizophrenia.	
76.	D. At least 18 years of age.	
77.	• ANXIETY ASSOCIATED WITH DEPRESSION	
78.	• MIXED ANXIETY-DEPRESSION	
79.	• DEPRESSION	
80. 81. 82. 83. 84.	Depression can be variously described as neurotic depression, reactive depression, major depressive disorder, etc, depending upon local psychiatric nosology. Usage has not been established in depression with psychiatric features, in bipolar disorders or in "endogenous" depression (i.e. severely depressed inpatients).	

85.	• PANIC DISORDERS	
86. 87. 88.	This includes panic disorder with or without agoraphobia. The essential feature of panic disorder is the unexpected panic attack, a sudden onset of intense apprehension, fear, or terror.	
89. 90. 91. 92. 93.	Panic disorder is an illness characterised by recurrent panic attacks. Later in the course of this disturbance, certain issues e.g. driving a car or being in a crowded place, may become associated with having a panic attack. These panic attacks are not triggered by situations in which the person is the focus of others' attention (as in social phobia).	
94.	*Diagnostic criteria for panic disorder:*	
95. 96. 97. 98.	A. At least three panic attacks within a three-week period in circumstances other than during marked exertion or in a life-threatening situation. The attacks are not precipitated by exposure to a circumscribed phobic stimulus.	
99. 100. 101. 102. 103. 104. 105.	B. Panic attacks are manifested by discrete periods of apprehension or fear, and at least four of the following symptoms appear during each attack: dyspnoea, palpitations, chest pain or discomfort, choking or smothering sensations, dizziness, vertigo or unsteady feelings, feelings of unreality, paraesthesias (tingling in hands or feet), hot and cold flushes, sweating, faintness, trembling or shaking, smothering sensations, dizziness.	
106. 107. 108. 109. 110. 111. 112.	XANOR is indicated: • ~~f~~For use of up to six months duration for anxiety and depression and • ~~f~~For up to eight months in the treatment of panic disorder with or without some phobic avoidance. The effectiveness for long-term use, exceeding six months has not been established.	Amended as per recommendation

113.		
114.	**4.2 Posology and method of administration**	
115. 116.	Patients should be periodically re-assessed, and dosage adjustments made, as appropriate.	
117. 118. 119. 120.	The optimum dose of XANOR tablets should be individualised based upon the severity of the symptoms and individual patient response. In patients who require higher doses, dosage should be increased cautiously to avoid adverse effects.	
121. 122. 123. 124. 125. 126. 127. 128.	When higher dosage is required, the evening dose should be increased before the daytime dose. In general, patients who have not previously received psychotropic medications will require somewhat lower doses than those previously treated with minor tranquillisers, antidepressants or hypnotics or those with a history of chronic alcoholism. ~~It is recommended that the general principle of using the lowest effective dose be followed in elderly or debilitated patients to preclude the development of ataxia or over sedation.~~	Moved below to Special populations as per recommendation
129.	**Posology**	
130. 131.	**XANOR tablets** / **Usual starting dose*** / **Usual dose range**	
132. 133.	Anxiety / 0,25 to 0,5 mg given 3 times daily / 0,5 to 4,0 mg daily, given in divided doses	
134. 135. 136. 137. 138.	Mixed anxiety/ depression Anxiety associated with depression / 0,5 mg given 3 times daily / 1,5 to 4,5 mg daily, given in divided doses	
139. 140.	Panic disorders / 0,5 – 1,0 mg given at bedtime or 0,5 mg / The dose should be adjusted to patient	

		three times daily	response. Dosage adjustments should be in increments no greater than 1 mg every three to four days. With XANOR tablets, additional doses can be added until a three times daily or four times daily schedule is achieved. The mean dose in a large multi-clinic study was 5,7 ± 2,27 mg with occasional patients requiring a maximum of 10 mg daily.	
	Geriatric patients or in the presence of debilitating disease	0,25 mg given two or three times daily	0,25 to 0,75 mg daily, given in divided doses; to be gradually increased if needed and tolerated	
	Anxiety	1 mg daily, in one or two doses	0,5 to 4,0 mg daily, in one or two doses	
	Mixed anxiety/ depression Anxiety associated with depression	1 mg daily, in one or two doses	0,5 to 4,5 mg daily, in one or two doses	

169. 170. 171. 172. 173. 174. 175. 176. 177. 178. 179. 180. 181. 182. 183.	Panic disorders	0,5 – 1,0 mg given at bedtime or 0,5 mg two times daily	In clinical trials the mean maintenance dose was between 5 and 6 mg per day given as a single daily dose or divided into two doses daily, with occasional patients needing up to 10 mg per day. The dose should be adjusted to patient response, with dose increments of no greater than 1 mg in the daily dose every three to four days	
184. 185. 186.	Geriatrics patients	0,5 to 1,0 mg daily, given in one or two doses	0,5 to 1 mg daily; may be gradually increased if needed and tolerated	
187. 188.	* If side effects occur, the dose should be ~~lowered~~decreased (see section 4.4).			Amended as per recommendation
189. 190. 191. 192. 193.	To discontinue treatment in patients taking XANOR tablets, the dosage should be reduced slowly in keeping with good medical practice. It is suggested that the daily dosage of XANOR be decreased by no more than 0,5 mg every three days. Some patients may require an even slower dosage reduction (see section 4.4).			
194.	**Special populations**			
195. 196.	It is recommended that the general principle of using the lowest effective dose be followed in elderly or debilitated patients to preclude			Moved from above as per recommendation

197.	the development of ataxia or over sedation.	
198. 199. 200. 201. 202. 203. 204.	In elderly patients, in patients with advanced liver disease or in patients with debilitating disease, the usual starting dose of XANOR is 0,25 mg, given two or three times daily, and of XANOR SR is 0,5 mg once daily. This may be gradually increased if needed and tolerated. The elderly may be especially sensitive to the effects of benzodiazepines. If side effects occur at the recommended starting dose, the dose may be lowered.	Added as per recommendation, and in line with XANAX USPI pg 22, para 6, and XANAX XR USPI, pg 22, para 3
205.	**Paediatric population**	Moved from section 4.4 below as per recommendation
206. 207.	The safety and efficacy of XANOR has not been established in children under the age of 18 years.	
208.	**Method of administration**	
209. 210. 211. 212.	XANOR SR tablets may be administered once daily, preferably in the morning. The XANOR SR tablets should be taken intact; they should not be chewed, crushed or broken.	
213.		
214.	**4.3 Contraindications**	
215. 216. 217.	• XANOR is contraindicated in patients with known hypersensitivity to benzodiazepines, alprazolam, or to any component of these formulations.	
218. 219.	• XANOR is not recommended for patients whose primary diagnosis is schizophrenia.	
220. 221. 222.	• Concomitant administration with antiretroviral protease inhibitors, ketoconazole and itraconazole, as the elimination of XANOR is delayed several fold.	Added as per recommendation, and in line with XANAX USPI pg 5, para 8, and XANAX XR USPI, pg 6, para 3
223.	• The safety and efficacy of XANOR has not been established in	Moved from section 4.4 below and amended as per recommendation

224.	children ~~under~~below the age of 18 years.	
225. 226. 227.	• Benzodiazepines are also contraindicated in patients with myasthenia gravis, severe respiratory insufficiency, sleep apnoea syndrome and severe hepatic insufficiency.	Added as per recommendation, and XANAX UK SmPC pg 2, para 9
228.		
229.	**4.4 Special warnings and precautions for use**	
230. 231.	XANOR usage has not been established in certain types of depression (see section 4.1).	
232. 233. 234.	Particular caution should be exercised with the elderly and debilitated who are at particular risk of over-sedation, respiratory depression and ataxia. (The initial oral dosage should be reduced in these patients).	Added as per recommendation, and SAHPRA guideline 2.20 Package Inserts for Human Medicines Standardised Texts, Jun 2015, v4
235. 236. 237. 238. 239. 240. 241. 242. 243.	XANOR must be used with caution in patients with: • ~~i~~Impaired renal function. ~~or~~ • Mild to moderate hepatic ~~function~~insufficiency.~~,~~ • ~~p~~Pulmonary disease or limited pulmonary reserve. • Patients suffering from anxiety accompanied by an underlying depressive disorder. • Patients receiving barbiturates or other central nervous system depressants. There is an additive risk of central nervous system depression when these medicines are taken together.	Amended as per recommendation, and in line with XANAX UK SmPC pg 2, para 11 Added as per recommendation, and in line with SAHPRA guideline 2.20 Package Inserts for Human Medicines Standardised Texts, Jun 2015, v4
244. 245. 246. 247. 248.	There have been rare reports of death in patients with severe pulmonary disease shortly after the initiation of treatment with XANOR. A decreased systemic alprazolam elimination rate (e.g. increased plasma half-life) has been observed in both alcoholic liver disease patients and obese patients receiving XANOR.	Added as per recommendation, and in line with XANAX USPI pg 10, para 3, and XANAX XR USPI, pg 10, para 8
249. 250. 251.	XANOR produces additive CNS depressant effects when co-administered with alcohol or other medicines producing CNS depression.	

252. 253. 254. 255. 256. 257. 258.	Habituation and emotional/physical dependence may occur with XANOR. The risk of dependence increases with higher doses and long-term use and is further increased in patients with a history of alcoholism or drug abuse. Caution should be particularly used when prescribing XANOR to patients who are prone to abuse drugs (e.g. alcoholics and drug addicts) because of their predisposition to habituation and dependence.	
259. 260. 261. 262. 263. 264. 265. 266.	Withdrawal symptoms have occurred following rapid decrease or abrupt discontinuance of XANOR. These can range from mild dysphoria and insomnia to a major syndrome which may include abdominal and muscle cramps, vomiting, sweating, tremor, and convulsions. In addition, withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy with XANOR and special care must be taken in the treatment of epileptic patients. See section 4.2 for dose reduction during withdrawal period.	
267. 268. 269.	XANOR should be avoided in psychotic patients and patients suffering from mental depression unless there is a marked component of anxiety in their illness.	
270. 271. 272. 273. 274. 275. 276. 277. 278. 279.	*Suicide* ~~Panic disorders have been associated with primary and secondary major depressive disorders and increased reports of suicide among untreated patients. Therefore, the same precaution must be exercised when using the higher doses of XANOR in treating patients with panic disorders as is exercised with the use of any~~ As with other psychotropic medicines, the usual precautions with respect to administration of the medicine and size of the prescription are indicated for severely ~~in treating~~ depressed patients or those in whom there is reason to expect concealed suicidal ideation or plans. Panic disorder has been	Amended as per recommendation, and brought in line with XANAX USPI pg 9, para 7, and XANAX XR USPI, pg 10, para 5

280. 281.	associated with primary and secondary major depressive disorders and increased reports of suicide among untreated patients.	
282. 283. 284.	*Mania* Episodes of hypomania and mania have been reported in association with the use of XANOR in patients with depression.	
285. 286. 287. 288. 289. 290. 291. 292. 293. 294. 295. 296. 297. 298. 299.	*Risk from concomitant use of opioids* Concomitant use of XANOR and opioids may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of sedative medicines such as benzodiazepines or related drugs such as XANOR with opioids should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe XANOR concomitantly with opioids, the lowest effective dose should be used, and the duration of treatment should be as short as possible (see also general dose recommendation in section 4.2). The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their environment to be aware of these symptoms (see section 4.5).	Added as per recommendation, and XANAX UK SmPC pg 3, para 2 – 4
300. 301. 302. 303. 304.	*Amnesia* Benzodiazepines may induce anterograde amnesia. The condition occurs most often several hours after ingesting the product and therefore to reduce the risk patients should ensure that they will be able to have uninterrupted sleep of 7 – 8 hours.	Added as per recommendation, and XANAX UK SmPC pg 4, para 2
305. 306. 307.	*Tolerance* Some loss of efficacy to the hypnotic effects of benzodiazepines may develop after repeated use for a few weeks.	Added as per recommendation, and XANAX UK SmPC pg 4, para 4

308. 309. 310.	Patients with rare hereditary problems of galactose intolerance, ~~the~~ ~~Lapp~~total lactase deficiency or glucose-galactose malabsorption should not take this medicine.	Amended to comply with Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' (SANTE-2017-11668) EMA/CHMP/302620/2017/EN corr. 1, as per latest PI guideline
311.	~~**Paediatric population**~~	
312. 313.	~~The safety and efficacy of XANOR has not been established in children under the age of 18 years.~~	Moved to section 4.3 above as per recommendation
314.		
315.	**4.5 Interaction with other medicines and other forms of interaction**	
316. 317. 318. 319. 320.	The steady state plasma concentrations of imipramine and desipramine have been reported to be increased an average of 31 and 20 %, respectively, by the concomitant administration of XANOR tablets in doses up to 4 mg/day. The clinical significance of these changes is unknown.	
321. 322. 323. 324. 325. 326. 327. 328. 329. 330. 331. 332. 333.	*Opioids* The concomitant use of sedative medicines such as benzodiazepines or related medicines such as XANOR with opioids increases the risk of sedation, respiratory depression, coma and death because of additive central nervous system (CNS) depressant effect. The dosage and duration of concomitant use should be limited (see section 4.4). Concomitant intake with alcohol is not recommended. XANOR should be used with caution when combined with CNS depressants. Enhancement of the central depressive effect may occur in cases of concomitant use with antipsychotics (neuroleptics), hypnotics, anxiolytics/sedatives, antidepressant agents, narcotic analgesics, anti-epileptic drugs, anaesthetics and sedative antihistamines. In the case of narcotic analgesics, enhancement of the euphoria may also occur	Added as per recommendation, and XANAX UK SmPC pg 4, para 8

334. 335. 336.	leading to an increase in psychic dependence. Pharmacokinetic interactions can occur when XANOR is administered along with medicines that interfere with its metabolism.	
337. 338. 339. 340. 341. 342. 343. 344. 345. 346. 347. 348. 349. 350. 351. 352. 353.	*CYP3A inhibitors* Pharmacokinetic interactions can occur when XANOR is administered along with medicines that interfere with its metabolism. Compounds which inhibit certain hepatic enzymes (particularly cytochrome P450 ~~III~~3A4) may increase the concentration of XANOR and enhance its activity. Data from clinical and *in vitro* studies with XANOR, and clinical studies with medicines metabolised similarly to XANOR provide evidence for varying degrees of interaction and possible interaction with XANOR for a number of medicines. Based on the degree of interaction and the type of data available, the following recommendations are made: • Caution and consideration of dose reduction is recommended when XANOR is co-administered with nefazodone, fluvoxamine, and cimetidine. • Caution is recommended when XANOR is co-administered with fluoxetine, oral contraceptives, sertraline, diltiazem, or macrolide antibiotics such as erythromycin and troleandomycin.	
354. 355. 356. 357. 358. 359. 360. 361.	*CYP3A4 inducers* Since XANOR is metabolised by CYP3A4, inducers of this enzyme may enhance the metabolism of XANOR. Interactions involving HIV protease inhibitors (e.g. ritonavir) and XANOR are complex and time dependent. Short-term, low doses of ritonavir resulted in a large impairment of XANOR clearance, prolonged its elimination half-life and enhanced clinical effects. However, upon extended exposure to ritonavir, CYP3A induction offset this inhibition. This interaction will	Added as per recommendation, and XANAX UK SmPC pg 5, para 2

362.	require a dose-adjustment or discontinuation of XANOR.	
363. 364. 365. 366. 367.	*Digoxin* Increased digoxin concentrations have been reported when XANOR was given, especially in elderly (> 65 years of age). Patients who receive XANOR and digoxin should therefore be monitored for signs and symptoms related to digoxin toxicity.	Added as per recommendation, and XANAX UK SmPC pg 5, para 3
368.		
369.	**4.6 Fertility, pregnancy and lactation**	
370.	**Pregnancy**	
371. 372. 373.	The safety of XANOR during pregnancy and lactation has not been established. The potential for congenital malformations in children of patients who have received XANOR during pregnancy exists.	
374. 375. 376. 377.	XANOR should not be administered during labour. Given during labour, it crosses the placenta and may cause the floppy-infant syndrome characterised by central respiratory depression, hypothermia and poor sucking.	
378.	**Breastfeeding**	
379. 380.	XANOR should not be administered to mothers breastfeeding their infants, since XANOR is excreted in human breast milk.	
381.		
382.	**4.7 Effects on ability to drive and use machines**	
383. 384. 385. 386. 387.	~~Caution p~~Patients should be cautioned about using XANOR while operating motor vehicles or other dangerous activities until it is established that they do not become impaired while taking XANOR. XANOR causes side effects such as somnolence, which may affect the ability to drive and use machines.	Added as per recommendation
388.		
389.	**4.8 Undesirable effects**	

390. The table below contains adverse events categorised as follows utilising
391. the incidence rates: Very common (≥ 1/10) ~~(≥ 10 %),~~; ~~C~~common (≥ 1/100
392. ~~and~~to < 1/10) ~~(≥ 1 % and < 10 %),~~; ~~U~~uncommon (≥ 1/1 000 ~~and~~to <
393. 1/100) ~~(≥ 0,1 % and < 1 %),~~; ~~R~~rare (≥ 1/10 000 ~~and~~to < 1/1 000) ~~(≥ 0,01~~
394. ~~% and < 0,1 %),~~; ~~V~~very rare (< 1/10 000) ~~(< 0,01 %)~~.

395. Undesirable effects associated with alprazolam therapy in patients
396. participating in controlled clinical studies were as follows:

397.
398.
399.

MedDRA System Organ Class	**Frequency**	**Undesirable effects**
400. 401. *Metabolism and nutrition disorders*	Common	Decreased appetite
402. 403. *Psychiatric disorders*	Common	Confusional state, depression, irritability, libido decreased
404. 405. 406.	Uncommon	Aggression, insomnia, loss of libido, mood disorder, nervousness
407.	Rare	Hallucinations, agitation, rage
408. 409. *Nervous system disorders*	Very common	Sedation, somnolence
410. 411. 412. 413. 414.	Common	Ataxia, balance impaired, coordination abnormal, dizziness, headache, memory impairment, dysarthria, hypersomnia, lethargy
415. 416.	Uncommon	Amnesia, increased activity, tremor
417.	Rare	Intellectual impairment, slurred

418.			speech	
419.	*Eye disorders*	Common	Vision blurred	
420.		Rare	Increased intraocular pressure	
421.	*Gastrointestinal disorders*	Common	Constipation, nausea, dry mouth	
422.				
423.		Uncommon	Diarrhoea, vomiting	
424.	*Hepatobiliary disorders*	Rare	Abnormal liver function	
425.				
426.	*Skin and subcutaneous tissue disorders*	Rare	Dermatitis	
427.				
428.				
429.	*Musculoskeletal and connective tissue disorders*	Uncommon	Muscle twitching, muscle weakness	
430.				
431.				
432.	*Renal and urinary disorders*	Uncommon	Enuresis, urinary frequency	
433.		Rare	Urinary retention	
434.	*Reproductive system and breast disorders*	Uncommon	Menstrual irregularities	
435.		Rare	Sexual dysfunction	
436.				
437.	*General disorders and administration site conditions*	Common	Fatigue	
438.				
439.				
440.				
441.	*Investigations*	Uncommon	Jaundice, weight decreased, weight increased	
442.				
443.	*Post-marketing surveillance*			
444.	The following post-marketing events have been reported with XANOR:			
445.	**MedDRA**	**Frequency**	**Undesirable effects**	

System Organ Class			
Endocrine disorders	Less frequent	Hyperprolactinaemia	
Psychiatric disorders	Less frequent	Hypomania, mania (see section 4.4), hallucination, anger, aggression, hostility, agitation, libido disorder, abnormal thinking, psychomotor hyperactivity	
Nervous system disorders	Less frequent	Dystonia	
	Less frequent	Autonomic nervous system imbalance	
Gastrointestinal disorders	Less frequent	Gastrointestinal disorder	
Hepatobiliary disorders	Less frequent	Hepatitis, abnormal hepatic function, jaundice	
Skin and subcutaneous tissue disorders	Less frequent	Dermatitis	
	Less frequent	Angioedema	
Renal and urinary disorders	Less frequent	Incontinence, urinary retention	
Reproductive system and breast disorders	Less frequent	Sexual dysfunction, irregular menstruation	
General disorders and administration site conditions	Less frequent	Peripheral oedema	

474.	*Investigations*	Less frequent	Increased intraocular pressure	
475.	*Reporting of suspected adverse reactions*			
476. 477. 478. 479. 480. 481.	Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8			
482.				
483.	**4.9 Overdose**			
484. 485. 486. 487. 488. 489. 490. 491.	Symptoms of overdose with XANOR are extensions of its pharmacological action and include drowsiness, slurred speech, motor incoordination, coma and respiratory depression. Serious sequelae are rare unless other medicines and/or ethanol are concomitantly ingested. Treatment of overdosage is primarily supportive of respiratory and cardiovascular function. The value of dialysis has not been determined. Flumazenil may be used as an adjunct to the management of respiratory and cardiovascular function associated with overdose.			
492.				
493.	**5. PHARMACOLOGICAL PROPERTIES**			
494.	**5.1 Pharmacodynamic properties**			
495.	Category and class: A 2.6 Tranquillisers			
496. 497. 498. 499. 500. 501.	Alprazolam is an anxiolytic agent of the benzodiazepine group. Benzodiazepines, including alprazolam, are thought to bind to central nervous system benzodiazepine receptors, thereby increasing the affinity of the receptor for gamma-aminobutyric acid (GABA). GABA, an inhibitory neurotransmitter, modulates the activity of other neurotransmitter systems, including the noradrenergic system.			

502.	**5.2 Pharmacokinetic properties**	
503. 504. 505. 506. 507. 508. 509. 510. 511. 512. 513. 514. 515. 516. 517. 518.	*Absorption* ~~The pharmacokinetics of alprazolam are linear over the recommended dosage range, with plasma concentrations being proportional to dose given.~~ Alprazolam is almost completely bioavailable following oral administration. The bioavailability and pharmacokinetic characteristics of XANOR tablets or XANOR SR tablets are comparable, except for a slower rate of absorption of alprazolam from XANOR SR tablets. The slower absorption rate for XANOR SR tablets results in peak plasma alprazolam concentrations that are approximately one-half that of an equivalent dose of XANOR tablets; peak concentrations occur within one to two hours after a single dose of XANOR tablets, and 5 to 11 hours after a single dose of XANOR SR tablets. The plasma elimination half-life of alprazolam has been found to be about 11 to 15 hours in healthy adults. A comparable elimination half-life for XANOR SR tablets indicates that the metabolism and elimination of alprazolam are the same for both dosage forms.	Added as per recommendation Moved below to Linearity/non-linearity Moved from below, and in line with XANAX USPI pg 2, para 4, and XANAX XR USPI, pg 2, para 3 – 4
519. 520. 521. 522. 523.	Steady-state plasma concentrations are achieved within three to four days of continuous dosing with either dosage form. When equivalent daily doses are given, steady-state peak and trough plasma alprazolam concentrations for XANOR SR tablets given once or twice a day are comparable to XANOR tablets given three or four times a day.	
524. 525.	*Distribution* *In vitro*, alprazolam is bound (80 %) to human serum protein.	Added as per recommendation Moved from below, and in line with XANAX USPI pg 2, para 5, and XANAX XR USPI, pg 3, para 1
526. 527. 528.	*Biotransformation* ~~Alprazolam and its metabolites are excreted primarily in the urine.~~ The predominant metabolites are alpha-hydroxy-alprazolam, 4-hydroxy	Added as per recommendation Moved below to Elimination

529. 530. 531. 532.	alprazolam, and a benzophenone derived from alprazolam. Although they possess some pharmacological activity, the plasma levels of these metabolites are extremely low during chronic dosing. ~~*In vitro*, alprazolam is bound (80 %) to human serum protein.~~	Moved above to Distribution
533. 534. 535. 536.	~~The plasma elimination half-life of alprazolam has been found to be about 11 to 15 hours in healthy adults. A comparable elimination half-life for XANOR SR tablets indicates that the metabolism and elimination of alprazolam are the same for both dosage forms.~~	Moved above to Absorption
537. 538.	*Elimination* Alprazolam and its metabolites are excreted primarily in the urine.	Added as per recommendation Moved from above, and in line with XANAX USPI pg 2, para 7, and XANAX XR USPI, pg 3, para 3
539. 540. 541. 542.	*Linearity/non-linearity* The pharmacokinetics of alprazolam are linear over the recommended dosage range, with plasma concentrations being proportional to dose given.	Added as per recommendation Moved from above
543. 544. 545. 546.	*Special populations* Alprazolam clearance has been reported to be delayed in patients with impaired hepatic and renal function, alcoholism, in elderly or obese patients, and by the co-administration of certain medicines.	Added as per recommendation
547.		
548.	**6. PHARMACEUTICAL PARTICULARS**	
549.	**6.1 List of excipients**	
550.	XANOR 0,25 mg, 0,5 mg, 1,0 mg and 2,0 mg tablets:	
551. 552. 553. 554. 555.	Colloidal silicon dioxide Docusate sodium with sodium benzoate Lactose hydrous Magnesium stearate Microcrystalline cellulose	

556. 557.	Starch with erythrosine sodium or FD & C blue as colourants	
558.	XANOR SR 0,5 mg, 1,0 mg and 2,0 mg tablets:	
559. 560. 561. 562. 563.	Cellulose methylhydroxypropyl Lactose anhydrous Magnesium stearate Silicon colloidal dioxide FD & C blue as colourant	
564.		
565.	**6.2 Incompatibilities**	
566.	Not applicable.	
567.		
568.	**6.3 Shelf life**	
569.	XANOR 0,25 mg, 0,5 mg, 1,0 mg tablets: 36 months	
570.	XANOR 2,0 mg tablets: 60 months	
571.	XANOR SR 0,5 mg, 1,0 mg, 2,0 mg tablets: 24 months	
572.		
573.	**6.4 Special precautions for storage**	
574.	Store at or below ~~30~~25 °C.	As per Type IA_{IN} overall variations dated 27 Sep 2019 (implemented 07 Oct 2019), the storage condition has been aligned to the outcome discussed in Module 3.2.P.8.1 Stability summary and conclusion
575.	Keep tablets packed in bottles tightly closed.	
576.	Keep tablets in the carton until use.	
577.	Protect from light.	
578.		
579.	**6.5 Nature and contents of container**	

580. 581.	XANOR 0,25 mg and 1,0 mg are packed in blister packs of 30 and 100 tablets.	
582. 583.	XANOR 0,5 mg is packed in blister packs of 30 and 100 tablets and in bottles containing 500 tablets.	
584.	XANOR 2,0 mg is packed in bottles containing 30 and 100 tablets.	
585.	XANOR SR tablets are packed in foil blisters of 60 tablets.	
586.	Not all pack sizes may be marketed.	
587.		
588.	**6.6 Special precautions for disposal**	
589.	No special requirements.	
590.		
591.	**7. HOLDER OF CERTIFICATES OF REGISTRATION**	
592.	Pfizer Laboratories (Pty) Ltd	
593.	85 Bute Lane	
594.	Sandton	
595.	2196	
596.	South Africa	
597.	Tel.: +27(0)11 320 6000 / 0860 734 937 (Toll-free South Africa)	
598.		
599.	**8. REGISTRATION NUMBERS**	
600.	XANOR 0,25 mg tablets: M/2.6/233	
601.	XANOR 0,5 mg tablets: M/2.6/234	
602.	XANOR 1,0 mg tablets: M/2.6/235	
603.	XANOR 2,0 mg tablets: 27/2.6/0096	
604.	XANOR SR 0,5 mg tablets: 29/2.6/0504	
605.	XANOR SR 1,0 mg tablets:29/2.6/0505	
606.	XANOR SR 2,0 mg tablets: 29/2.6/0506	
607.		

608.	**9. DATE OF FIRST AUTHORISATION**	
609.	XANOR 0,25 mg, 0,5 mg, 1,0 mg tablets: 23 May 1983	
610.	XANOR 2,0 mg tablets: 20 October 1993	
611.	XANOR SR 0,5 mg, 1,0 mg, 2,0 mg tablets: 21 June 1996	
612.		
613.	**10. DATE OF REVISION OF THE TEXT**	
614.	07 March 2014	
615.		
616.	**BOTSWANA: S1C**	
617.	XANOR 0,25 mg – Reg. no.: B9312185	
618.	XANOR 0,5 mg – Reg. no.: B9312190	
619.	XANOR 1,0 mg – Reg. no.: B9312195	
620.		
621.	**NAMIBIA: NS3**	
622.	XANOR 0,25 mg – Reg. no.: 90/2.6/001366	
623.	XANOR 0,5 mg – Reg. no.: 90/2.6/001367	
624.	XANOR 1,0 mg – Reg. no.: 90/2.6/001368	
625.	XANOR 2,0 mg – Reg. no.: 04/2.6/0746	
626.	XANOR SR 0,5 mg – Reg. no.: 04/2.6/0747	
627.	XANOR SR 1,0 mg – Reg. no.: 04/2.6/0748	
628.	XANOR SR 2,0 mg – Reg. no.: 04/2.6/0749	